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SYNTHESIS OF SOME NEWER PYRIMIDINONE DERIVATIVES AS POTENTIAL ANALGESICS AND ANTI-INFLAMMATORY AGENTS

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ABSTRACT

A number of substituted chalcones (1a-1o) were synthesized by the reaction of substituted benzaldehyde and substituted acetophenone in presence of ethanolic sodium hydroxide solution. On further treating these substituted chalcones (1a-1o) with urea in alkaline medium, yielded a series of 4,6 disubstituted pyrimidine-2-one derivatives (2a-2o). The structures of the newly synthesized compounds have been established on the basis of IR, ^{1}H-NMR, MS (ESI) data and elemental analysis. All the compounds were screened for their analgesic activity by Acetic acid induced writhing method and anti-inflammatory activity by Carrageenan induced hind paw oedema assay.

Keywords: *Pyrimidine; Chalcones; Analgesic activity; Anti-inflammatory activity*.

INTRODUCTION

Cyclooxygenase (COX) is the rate limiting enzyme of the prostanoid biosynthetic pathway, it catalyses the conversion of arachidonic acid to various inflammatory mediators such as prostaglandin, prostacyclin and thromboxane .The enzyme cyclooxygenase exist in two isoforms COX-1 and COX-2. The association of COX-2 with induced inflammation has led to the fact that the selective inhibition of COX-2 over COX-1 might provide good anti-inflammatory agents with reduced side effects than classical NSAIDs but careful prospective examination of coxibs has exhibited unexpected cardiovascular adverse effect[1,2]. Therefore development of novel compounds having anti-inflammatory and analgesic activities with an improved safety profile is very necessary.

The synthesis of pyrimidine derivatives has engrossed substantial attention from organic and medicinal chemists for many years. As several pyrimidine derivatives are known to be associated with multiple biological activities like analgesic[2,3], anti-inflammatory[4,5], antitumor[6], antiviral[7] and antimicrobial[8-10]. This stimulated our interest for the synthesis of 4,6-disubstituted pyrimidine-2-one (2a-2o). The structures of the synthesized compounds have been established on the basis of IR, ^{1}H NMR, MS (ESI) data and elemental analysis.

EXPERIMENTAL

All the compounds (2a-2o) were synthesized by using laboratory grade chemicals. The melting points were determined by open capillary method using Thiele's tube and uncorrected. IR spectrum of compounds using KBr pellets were recorded on a Shimadzu FTIR-8400S spectrophotometer, ^{1}H NMR spectra were recorded on Bruker DRX-300 (300-D MHz, FT NMR) spectrophotometer using TMS as an internal standard, $CDCl_3$ as a solvent. Mass spectra were obtained using LC-MS (Shimadzu-2010AT) under Electron Spray Ionization (ESI) technique and elemental analysis was performed using Elemental Vario EL III, Carlo-Erba 1108. Purity of the compounds was checked by TLC on precoated TLC silica gel 60 aluminium sheets by using *n*-hexane: ethyl acetate (8:2) as solvent system.

General procedure for the synthesis of 3-(Substitutedphenyl)-1-(substitutedphenyl)prop-2-en-1-one (1a-1o)

Ethanolic solution of sodium hydroxide (12 ml, 5%) was added to substituted acetophenone (0.43 mol) and then substituted benzaldehyde (0.43 mol) was added, stirred vigorously until mixture was thick, the mixture was kept in the refrigerator overnight, product was filtered, washed with cold water and recrystallized from ethanol to give pure crystals of compounds (1a-1o).

General procedure for the synthesis of 4,6-disubstituted pyrimidine-2(1*H*)-one (2a-2o).

3-(substitutedphenyl)-1-(substitutedphenyl)prop-2-en-1-one (0.1 mol) and urea (0.01 mol) were dissolved in ethanolic solution of sodium hydroxide (20ml, 5%) and it was refluxed for 9hr. After refluxing, it was cooled and poured in cold water. The resultant reddish brown solid was filtered, washed with cold water and recrystallized from ethanol to give reddish brown semisolid compounds which were again recrystallized from ethanol to give pure compounds (2a-2o).

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Scheme:

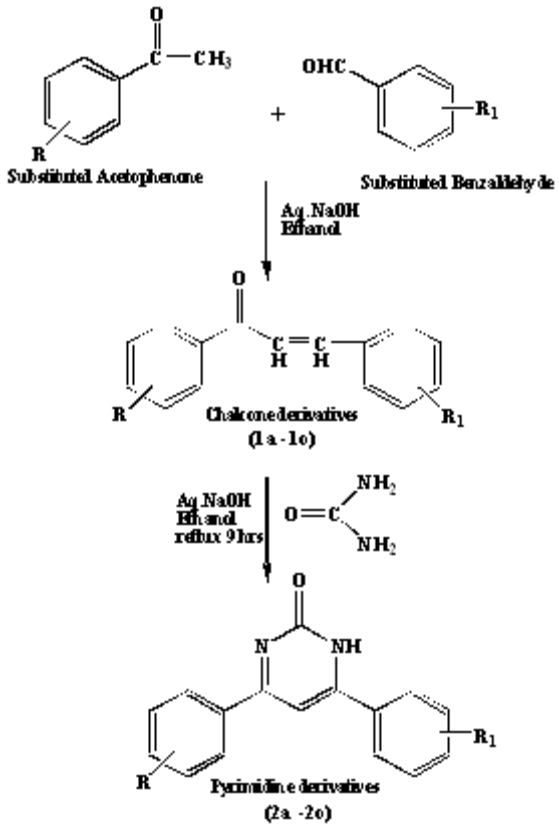

Fig. 1. Synthesis of 4, 6-disubstituted pyrimidine-2-one (2a-2o)

The spectral data of final compounds are given below: **4-Phenyl-6-(3'-fluorophenyl)pyrimidin-2(1*H*)-one, 2a: IR (KBr) □:** 3375.41 (N-H stretching), 3022.24 (aromatic C-H stretching), 1662.28 (C=O stretching), 1593.72 (C=C stretching), 1565.33 (C=N stretching), 1276.28 (C-N stretching), 1222.28 (C-F stretching), 754.97 cm^{-1} (disubstituted benzene deformation). **^{1}H NMR ($CDCl_3$):** □ 7.09-7.34 (m, 8H, Ar-H), 7.88-7.84 (d, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 8.41 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 266.27; **Fragments:** 189.04, 171.05, 95.02, 77.03. **Elemental analysis:** Calcd for $C_{16}H_{11}FN_2O$: C, 72.17; H, 4.16; F, 7.14; N, 10.52.Found $C_{16}H_{11}FN_2O$: C, 72.12; H, 4.11; F, 7.12; N, 10.49 %.

4-(4'-Fluorophenyl)-6-(2''-chlorophenyl)pyrimidin-2(1*H*)-one, 2b: IR (KBr) □: 3324.70 (N-H stretching), 3031.89 (aromatic C-H stretching), 1676.03 (C=O stretching), 1589.88 (C=C stretching), 1556.72 (C=N stretching),1323.08 (C-N stretching), 1218.28 (C-F stretching),775.56 (C-Cl stretching), 754.12 cm^{-1} (disubstituted benzene deformation). **^{1}H NMR ($CDCl_3$):** □6.90-7.35 (m, 6H, Ar-H), 7.70-7.82 (d, 1H, Ar-H), 7.90-8.01 (d, 2H, Ar-H), 8.33 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 300.70; **Fragments:** 205.01, 189.02, 96.03, 95.06. **Elemental analysis:** Calcd for $C_{16}H_{10}ClFN_2O$: C, 63.90; H, 3.35; Cl, 11.79; F, 6.32; N, 9.32. Found $C_{16}H_{10}ClFN_2O$: C, 63.88; H, 3.32; Cl, 11.76; F, 6.30; N, 9.30 %.

4-(4'-Fluorophenyl)-6-(3''-chlorophenyl)pyrimidin-2(1*H*)-one, 2c: IR (KBr) □: 3352.50 (N-H stretching), 3010.80 (aromatic C-H stretching), 1672.31 (C=O stretching), 1586.84 (C=C stretching), 1568.01 (C=N stretching),1320.18 (C-N stretching),1232.40 (C-F stretching), 788.66 (C-Cl stretching), 760.37 cm^{-1} (disubstituted benzene deformation).**^{1}H NMR ($CDCl_3$):** □7.23-7.40 (m, 4H, Ar-H), 7.67-7.70 (d, 2H, Ar-H), 7.77 (s, 1H, Ar-H), 7.80-7.98 (d, 2H, Ar-H), 8.66 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 300.71; **Fragments:** 205.01, 189.04, 96.05, 95.06. **Elemental analysis:** Calcd for $C_{16}H_{10}ClFN_2O$: C, 63.90; H, 3.35; Cl, 11.79; F, 6.32; N, 9.32.Found $C_{16}H_{10}ClFN_2O$: C, 63.88; H, 3.32; Cl, 11.76; F, 6.28; N, 9.30 %.

4-(4'-Fluorophenyl)-6-(3''-methoxyphenyl)pyrimidin-2(1*H*)-one, 2d: IR (KBr) □: 3371.40 (N-H stretching), 3020.40 (aromatic C-H stretching), 1680.32 (C=O stretching), 1598.38 (C=C stretching),1562.30 (C=N stretching), 1310.18 (C-N stretching), 1275.70 (C-O stretching), 1216.40 (C-F stretching), 768.46 cm^{-1} (disubstituted benzene deformation). **^{1}H NMR ($CDCl_3$):** □3.84(s, 3H, -OCH_3), 6.90-6.93 (d, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 7.09-7.97 (m, 6H, Ar-H), 8.01-8.03 (d, 1H, Ar-H), 8.52 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 296.30.**Fragments:** 201.06, 189.04, 107.05, 95.02. **Elemental analysis:** Calcd for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; F, 6.41; N, 9.45. Found $C_{17}H_{13}FN_2O_2$: C, 68.89; H, 4.40; F, 6.38; N, 9.42 %.

4-(4'-Methoxyphenyl)-6-(4''-fluorophenyl)pyrimidin-2(1*H*)-one, 2e: IR (KBr) □: 3364.72 (N-H stretching), 3021.30 (aromatic C-H stretching), 1678.30 (C=O stretching), 1567.40 (C=N stretching), 1591.20 (C=C stretching), 1320.07 (C-N stretching), 1263.50(C-O stretching), 1230.40 (C-F stretching), 786.30 cm^{-1} (disubstituted benzene deformation).**^{1}H NMR ($CDCl_3$):** □ 3.43(s, 3H, -OCH_3), 6.99-7.03 (d, 2H, Ar-H), 7.16-7.48 (m, 5H, Ar-H), 7.90-7.96 (d, 2H, Ar-H), 8.46 (s, 1H, N-H, D_2O exchangeable).**MS (ESI) (m/z):**$[M]^+$ 296.31;**Fragments:** 201.06, 189.04, 107.05, 95.04. **Elemental analysis:**Calcd for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; F, 6.41; N, 9.45.Found $C_{17}H_{13}FN_2O_2$: C, 68.90; H, 4.40; F, 6.38; N, 9.42 %.

4-(4'-Fluorophenyl)-6-(2''-hydroxyphenyl)pyrimidin-2(1*H*)-one, 2f: IR (KBr) □: 3522.30 (O-H stretching), 3342.50 (N-H stretching), 3011.80 (aromatic C-H stretching),1675.21 (C=O stretching), 1588.70 (C=C stretching),1572.21 (C=N stretching), 1326.01 (C-N stretching), 1224.47 (C-F stretching), 788.30 cm^{-1} (disubstituted benzene deformation).**^{1}H NMR ($CDCl_3$):** □6.90-6.96 (d, 1H, Ar-H), 6.98-7.38 (m, 6H, Ar-H), 7.80-7.98 (d, 2H, Ar-H), 8.56 (s, 1H, N-H, D_2O

exchangeable), 9.42 (s, 1H. O-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 282.27;**Fragments:**189.04, 187.05, 95.08, 95.02, 93.03. **Elemental analysis:** Calcd for $C_{16}H_{11}FN_2O_2$: C, 68.08; H, 3.93; F, 6.73; N, 9.92.Found $C_{16}H_{11}FN_2O_2$: C, 68.02; H, 3.90; F, 6.69; N, 9.88 %.

4-(4'-Chlorophenyl)-6-(2''-chlorophenyl)pyrimidin-2(1*H*)-one, 2g: IR (KBr)□: 3331.70 (N-H stretching), 3031.25 (aromatic C-H stretching), 1656.20 (C=O stretching), 1598.25 (C=C stretching), 1570.81 (C=N stretching), 1323.08 (C-N stretching), 782.42 (C-Cl stretching), 764.83 cm^{-1} (disubstituted benzene deformation).**^{1}H NMR ($CDCl_3$):** □7.25-7.65 (m, 6H, Ar-H), 7.70-7.82 (d, 1H, Ar-H), 7.98-8.00 (d, 2H, Ar-H), 8.15 (s, 1H, N-H, D_2O exchangeable).**MS (ESI) (m/z):** $[M]^+$ 317.10;**Fragments:** 205.01, 111.20, 95.02.**Elemental analysis:**Calcd for $C_{16}H_{10}Cl_2N_2O$: C, 60.59; H, 3.18; Cl, 22.36; N, 8.83.Found $C_{16}H_{10}Cl_2N_2O$: C, 60.54; H, 3.12; Cl, 22.32; N, 8.82 %.

4-(4'-Chlorophenyl)-6-(3''-methoxyphenyl)pyrimidin-2(1*H*)-one, 2h: IR (KBr) □: 3353.98 (N-H stretching), 3011.90 (aromatic C-H stretching), 1670.24 (C=O stretching), 1592.80 (C=C stretching), 1564.80 (C=N stretching), 1307.65 (C-N stretching), 1253.64 (C-O stretching), 786.06 (C-Cl stretching), 752.19 cm^{-1} (disubstituted benzene deformation). **^{1}H NMR ($CDCl_3$):** □, 3.64(s, 3H, $-OCH_3$), 6.57-6.67 (d, 2H, Ar-H), 6.94-7.57 (m, 5H, Ar-H), 7.90-7.99 (d, 2H, Ar-H), 8.43 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 357.2; **Fragments:** 248.96, 201.06, 111.06, 107.05, 95.02.**Elemental analysis:** Calcd for $C_{17}H_{13}ClN_2O_2$: C, 64.54; H, 4.06; Cl, 11.91; N, 14.11.Found $C_{17}H_{13}ClN_2O_2$: C, 64.50; H, 4.01; Cl, 11.88; N, 14.10 %.

4-(4'-Methoxyphenyl)-6-(2''-chlorophenyl)pyrimidin-2(1*H*)-one, 2i: IR (KBr) □: 3324.40 (N-H stretching), 3006.82 (aromatic C-H stretching), 1678.22 (C=O stretching), 1588.70 (C=C stretching), 1567.60 (C=N stretching), 1359.72 (C-N stretching), 1240.60 (C-O stretching), 790.92 (C-Cl stretching), 756.04 cm^{-1} (disubstituted benzene deformation).**^{1}H NMR ($CDCl_3$):** □3.49 (s, 3H, $-OCH_3$), 6.99-7.03 (d, 2H, Ar-H), 7.12-7.56 (m, 6H, Ar-H), 7.70-7.82 (d, 1H, Ar-H), 8.35 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 312.75; **Fragments:** 205.01, 201.06, 107.05, 111.09, 95.02. **Elemental analysis:** Calcd for $C_{17}H_{13}ClN_2O_2$: C, 64.54; H, 4.06; Cl, 11.91; N, 14.11.Found $C_{17}H_{13}ClN_2O_2$: C, 64.52; H, 4.04; Cl, 11.90; N, 14.08 %.

4-(4'-Aminophenyl)-6-(2''-chlorophenyl)pyrimidin-2(1*H*)-one, 2j: IR (KBr) □: 3378.60 (N-H stretching), 3312 (N-H stretching of NH_2), 3015.80 (aromatic C-H stretching), 1668.30 (C=O stretching), 1592.88 (C=C stretching), 1560.84 (C=N stretching), 1323.08 (C-N stretching), 792.40 (C-Cl stretching), 760.30 cm^{-1} (disubstituted benzene deformation).**^{1}H NMR ($CDCl_3$):** □4.01(s, 2H, $-NH_2$), 6.90-6.92 (d, 2H, Ar-H), 7.10-7.56 (m, 6H, Ar-H), 7.78-7.80 (d, 1H, Ar-H), 8.51 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 297.74; **Fragments:** 205.01, 186.05, 111.05, 95.02, 92.05. **Elemental analysis:**Calcd for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; Cl, 11.91; N, 14.11.Found $C_{16}H_{12}ClN_3O$: C, 64.50; H, 4.01; Cl, 11.88; N, 14.10 %.

4-(4'-Bromophenyl)-6-(2''-chlorophenyl)pyrimidin-2(1*H*)-one, 2k: IR (KBr) □: 3327.98 (N-H stretching), 3028.30 (aromatic C-H stretching), 1677.95 (C=O stretching), 1596.88 (C=C stretching), 1581.52 (C=N stretching), 1336.58 (C-N stretching), 784.49 (C-Cl stretching), 756.04 (disubstituted benzene deformation), 633.77 (C-Br stretching)cm^{-1}. **^{1}H NMR ($CDCl_3$):** □6.95-7.63 (m, 6H, Ar-H), 7.70-7.75 (d, 1H, Ar-H), 7.80-7.97 (d, 2H, Ar-H), 8.22 (s, 1H, N-H, D_2O exchangeable).**MS (ESI) (m/z):** $[M]^+$ 361.62;**Fragments:** 205.01, 154.95, 111.04, 95.02. **Elemental analysis:** Calcd for $C_{16}H_{10}BrClN_2O$: C, 53.14; H, 2.79; Br, 22.10; Cl, 9.80; N, 7.75; Found $C_{16}H_{10}BrClN_2O$: C, 53.12; H, 2.72; Br, 22.08; Cl, 9.78; N, 7.72 %.

4-(4'-Bromophenyl)-6-(3''-methoxyphenyl) pyrimidin-2(1*H*)-one, 2l: IR (KBr) □: 3382.91 (N-H stretching), 3016.90 (aromatic C-H stretching), 1665.03 (C=O stretching), 1583.45 (C=C stretching), 1572.81 (C=N stretching), 1323.08 (C-N stretching), 1213.14 (C-O stretching), 779.19 cm^{-1} (disubstituted benzene deformation). 641.49 (C-Br stretching)cm^{-1}. **^{1}H NMR ($CDCl_3$):** □3.51(s, 3H, $-OCH_3$), 6.88-6.92 (d, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 7.29-7.59 (m, 5H, Ar-H), 7.78-7.97 (d, 2H, Ar-H), 8.29 (s, 1H, N-H, D_2O exchangeable). **MS (ESI) (m/z):** $[M]^+$ 357.2; **Fragments:** 248.96, 201.06, 107.05, 111.06, 95.02. **Elemental analysis:** Calcd for $C_{17}H_{13}BrN_2O$: C, 57.16; H, 3.67; Br, 22.37; N, 7.84. Found $C_{17}H_{13}BrN_2O$: C, 57.14; H, 4.01; Cl, 11.88; N, 14.10 %.

4-(3'-Bromophenyl)-6-(4''-methoxyphenyl)pyrimidin-2(1*H*)-one, 2m: IR (KBr) □: 3321.80 (N-H stretching), 3014.40 (aromatic C-H stretching), 1661.30 (C=O stretching), 1592.40 (C=C stretching), 1568.81 (C=N stretching), 1344.08 (C-N stretching), 1280.20(C-O stretching), 764.37 (disubstituted benzene deformation), 645.40 (C-Br stretching) cm^{-1}. **^{1}H NMR ($CDCl_3$):** □3.53(s, 3H, $-OCH_3$), 6.57-6.67 (d, 2H, Ar-H), 7.12 (s, 1H, Ar-H), 7.25-7.50 (m, 5H, Ar-H), 7.62-7.67 (d, 1H, Ar-H), 8.27 (s, 1H, N-H, D_2O exchangeable), **MS (ESI) (m/z):**$[M]^+$ 357.20; **Fragments:** 248.96, 201.06, 111.06, 107.05, 95.02. **Elemental analysis:** Calcd for $C_{17}H_{13}BrN_2O_2$: C, 57.16; H, 3.67; Br, 22.37; N, 7.84. Found $C_{17}H_{13}BrN_2O_2$: C, 57.10; H, 3.61; Br, 22.33; N, 7.80 %.

4-(4'-Bromophenyl)-6-(2'',5''dihydroxyphenyl) pyrimidin-2(1*H*)-one, 2n: IR(KBr) □: 3520.30 (O-H stretching), 3321.70 (N-H stretching), 3018.40 (aromatic C-H stretching), 1674.20 (C=O stretching),

1586.68 (C=C stretching), 1571.75 (C=N stretching), 1315.20 (C-N stretching), 1225.30(C-O stretching), 644.47 (C-Br stretching) cm^{-1}.**^{1}H NMR ($CDCl_3$):** 6.57 (s, 1H, Ar-H), 6.67-6.70 (d, 2H, Ar-H), 7.20-7.59 (m, 3H, Ar-H), 7.78-7.97 (d, 2H, Ar-H), 8.45 (s, 1H, N-H, D_2O exchangeable), **9.20 (s,** 2H, OH, D_2O exchangeable).**MS (ESI) (m/z):** $[M]^+$ 308.30; **Fragments:** 201.06, 190.02, 107.05, 95.02. **Elemental analysis:** Calcd for $C_{16}H_{11}BrN_2O_3$: C, 53.50; H, 3.09; Br, 22.25; N, 7.80.Found $C_{16}H_{11}BrN_2O_3$: C, 53.48; H, 3.02; Br, 22.19; N, 7.78 %.

4-(4'-Methoxyphenyl)-6-(4''-methoxyphenyl) pyrimidin-2(1*H*)-one, 2o: IR (KBr) : 3312.10 (N-H stretching), 3015.90 (aromatic C-H stretching), 1656.22 (C=O stretching), 1588.23 (C=C stretching), 1558.78 (C=N stretching), 1308.50 (C-N stretching), 1224.60 (C-O stretching), 780.37 (disubstituted benzene deformation) cm^{-1}.**^{1}H NMR ($CDCl_3$):** 3.61(s, 6H, -OCH_3), 6.33-6.57 (d, 4H, Ar-H), 7.25-7.96 (m, 5H, Ar-H), 8.35 (s, 1H, N-H, D_2O exchangeable).**MS (ESI) (m/z):** $[M]^+$ 308.30; **Fragments:** 201.06, 107.05, 95.02. **Elemental analysis:** Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09.Found $C_{18}H_{16}N_2O_3$: C, 70.10; H, 5.20; N, 9.07 %.

Physical data of synthesized compounds (2a-2o) i.e., substituents, molecular formula, melting point, R_f value percent yield are given in Table 1

Table 1: *Physical data of synthesized compounds (2a-2o)*

Compound	R	R_1	Molecular formula	M.P (°C)	R_f value	Yield (%)
2a	H	3-F	$C_{16}H_{11}FN_2O_3$	76-78	0.78	69.50
2b	4-F	2-Cl	$C_{16}H_{10}ClFN_2O_3$	92-94	0.49	64.20
2c	4-F	3-Cl	$C_{16}H_{10}ClFN_2O_3$	95-97	0.44	68.30
2d	4-F	3-OCH_3	$C_{17}H_{13}FN_2O_4$	80-82	0.55	70.50
2e	4-OCH_3	4-F	$C_{17}H_{13}FN_2O_4$	87-89	0.42	68.20
2f	4-F	2-H	$C_{16}H_{11}FN_2O_3$	90-91	0.44	65.90
2g	4-Cl	2-Cl	$C_{16}H_{10}Cl_2N_2O_3$	74-76	0.46	62.60
2h	4-Cl	4-OCH_3	$C_{17}H_{13}ClN_2O_4$	88-90	0.64	65.50
2i	4-OCH_3	2-Cl	$C_{17}H_{13}ClN_2O_4$	84-86	0.54	66.50
2j	4-NH_2	2-Cl	$C_{16}H_{12}ClN_3O_3$	96-98	0.58	64.50
2k	4-Br	2-Cl	$C_{16}H_{10}BrClN_2O_3$	98-100	0.78	70.50
2l	4-Br	3-OCH_3	$C_{17}H_{13}BrN_2O_4$	97-99	0.51	62.50
2m	3-Br	4-OCH_3	$C_{17}H_{13}BrN_2O_4$	93-95	0.41	72.50
2n	4-Br	2,5-di-OH	$C_{16}H_{11}BrN_2O_5$	100-101	0.72	72.40
2o	4-OCH_3	4-OCH_3	$C_{18}H_{16}N_2O_4$	108-110	0.47	64.50

**n-hexane: ethyl acetate (8:2)*

Biological activity

Albino rats (Wistar strain) of either sex weighing 100-200g were used for anti-inflammatory and analgesic activity. International principles and local regulations concerning the care and use of laboratory animals were observed. The animal had free access to standard commercial diet and water *ad libitum* and were kept in rooms maintained at 23 ± 2 °C with a 12 h light dark cycle. The protocol was approved by the Animal Ethics Committee of Rajiv Academy for Pharmacy, Mathura, U.P.(IEAC/RAP/2983/2010).

Anti-inflammatory activity

The synthesized compounds were evaluated for their anti-inflammatory activity using the Carrageenan induced hind paw oedema assay model of inflammation by using the method of Winter et al[11]. The animals were randomly allocated to groups of six animals each and were fasted for 12 h before the experiment. Control group received only 1% (w/v) PEG-6000 solution. Standard drug Indomethacin was administered orally at 10 and 20 mg kg^{-1} dose. Carrageenan solution in distilled water(1%, 0.1 ml) was injected subcutaneously into the sub-plantar region of the left hind paw of each rat, one hour after the administration of the test compounds (10, 20 and 40 mg kg^{-1}) or standard drug (10 and 20 mg kg^{-1}). The left hind paw volume was measured before and after 3 h of carrageenan treatment by means of a plethysmometer. Paw oedema volume was compared with vehicle control group and percent inhibition was calculated as 1- (oedema volume in the drug treated group/oedema volume in the control group)× 100. Results are reported in Table-2.

Table 2: *Anti-inflammatory activity of synthesized compounds (2a-2o) after 180 min of carrageenan administration*

Compound No.	Dose (mg/kg)	Number of rats	Inhibition of oedema (%) ±SEM	ED50 (mg/kg)
2a	10	6	42.40±1.20*	14.45
	20	6	58.61±1.82*	
	40	6	80.50±1.86*	
2b	10	6	44.40±1.16*	12.80
	20	6	56.40±1.20*	
	40	6	82.40±1.28*	
2c	10	6	40.60±1.14**	17.87
	20	6	51.20±1.27**	
	40	6	78.22±1.92**	
2f	10	6	40.60±1.12**	19.30
	20	6	52.40±1.06**	
	40	6	74.40±1.86**	
2g	10	6	38.20±1.08**	22.90
	20	6	50.20±1.14**	
	40	6	62.40±1.22**	
2h	10	6	18.4±0.88	Not determinable
	20	6	24.50±1.01	
	40	6	42.60±1.16	
2i	10	6	20.20±0.89	Not determinable
	20	6	31.50±1.06	
	40	6	45.20±1.20	
2j	10	6	48.40±1.08*	12.20
	20	6	56.20±1.12*	
	40	6	84.40±1.80*	
2k	10	6	38.20±1.14**	16.05
	20	6	51.21±1.29**	
	40	6	80.40±1.88**	
2n	10	6	40.60±1.19**	21.80
	20	6	52.40±1.24**	
	40	6	69.50±1.80**	
indomethacin	10		44.60±0.89**	11.50
	20	6	85.60±0.96**	

All the values are in Mean ± SEM (n=6). Statistical analysis of data was carried out by one way ANOVA, p<0.05, **p< 0.01 as compared to control. (** = significantly different from control).*

Analgesic activity

Analgesic activity was evaluated by Acetic acid induced writhing method[12]. Twenty four hours prior to actual testing a large number of albino rats (100-200g) received intraperitoneally 10 ml kg^{-1} 1% glacial acetic acid. Animals were observed for writhing movements. Only those showing one or other type of writhing

movements (positive responders) were chosen for the test on the next day. On the test day the responders received compounds half an hour prior to glacial acetic acid challenge. The test compounds were administered intraperitoneally at the dose of 10, 20 and 40 mg kg^{-1} as a suspension in 1% PEG-6000. Diclofenac sodium was used as a standard drug at the dose of 10 and 20 mg kg^{-1}. Then the animals were observed for the total number of writhings for 10 min following glacial acetic acid injection. The percent inhibition of writhing movements were calculated as (average writhes in control group - average writhes in treated group/ average writhes in control group)× 100. The results are reported in Table-3.

Table 3: *Analgesic activity of synthesized compounds (2a-2o)*

Compound no.	Dose (mg/kg)	No. of rats	% Inhibition ± SEM	ED_{50} (mg/kg)
2b	10 20 40	6	24.30 ± 1.22 34.20 ± 0.94 56.44 ± 1.10	31.60
2c	10 20 40	6	25.22 ± 1.16 40.80 ± 0.92 58.20 ± 1.10	27.50
2d	10 20 40	6	40.62 ± 1.12* 56.40 ± 1.16* 74.21 ± 1.28*	12.58
2e	10 20 40	6	39.22 ± 1.05** 51.41 ± 1.21** 72.41 ± 1.31**	16.20
2f	10 20 40	6	42.40 ± 1.29* 55.21 ± 1.16* 79.82 ± 1.20*	14.45
2g	10 20 40	6	16.44 ± 0.76 24.82 ± 0.92 32.40 ± 1.10	Not determinable
2h	10 20 40	6	44.91 ± 1.21** 52.43 ± 1.12** 82.22 ± 1.18**	13.18
2i	10 20 40	6	46.42 ± 1.08** 55.41 ± 1.19** 83.28 ± 1.35**	12.08
2k	10 20 40	6	47.92 ± 1.11** 57.81 ± 1.20** 80.43 ± 1.28**	15.13
2l	10 20 40	6	37.20 ± 0.82** 54.61 ± 1.16** 77.24 ± 1.22**	15.80
2o	10 20 40	6	39.42 ± 1.04* 52.46 ± 1.08* 81.38 ± 1.19*	14.45
Diclofenac sodium	10 20	6	45.60 ± 0.75* 84.60 ± 0.86*	10.40

All the values are in Mean ± SEM (n=6). Statistical analysis of data was carried out by one way ANOVA, p<0.05, **p< 0.01 as compared to control.*
*(** = significantly different from control)*

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Dunnett's t-test for multiple comparisons of all compounds in various assays. Data are expressed as mean ± SEM. The significance of difference was accepted at $p<0.05$ and $p<0.01$.

RESULT AND DISCUSSION

A series of 4,6-disubstituted pyrimidine-2-one derivatives (2a-2o) were synthesized and characterized by analytical and spectral data. The structure elucidation was done by interpreting FTIR spectra, ^{1}H-NMR, mass spectroscopy and elemental analysis. The IR and NMR spectra of these compounds showed the presence of peaks due to N-H and carbonyl(C=O) group. The molecular ion recorded in the mass spectrum is in the agreement with the molecular weight of the compounds. Table-1 gives the physiochemical data of all the synthesized compounds (2a-2o).

The biological screening results revealed that the compounds 2a, 2b, 2c, 2f, 2g, 2j, 2k and 2n displayed significant anti-inflammatory activity. Among all these compounds, 2j was found to be the most potent compound having *o*-chloro group at one phenyl ring and *p*- amino group at other phenyl ring with ED_{50} 12.20 mg/kg. The other compounds having electron withdrawing groups on phenyl ring showed good anti-inflammatory activity (Table-2).

The compounds 2d, 2e, 2f, 2h, 2i, 2l, 2m and 2o displayed significant analgesic activity. The results shown in Table-3 revealed that the presence of methoxy group (electron releasing) at C-3 and C-4 positions of phenyl ring with electron withdrawing groups like chloro, fluoro and bromo on other phenyl ring showed good analgesic activity.Among all the tested compounds 2i with ED_{50} 12.08 mg kg^{-1} displayed maximum analgesic activity as compared to diclofenac sodium standard drug (Table-2).

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