

Analgesic and anti-inflammatory activities of several 4-substituted-6-(3'-nitrophenyl)pyridazin-(2H)-3-one derivatives

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Several 6-aryl-4-substituted benzylidene/furfurylidene pyridazin(2H)-3-one derivatives (4a-f) were synthesized and evaluated as analgesic and anti-inflammatory agents in mice and rats, respectively. All compounds were tested by using Eddy's hot plate and the carrageenan-induced hind paw oedema method for the evaluation of analgesic and anti-inflammatory activities, respectively. Results showed that compounds 4f, 4b, 4d, and 4e exhibited higher analgesic and anti-inflammatory activities than other remaining compounds. All title compounds (4a-f) were characterized by IR, NMR and Mass spectroscopy.

Uniterms: Pyridazinone/evaluation/experimental study. Analgesics/evaluation/experimental study. Anti-inflammatories/evaluation/experimental study.. Synthetic compounds/evaluation/experimental study..

Diversos derivados benzilideno/furfurilideno piridazin(2H)-3-ona 6-aril-4-substituídos (4a-f) foram sintetizados e avaliados como analgésicos e anti-inflamatórios em camundongos e ratos, respectivamente. Todos os compostos foram testados utilizando-se o método de placa quente de Eddy e o de edema de pata induzido por carragenana para a avaliação das atividades analgésica e anti-inflamatória, respectivamente. Os resultados mostraram que os compostos 4f, 4b, 4d e 4e exibiram atividade analgésica e anti-inflamatória mais alta do que os compostos restantes. Todos os compostos (4a-f) foram caracterizados por IV, RMN e espectrometria de massas.

Unitermos: Piridazinona/avaliação/estudo experimental. Analgésicos/avaliação/estudo experimental. Anti-inflamatórios/avaliação/estudo experimental. Compostos sintéticos/avaliação/estudo experimental.

INTRODUCTION

The classical non-steroidal anti-inflammatory drugs (NSAIDs) are useful for the treatment of inflammation, pain and fever. The actions of NSAIDs are based on the inhibition of the enzyme cyclooxygenase (COX), which catalyzes the metabolism arachidonic acid (AA) to prostaglandin H₂ (PGH₂). PGH₂ is further metabolized to prostanoids, prostaglandins (PGs) and thromboxane-A₂ (TXA₂). Various physiological effects of PGs include acute and chronic inflammatory reactions, blood pressure (BP) change, platelet aggregation, induction of labor and intensification of pain and fever. However, long-term usage of NSAIDs is associated with several side effects

including gastrointestinal (GI) lesions, bleeding, as well as hepato- and nephro-toxicities (Hallas *et al.*, 1995; Mccarthy, 1998; Raskin, 1999). In designing new drug molecules, developing safer analgesic and anti-inflammatory drugs without such side effects has recently been the goal of many researchers. Different pharmacophores with a different mode of action in the structure may lead to compounds having efficiency in biological activity.

Research has been directed in recent years, where a substantial number of 6-aryl-pyridazin-3(2H)ones have been reported to possess various types of biological activities such as antimicrobial, antifeedant, herbicidal, antihypertensive, antipyretic, antiplatelet, anticancer, anticonvulsant, antitubercular, cardiotoxic and other anticipated activities (Jing *et al.*, 2007; Islam *et al.*, 2008). On the other hand, a considerable number of pyridazine-3(2H)one derivatives are endowed with analgesic and anti-inflammatory properties (Siddiqui *et al.*, 2004; Dogruer,

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et al., 2007). Among the various pyridazine compounds, 3-amino-6-methyl-pyridazine-4-thiol (*ES-1007*) (1) is marketed in Germany (Pyridazine analogue) and 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (*emorfazone*) (1) is being marketed as pentoil and nandron in Japan as an analgesic and anti-inflammatory drug (Rubat, *et al.*, 1992, Pinna *et al.*, 1992; Flouzat *et al.*, 1993).

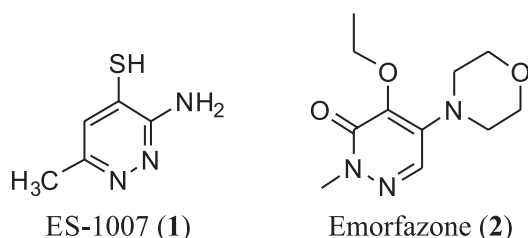


FIGURE 1 - Structure of pyridazinone compound ES-1007 and emorfazone.

Diverse pharmacological activities of the compounds containing pyridazinone moieties (Dogruer, *et al.*, 2003; Şukuroglu, *et al.*, 2006; Baytas, *et al.*, 2012) have prompted us to synthesize new compounds with analgesic and anti-inflammatory activities that may be potent, selective and less toxic.

Stimulated by these findings, our attention has been focused on the synthesis and evaluation of some 6-nitrophenylpyridazin-3(2*H*)-one derivatives (4a-f) as analgesic and antiinflammatory agents using the hot plate model and carrageenan-induced oedema model, respectively. Aspirin and indomethacin were used as reference drugs for analgesic and antiinflammatory activities, respectively. All title compounds (4a-f) have nitrophenyl at position 6 and a benzylidene/furfurylidine ring at position 4 on the pyridazinone ring. The results of the biological screening indicated that all compounds (4a-f) possess significant anti-inflammatory and analgesic activities.

MATERIAL AND METHODS

All the title compounds 6-(3'-nitrophenyl)-4-benzylidene-2,3,5-trihydro-pyridazin-3-one (4a-f) were synthesized by condensation of 6-(3'-nitrophenyl)-4,5-dihydro pyridazin-3(2*H*)-one (3) with different aromatic aldehydes (benzaldehyde, 4-hydroxy-3-methoxy benzaldehyde, 4-hydroxybenzaldehyde, 2-methoxy benzaldehyde, venilline and furfuraldehyde). Compound (3) was synthesized by cyclization of β -m-nitro benzoyl propionic acid (2) with hydrazine hydrate. A compound (2) was prepared by nitration of benzoyl propionic acid (1) by nitrating mixture (conc. HNO_3 and conc. H_2SO_4). Compound (1) was prepared by Friedal craft reaction of benzene with succinic anhydride in the presence of anhydrous aluminium chloride. All the compounds (4a-f) were previously synthesized by the same author and evaluated as anticonvulsants (Siddiqui *et al.*, 2007; Asif, *et al.*, 2011).

Characterization and spectral analysis of synthesized compounds

β -Benzoyl propionic acid (1)

Melting point: 120 °C, yield 70% R_f value 0.77, molecular formula $\text{C}_{10}\text{H}_{10}\text{O}_3$, molecular weight 178.18. Elemental analysis: (found/ calculated) H: 5.65/5.73 and C: 67.40/67.88. IR Spectra: 3250 cm^{-1} (OH), 1720 cm^{-1} (C=O), ^1H NMR(CDCl_3) ppm 2.82 (2H, t, CH_2), 3.32 (2H, t, CH_2), 7.74 (CH_2 , m, H-3, 5), 7.79 (2H, m, H-2, 6), MS (m/z): 174 (M^+).

β -m-nitro benzoyl propionic acid (2)

Melting point: 108 °C, yield 50 %, R_f value 0.70, molecular formula $\text{C}_{10}\text{H}_9\text{NO}_5$, molecular weight 223.18. Elemental analysis: (found/ calculated), H: 4.06/4.054, C: 53.81/53.62 and N: 6.27/6.87. IR Spectra: 3091 cm^{-1}

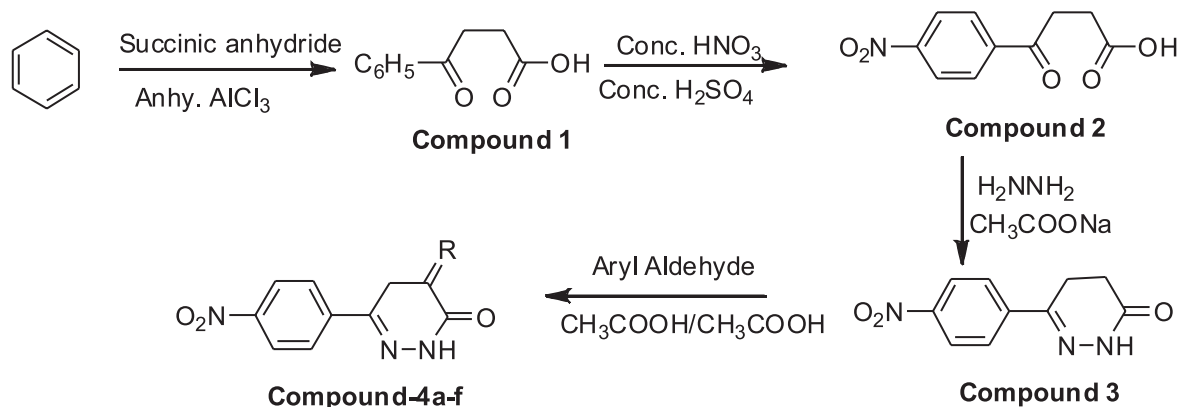


FIGURE 2 - Synthetic route for pyridazinone derivatives.

(CH), 1705 cm^{-1} (C=O), 1353 cm^{-1} (NO_2), 1617 cm^{-1} (C=C). ^1H NMR (DMSO) ppm 3.0 (t, 2H, CH_2), 3.36 (t, 2H, CH_2), 7.30- 8.2 (m, Ar-H), 8.82 (s, H, Ar-H), MS (m/z): 224 (M^+).

6-(3'-nitrophenyl)-4,5-dihydro pyridazin-3-one (3)

Yield 52%, melting point: 95 °C, R_f value 0.62, molecular formula $\text{C}_{10}\text{H}_9\text{NO}_5$, molecular weight 193.2. Elemental analysis: (found/calculated), H: 5.73/5.32, C: 62.16/62.87, N:7.24/7.47. IR (cm^{-1})1685(C=O), 1352(NO_2), 3100(CH), 3550(NH), ^1H NMR (CDCl_3) (ppm): 2.45 (t, 2H, CH_2 -C-C $_6\text{H}_5$), 2.93 (t, 2H, CH_2 -CONH), 7.41(m, 3H, Ar-H3', Ar-H-5'), 7.74 (d, 2H, Ar-H2', Ar-H-6'), 10.94 (s, 1H, CONH), MS (m/z): 219 (M^+).

6-(3'-nitrophenyl)-4-benzylidene-2,3,5-trihydro-pyridazin-3-one (4a-f)

• 6-(3'-nitrophenyl)-4-benzylidene-2,3,5 trihydro-pyridazin-3-one (4a)

Melting point: 132 °C, yield 65%, molecular formula $\text{C}_{17}\text{H}_{13}\text{O}_3\text{N}_3$, molecular weight 307.309 Elemental analysis: (found/calculated), H: 4.26/4.63, C: 66.44/66.20 and N: 13.67/13.32. IR cm^{-1} -1360 cm^{-1} (NO_2), 1700 cm^{-1} (C=O), 1580 cm^{-1} (C=C) exo, 3450 cm^{-1} (NH). ^1H NMR (CDCl_3) ppm 2.3 (s, 2H, CH_2), 7.47-7.88 (m, H, Ar-H), 8.5 (d, H, Ar-H), 8.3 (d, H, Ar-H), 7.0 (s, H, NH), 8.9 (s, H, Ar-H), MS (m/z): 307 (M^+).

• 6-(3'-nitrophenyl)-4-(4-hydroxy-3-methoxy)benzylidene-2,3,5-trihydro-pyridazin-3-one (4b)

Melting point: 127 °C, yield 50%, molecular formula $\text{C}_{17}\text{H}_{13}\text{O}_4\text{N}_3$, molecular weight 323.308. Elemental analysis: (found/calculated), H: 4.05/4.025, C: 63.15/63.56 and N: 2.99/12.66. IR- cm^{-1} 1700 cm^{-1} (C=C), 1350 cm^{-1} (NO_2), 3450 cm^{-1} (C=C), 1580 cm^{-1} (C=C) exo, 1310 cm^{-1} (C-O). ^1H NMR (CDCl_3) ppm 7.4-7.8 (m, H, nitro Ar-H), 7.0 (s, H, NH), 7.6 (s, H, Ar-H), 7.4 (d, H, Ar-H), 7.7 (m, H, Ar-H), 3.8 (s, 3H, OCH_3), 6.9 (s, H, Ar-H), 7.26 (s, H, CH), 4.08 (s, H, OH), MS (m/z): 353 (M^+).

• 6-(3'-nitrophenyl)-4-(4-hydroxy)benzylidene-2,3,5-trihydro-pyridazin-3-one (4c)

Melting point: 139 °C, yield 55%, molecular formula $\text{C}_{17}\text{H}_{13}\text{O}_4\text{N}_3$, molecular weight 323.308. Elemental analysis: (found/calculated), H: 4.05/4.031, C: 63.15/63.42 and N: 12.99/12.46. IR cm^{-1} -1685 cm^{-1} (C=O), 1350 cm^{-1} (NO_2), 3450 cm^{-1} (NH), 3600 cm^{-1} (OH), 1580 cm^{-1} (C=C). ^1H NMR (DMSO) ppm: 2.0 (s, H, CH), 4.0 (s, H, OH), 7.3 (s, H, CH), 6.9 (d, H, Ar-H), 7.78 (t, H, Ar-H), 6.8 (s, H, NH), 7.7 (s, H, Ar-H), MS (m/z): 323 (M^+).

• 6-(3'-nitrophenyl)-4-(2-methoxy)benzylidene-2,3,5-trihydro-pyridazin-3-one (4d)

Melting point: 146 °C, yield 50%, molecular formula $\text{C}_{18}\text{H}_{12}\text{O}_4\text{N}_3$, molecular weight 334.311. Elemental analysis: (found/calculated), H: 3.61/3.73, C: 64.66/64.49 and N: 12.56/12.59. IR cm^{-1} -1685 cm^{-1} (C=O), 1352 cm^{-1} (NO_2), 3450 cm^{-1} (NH), 1580 cm^{-1} (C=C), 1300 cm^{-1} (C=O). ^1H NMR (CDCl_3) ppm: 2.2 (s, 2H, CH_2), 4.07 (s, H, OCH_3), 7.5 (s, H, NH), 7.4 – 8.2 (m, H, Ar-H), 4.0 (s, H, NH), MS (m/z): 337 (M^+).

• 6-(3'-nitrophenyl)-4-(4-*N,N*-dimethyl-amino)benzylidene-2,3,5-trihydro-pyridazin-3-one (4e)

Melting point: 158 °C, yield 60%, molecular formula $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_4$, molecular weight 350.37. Elemental analysis: (found/calculated), H: 5.17/5.43, C: 65.13/65.23 and N:15.99/15.65. IR cm^{-1} -1685 cm^{-1} (C=O), 1352 cm^{-1} (NO_2), 3450 cm^{-1} (NH), 1580 cm^{-1} (C=C). ^1H NMR (CDCl_3) ppm 3.9 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 2.0 (s, 2H, CH_2), 7.2 (s, H, NH), 6.7 (d, H, Ar-H), 7.7 (t, H, Ar-H), 8.6 (s, H, Ar-H), 8.8 (d, H, Ar-H), MS (m/z): 351 (M^+).

• 6-(3'-nitrophenyl)-4-(furfurylidene)-2,3,5-trihydro-pyridazin-3-one (4f)

Melting point: 157 °C, yield 65%, molecular formula $\text{C}_{15}\text{H}_{11}\text{O}_4\text{N}_3$, molecular weight 297.27. Elemental analysis: (found/calculated), H: 3.72/3.79, C: 60.60/60.68 and N: 14.13/14.53. IR cm^{-1} -1650 cm^{-1} (C=O), 1352 cm^{-1} (NO_2), 3440 cm^{-1} (NH). ^1H NMR (DMSO) ppm 2.5 (s, 2H, CH_2), 6.5 (m, H, fur-H), 6.9 (d, H, fur-H), 7.7 (t, H, fur-H), 7.5 (s, H, NH), 7.6 (m, H, nitro Ar-H), 8.4 – 8.8 (m, H, nitro Ar-H), MS (m/z): 298 (M^+).

Preparation of test samples for bioassay

All test samples (50 mg/kg) were suspended in a mixture of distilled water and 0.5% sodium carboxyl methylcellulose (CMC) and were given intraperitoneally (i.p.) to the test animals. The animals of the control group received the same experimental handling except that the test drug treatment was replaced with appropriate volumes of the vehicle. Indomethacin (10 mg/kg) for anti-inflammatory and aspirin at 0.5% CMC (50 mg/kg) for analgesic activity were used as reference drugs.

Experimental animals

Male Swiss albino rats (150-200 g) were used for anti-inflammatory activity and mice (30- 35 g) were used for analgesic activity. All of the animals were left for 2 days in the laboratory for acclimatization before the day

TABLE I - Structures of 6-(3'-nitrophenyl)-4-benzylidene-2,3,5-trihydro-pyridazin-3-one (4a-f)

| SNo. | Compounds | R |
|------|---|---|
| 1 | 6-(3'-nitrophenyl)-4-benzylidene-2,3,5 trihydro-pyridazin-3-one (4a) | |
| 2 | 6-(3'-nitrophenyl)-4-(4-hydroxy-3-methoxy)benzylidene-2,3,5-trihydro-pyridazin-3-one (4b) | |
| 3 | 6-(3'-nitrophenyl)-4-(4-hydroxy)benzylidene-2,3,5-trihydro-pyridazin-3-one (4c) | |
| 4 | 6-(3'-nitrophenyl)-4-(2-methoxy)benzylidene-2,3,5-trihydro-pyridazin-3-one (4d) | |
| 5 | 6-(3'-nitrophenyl)-4-(4-N,N-dimethyl-amino)benzylidene-2,3,5-trihydro-pyridazin-3-one (4e) | |
| 6 | 6-(3'-nitrophenyl)-4-(furfurylidene)2,3,5-trihydro-pyridazin-3-one (4f) | |

of experiment, and on the last day they were given water only. A minimum of 5 animals were used in each group. All pharmacological activities were carried out as per CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) norms (Regn No: 1145/a/07/CPCSEA), after obtaining the approval from the Institutional Animal Ethics Committee of the Department of Pharmacy, GRD (PG) Institute of Management & Technology, Dehradun, India.

Analgesic activity

Eddy's hot plate method

Heat was used as the source of pain. Animals were individually placed on the hot plate, maintained at a constant temperature (55 °C), and the reaction of animals, such as paw licking or jump response was taken as the end response. Analgesic compounds increased the reaction time. This method was described by Eddy & Leimbach (A cut-off period of 15 sec is observed to avoid damage to the paw). The control, standard and test compounds were administered to animals by the i.p route and the reaction of time of animals on the hot plate was noted at 10, 20, 30, 40 & 50 min interval after drug administration by using a Techno heated plate analgesic apparatus. A group of albino mice were treated i.p. with a dose of 50 mg/kg

body weight. The standard drug Aspirin (50 mg/kg) was used as the reference drug (Kulkarni, 1999). The results are tabulated in Table II.

Anti-inflammatory activity

Carrageenan-induced hind paw oedema test

For the determination of anti-inflammatory effect, the carrageenan-induced paw oedema model (Winter *et al.*, 1962) was employed. Sixty minutes after the i.p administration of control, test samples and reference drug, each rat was injected with a freshly prepared 0.1 mL of 1% carrageenan suspension in physiological saline (0.9% NaCl) into subplantar tissue of the right hind paw. For the control, 10 mL/kg saline solution was administered. Paw oedema was measured every 90 min for 6h after induction of inflammation. Mean values of the treated groups were compared with those of the control group and analyzed using statistical methods (Table III, IV).

Acute toxicity

All animals used in the analgesic and inflammatory experiments were observed for 48 h and mortality of animals recorded where present for each group at the end of observation period.

TABLE II - Analgesic activity of the synthesized compounds

| Compd. No. | Time (min) | | | | | |
|----------------|-------------|-------------|-------------|--------------|--------------|--------------|
| | 10 | 20 | 30 | 60 | 90 | 120 |
| Control | 3.42±0.03 | 3.48±0.02 | 3.64±0.04 | 3.50±0.03 | 3.76±0.04 | 3.64±0.05 |
| 4a | 4.53 ± 0.02 | 5.73 ± 0.01 | 6.68 ± 0.02 | 9.42 ± 0.01 | 11.50 ± 0.01 | 12.12 ± 0.01 |
| 4b | 4.34 ± 0.01 | 5.72± 0.01 | 7.00± 0.01 | 9.68 ± 0.01 | 10.16± 0.01 | 11.53 ± 0.01 |
| 4c | 3.76± 0.01 | 4.45±0.01 | 5.86± 0.01 | 7.54± 0.01 | 9.96± 0.01 | 10.41± 0.01 |
| 4d | 3.84± 0.01 | 4.68±0.01 | 5.94 ± 0.01 | 6.79± 0.01 | 8.92 ± 0.01 | 9.62 ± 0.01 |
| 4e | 6.33± 0.02 | 7.63±0.02 | 8.44± 0.02 | 9.68 ± 0.02 | 10.84 ± 0.01 | 12.14 ± 0.01 |
| 4F | 7.54± 0.01 | 9.65± 0.01 | 10.36±0.01 | 11.04± 0.01 | 12.01± 0.01 | 12.53± 0.02 |
| Aspirin | 8.54 ± 0.01 | 10.58± 0.01 | 11.47±0.01 | 11.71 ± 0.01 | 12.73± 0.01 | 12.98± 0.01 |

All results are significantly different from control at $ap < 0.001$.

$$\text{Percentage Inhibition} = \frac{\text{Mean paw inflammation of control} - \text{Mean paw inflammation of test}}{\text{Mean paw inflammation of control}} \times 100$$

TABLE III - Anti-inflammatory Activities of the Compounds

| Compounds | Anti-inflammatory Activity | | | |
|---------------------|--------------------------------------|--------------|-------------|-------------|
| | Change in mean paw volume (ml) ± SEM | | | |
| | 90 min | 180 min | 270 min | 360 min |
| Control | 0.41 ± 0.03 | 0.50 ± 0.01 | 0.57 ± 0.03 | 0.65 ± 0.04 |
| 4a | 0.35 ± 0.02 | 0.41 ± 0.04 | 0.44 ± 0.04 | 0.49 ± 0.04 |
| 4b | 0.29 ± 0.03 | 0.32 ± 0.03 | 0.36 ± 0.03 | 0.41 ± 0.03 |
| 4c | 0.34 ± 0.01 | 0.37 ± 0.02 | 0.39 ± 0.03 | 0.42 ± 0.03 |
| 4d | 0.31 ± 0.03 | 0.34 ± 0.02 | 0.37 ± 0.01 | 0.41 ± 0.01 |
| 4e | 0.35 ± 0.05 | 0.39 ± 0.009 | 0.42 ± 0.03 | 0.44 ± 0.03 |
| 4f | 0.29 ± 0.03 | 0.32 ± 0.01 | 0.35 ± 0.02 | 0.39 ± 0.02 |
| Indomethacin | 0.26 ± 0.008 | 0.30 ± 0.03 | 0.32 ± 0.02 | 0.36 ± 0.02 |

All results are significantly different from control at $ap < 0.001$.

TABLE IV – Percentage inhibition of carrageenan-induced paw oedema (4a-f)

| Compound. No. | Inhibition of oedema % | | | |
|---------------------|------------------------|---------|---------|---------|
| | 90 min | 180 min | 270 min | 360 min |
| 4a | 14.63 | 18.00 | 22.80 | 28.71 |
| 4b | 29.27 | 36.00 | 36.84 | 36.92 |
| 4c | 17.07 | 26.00 | 30.00 | 35.38 |
| 4d | 24.39 | 32.00 | 35.08 | 36.92 |
| 4e | 14.63 | 22.00 | 26.31 | 32.30 |
| 4F | 29.27 | 36.00 | 38.59 | 40.00 |
| Indomethacin | 34.14 | 37.00 | 42.35 | 44.53 |

All results are significantly different from control at $ap < 0.001$.

Statistical analysis

Results were expressed as means \pm s.e.m. Statistical significance was analyzed by using the one-way analysis of variance followed by Tukey's Multiple Comparison Test where $p < 0.05$ was accepted to be a significant difference.

RESULTS AND DISCUSSION

All the 6-(3'-nitrophenyl)-2,3,5-trihydro pyridazin-3-one derivatives (4a-f) exhibited analgesic activities (Table I) that lasted for 120 minutes with potency that increased with time. All compounds were less potent than the reference drug Aspirin, but the most potent compounds were (4e and 4f) and least potent compound was 4d. Thus, the degree of potency in ascending order was 4d, 4c, 4b, 4a, 4e, and 4f. All the tested compounds showed anti-inflammatory activity (Table III). Compounds 4b, 4f and 4d showed high protection against induced oedema after 360 min. whereas compounds 4a, 4c, 4e showed less potency. The degree of anti-inflammatory potency in ascending order was: 4a, 4e, 4c, 4d, 4b, and 4f by % Inhibition of carrageenan-induced paw oedema (Table IV). Substitution on the pyridazinone ring at position 4 by furfurylidine was considered to have greater anti-inflammatory and analgesic activity. For acute toxicity, no animals died during a 48-hr. period of observation after experiments.

The discovery of novel, potent and safer non-steroidal anti-inflammatory drugs (NSAIDs) represents a challenging goal (Van, Botting, 1995) because resistance to NSAIDs is widespread. Therefore, there is an increasing need for identification of lead structures that may be of use in designing new, potent drugs with less toxic effects (Takaya *et al.*, 1979; Heinisch *et al.*, 1990). In addition, some pyridazinone derivatives have been found to exhibit potent NSAIDs activity through the selective COX-2 inhibitory mechanism (Chintakunta *et al.*, 2002) and some pyridazinone compounds were also found to be more potent than reference drugs.

Further investigations in the future should determine analgesic and anti-inflammatory potency for title compounds, the effect of specific substituents and their positions in the molecules, and their related toxicity. In fact, the presence of a nitro-aryl moiety in all analogs raises a concern regarding liver toxicity; due to the action of NADPH-cytochrome P450 reductases, and will also be studied. In addition, we shall study the compound without a nitro group and study the impact of the nitro group on aryl moiety for analgesic and anti-inflammatory potency. Other substituted arylidines, with or without hetero

atoms, will be tested in order to confirm the most active compounds of this group.

CONCLUSION

In conclusion, we reported here several pyridazinone compounds as analgesic and anti-inflammatory agents. Initial results demonstrated that the pyridazine ring may contribute to their analgesic and anti-inflammatory activities. These nitrophenyl pyridazinones have an m-nitrophenyl ring at position 6 and benzylidene/furfurylidine at position 4. On the basis of these results, furfurylidine derivatives seem to be more potent for both analgesic and anti-inflammatory activities than other substituted benzylidene derivatives.

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REFERENCES

- ASIF, M.; SINGH, A.; LAKSHMAYYA Synthesis and anticonvulsant activity of 6-(3'-nitrophenyl)-4-substituted benzylidene-2, 3, 5-trihydro pyridazin-3-one. *Middle-East J. Sci. Res.*, v.9, n.4, p.481-485, 2011.
- BAYTAS, S.; TURANDURAL, N.N.; OZKAN, Y.; SIMSEK, H.B.; GURSEL, T.; UNLU, S. Synthesis, anti-inflammatory, antiplatelet and in silico evaluations of (E)-3-(3-(2,3-dihydro-3-methyl-2-oxo-3H-benzoxazole-6-yl)-1-phenyl-1H-pyrazole-4-yl)acrylamides. *Turk. J. Chem.*, v.36, p.367-382, 2012.
- CHINTAKUNTA, V.K.; AKELLA, V.; VEDULA, M.S.; MAMNOOR, P.K.; MISHRA, P.; CASTURI, S.R.; VANGOORI, A.; RAJAGOPALAN. R. 3-O-substituted benzyl pyridazinone derivatives as COX inhibitors. *Eur. J. Med. Chem.*, v.37, p.339-347, 2002.
- DOGRUER, D.S.; SAHIN, M.F.; UNLU, S.; ITO, S. Studies on some 3(2H)-pyridazinone derivatives with antinociceptive activity. *Arch. Pharm. Pharm. Med. Chem.*, v.333, p.79-86, 2000.

- DOGRUER, D.S.; SAHIN, M.F.; KÜPELI, E.; YEŞİLADA, E. Synthesis and analgesic and anti-inflammatory activity of new pyridazinones. *Turk. J. Chem.*, v.27, p.727-738, 2003.
- DOGRUER, D.S.; UNLU, S.; KUPELI, E.; BANOGLU, E.; SAHIN, M.F. Synthesis of 2-[5,6-diphenyl-3(2H)-pyridazinone-2-yl] acetamide and 3-[5,6-diphenyl-3(2H)-pyridazinone-2-yl]propanamide derivatives as Analgesic and anti-inflammatory agents. *Turk. J. Pharm. Sci.*, v.4, p.57-70, 2007.
- FLOUZAT, C.; BRESSON, Y.; MATTIO, A. Novel non opioid non antiinflammatory analgesics: 3-(aminoalkyl) and 3-[(4-aryl-1-piperazinyl) alkyl] oxazolo [4,5-b] pyridin-2(3H)ones. *J. Med. Chem.*, v.36, p.497-503, 1993.
- GIOVANNONI, M.P.; VERGELLI, C.; GHELARDINI, C.; GALEOTTI, N.; BARTOLINI, A.; PIAZ, V.D. [(3-Chlorophenyl) piperazinylpropyl] pyridazinones and analogues as potent antinociceptive agents. *J. Med. Chem.*, v.46, p.1055-1059, 2003.
- GOKCE, M.; DOGRUER, D.; FIAHIN, M.F. Synthesis and antinociceptive activity of 6-substituted-3-pyridazinone derivatives. *Farmaco*, v.56, p. 233-237, 2001.
- HALLAS, J.; LAURITSEN, J.; VILLADSEN, H.D.; GRAM, L.F. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. *Scand. J. Gastroenterol.*, v.30, p.438-444, 1995.
- HEINISCH, G.; FRANK, H. Pharmacologically active pyridazine derivatives. *Prog. Med. Chem.*, v.27, p.1-35, 1990.
- JING, T.; DUO-ZHI, W.; LING-HUA, C. Synthesis of 5-(6-Pyridazinone-3-yl)-2-lycosylamino-1,3,4-oxadiazoles. *J. Chinese Chem. Soc.*, v.54, p.1287-1292, 2007.
- KULKARNI, S.K. *Handbook of experimental pharmacology*. 3.ed. New Delhi: Vallabh publication, 1999. p.131-133.
- MCCARTHY D. Nonsteroidal antiinflammatory drug-related gastrointestinal toxicity: definition and epidemiology. *Am. J. Med.*, v.105, n.5A, p.3S-9S, 1998.
- ISLAM, M.; SIDDIQUI, A.A.; RAJESH, R. Synthesis, antitubercular, antifungal and antibacterial activities of 6-Substituted Phenyl-2-(3'-Substituted Phenyl Pyridazin-6'-yl)-2,3,4,5-Tetrahydropyridazin-3-one. *Acta Poloniae Pharm.*, v.65, n.3, p.353-362, 2008.
- PIAZ, V.D.; GIOVANNONI, M.P.; CICIANI, G.; BARLOCCO, D.; GIARDINA, G.; PETRONE, G.; CLARKE, G.D. 4,5-Functionalized-6-phenyl-3(2H)-pyridazinones: synthesis and evaluation of antinociceptive activity. *Eur. J. Med. Chem.*, v.31, p.65-70, 1996.
- PINNA, G.A.; SARDU, F.; CURZU, M.M. Synthesis and pharmacological activity of 4-carbamoyl-5-aryl-6-methyl-4,5-dihydropyridazin-3(2H)-ones. *Farmaco*, v.47, p.449-463, 1992.
- RASKIN, J.B. Gastrointestinal effects of nonsteroidal antiinflammatory therapy. *Am. J. Med.*, v.106, p.3S-12S, 1999.
- RUBAT, C.; COUDERT, P.; ALBUISSON, E.; BASTIDE, J.; COUQUELET, J.; TRONCHE, P. Synthesis of mannich bases of arylidenepyridazinones as analgesic agents. *J. Pharm. Sci.*, v.81, p.1084-1087, 1992.
- SIDDIQUI, A.A.; KUSHNOOR, A.; WANI, S.M. Synthesis and hypotensive activity of some 6-(substituted aryl)-4-methyl-2,3-dihydropyridazin-3-ones. *Indian J. Chem-B*, v.43B, p.1574-1579, 2004.
- SIDDIQUI, A.A.; ISLAM, M.; ASIF, M.; ASTHANA, C. Synthesis and anticonvulsant activity of 6-(3'-nitrophenyl)-4-substituted benzylidene-2,3,5-trihydropyridazin-3-one. *J. Ultrachem.*, v.3, p.173-178.
- SUKUROGLU, M.; KUPELI, E.; BANOGLU, E.; UNLU, S.; YESILADA, E.; ŞAHIN, M.F. Synthesis and analgesic activity of some 4,6-disubstituted-3(2H)-pyridazinone derivatives. *Arzneim. -Forsch.*, v.56, p.337-345, 2006.
- TAKAYA, M.; SATO, M.; TERASHIMA, K.; TANIZAWA, H.A. New nonsteroidal analgesic antiinflammatory agent. Synthesis and activity of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone and related compounds. *J. Med. Chem.*, v.22, p.53-58, 1979.
- VAN, J.R.; BOTTING, R.M. New insights into the mode of action of antiinflammatory drugs. *Inflamm. Res*, v.44, p.1-10, 1995.
- WINTER, C.A.; RISELY, E.A.; NUSS, G.W. Carrageenan-induced oedema in hind paw of rat as an assay of anti-inflammatory drugs. *Exp. Biol. Med.*, v.111, p.19-26, 1962.