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SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF SOME NEW PYRIDAZINONE DERIVATIVES

B. Chandrakanth[1*], V. Girija Sastry[2] and R. Vasanthi[3]

[1]Department of Pharmaceutical Chemistry, Aurobindo College of Pharmaceutical Sciences, Gangadevipally, Warangal, Telangana State.
[2]Department of Pharmaceutical Chemistry, A.U College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India.
[3]Department of Pharmaceutical Chemistry, Nalanda College of Pharmacy, Nalgonda, Telangana State.

***Author for Correspondence: B. Chandrakanth**
Department of Pharmaceutical Chemistry, Aurobindo College of Pharmaceutical Sciences, Gangadevipally, Warangal, Telangana State.

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ABSTRACT

The present study deals with synthesis of some seventeen novel 2-(4-methanesulfonyl-phenyl)-6-aryl-4,5-dihydro*2H*-pyridazi-3-one (P-1 to P-17) were synthesized by condensation of appropriate β-aroylpropionic acids (VI) and 4-Methanesulfonyl-phenylhydrazine (III) and their spectral characterization by means of IR, ^{1}H NMR and ^{13} C NMR and Results the compound were screened anti-inflammatory activity and in-vitro anti-cancer activity.

KEYWORDS: 4-Methanesulfonyl-phenylhydrazine, β-Aroylpropionic, , Anti-inflammatory activity, COX inhibitors.

INTRODUCTION

Pyridazinone nucleus has been done in the past and it has been found to possess variety of biological activities and these compounds exhibits diversified pharmacological activities due to presence of pyridazinone moieties. In recent years a substantial number of pyridazinones have been reported to potent anti-inflammatory[1], analgesic[2, 3], COX inhibitor [4], aldose reductase inhibitors[5], anticancer effects[6, 7] agents.

Moreover pyridazinone nucleus is present in some drugs e.g. emorphazone (analgesic) and zardaverine (phosphodiestrase inhibitor). 4-Methanesulfonyl phenyl moiety is present in large variety of pharmaceuticals covering a wide range of biological activities. Derivatives possessing this moiety are being reported as anti-inflammatory, selective COX-2 inhibitors[8], antimicrobial and anti-proliferative agents.[9]

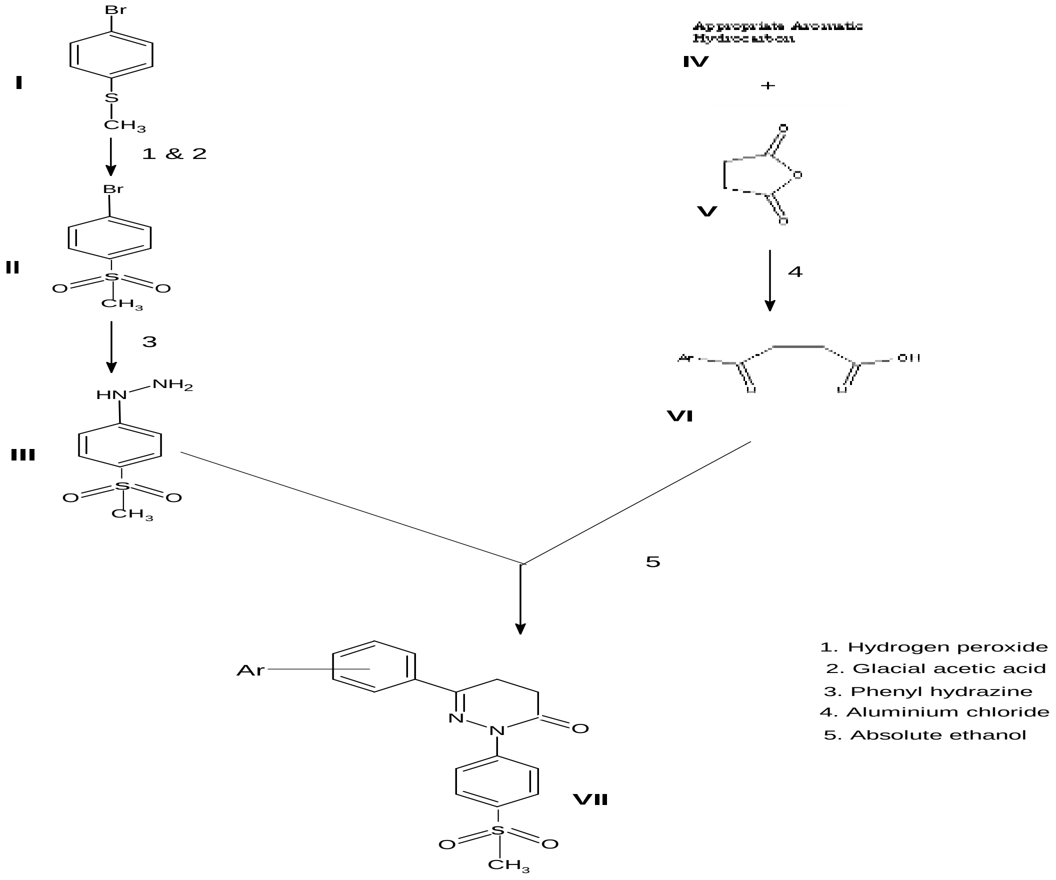
Moreover 4-methanesulfonyl phenyl moiety is present in number of clinically used antiinflammatory drugs e.g. etoricoxib, rofecoxib, firocoxib etc. These facts promoted us to synthesize novel 2-(4-methanesulfonyl-phenyl)-6aryl-4,5-dihydro-*2H*-pyridazi-3-one molecules and to evaluate them as for anti-inflammatory (*in-vivo*) and anti-cancer (*in-vitro* and *in-vivo*) agents.

MATERIALS AND METHOD

All the chemicals used in the synthesis were obtained from standard commercial sources The organic solvents such as methanol, toluene, ethyl acetate, formic acid and hexane were of spectral grade. Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The separations of the compounds were checked on TLC under UV lamp and also by spraying the plates with 10 % sulphuric acid in methanol.

All the melting points were determined in open capillaries, using Boitus melting point apparatus, expressed in °C and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra of the compounds were recorded on Bruker spect. Spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. The IR spectra of the compounds were recorded on Bruker spect and perkin .Elmer (spectrum BX series). Elemental analyses were carried out with Carlo Erba 1108 elemental analyzer apparatus.

Synthesis scheme

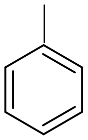
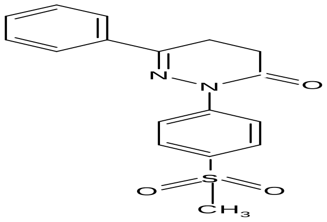
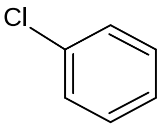
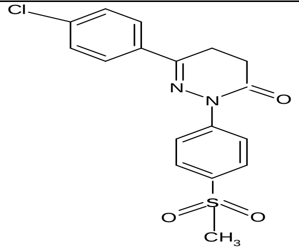
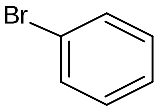
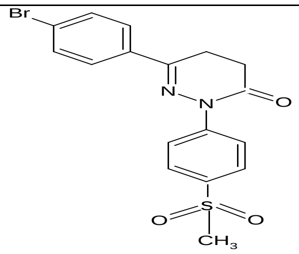


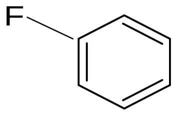
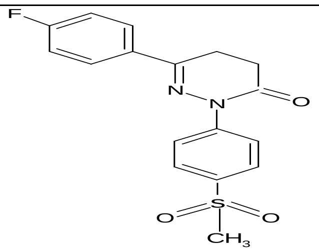
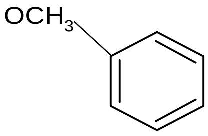
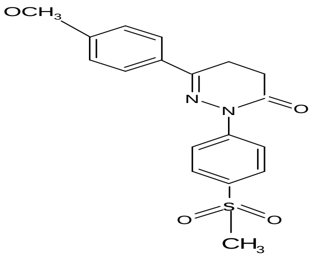
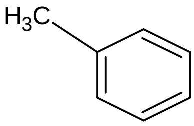
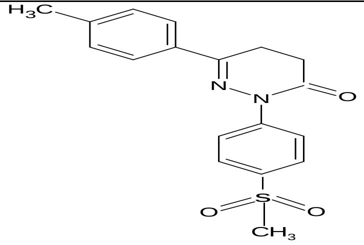
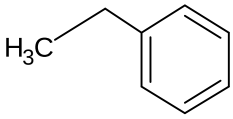
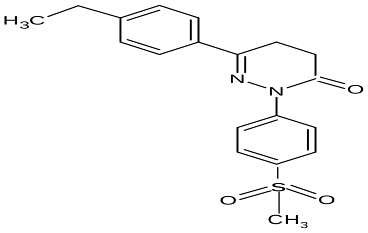
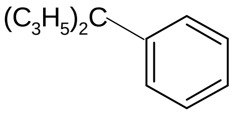
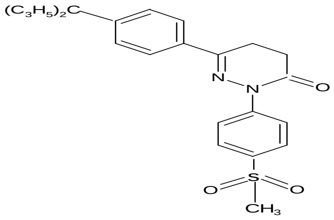
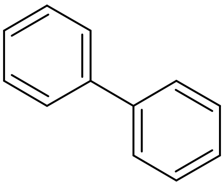
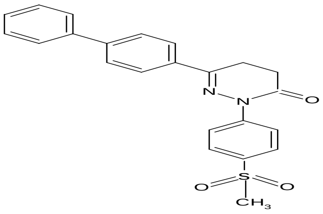
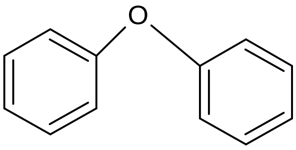
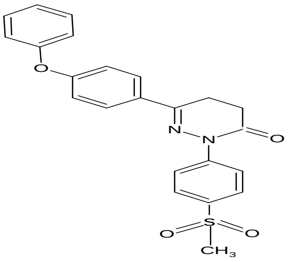
P - (1-17)

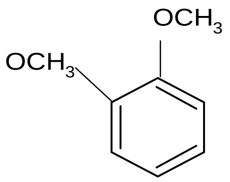
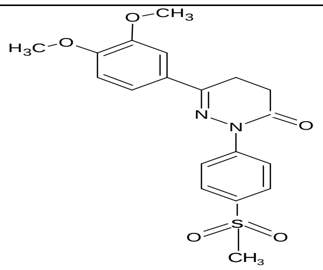
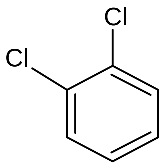
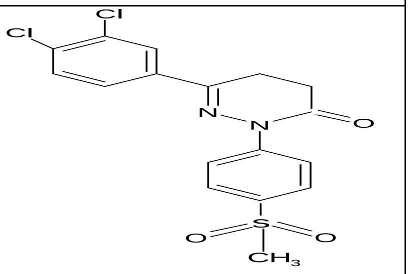
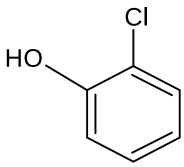
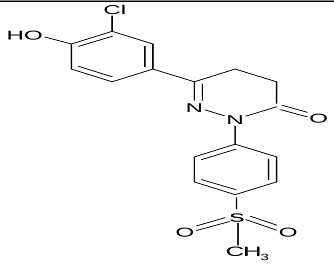
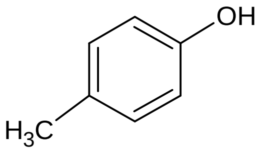
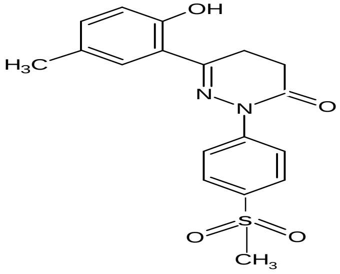
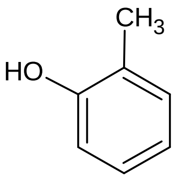
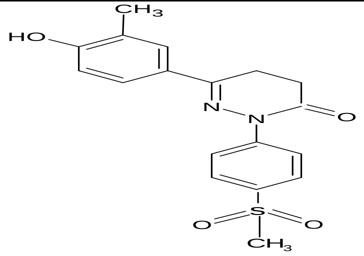
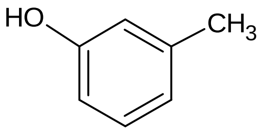
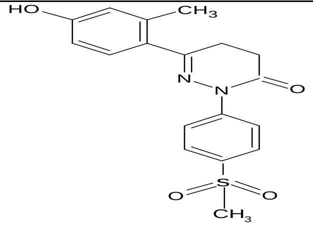
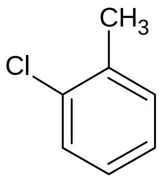
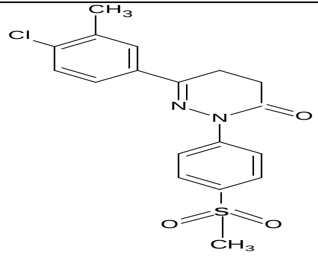
Fig.1. Synthesis Scheme for β-aroylpropionic acids (VI) and 4-Methanesulfonyl-phenylhydrazine (III)

Substituted β- aroylpropionic acids used for synthesis

Table.1. Substrates used for the reaction process to form target compounds.

Sample Code	Substrate	Compound
P-1 Mol. Wt = 329 $C_{17}H_{16}N_2O_3S$		
P-2 Mol. Wt = 373 $C_{17}H_{15}ClN_2O_3S$		
P-3 Mol. Wt = 407 $C_{17}H_{15}BrN_2O_3S$		

P-4 Mol. Wt = 346 $C_{17}H_{15}FN_2O_3S$		
P-5 Mol. Wt = 358 $C_{18}H_{18}N_2O_4S$		
P-6 Mol. Wt = 358 $C_{18}H_{18}N_2O_3S$		
P-7 Mol. Wt = 356 $C_{19}H_{20}N_2O_3S$		
P-8 Mol. Wt = 418.5 $C_{21}H_{24}N_2O_3S$		
P-9 Mol. Wt = 404 $C_{23}H_{20}N_2O_3S$		
P-10 Mol. Wt = 420 $C_{23}H_{20}N_2O_4S$		

P-11 Mol. Wt = 388 $C_{19}H_{20}N_2O_5S$		
P-12 Mol. Wt = 397 $C_{17}H_{14}Cl_2N_2O_3S$		
P-13 Mol. Wt = 397 $C_{17}H_{15}ClN_2O_4S$		
P-14 Mol. Wt = 346 $C_{18}H_{18}N_2O_4S$		
P-15 Mol. Wt = 358 $C_{18}H_{18}N_2O_4S$		
P-16 Mol. Wt = 358 $C_{18}H_{18}N_2O_4S$		
P-17 Mol. Wt = 360 $C_{18}H_{17}$ Cl N_2O_3S		

Experimental Procedures

General method for synthesis of Substituted β-aroylpropionic acids to the condensation with 4-Methanesulfonyl-phenylhydrazine

I Synthesis of 4-Methanesulfonyl-Phenylhydrazine (III)

4-Methanesulfonyl-phenyl-hydrazine was synthesized from *p*-bromophenyl methyl sulfide (III) by reported method with minor modifications.[10]].

a. Synthesis of *p*-bromophenyl methylsulfone (II)

Hydrogen peroxide (30 ml of 30%, 0.27 mole) was added to a solution of 7.7g, (0.05 mole) of *p*-bromophenyl methyl sulfide in 40 cc of glacial acetic acid. The solution was refluxed for 30 min. The reaction mixture was allowed to cool to room temperature and water was added to it. The white precipitate formed (*p*-bromophenyl methylsulfone) (IV) was filtered and washed with water. Further it was recrystallized from methanol as white solid crystals are formed.

b. Synthesis of 4-Methanesulfonyl-Phenylhydrazine (III)

p-Bromophenyl methylsulfone (0.01 M) was dissolved in hydrazine hydrate (0.02 mole) and refluxed at 150-150^{o}C for 1hr. Reaction mixture was allowed to cool and then poured on crushed ice to obtain white solid. This was filtered and washed with excess water. Further it was recrystallized from methanol as white solid crystals are formed

II Synthesis of β-Aroylpropionic Acids (or) 1,4 Keto acids (VI)

β-Aroylpropionic acids (VI) were prepared by Fridel Crafts succinoylation of substituted aromatic hydrocarbons through reported methods[11] with minor modification.

To liquid aromatic hydrocarbon (30 ml) (IV), anhydrous aluminium chloride (16.6 g, 0.125 mole) was added. It was stirred on magnetic stirrer at room temperature for 30 minutes. To it succinic anhydride (5 g, 0.05 mole) (V) was added in five portions with continuous stirring. Stirring was continued for another six hours at room temperature. It was left at room temperature for 48 hours and then decomposed by adding ice-cold hydrochloric acid (50 %, 100 ml). The precipitated solid was treated with saturated sodium bicarbonate solution to give a solid mass. It was filtered, washed with cold water, dried and crystallized from appropriate solvent (VI).

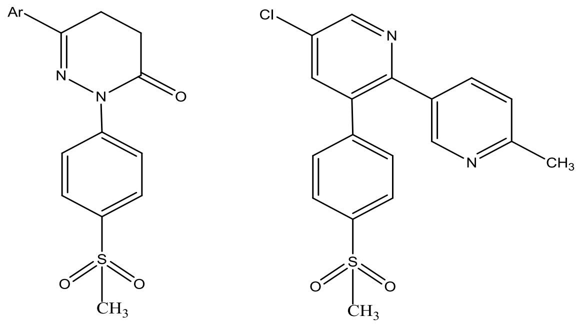
III Synthesis of 2-(4-Methanesulfonyl-Phenyl)-6-Aroyl4,5-Dihydro-2H-Pyridazi-3-One (VII)

On complete dissolution of (4-methanesulfonyl-phenyl)-hydrazine (0.001 mole) (III) in absolute ethanol (25 ml) was added desired β-aroylacrylic acid (0.001 mole) (VI) and the mixture was heated to reflux for 6-12 hours. The volume was reduced to half by evaporating the solvent and left at room temperature when the product separated out as a crystalline solid. It was filtered and then converted into fine powder, which was stirred with 5 % sodium bicarbonate solution (25 ml). It was filtered, washed with 2 % acetic acid and then with water. It was dried and crystallized from methanol or acetone to give TLC pure compound (VII).

Biological activity

Anti-inflammatory activity

Since the Pyridazinone derivatives were reported to possess anti-inflammatory activity, the Pyridazinone derivatives prepared during the course of the present work were tested for anti-inflammatory activity. In the present studies seventeen pyridazinones bearing methanesulfonylphenyl moiety (P-3 to P-17) were evaluated for their anti-inflammatory activity by using carageenan induced hind paw edema model in Wistar strain albino rats (either sex). Rats of Wistar strain (either sex) obtained from Central animal house of the university were used. CMC 1 %, w/v in distilled water was used as vehicle for dosing (10 ml/kg b.w.). Etoricoxib (0.05mmole/kg) was used as standard as it shows structural resemblance with the test compounds. All the treatments suspended in vehicle were given orally.



Test Drug

Etoricoxib

(P-1 to P-17)

The anti-inflammatory activity of target compounds (P-1 to P-17) was evaluated by applying carrageenan-induced hind paw edema bioassay in rats. Results were compared with etoricoxib as it has some chemical structural resemblance with target compounds. The results are summarized in supplementary Table-2.

RESULTS AND DISCUSSON

Physico-chemical properties and spectral data of the synthesized compounds

The yields of all the synthesized compounds were found to be satisfactory within the range of 31 to 59%. The spectral data generated upon analysis were found in accordance with the anticipated structure of the synthesized compounds.

P-1: *2-(4-Methanesulfonyl-phenyl)-6-phenyl-4,5-dihydro-2H-pyridazi-3-one*

Yield (%) : 31; **Melting point**:167-168 ^{o}C; **R_f value** : 0.44; **IR** (KBr,cm^{-1}):1548-1616 cm^{-1} (C=O), 1398-1462 cm^{-1} (C=N) and 1195-1261 cm^{-1} & 1020-1074 cm^{-1} (SO_2C); **^{1}H NMR** (δ ppm): 2.79 (2H, t, J = 8.1 Hz, -

CH$_2$ at C-5), 3.14(2H, t, J = 8.1 Hz, -CH$_2$ at C-4) 3.20 (3H, s, SO$_2$CH$_3$), 7.47-7.49 (3H, m, H-3', H-4',H- 5'), 7.86-7.91 (4H, m H-2', H-6', H-3", H-5"), 7.98 (2H, d, J =9.0 Hz, H-2", H-6").

P-2: ***6-(4-Chloro-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%): 56; **Melting point** : 157-159 °C ; **R$_f$ value** : 0.37; **IR** (KBr, cm-1): 1117 cm-1 and 1257 cm-1 (SO$_2$C); 1664 cm-1 (C=O), 1548 cm-1 C=N ;**^{1}H NMR** (δ ppm) : 2.79 (2H, t, J = 8.4 Hz, -CH$_2$ at C-5), 3.17 (2H, t, J = 8.4 Hz, -CH$_2$ at C-4), 3.24 (3H, s, SO$_2$CH$_3$) 7.55 (2H, d, J = 8.7 Hz, H-3", H-5"), 7.87 (2H, d, J = 6.3 Hz, H- 3', H-5'), 7.90 (2H, d, J = 6.3 Hz, H-2', H-6'), 7.98 (2H, d, J = 8.7 Hz, H-2", H-6"); **^{13}C NMR** (δ) : 22.14, 27.34, 43.63, 124.74, 127.39, 128.03, 128.64, 134.01, 134.80, 137.50, 145.12, 152.06, 165.71.

P-3: ***6-(4-Bromo-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one.***
Yield (%): 42; **Melting point**: 161-162 °C ; **R$_f$ value**: 0.34; **IR** (KBr,cm-1) : 1155 cm-1 and 1226 cm-1 (SO$_2$C), 1608 cm-1 (C=O), 1579 cm-1 (C=N); **^{1}H NMR** (δ ppm) : 2.79 (2H, t, J = 7.5 Hz, -CH$_2$ at C-5), 3.15 (2H, t, J = 7.8 Hz, -CH$_2$ at C-4), 3.24 (3H, s, SO$_2$CH$_3$), 7.48-7.50 (2H, m, H-3', H-5'), 7.89 7.92 (4H, m, H-2', H-6', H-3", H-5"), 7.98 (2H, d, J = 8.7 Hz, H-2", H-6")

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P-4: ***6-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%): 59; **Melting point**: 161-169 °C; **R$_f$ value**: 0.47 ; **IR** (KBr, cm-1): 1257 cm-1 & 1163 cm-1 (SO$_2$C), 1666 cm-1(C=O), 1529 cm-1 (C=N); **^{1}H NMR** (δ ppm) : 2.78 (2H, t, J = 8.1 Hz, -CH$_2$ at C-5), 3.15(2H, t, J = 9.0 Hz, -CH$_2$ at C-4), 3.23 (3H, s, SO$_2$CH$_3$), 7.28-7.34 (2H, m, H-3',H-5'), 7.86-7.98 (6H, m, H-2', H-6', H-3",H-5", H-2", H-6"); **^{13}C NMR** (δ) 22.27, 27.41, 43.64, 115.46, 115.64, 124.36, 27.37, 128.60, 128.67, 131.68,131.71, 137.40, 145.16, 152.29, 162.22,164.19,165.72.

P-5: ***6-(4-methoxy-phenyl)-2-(4-Methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%): 57; **Melting point**:170-171° C; **R$_f$ value**: 0.39; **IR** (KBr) : 1340 cm^{-1} and 1255 cm^{-1} (SO$_2$C), 1581 cm^{-1} (C=O),1616 cm^{-1} (C=N) **^{1}H NMR** (δ ppm) : 2.76 (2H, t, J = 8.1 Hz, -CH2 at C-5), 3.13 (2H, t, J= 7.8 Hz, -CH$_2$ at C-4), 3.23 (3H, s, SO$_2$CH$_3$), 3.81 (3H, s, OCH$_3$), 7.03 (2H, d, J = 9.0 Hz, H-3', H-5'), 7.84 (2H, d, J = 9.0 Hz, H-2', H-6'), 7.89 (2H, d, J =8.7 Hz, H-3", H-5"), 7.97 (2H, d, J = 8.7 Hz, H-2", H-6").**^{13}C NMR** (δ) : 22.07, 27.58, 43.64, 55.27, 113.97, 124.20, 127.35,127.47,127.88, 137.19,145.28, 153.05, 160.82, 165.86

P-6: ***6-p-tolyl-2-(4-Methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 54 **Melting point** : 169-170° C **R$_f$ value** : 0.40; **IR** (KBr, cm-1):1348 cm-1 and 1224 cm-1 (SO$_2$C), 1654 cm-1 (C=O), 1597 cm-1 (C=N) ; **^{1}H NMR** (δ) : 2.36 (3H, s, CH$_3$ at C-4'), 2.77 (2H, t, J = 8.1 Hz, -CH$_2$ at C-5), 3.14 (2H, t, J = 8.1 Hz, - CH$_2$ at C-4), 3.23 (3H, s, SO$_2$CH$_3$), 7.29 (2H, d, J = 7.8 Hz, H-3', H-5'), 7.78 (2H, d, J = 7.8 Hz, H-2', H-6'), 7.89 (2H, d, J = 8.7 Hz, H-3", H-5"), 7.99 (2H, d, J = 8.7 Hz, H-2", H-6") ; **^{13}C NMR** (δ): 21.39, 22.65, 28.03, 44.15, 124.83, 126.71, 127.86, 129.69, 132.88, 137.85, 140.40, 145.76, 153.75,166.36 .

P-7: ***6-(4-Ethyl-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 59; **Melting point** : 165-166° C; **R$_f$ value** : 0.58 ; **IR** (KBr, cm-1) : 1301 cm-1 and 1232 cm-1 (SO$_2$C), 1637 cm-1 (C=O), 1548 cm-1 (C=N) **^{1}H NMR** (δ, ppm) : 1.19 (3H, t, J = 7.5 Hz, -CH$_2$-CH$_3$), 2.66 (2H, q, J = 7.5 Hz, -CH$_2$-CH$_3$),2.77 (2H, t, J = 8.1 Hz, -CH$_2$ at C-5), 3.15 (2H, t, J = 7.8 Hz, -CH$_2$ at C-4), 3.24 (3H, s, SO$_2$CH$_3$), 7.32 (2H, d, J = 6.9 Hz, H-3', H-5'), 7.80 (2H, d, J = 6.6 Hz, H-2', H-6'), 7.89 (2H, d, J = 8.7 Hz, H-3", H-5"), 7.97 (2H, d, J = 8.7 Hz, H-2", H-6"); **^{13}C NMR** (δ): 15.91, 22.69, 28.03, 28.47, 44.14, 124.78, 126.81, 127.88, 133.15, 137.81, 145.74, 146.65, 153.80, 166.36.

P-8: ***6-(4-tert-Butyl-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 53; **Melting point** : 179-180° C; **R$_f$ value** : 0.53; **IR** (KBr , cm-1) : 1305 cm-1 and 1230 cm-1 (SO$_2$C), 1646 cm-1 (C=O), 1546 cm-1 (C=N); **^{1}H NMR** (δ , ppm) : 1.29 [9H, s, -C(CH$_3$)$_3$], 2.77 (2H, t, J = 8.1 Hz,-CH$_2$ at C-5), 3.14 (2H, t, J = 8.7 Hz, -CH$_2$ at C-4), 3.23 (3H, s, SO$_2$CH$_3$), 7.49 (2H, d, J = 8.4 Hz, H-3', H-5'), 7.80 (2H, d, J = 8.4 Hz H- 2', H-6'), 7.89 (2H, d, J = 8.7 Hz, H-3", H-5"), 7.98 (2H, d, J = 8.7 Hz, H-2", H-6"); **^{13}C NMR** (δ): 22.23, 27.55, 30.89, 34.49, 43.64, 124.21, 125.38, 126.07, 127.35, 132.42, 137.29, 145.23,152.89, 153.31, 165.85.

P-9: ***6-Biphenyl-4-yl-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 59; **Melting point** : 147-148° C; **R$_f$ value** : 0.62 ; **IR** (KBr, cm^{-1}) : 1301 cm^{-1} and 1163 cm^{-1} (SO$_2$C), 1599 cm^{-1} (C=O), 1545 cm^{-1} (C=N) ; **^{1}H NMR (δ, ppm) :** 2.81 (2H, t, J = 8.1 Hz, -CH$_2$ at C-5), 3.21 (2H, t, J = 8.4 Hz, -CH$_2$ at C-4), 3.25 (3H, s, SO$_2$CH$_3$), all aromatic protons appeared between δ 7.82 – 8.01; **^{13}C NMR (δ) :** 22.20, 27.51, 30.64, 43.64, 118.04, 119.19, 124.09, 124.31, 127.36, 128.27, 130.08, 130.17, 137.33, 145.29, 152.70, 155.82, 158.49, 165.80.

P-10: ***6-(4-phenoxy-phenyl)-2-(4-Methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 51; **Melting point** : 168-169° C ; **R$_f$ value** : 0.58 ; **IR** (KBr, cm^{-1}) : 1301 cm^{-1} and 1180 cm^{-1} (SO$_2$C), 1716 cm^{-1} (C=O), 1539 cm^{-1} (C=N).**^{1}HNMR (δ, ppm) :** 2.78 (2H, t, J = 8.1 Hz, -CH$_2$ at C-5), 3.16 (2H, t, J = 8.4Hz, -CH$_2$ at C-4), 3.24 (3H, s, SO$_2$CH$_3$), all

aromatic protons appeared between δ 7.07- 7.98. **^{13}C NMR (δ) :** 14.00, 20.98, 29.61, 29.84, 44.26, 51.50, 60.16, 112.41, 126.17, 126.21, 126.50, 126.66, 127.55, 128.70, 128.94, 129.81, 129.83, 136.30, 136.35, 139.49, 139.77, 144.87,144.98, 149.74, 171.92, 172.38.

P-11: ***6-(4-Dimethoxy-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) :57; **Melting point**: 173-174^o C; **R$_f$ value** : 0.48; **IR** (KBr, cm^{-1}) : 1311 cm^{-1} and 1178 cm^{-1} (SO_2C), 1597 cm^{-1} (C=O), 1514 cm^{-1} (C=N). **^{1}H NMR (**δ, ppm **) :** 2.76 (2H, t, J = 8.1 Hz, $-CH_2$ at C-5), 3.15 (2H, t, J = 7.8 Hz, $-CH_2$ at C-4), 3.23 (3H, s, SO_2CH_3), 3.81 (6H, s, OCH_3 X 2 at C-3' and C-4'), 7.04 (1H, d, J = 8.4 Hz, H-6'), 7.41- 7.46 (2H, m, H-2', H-5'), 7.90 (2H, d, J = 9.0 Hz, H-3", H-5"), 7.98 (2H, d, J = 9.0 Hz, H-2", H-6"); **^{13}C NMR :** 22.10, 27.62, 43.61, 55.50, 55.54, 109.00, 111.20, 119.90, 124.24, 127.37, 127.60, 137.23, 145.26, 148.66, 150.72, 153.25, 165.98.

P-12: ***6-(4-Dichloro-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%): 42; **Melting point**: 206-208^o C; **R$_f$ value** : 0.41; **IR (KBR, cm^{-1})** : 1301 cm^{-1} and 1157 cm^{-1} (SO_2C), 1637 cm^{-1} (C=O), 1548 cm^{-1} (C=N); **^{1}H NMR (** δ, ppm **) :** 2.81 (2H, t, J = 8.1 Hz, $-CH_2$ at C-5), 3.17 (2H, t, J = 7.8 Hz, $-CH_2$ at C-4), 3.24 (3H, s, SO_2CH_3), 7.75 (1H, d, J =8.7 Hz, H-6'), 7.84-7.88 (3H, m, H-2", H-6", H-5"), 7.98 (2H, d, J = 8.7 Hz, H-3", H-5"), 8.08 (1H, d, J =2.1 Hz, *meta* coupled H-2'). **^{13}C NMR (**δ**) :** 22.91, 27.20, 43.61, 124.63, 126.38,127.43, 127.96, 130.78, 131.58, 132.57, 135.81, 137.66, 144.99, 150.98, 165.63 .

P-13:*6-(3-Chloro-4-hydroxy-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazin-3-one*
Yield (%) : 48; **Melting point**: 230-231^o C; **R$_f$ value:** 0.6; **IR** (KBr, cm-1): 1117 cm-1 and 1257 cm-1 (SO_2C); 1664 cm-1 (C=O), 1548 cm-1 C=N ; **^{1}H NMR** (δ, ppm) : 2.75 (2H, t, J = 8.1 Hz, -CH2 at C-5), 3.11 (2H, t, J = 7.8 Hz, -CH2 at C-4), 3.24 (3H, s, SO2CH3), 7.04 (1H, d, J = 8.7 Hz, H-6'), 7.69 (1H, d, J = 8.7 Hz, H-5'), 7.84-7.89 (3H, m, H-2' H-3", H-5"), 7.98 (2H, d, J = 8.7 Hz, H-2", H-6"), 10.77 (1H, s, OH); **^{13}C NMR** (δ) : 21.98, 27.48, 30.62, 43.65, 116.49, 120.12, 124.35, 126.43, 127.15, 127.36, 127.77,137.27, 145.21, 152.12, 154.84, 165.76.

P-14*:* ***6-(2-Hydroxy-5-methyl-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro- 2H-pyridazi-3-one***
Yield (%) : 59; **Melting point** : 248-249^o C; **R$_f$ value:** 0.47 ; **IR** (KBr, cm^{-1}): 1367 cm^{-1} and 1153 cm^{-1} (SO_2C), 1680 cm^{-1} (C=O), 1597 cm^{-1} (C=N). **^{1}H NMR (**δ, ppm**) :** 2.17 (3H, s, CH_3 at C-5'), 2.73 (2H, t, J = 8.4 Hz, $-CH_2$ at C-5), 3.09 (2H, t, J = 8.0 Hz, $-CH_2$ at C-4), 3.24 (3H, s, SO_2CH3), 6.85 (1H, d, J = 8.4 Hz, H-3'), 7.56 (1H,*ortho-meta* coupled double doublet, J = 2.5 Hz, J = 8.0 Hz, H-4'), 7.63 (1H, d, J = 1.2 Hz, *meta* coupled H-6'), 7.89 (2H, d, J = 8.8 Hz, H-3", H-5"), 7.97 (2H, d, J = 8.8 Hz, H-2", H-6"), 9.88 (1H, s, OH). **^{13}C NMR (**δ**) :** 16.00,22.01,27.68, 43.64, 124.12, 124.13,124.26, 125.45, 125.68, 127.33, 128.80, 137.12, 145.35, 153.62,157.57,165.95.

P-15: ***6-(4-Hydroxy-3-methyl-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 41; **Melting point** : 243-244^o C; **R$_f$ value** : 0.33; **IR** (KBr, cm^{-1}) : 1359 cm^{-1} and 1157 cm^{-1} (SO_2C), 1630 cm^{-1}(C=O), 1599 cm^{-1} (C=N) ; **^{1}H NMR (**δ, ppm**) :** 2.50 (3H, s, CH_3 at C-3'), 2.73 (2H, t, J = 8.4 Hz, $-CH_2$ at C-5), 3.09 (2H, t, J = 7.5 Hz, - CH_2 at C-4), 3.23 (3H, s, SO_2CH_3), 6.85 (1H, d, J = 8.4 Hz, H-5'), 7.55 (1H,*ortho-meta* coupled double doublet, J = 2.5 Hz, J = 8.7 Hz, H-6'), 7.63 (1H, d, J = 2.1 Hz, *meta* coupled H-2'), 7.89 (2H, d, J = 9.0 Hz, H-3", H-5"), 7.96 (2H, d, J = 9.0 Hz, H-2", H-6"), 9.86 (1H, s, OH) ; **^{13}C NMR (**δ **) :** 15.99, 22.02, 27.67, 43.64, 114.51, 124.13, 124.26, 125.45, 125.69, 127.33, 128.80, 137.12, 145.36, 153.61,157.57, 165.95.

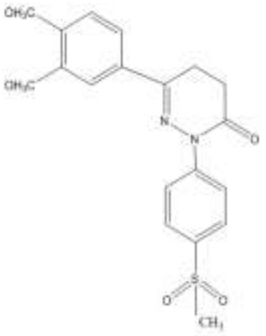
P-16: ***6-(4-Hydroxy-2-methyl-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 39; **Melting point**: 248-250^o C; **R$_f$ value**: 0.47; **IR** (KBr, cm^{-1}) : 1383 cm^{-1} and 1579 cm^{-1} (SO_2C), 1653 cm^{-1} (C=O), 1577 cm^{-1} (C=N); **^{1}H NMR** (δ, ppm) **:** 2.28 (3H, s, CH_3 at C-2'), 2.77 (2H, t, J = 7.8 Hz, -CH_2 at C-5), 3.14 (2H, t, J = 8.4 Hz, $-CH_2$ at C-4), 3.25 (3H, s, SO_2CH_3), 6.75 (1H, s, H-3'), 6.77 (1H,d, J = 7.2 Hz, H-5'), 7.51 (1H, d, J = 8.4 Hz, H-6'), 7.80 (2H, d, J =8.7 Hz, H-3", H-5"), 8.00 (2H, d, J = 8.7 Hz, H-2", H-6"), 11.04 (1H, s, OH); **^{13}C NMR (**δ**) :** 16.50, 22.52, 28.44, 44.14, 114.99, 124.60, 124.70, 125.96, 127.84, 129.31, 137.64, 158.07, 166.46.

P-17: ***6-(4-Chloro-3-methyl-phenyl)-2-(4-methanesulfonyl-phenyl)-4,5-dihydro-2H-pyridazi-3-one***
Yield (%) : 39; **Melting point** : 255-256^o C; **R$_f$ value** : 0.44; **IR** (KBr, cm-1) : 1365 cm^{-1} and 1161 cm^{-1} (SO_2C), 1660 cm^{-1} (C=O), 1566 cm^{-1} (C=N) ; **^{1}H NMR** (δ, ppm) **:** 2.38 (3H, s, CH_3), 2.78 (2H, t, J = 8.4 Hz, -CH_2 at C-5), 3.16 (2H, t, J = 7.5 Hz, $-CH_2$ at C-4), 3.24 (3H, s, SO_2CH_3), 7.52 (1H, d, J = 8.7 Hz, H-5'), 7.73 (1H,*ortho- meta* coupled double doublet, J = 1.8 Hz, J = 8.1 Hz, H-6'), 7.86.90 (3H, m, H-2', H-3", H-5"), 7.97 (2H, d, J= 8.5 Hz, H-2", H-6").

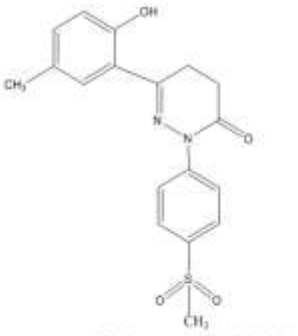
Anti-inflammatory activity data of the synthesized compounds

The anti-inflammatory activity of target compounds (P-1 to P-17) was evaluated by applying carrageenan-induced hind paw edema bioassay in rats. Results were compared with etoricoxib as it has some chemical structural resemblance with target compounds. The results are summarized in supplementary Table-2-2. These compounds (P-1 to P-17) showed moderate to strong anti-inflammatory activity (6.6- 66.6 % at 3h and 21.0- 86.4 % at 5h). The anti- inflammatory activity of P-11 and P-14 at 5h was almost comparable to that exhibited by standard drug etoricoxib.

With regard to structural activity relationship (SAR) it was observed that introduction of alkyl group at C-4′ position caused elevation in the activity and it was further increased when the bulk of alkyl was increased (P-1 vs P-6 to P-8) at both 3h and 5h. Introduction of oxy group (hydroxyl, methoxyl and phenoxyl) in phenyl ring also seems some favorable for increasing the activity as compounds P-5, P-10, P-11, P-13, P-14, P-15 and P-16 showed better activity than that of P-1. Introduction of chlorine or bromine atom at C-4′ diminished the activity at both study time 3h and 5h (P-1 vs P-2, P-1 vs P-12, P-1 vs P-3) while the introduction of fluorine at same position increased the activity (P-1 vs P-4). Compound P-9 with phenyl moiety at C-4′ exhibited least activity in this study.



P-11 (Fairly active at 5 h)



P-14 (Equally potent as etoricoxib at 5h)

Table-2: Effect of pyridazinones on carageenan induced hind paw edema in rats

Group	Treatment (0.05mmole/kg)	Ar	Increase in paw volume ml ± SEM after carageenan administration	
			3 hours	5 hours
1	Vehicle	-	0.30 ± 0.02	0.38 ± 0.04
2	Etoricoxib	-	0.05 ± 0.02*** (83.3%)	0.05 ± 0.02** (86.8%)
3	P-1	Phenyl	0.22 ± 0.02* (26.6%)	0.2 ± 0.01** (47.3%)
4	P-2	4-Chlorophenyl	0.22 ± 0.03** (26.6%)	0.24 ± 0.02* (36.8%)
5	P-3	4-Bromophenyl	0.27 ± 0.01 (10.0%)	0.26 ± 0.01* (31.5%)
6	P-4	4-Flourophenyl	0.12 ± 0.02* (60.0%)	0.1 ± 0.01* (73.6%)
7	P-5	4-Methoxyphenyl	0.16 ± 0.04** (46.7%)	0.12 ± 0.01** (68.4%)
8	P-6	4-Methylphenyl	0.16 ± 0.02** (44.6%)	0.15 ± 0.02*** (60.5%)
9	P-7	4-Ethylphenyl	0.16 ± 0.02* (46.7%)	0.13 ± 0.02** (65.7%)
10	P-8	Tert.butylphenyl	0.15 ± 0.02** (50.0%)	0.12 ± 0.02* (68.4%)
11	P-9	Biphenyl	0.28 ± 0.01* (6.6%)	0.3 ± 0.01* (21.0%)
12	P-10	Phenoxyphenyl	0.15 ± 0.02** (50.0%)	0.13 ± 0.01** (65.7%)
13	P-11	3,4- Dimethoxyphenyl	0.1 ± 0.01*** (66.6%)	0.06 ± 0.03** (82.4%)
14	P-12	3,4- Dichlorophenyl	0.22 ± 0.03* (26.6%)	0.25 ± 0.02* (34.2%)
15	P-13	3-Chloro-4-hydroxyphenyl	0.17 ± 0.01** (43.3%)	0.17 ± 0.02** (55.2%)
16	P-14	2-Hydroxy-5-methylphenyl	0.1 ± 0.01*** (66.6%)	0.05 ± 0.02** (86.8%)
17	P-15	4-Hydroxy-3-methylphenyl	0.22 ± 0.01* (26.6%)	0.15 ± 0.02** (60.5%)
18	P-16	4-Hydroxy-2-methylphenyl	0.2 ± 0.03* (33.3%)	0.22 ± 0.02** (42.1%)
19	P-17	4-Chloro-3- methylphenyl	0.25 ± 0.02* (16.6%)	0.3 ± 0.02* (21.0%)

**p <0.01, ***p<0.001, compared to control (one-way ANOVA followed by Dunnett's test). Values are presented as mean ± S.E.M. (n = 6).Values in parentheses represent percent inhibitions.

CONCLUSION

Various substituted pyridazinones bearing methanesulfonylphenyl were synthesized by refluxing the mixture of appropriate β-aroylpropionic acid and (4-Methanesulfonyl-phenyl)-hydrazine in absolute alcohol for 6-12 hours. The derivatives were characterized for chemical properties and biological properties. The pyridazinone derivatives were found to possess moderate to strong anti-inflammatory activity in Wistar strain albino rats.

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