Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2010, 2(5): 118-125
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Synthesis and anti-inflammatory activity of some [4, 6-(4 substituted aryl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin- 5-yl]-acetic acid derivatives

Santosh N. Mokale,* Padma S. Singu, Sushil S. Bahekar

Dr. Rafiq Zakaria Campus, Y. B. Chavan College of Pharmacy, Aurangabad

---

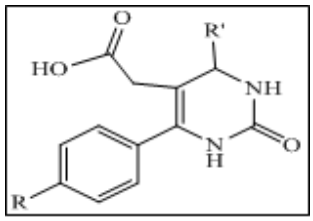
ABSTRACT

A series of [4,6-(substituted aryl)-2-oxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid has been synthesized by the base catalyzed condensation of 4-(4-substituted phenyl)-4-oxo butanoic acid, urea with aldehyde in ethanol. All the synthesized compounds were subjected to preliminary testing for anti-inflammatory activity according to the method of Winter et al. Most of the compounds showed significant anti-inflammatory activity.

Keywords: Anti-inflammatory, NSAIDs, Tertahydropyrimidines, Acetic acid.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) exhibit their effect by inhibiting COX enzymes and by blocking the synthesis of proinflammtory prostaglandin's [1-2]. It was found that large numbers of pyrimidine derivatives of pharmacological importance [3-4] were synthesized. It was also observed that aryl acetic acid derivatives have major contribution in Non Steroidal Anti-Inflammatory Agents. Acidic side chain was frequently used on heterocyclic nucleus to have more potent anti-inflammatory agent.



In view of this, it was proposed to synthesize heterocyclic acetic acids containing 2-oxo-pyrimidine moiety with the hope to have new compound with better anti-inflammatory activity than existing.

MATERIALS AND METHODS

Chemicals were obtained from commercial sources and used without further purification. Succinic anhydride was prepared in our laboratory with further purification. The [4,6-(4-substituted aryl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acetic acid derivatives were synthesized as per Scheme-1. Their sharp melting points were taken in open capillaries on Scientific Melting Point Apparatus and were quoted as uncorrected values. Thin layer chromatography (Rf-value) confirmed the purity of these compounds. The Infrared spectra using JASCO FT-IR Spectrophotometer 4000 were obtained in KBr powder and peaks are expressed in terms of wavenumber (cm^{-1}). The ^{1}H NMR spectra were obtained using BRUKER AVANCE II 400 SPECTROMETER with TMS as internal standard. The mass spectra were obtained using Time Of Flight Mass Spectrometer.

General procedure

Synthesis of Succinic Anhydride (I)[5] In a 500 ml RBF, provided with a reflux condenser protected by a calcium chloride drying tube, placed 29.50 gm (0.25 mol) of Succinic acid and 51 gm (47.25 ml, 0.5 mol) of redistilled acetic anhydride. Refluxed the mixture gently on a water bath with occasional shaking until a clear solution was obtained and then for a further hour to ensure the completeness of the reaction. Removed the complete assembly from the water bath, allowed it cool (observed the formation of crystals) and finally cooled in ice. Collected on a Buchner funnel and dried. m.p. 120°C, Rf 0.8, yield 32 gm, 87.45%.

Synthesis of 4-(4-substituted phenyl)-4-oxo butanoic acid derivatives (IIa-IId) In RBF provided with a reflux condenser protected by calcium chloride guard tube, placed 0.5 mol of substituted benzene and 7.5 gm (0.75 mol) of **I**. Stirred the mixture & added 22 gm (0.165 mol) of powdered anhydrous $AlCl_3$ all at once. The reaction started immediately. HCl was evolved and the mixture became hot. Heated in an oil bath to gentle refluxing, with continued stirring for one hour. Allowed to cool, immersed the flask in a bath of cool water and slowly added 33.33 ml of water and 11 ml of conc. HCl and separated the benzene with the separating funnel into a beaker and kept overnight. Dissolved the crude acid in a solution of 8.88 gm of anhydrous sodium carbonate in 55.55 ml of water by boiling for 10-15 min, filtered the solution with suction to remove the small amount of Aluminium hydroxide and washed with two 5.55 ml portions of hot water. Treated the hot filtrate with decolorizing carbon, boiled for 5 min and filtered at the pump through a Buchner funnel. Cooled the hot filtrate to about 50°C and cautiously acidified with 14-15 ml of conc. HCl. Cooled to 0°C in a freezing mixture of ice and salt, filtered, washed thoroughly with cold water, dried for 12 hours upon filter papers. The physical characteristics of the compounds **(IIa-IId)** are given in Table 1.

Synthesis of [4,6-(4-substituted aryl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acetic acid derivatives (IIIa-IIIj)[4,6]

A mixture of each compounds **II** (0.009 mol), Urea (0.009 mol), substituted aldehyde (0.009 mol) and K_2CO_3 (0.009 mol) in 15 ml ethanol was refluxed in oil bath for 8 hours. The reaction

mixture was cooled and the solid obtained was filtered and dissolved in hot water and filtered. The filtrate was neutralized with acetic acid. The solid obtained was filtered, dried and recrystallized from ethyl acetate.

2-(6-(4-chlorophenyl)-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4- tetrahydropyrimidin-5-yl)acetic acid (IIIa): Yield 33.41% , m.p. 102 °C; ^{1}H NMR ($CHCl_3$, 400MHz) δ: 1.24 – 1.25 (s, 2H, CH_2), 3.65 – 3.79 (s, 9H, OCH_3), 3.81 – 3.97 (s, 1H, CH), 2.05 – 2.17 (s, 2H, NH broad), 6.23 – 6.68 (m, 2H, ArH), 7.13 – 7.90 (m, 4H, ArH), 9.87 (s, 1H, OH); IR (KBr) *v*: 3458, 1557, 1328, 3512, 1696, 1418, 907, 3079, 1942, 1589, 1185, 2834, 756 cm^{-1} ; MS ES+ () *m/z* (%): found 431.1 (M^+,), calcd 432.86 (M^+).

2-(4-(4-hydroxyphenyl)-2-oxo-6-p-tolyl-1,2,3,4-tetrahydropyrimidin-5-yl)acetic acid (IIIb): Yield 33%, m.p. 150 °C; ^{1}H NMR (DMSO, 400MHz) δ: 1.22 – 1.24 (s, 2H, CH_2), 2.39 – 2.75(s, 3H, -CH_3), 6.55 – 6.93(m, 1H, ArOH), 3.79 – 3.94 (s, 1H, CH), 2.08 – 2.10 (s, 2H, NH broad), 7.23 – 7.77 (m, 8H, ArH), 9.90 (s, 1H, OH); IR (KBr) *v*: 3500, 850, 1228, 3512, 1706, 1425, 945, 3050, 1912, 1512, 1180, 2923, 3616 cm^{-1} ; MS ES+ () *m/z* (%): found 337.7 (M^+,), calcd 338.37 (M^+).

2-(4-(4-(dimethylamino)phenyl)-2-oxo-6-p-tolyl-1,2,3,4-tetrahydropyrimidin-5-yl)acetic acid (IIIc): Yield 30.12%, m.p. 97 °C; ^{1}H NMR ($CHCl_3$, 400MHz) δ: 1.25 (s, 2H, CH_2), 2.41 – 2.82 (s, 3H, -CH_3), 3.09 – 3.31(s, 6H, -NCH_3-), 3.77 – 3.95 (s, 1H, CH), 6.69 – 6.71 (s, 2H, NH broad), 7.25 – 7.89 (m, 8H, ArH), 9.73 (s, 1H, OH); IR (KBr) *v*: 3450, 599, 1328, 3542, 1716, 1365, 945, 3026, 1812, 1412, 1100, 2962, 2803 cm^{-1} ; MS ES+ () *m/z* (%): found 366 (M^+,), calcd 365.44 (M^+).

2-(6-(4-chlorophenyl)-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidin- 5-yl)acetic acid (IIId): Yield 55.86% , m.p. 100 °C; ^{1}H NMR ($CHCl_3$, 400MHz) δ: 1.24 – 1.25 (s, 2H, CH_2), 3.65 – 3.79 (s, 9H, OCH_3), 3.81 – 3.97 (s, 1H, CH), 2.05 – 2.17 (s, 2H, NH broad), 7.01 – 7.54 (m, 7H, ArH), 9.99 (s, 1H, OH); IR (KBr) *v*: 3450, 1555, 1330, 3510, 1689, 1410, 900, 3069, 1932, 1575, 1156, 2812 cm^{-1} ; MS ES+ () *m/z* (%): found 398.42 (M^+,), calcd 398.42 (M^+).

2-(4-(4-hydroxyphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)acetic acid (IIIe): Yield 41.23%, m.p. 130 °C; ^{1}H NMR (DMSO, 400MHz) δ: 1.18 - 1.25 (s, 2H, CH_2), 6.53 – 6.95 (m, 1H, ArOH), 3.30 – 3.74 (s, 1H, CH), 2.00 – 2.88 (s, 2H, NH broad), 7.12 – 7.99 (m, 9H, ArH), 9.81 (s, 1H, OH); IR (KBr) *v*: 3503, 855, 1220, 3509, 1718, 1420, 940, 3052, 1908, 1519, 1170, 3610 cm^{-1} ; MS ES+ () *m/z* (%): found 323 (M^+,), calcd 324.34 (M^+).

2-(6-(4-fluorophenyl)-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl) acetic acid (IIIf): Yield 48.85%, m.p. 145 °C; ^{1}H NMR (DMSO, 400MHz) δ: 1.25 (s, 2H, CH_2), 6.47 – 6.96 (m, 1H, ArOH), 2.81 (s, 1H, CH), 2.15 – 2.59 (s, 2H, NH broad), 7.07 – 7.82 (m, 8H, ArH), 9.81 – 10.01 (s, 1H, OH); IR (KBr) *v*: 3510, 679, 1248, 3522, 1708, 1385, 905, 3045, 1912, 1423, 990, 3616, 1112 cm^{-1} ; MS ES+ () *m/z* (%): found 343.2 (M^+,), calcd 342.33 (M^+).

2-(6-(4-fluorophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrim- idin-5-yl)acetic acid (IIIg): Yield 29.12%, m.p. 125 °C; ^{1}H NMR ($CHCl_3$, 400MHz) δ: 1.19 (s, 2H,

CH_2), 3.61 – 3.70 (s, 3H, -OCH_3) 6.39 – 6.89 (m, 1H, ArOH), 2.79 (s, 1H, CH), 2.09 – 2.50 (s, 2H, NH broad), 7.16 – 7.77 (m, 7H, ArH), 9.99 – 10.02 (s, 1H, OH); IR (KBr) *v*: 3507, 609, 1348, 3516, 1701, 1355, 935, 3045, 1712, 1523, 1190, 3646, 1012, 2834 cm^{-1} ; MS ES+ () *m/z* (%): found 373.2 (M^+,), calcd 372.36 (M^+).

2-(6-(4-chlorophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2,3,4–tetrahydropyri-midin-5-yl)acetic acid (IIIh): Yield 28.16%, m.p. 110 °C; ^1H NMR ($CHCl_3$, 400MHz) δ: 1.25 (s, 2H, CH_2), 3.09 – 3.79 (s, 3H, -OCH_3) 6.96 – 6.99 (m, 1H, ArOH), 3.89 – 3.97 (s, 1H, CH), 2.10 – 2.84 (s, 2H, NH broad), 7.01 – 7.94 (m, 7H, ArH), 9.70 - 9.83 (s, 1H, OH); IR (KBr) *v*: 3500, 600, 1340, 3520, 1700, 1375, 955, 3044, 1712, 1523, 1188, 3647, 756, 2822 cm^{-1} ; MS ES+ () *m/z* (%): found 373.2 (M^+,), calcd 388.81 (M^+).

2-(4-(4-hydroxy-3-methoxyphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl) acetic acid (IIIi): Yield 34.59%, m.p. 130 °C; ^1H NMR ($CHCl_3$, 400MHz) δ: 1.25 – 1.59 (s, 2H, CH_2), 3.34 – 3.97 (s, 3H, -OCH_3) 6.51 – 6.99 (m, 1H, ArOH), 4.00 (s, 1H, CH), 2.16 – 2.83 (s, 2H, NH broad), 7.01 – 7.54 (m, 8H, ArH), 9.83 (s, 1H, OH); IR (KBr) *v*: 3500, 600, 1358, 3510, 1703, 1360, 934, 3045, 1711, 1523, 1190, 3645, 2843 cm^{-1} ; MS ES+ () *m/z* (%): found 354.3 (M^+,), calcd 354.37 (M^+).

2-(2-oxo-6-p-tolyl-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-yl)acetic acid (IIIj): Yield 25.94% , m.p. 120 °C; ^1H NMR ($CHCl_3$, 400MHz) δ: 1.25 (s, 2H, CH_2), 2.17 – 2.47 (s, 3H, -CH_3), 3.56 – 3.79 (s, 9H, OCH_3), 3.80 – 3.94 (s, 1H, CH), 6.78 (s, 2H, NH broad), 7.13 – 7.34 (m, 6H, ArH), 9.87 (s, 1H, OH); IR (KBr) *v*: 3458, 1557, 1328, 3512, 1696, 1418, 907, 3079, 1942, 1589, 1185, 2834, 2923 cm^{-1} ; MS ES+ () *m/z* (%): found 411.99 (M^+,), calcd 412.45 (M^+).

RESULTS AND DISCUSSION

Synthesis

The [4,6-(4-substituted aryl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acetic acid derivatives **(IIIa-IIIj)** have been synthesized by the reaction of 4-(4-substituted phenyl)-4-oxo butanoic acid with urea and substituted aldehyde in alcohol as solvent in presence of potassium carbonate.

Biological activity

Compounds **(IIIa-IIIj)** were subjected to preliminary testing for anti-inflammatory activity according to the method of Winter *et* a[7]. The results for anti-inflammatory activity are given in Table No. 2. The result suggested that all the compounds possess good anti-inflammatory activity with percent inhibition ranging from 15.81% to 49.97%, where as the standard drug possess percent inhibition from 26.5% to 51.96%. Most of the compounds showed significant anti-inflammatory activity hence the potency of the compounds is considered based upon onset and duration of action. In this regard **IIIe**, **IIIg** had been significant towards onset of action and results were comparable to that of reference standard. On the other hand **IIIf**, **IIIh**, **IIIi** have showed delayed onset of action and found to be effective since 2nd hour. All above five compounds showed consistent action till 24 hours when compared against vehicle treated control rats. **IIIe** and **IIIg** are most effective compounds with respect to onset and duration of its anti-inflammatory action. Whereas **IIIf**, **IIIh** and **IIIi** can be better option if delayed onset of action is

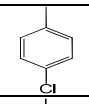
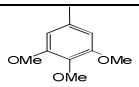
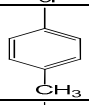
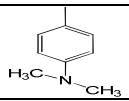
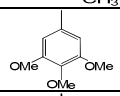
not a matter. This difference in onset may be due to release of different inflammatory mediators with respect to time indicating different mechanism of action.

As far as the structure-activity relationship is concerned, among all the synthesized 2-oxo-pyrimidne acetic acid derivatives, the compounds having the 3-OMe-4-OH phenyl group at C_4 and phenyl, *p*-chlorophenyl, *p*-fluorophenyl group at C_6 showed remarkable activity, in which phenyl, *p*-chlorophenyl group at C_6 enhances the activity. The presence of *p*-OH at C_4 and phenyl and p-fluorophenyl group at C_6 also showed good activity. It has been observed that replacement of phenyl and *p*-fluorophenyl group by *p*-tolyl group at C_6 reduced the activity. The presence of 3,4,5-trimethoxy phenyl group at C_4 and *p*-chlorophenyl and *p*-tolyl group at C_6 also showed good activity. Replacement of *p*-tolyl and *p*-chloro by phenyl at C_6 reduced the activity. The presence of *p*-dimethylamino phenyl and 3,4,5-trimethoxy phenyl group at C_4 with *p*-tolyl and phenyl at C_6 showed moderate activity. SAR studies reveal that presence of 3-OMe-4-OH phenyl group is important for activity. It indicates that there should be proper balance between hydrophilicity and lipophilicity of the molecule so as to show anti-inflammatory activity.

Table no. 1: Characterization data for 4-(4-substituted phenyl) 4-oxo butanoic acid derivatives

No.	R	Molecular Formula	Molecular Weight	% Yield	Melting Point*	Rf Value**
IIa	H	$C_{10}H_{10}O_3$	178	24.65	120	0.72
IIb	CH_3	$C_{11}H_{12}O_3$	192.2	18.65	105	0.83
IIc	Cl	$C_{10}H_9O_3Cl$	212.5	12.54	125	0.69
IId	F	$C_{10}H_9O_3F$	196.11	18	76	0.56

Table no. 5: Characterization data for [4,6-(4-substituted aryl)-2oxo-1,2,3,4 tetrahydropyrimidin-5-yl]-acetic acid derivatives

Sr. No.	Comp. Code	R	R'	Molecular Formula	Molecular Weight
1.	IIIa			$C_{21}H_{21}ClN_2O_6$	432.86
2.	IIIb			$C_{19}H_{18}N_2O_4$	338.37
3.	IIIc			$C_{21}H_{23}N_3O_3$	365.44
4.	IIId			$C_{21}H_{22}N_2O_6$	398.42
5.	IIIe			$C_{18}H_{16}N_2O_4$	324.34

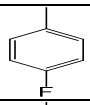
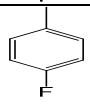
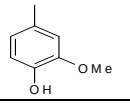
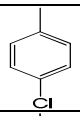
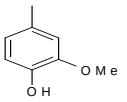
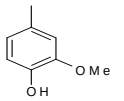
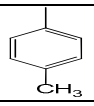
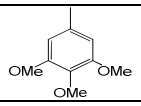
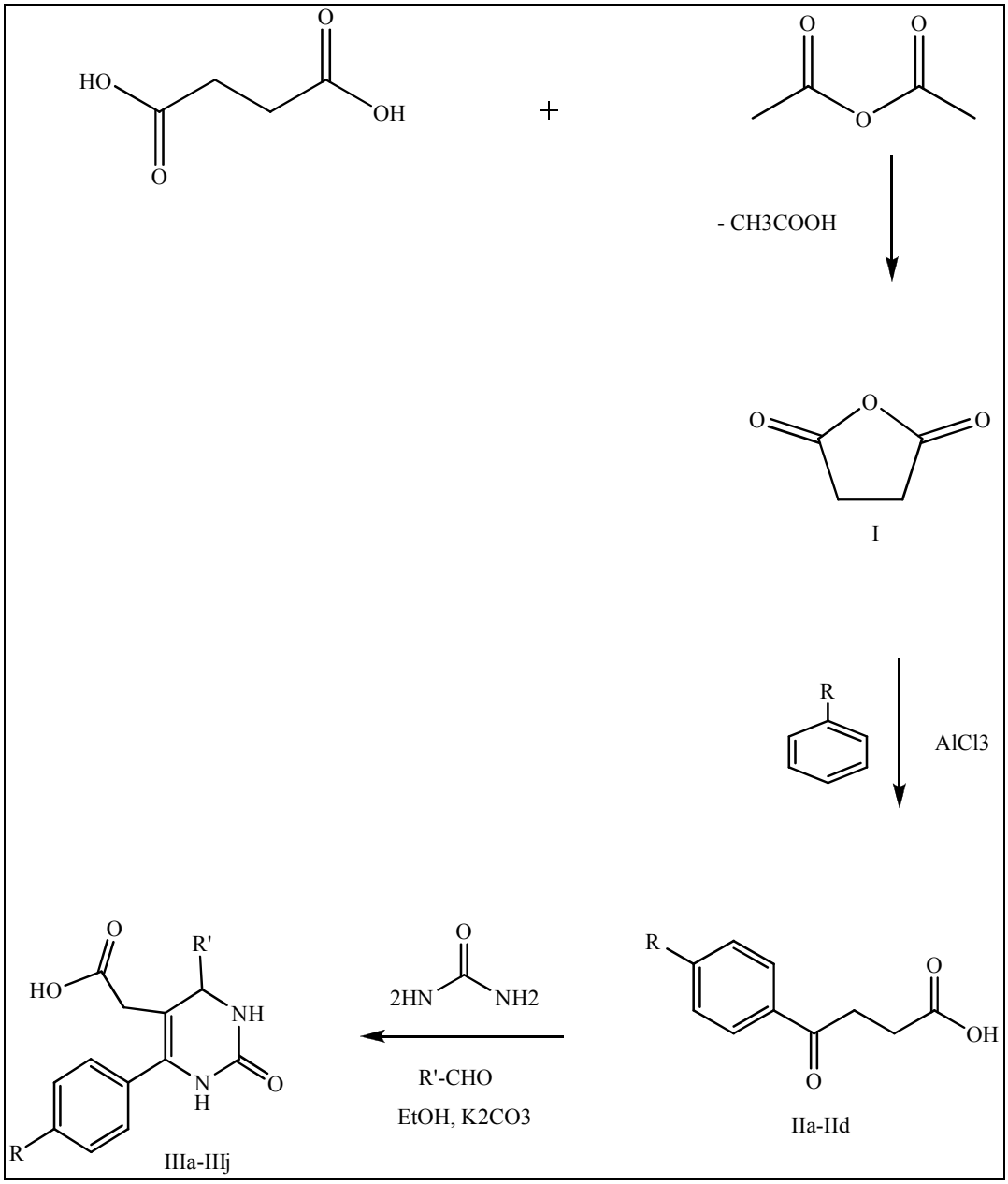
6.	IIIf			$C_{18}H_{15}FN_2O_4$	342.33
7.	IIIg			$C_{19}H_{17}FN_2O_5$	372.36
8.	IIIh			$C_19H_{17}ClN_2O_5$	388.81
9.	IIIi			$C_{19}H_{18}N_2O_5$	354.37
10.	IIIj			$C_{22}H_{24}N_2O_6$	412.45

Table no. 2: Mean paw volume (ml) and % inhibition of compounds IIIa-IIIj

No.	Mean Paw Volume (ml) ± SEM					% Inhibition of Edema				
	1 hr.	2 hr.	3 hr.	4 hr.	24 hr.	1 hr.	2 hr.	3 hr.	4 hr.	24 hr.
Control	1.925 ± 0.101	1.905 ± 0.046	1.631 ± 0.059	1.443 ± 0.046	1.396 ± 0.053	--	--	--	--	--
IIIa	1.143 ± 0.008**	1.21 ± 0.030**	1.001 ± 0.018**	1.043 ± 0.030**	1.08 ± 0.077**	40.62	36.48	38.62	27.72	22.63
IIIb	1.385 ± 0.041**	1.665 ± 0.070**	1.373 ± 0.046**	1.17 ± 0.023**	1.083 ± 0.012**	28.05	12.59	15.81	18.91	22.42
IIIc	1.361 ± 0.070**	1.265 ± 0.072**	1.068 ± 0.051**	0.976 ± 0.049**	1 ± 0.021**	29.29	33.59	34.51	32.36	28.36
IIId	1.361 ± 0.023**	1.278 ± 0.043**	1.185 ± 0.065**	0.943 ± 0.015**	0.971 ± 0.007**	29.29	32.91	27.34	34.65	30.44
IIIe	1.131 ± 0.031**	1.143 ± 0.022**	1.01 ± 0.031**	0.816 ± 0.030**	0.843 ± 0.028**	41.24	40	38.07	43.45	39.61
IIIf	1.265 ± 0.018**	1.096 ± 0.061**	1.058 ± 0.034**	0.905 ± 0.026**	0.935 ± 0.012**	34.28	42.46	35.13	37.28	33.02
IIIg	1.143 ± 0.028**	1.081 ± 0.017**	0.933 ± 0.007**	0.871 ± 0.030**	0.851 ± 0.021**	40.62	43.25	42.79	39.63	39.04
IIIh	1.201 ± 0.028**	0.953 ± 0.031**	0.983 ± 0.024**	0.843 ± 0.008**	0.858 ± 0.027**	37.61	49.97	39.73	41.58	38.53
IIIi	1.261 ± 0.011**	0.99 ± 0.062**	0.908 ± 0.044**	0.823 ± 0.018**	0.833 ± 0.019**	34.49	48.03	44.32	42.96	40.32
IIIj	1.278 ± 0.029**	1.013 ± 0.021**	1.065 ± 0.009**	0.94 ± 0.020**	1.095 ± 0.008**	33.61	42.09	34.7	34.85	21.56
Diclofenac	1.168 ± 0.016**	0.915 ± 0.032**	0.806 ± 0.024**	0.821 ± 0.018**	1.026 ± 0.035**	39.32	51.96	50.58	43.1	26.5

*Test compounds = 20 mg/kg, Reference Standard, Diclofenac Sodium = 25mg/kg, Mean +/- SEM N=6, [**p<0.05] Statistical analysis is done by one-way ANOVA followed by Dunnet's test.*

Scheme-1



Acknowledgement
The authors thankful to the Mrs. Fatima Rafiq Zakaria Chairman, Maulana Azad Educational Trust and Dr. M.H.G. Dehghan, Principal, Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus , Aurangabad 431 001 (M.S.), India for providing the laboratory facility

REFERENCES

[1] Vane JR, *Nature* (New Biol.) **1971**; 231.

[2] Smith JB, Willis AL, *Nature* (New Biol.) **1971**; 235.
[3] Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. *New Engl. J. Med*. **1992**; 327: 749.
[4] Bahekar SS, Shinde DB. *Bioorg. & Med. Chem. Lett*. **2004**; 14:1733.
[5] Furniss BS, Tatchell AR, Smith PW. Vogel's Textbook of Practical Organic Chemistry. 5th ed. New Delhi, **2005**, pp. 695.
[6] http://www.organic-chemistry.org/namedreactions/biginelli-reaction.shtm
[7] Winter CA, Risley EA, Nuss GW. *Proc. Soc. Exp. Biol. Med*. **1962**; 111: 544.