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ANTI-INFLAMMATORY ACTIVITY OF SOME NEW DIHYDROPYRIMIDINES DERIVATIVES

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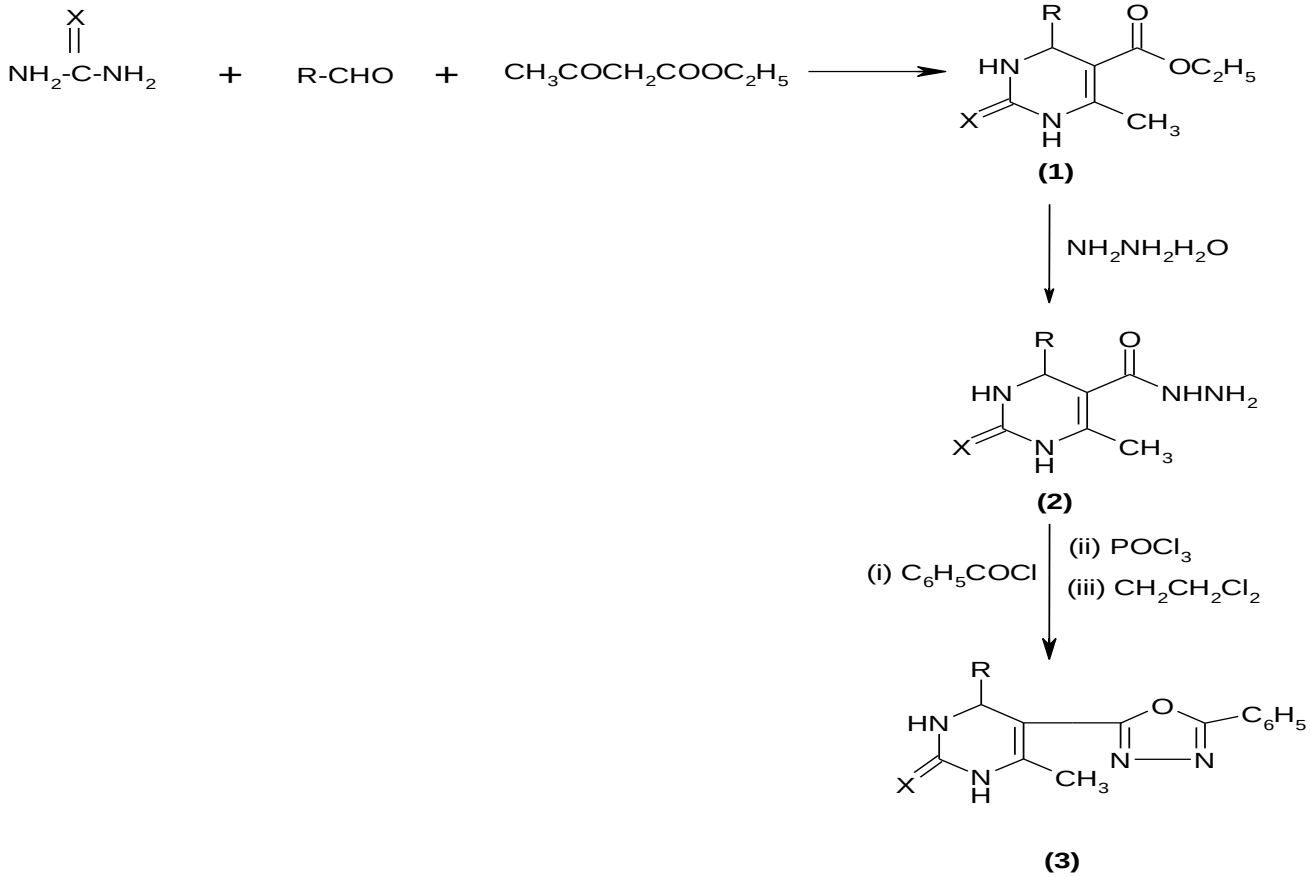
ABSTRACT

A series of 6- methyl- 2 - oxo N- (4- oxo- 2- substituted phenyl- 1, 3- thiazolidin- 3- yl)- 4- substituted phenyl- 1, 2, 3, 4- tetrahydropyrimidine- 5- carboxamide have been synthesized and evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema method. The reaction was carried out simply by heating a mixture of three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one pot, tree-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3, 4- dihydropyrimidine- 2 (1H) - one. The synthetic potential of this new heterocyclic synthesis remained unexplored for quite some time. In the 1970s and 1980s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multi functionalized dihydropyrimidines. The resulting dihydropyrimidinones and their sulphur analogs posses antibacterial, antiviral, antitumor, anti-inflammatory, antihypertensive as well as calcium channel blocker properties.

INTRODUCTION: In 1893 Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea. The reaction was carried out simply by heating a mixture of three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one pot, tree-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3, 4-dihydropyrimidine- 2 (1H) - one. The synthetic potential of this new heterocyclic synthesis remained unexplored for quite some time. In the 1970s and 1980s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multi functionalized dihydropyrimidines [1-4]. The resulting dihydropyrimidinones and their sulphur analogs posses antibacterial, antiviral, antitumor, anti-inflammatory, antihypertensive as well as calcium channel blocker properties [5-6]. Literature survey revealed that slight modification in the structure can result in qualitative as well as quantitative changes in activity, which prompted us to undertake the synthesis of various dihydropyrimidinones derivatives. The synthesized compounds were evaluated for anti-inflammatory activity by carrageenan induced rat paw edema method and results are compared with standard drug Diclofenac sodium.



SCHEME 1

EXPERIMENTAL:

Ethyl -6- methyl- 2- oxo- 4- substituted phenyl- 1,2,3,4-tetrahydropyrimidine-5-carboxylate (1): To a mixture of urea (0.15 mole), substituted aldehyde (0.10 mole) and ethylacetoacetate (0.10 mole) in ethanol (75 ml), 4 drops of concentrated hydrochloric acid was added and heated for 1.5 hrs at 70^0C. The reaction mixture was poured into ice water (100 ml) with stirring and left overnight at room temperature. Filtered and residue dried at room temperature, recrystallised from ethanol.

IR (KBr) 1645 cm^{-1} (amide C=O), 1714 cm^{-1} (ester C=O), 3246 cm^{-1} (-NH).

^{1}H NMR (DMSO-d_6): δ 1.07(t, 3H, CH_3- ester); 2.25 (s, 3H, dihydropyridyl- CH_3); 3.93 (q, 2H, CH_2- ester); 5.15 (d, 1H, dihydropyridyl- CH); 7.2-7.5 (m, 4H, Ar-H) 7.7 (s, 1H, 3-NH); 9.25 (s, 1H, 1- NH).

6- Methyl- 2 - oxo - 4 - substitutedphenyl- 1, 2, 3, 4- tetrahydropyrimidine- 5- carbohydrazide (2): To a hot solution of 1 (0.01mole) in ethanol (150 ml), was added hydrazine hydrate (99%, 0.015 mole) and the reaction mixture was heated under reflux for 3 hrs. The solvent was removed to possible extent by distillation and the product thus separated was filtered and purified by recrystallization from ethanol to get a colorless crystalline solid.

IR (KBr) 1647 cm^{-1} (amide C=O), 3247 cm^{-1} (- H).

^{1}H NMR (DMSO- d_6) δ 2.25 (s, 3H, dihydropyridyl- CH_3); 4.0 (s, 2H, NH_2); 5.1(d, 1H,-NH); 7.22-7.5(m, 4H, Ar-H); 7.77 (s, 2H, 3-NH/CH); 9.25 (s, 1H, 1-NH)

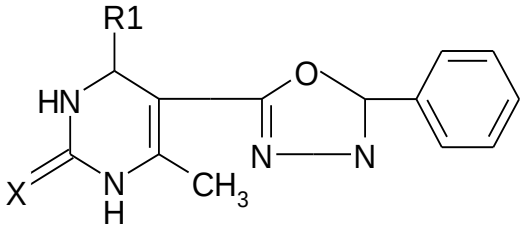
6- Methyl- 4 - aryl- 5- (5- phenyl- 1, 3, 4- oxadiazol- 2- yl)- 1, 2, 3, 4- tetrahydropyrimidine- 2 (1*H*) - one (3): To a solution of benzoyl chloride (0.01 mole) in dichloroethane (10 ml) and compound 2 (0.01 mole), phosphorous oxychloride (5ml) was added and content were refluxed for 8 hrs on an oil bath. After the reaction, excess of solvent and $POCl_3$ were distilled at reduced pressure. Reaction mass was cooled and poured into ice, left overnight. The product was obtained by filtration and purified by recrystallization from aqueous ethanol (Table-1).

IR (KBr) 1689 cm^{-1} (amide C=O), 1026 cm^{-1} (C-O-C), 1603 &1582 cm^{-1} (C=N).

^{1}H NMR (DMSO- d_6) δ 1.28 (s, 6H, CH_3- N- CH_3); δ 2.1 (s, 3H, - CH_3); δ 2.65(s, 1H, - CH); 7.43-7.47 (d, 4H, Ar- H, attached with dihydropyrimidine); 7.55 (s, 1H, 1- NH); 7.57 (s, 1H, 1NH); 7.95- 8.15 (d, 5H, Ar-H, attached with oxadiazoles).

TABLE 1:

SL. NO.	R1	X	% YIELD	M. P. (^{o}C)	MOL. FORMULA
3a	Phenyl	O	72%	200	$C_{14}H_{16}O_3N_2$
3b	4-Methoxyphenyl	O	78%	116	$C_{15}H_{18}O_4N_2$
3c	4-Dimethylaminophenyl	O	71%	115	$C_{16}H_{21}O_3N_3$
3d	4-Nitrophenyl	O	72%	121	$C_{14}H_{15}O_5N_3$
3e	2-Hydroxyphenyl	O	64%	114	$C_{14}H_{16}O_4N_2$
3f	3-Hydroxy-4-mehtylphenyl	O	68%	132	$C_{15}H_{18}O_5N_2$
3g	3-Bromophenyl	O	71%	128	$C_{14}H_{15}O_3N_2Br$



COMPOUND 3

ANTI- INFLAMMATORY ACTIVITY: The synthesized compounds were screened for in vivo anti-inflammatory activity by carrageenan induced rat paw edema method [7]. The percentage inhibition of paw edema was calculated for the synthesized compounds using the formula [8] and compared with control and standard drug Diclofenac sodium (table 2).

TABLE 2:

COMPOUND	ANTI- INFLAMMATORY ACTIVITY (% INHIBITION)		
	1hr	2hr	3hr
Control	-	-	-
Diclofenac sodium	28.69	48.99	71.30
3a	21.56	44.64	67.19
3b	23.70	49.99	68.78
3c	22.30	47.60	68.66
3d	29.68	47.89	70.39
3e	25.66	45.90	60.66
3f	27.66	46.56	69.99
3g	31.34	51.26	74.89

RESULTS AND DISCUSION: The structures of synthesized compounds were confirmed by IR and ^{1}HNMR spectral analysis. The compounds (3a-3g) were obtained by appropriate methods. The yield was found to be in range of 64-72%. Compounds 3d and 3g was found to possess better activity.

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