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Microwave assisted synthesis and biological evaluation of tetrahydropyrimidine derivatives

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ABSTRACT

Twelve [6- (2-methoxy-phenyl)-2-oxo-4-phenyl / substituted phenyl-1, 2,3, 4- tetrahydropyrimidine-5-yl] acetic acid derivatives have been synthesized in a two-step reaction. In the first step benzene or substituted benzene react with succinic anhydride in presence of aluminum trichloride (Friedel Craft reaction) to obtain 4-(substituted phenyl)-4-oxo- butanoic acid. Second step involves synthesis of [6-(2-methoxy-phenyl)-2-oxo-4-phenyl/substituted phenyl-1,2,3,4-tetrahydro pyrimidine -5-yl] acetic acid by reaction between4-(substituted phenyl)-4-oxo- butanoic acid, urea and substituted aldehydes (Biginelli reaction). Their structures are confirmed by IR, ^{1}H NMR. T.L.C. of synthesized compounds performed in chloroform: ethanol (3:1) solvent system. The anti-inflammatory activity of all compounds has been recorded on the basis of reference standard Indomethacin. All the compounds showed tendency to cause a fall in oedema and showed anti-inflammatory activity. The anti-inflammatory data shows that use of anisole in first step plays important role in the activity. Anti-inflammatory activity of all compounds was taken by Carrageenan induced rat paw oedema as described by Winter et al. on albino rats.

Keywords: Pyrimidine, Anti-inflammatory activity, aryl alkanoic acid, NSAID'S.

INTRODUCTION

NSAIDs are a mainstay in the treatment of inflammatory disease and are among the most widely used drugs worldwide [1]. The main limitation in using NSAIDs lies in their side effects, which include gastrointestinal ulcerogenic activity and bronchospasm [2]. In recent years, several novel approaches to reducing the GI toxicity of NSAIDs have been taken, with promising results.

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications [3]. The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity [4].

The literature indicated that compounds having pyrimidine nucleus possess broad range of biological activities, like 5-fluorouracil as anticancer [5]; idoxuridine and trifluoridine as antiviral [6] zidovudine and stavudine as antiHIV [7]; trimethoprim, sulphamethiazine and sulphadiazine as antibacterial [8]; sulphadoxin as antimalarial and antibacterial [9]; minoxidil and prazosin as antihypertensive [10]; barbiturates e.g. phenobarbitone as sedative [11], hypnotics and anticonvulsant [12]; propylthiouracil as antithyroid [13]; thionzylamine as H_1 –antihistamine [14]; and toxoflavin as antibiotics [15].

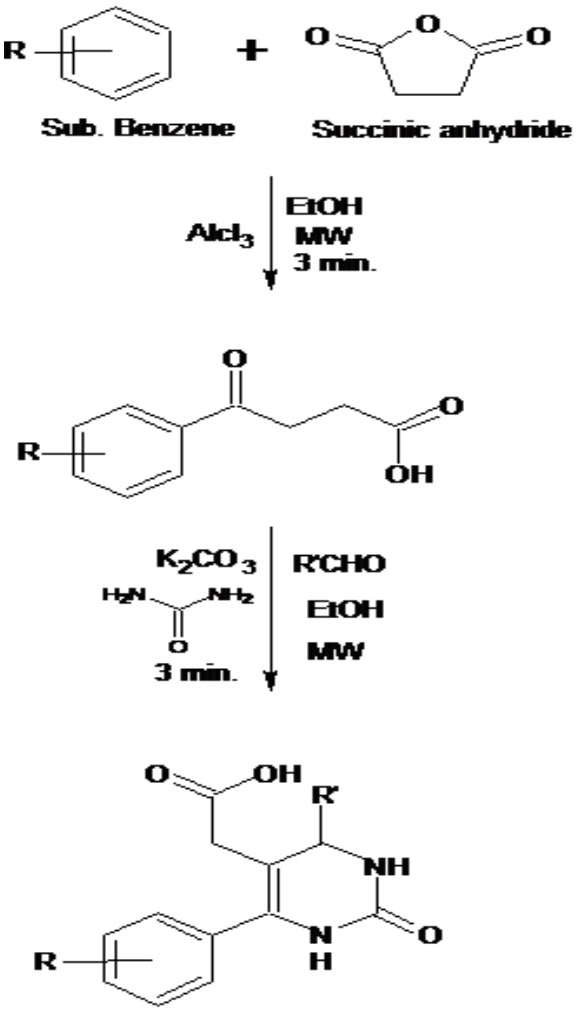
The main mechanism of action of NSAIDs is the inhibition of the enzymes possessing cyclooxygenase (COX) activity, which are involved in the formation of prostaglandins and thromboxanes from arachidonic acid contained in cellular membranes [16]. The relationship between the risk of serious GI side effects and the use of nonselective NSAIDs is well established[17]. Side effects to NSAIDs vary from person to person. Common side effects to all NSAIDs are abdominal pain, diarrhoea, nausea, and fluid retention [18].

Synthetic approaches based on chemical modification of some 1,2,3,4 tetrahydro pyrimidine derivatives are undertaken with the aim of improving safety profile. Encouraged by the findings of an exhaustive literature survey, we aimed to develop potent and nontoxic drug.

METHODOLOGY

The first step of reaction is by acylation of substituted benzene and succinic anhydride in the presence of aluminium chloride. The final step in the mechanism is believed to be the condensation between the aldehyde and urea, with some similarities to the Mannich Condensation. The imminium intermediate generated acts as an electrophile for the nucleophilic addition of the ketoesterenol and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give cyclized product [19,20].

Scheme -



Step – I. Synthesis of the 4-(substituted phenyl) -4-oxo- butanoic acids[21]

Microwave assisted synthesis were carried out using substituted benzene, succinic anhydride and a powdered aluminum chloride. Alcohol used as energy transfer medium. Stirring was provided manually and temperature maintained at constant value for three to five minutes.

Allowed to cool the resulting reaction mixture, added 15 ml of water. The 4-(substituted phenyl) -4-oxo-butanoic acid separated as colorless oil, which soon solidified. Cool in ice, filter off acid at the pump and wash with cold water.

Step – II. Synthesis of [4, 6-(4-substituted aryl)-2-oxo- 1, 2, 3, 4-tetrahydro-pyrimidin-5-yl]-ethanoic acid [22]

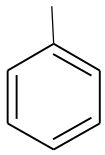
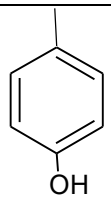
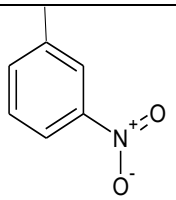
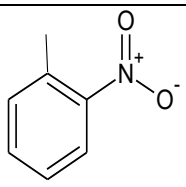
An equimolar reaction mixture of 4-(substituted phenyl) -4-oxo- butanoic acid (0.0022 mol) urea (0.002 mol), substituted aldehyde (0.0022 mol) and K2CO3 (0.0022 mol) in 7 ml ethanol were refluxed for three to five minutes. The reaction mixture was cooled and the solid obtained was dissolved in hot water and filtered. The filtrate was neutralized with acetic acid. The product thus obtained was recrystallized from methanol.

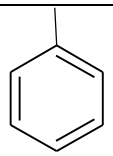
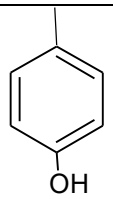
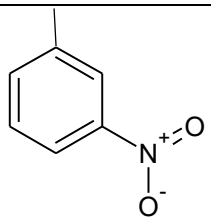
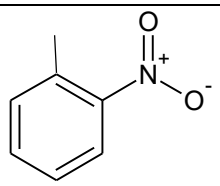
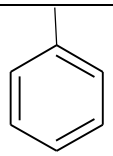
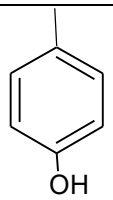
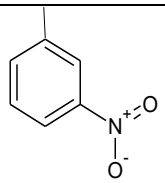
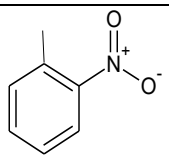
RESULTS AND DISCUSSION

Table 1: Characterization data for 4-(substituted phenyl) -4- oxo- butanoic acids.

Comp.	R	Molecular formula	Molecular weight	% Yield	M.P.
A	CH_3	$C_{11}H_{12}O_3$	192.23	86.12	127^0-128^0
B	H	$C_{10}H_{09}O_3$	177.19	87.48	120^0-121^0
C	OCH_3	$C_{11}H_{12}O_4$	208.23	78.02	136^0-137^0

Table 2. Characterization data for of [6-(2-methyl-phenyl)-2-oxo-4-phenyl/substituted phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-yl] acetic acid.

Comp code	R	R^1	Mol. Formula/Wt	% Yield	M.P.	Rf value Chloroform :Ethanol (3:1)
A1	CH_3		$C_{19}H_{18}N_2O_3$ 322.38	80.78	123	0.661
A2	CH_3		$C_{19}H_{18}N_2O_4$ 338.38	73.43	133	0.592
A3	CH_3		$C_{19}H_{17}N_3O_5$ 367.38	60.45	128	0.622
A4	CH_3		$C_{19}H_{17}N_3O_5$ 367.38	61.09	131	0.643

B1	H		$C_{18}H_{15}N_2O_3$ 307.38		118	0.580
B2	H		$C_{18}H_{15}N_2O_4$ 323.38	69.86	128	0.611
B3	H		$C_{18}H_{15}N_3O_5$ 355.37	68.13	122	0.592
B4	H		$C_{18}H_{15}N_3O_5$ 355.37	57.65	127	0.573
C1	OCH_3		$C_{19}H_{18}N_2O_4$ 339.37	77.57	122	0.540
C2	OCH_3		$C_{19}H_{18}N_2O_5$ 354.38	78.87	131	0.602
C3	OCH_3		$C_{19}H_{18}N_2O_6$ 383.38	65.56	127	0.491
C4	OCH_3		$C_{19}H_{17}N_3O_6$ 383.38	63.89	132	0.511

Spectroscopic data

A1- 3-[6-(4-methylphenyl)-2-oxo-4-phenyl-1, 2.3.4-tetrahydropyrimidine-5-yl] propionic acid-

IR (KBr,cm^{-1}) 3430 (O-H)str.,3068 (Ar-C-H)str,2966 (C-H)str, 1697(C=O)str,1574 (C=C)str,1109(C-N)str.

^1H NMR ($CDCl_3$) 7.2-8 (9 H (s) of Ar-H), 6.9 (3 H (s) of pyrimidine), 11.0 (1 H (s) of –COOH), 1.2(3 H (s) of CH_3), 1.42 (2H (t) of CH_2).

A2-3-[6-(4-methylphenyl)-2-oxo-4-hydroxy-phenyl-1,2.3.4-tetrahydropyrimidine-5-yl]propanoic acid-3337 (O-H) str.,3068 (Ar-C-H) str,1123 (C-N) str, 1698(C=O) str,1574 (C=C) str

A3-3-[6-(4-methylphenyl)-4-(3-Nitrophenyl)-2-oxo-1,2.3.4-tetrahydropyrimidine-5-yl]propanoic acid-3437 (O-H) str.,3068 (Ar-C-H) str, 1699(C=O) str,1534 (C=C) str,1073(C-N) str. 1351(NO_2) str.

A4-3-[6-(4-methylphenyl)-4-(2-Nitrophenyl)-2-oxo-1,2.3.4-tetrahydropyrimidine-5-yl]propanoic acid-3437 (O-H) str.,3068 (Ar-C-H) str, 1698(C=O) str,1574 (C=C) str,1073(C-N) str. 1377(NO_2) str.

B1-4, 6-diphenyl-2-oxo-1, 2, 3, 4 – tetrahydropyrimidin-5yl-propionic acid –IR (KBr,cm^{-1})3423(O-H)str.,3063(Ar-C-H)str,2935,2850 (C-H)str, 1680(C=O)str,1598 (C=C)str,3172(N-H)str.
^{1}H NMR ($CDCl_3$)7.2-8 (9 H (s) of Ar-H), 6.9 (3 H (s) of pyrimidine), 11.0 (1 H (s) of –COOH), 1.42 (2H (t) of CH_2).
B2-4-p-hydroxy-6-phenyl-2-oxo-1, 2, 3, 4 – tetrahydropyrimidin-5yl-propionic acidIR (KBr,cm^{-1})3441(O-H)str.,3030 (Ar-C-H)str,2850 (C-H)str, 1690(C=O)str,1550(C=C)str,3172(N-H)str., 1102(C-N)str., 1650(C=O) amide str.
B3–4-m-nitrobenzen-6-phenyl-2-oxo-1,2,3,4–tetrahydropyrimidin-5yl-propionic acidIR (KBr,cm^1)3338(OH)str.,3068(ArCH)str,2211,2898(CH)str,1697(C=O)str,1574(C=C)str,1344(NO_2)str., 1185(C-N)str.
B4-4-o-nitrobenzen-6-phenyl-2-oxo-1,2,3,4–tetrahydropyrimidin-5yl-propionicacidIR (KBr,cm^1)3394(OH)str., 3040(ArCH)str,2966(CH)str,1697(C=O)str,1574(C=C)str,1313(NO_2)str. 1193(C-N)str.,3170(N-H)str.
C1 - 3-[6-(4-methoxyphenyl)-4-phenyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl] propionic acid
IR (KBr,cm^{-1})3398(O-H)str.,3032 (Ar-C-H)str,2930 Me- (C-H)str, 1690(C=O)str,1570 (C=C)str,3140(N-H)str,1188(C-N)str,1390 methoxy (C=O)str.
^{1}H NMR ($CDCl_3$) 7.2-8 (9 H (s) of Ar-H), 6.9 (3 H (s) of pyrimidine), 11.0 (1 H (s) of –COOH), 1.42 (2H (t) of CH_2),3.9 (3 H (s) of OCH_3).
C2--3-[6-(4-methoxyphenyl)-4-(4-Hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl] propionic acidIR (KBr,cm^{-1})3390(O-H)str.,3030(Ar-C-H)str,2950Me-(C-H)str, 1650(C=O)str,1580(C=C)str,3125(N-H)str,1292(C-N)str,1399 methoxy (C=O)str.
C3-3-[6-(4-methoxyphenyl)-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]propionic acidIR (KBr,cm^{-1})3398(O-H)str.,3032 (Ar-C-H)str,2930 Me- (C-H)str, 1690(C=O)str,1570 (C=C)str,3140(N-H)str,1188(C-N)str,1390 methoxy (C=O)str, 1321(NO_2)str.
C4-3-[6-(4-methoxyphenyl)-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]propionic acidIR (KBr,cm^{-1})3390(O-H)str.,3030(Ar-C-H)str,2950 Me- (C-H)str, 1650(C=O)str,1580(C=C)str,3125(N-H)str,1292(C-N)str,1399 methoxy (C=O)str, 1313(NO_2)str.

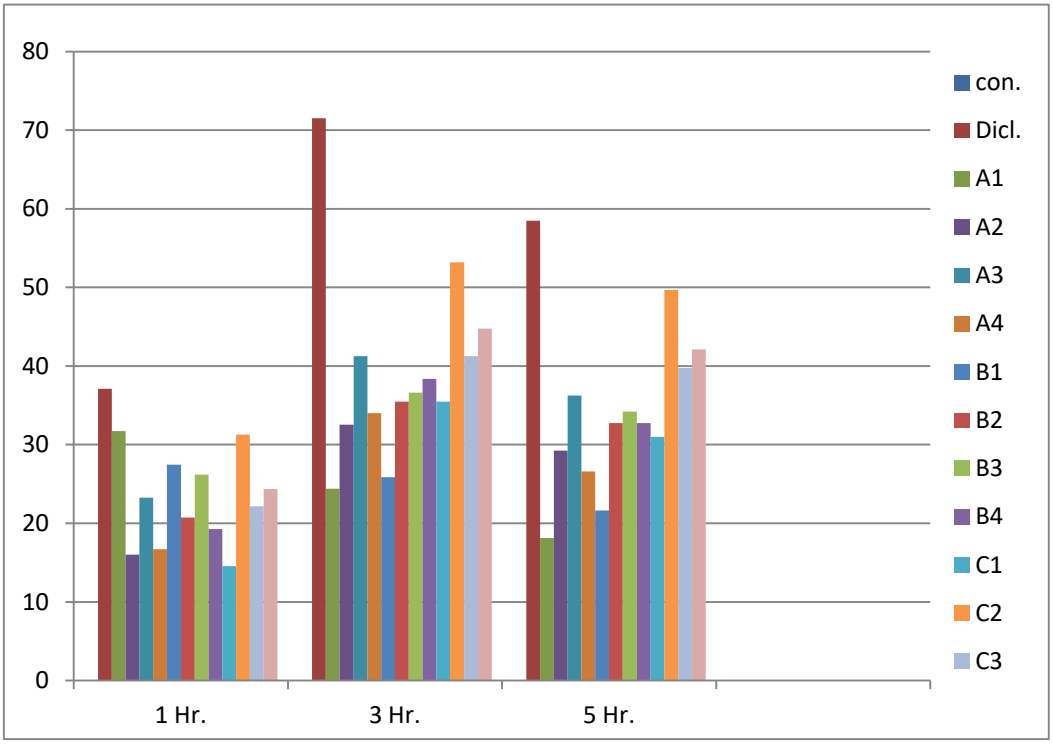


Fig. 1 - statistical graph showing comparisons in anti-inflammatory activity.

Table 3. Anti-inflammatory activity statistical data

Group	Dose	Carrageenan induced paw edema					
		1 Hr.		3 Hr.		5 Hr.	
		EV	EI	EV	EI	EV	EI
control	saline	2.68 ±0.19	-	3.44±0.35		3.42±.32	
Indomethacin	10 mg/kg	1.63±0.25	37.09	0.98±0.02**	71.51	1.40±.25*	56.47
A1		2.36±0.11	31.74	2.58±.06*	24.41	2.80±.05	17.12
A2		2.31±0.03	16.00	2.32±.07*	32.55	2.42±.02	27.23
A3		2.00±0.09	23.27	2.02±.12*	41.27	2.18±.01	36.25
A4		2.29±0.047	16.72	2.27±.03*	33.01	2.51±.017	26.60
B1		2.34±0.016	27.45	2.53±00*	25.87	2.68±.011	21.63
B2		2.18±0.011	20.72	2.22±.05*	35.46	2.30±.052	30.74
B3		2.03±0.034	26.18	2.18±.10**	36.62	2.25±0.60	34.21
B4		2.23±0.060	19.27	2.12±.01*	37.37	2.30±.052	30.74
C1		2.30±0.062	14.54	2.25±.06*	35.46	2.36±.053	30.99
C2		1.89±0.084	31.27	1.60±.06**	53.19	1.72±.027*	49.70
C3		2.14±0.050	22.18	2.02±.10**	41.27	2.06±.024	39.76
C4		2.08±0.103	24.36	1.90±.01**	44.76	1.98±.057	41.10

Values are expressed as mean ± SEM (n=6). EV – Oedema volume, EI – Oedema inhibition.
Significant at p< 0.05, ** highly significant at p<0.01, *** Very highly significant at p<0.001

Evaluation of anti-inflammatory activity using carrageen an induced rat paw edema mode [23]. Albino rats of either sex (150-200 g) were divided into different groups, containing six animals each. Animals were fasted for 12 h before experiment and only water was allowed. While the first group was a control one and received vehicle (Tween 80 in propylene glycol (10% v/v), 0.5 ml per rat), the second group received Diclofenac sodium (10 mg/kg). The entire remaining group received the test compounds at the same dose orally. All the suspensions for oral dose were prepared in the vehicle mentioned above and administered in a constant volume of 0.5 ml per rat.

CONCLUSION

Twelve [6-(2-methoxy-phenyl)-2-oxo-4-phenyl/ substituted phenyl-1,2,3,4- tetrahydropyrimidine-5-yl] acetic acid derivatives have been synthesized in a two-step reaction.

Their structures are confirmed by IR, ^{1}H NMR and TLC.The anti-inflammatory activity of all compounds has been recorded on the basis of reference standard indomethacin.All the compounds showed tendency to cause a fall in oedema and showed anti-inflammatory activity.The anti-inflammatory data shows that use of methoxy at 4th position of phenyl in product shows increase in activity (c1-c4).

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Conflicts of interest: The authors stated that no conflicts of interest.

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