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SYNTHESIS AND EVALUTION OF NOVEL 3, 4-DIHYDRO PYRIMIDINE-2(1H)-ONE DERIVATIVE AS ANALGESIC AGENTS

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ABSTRACT

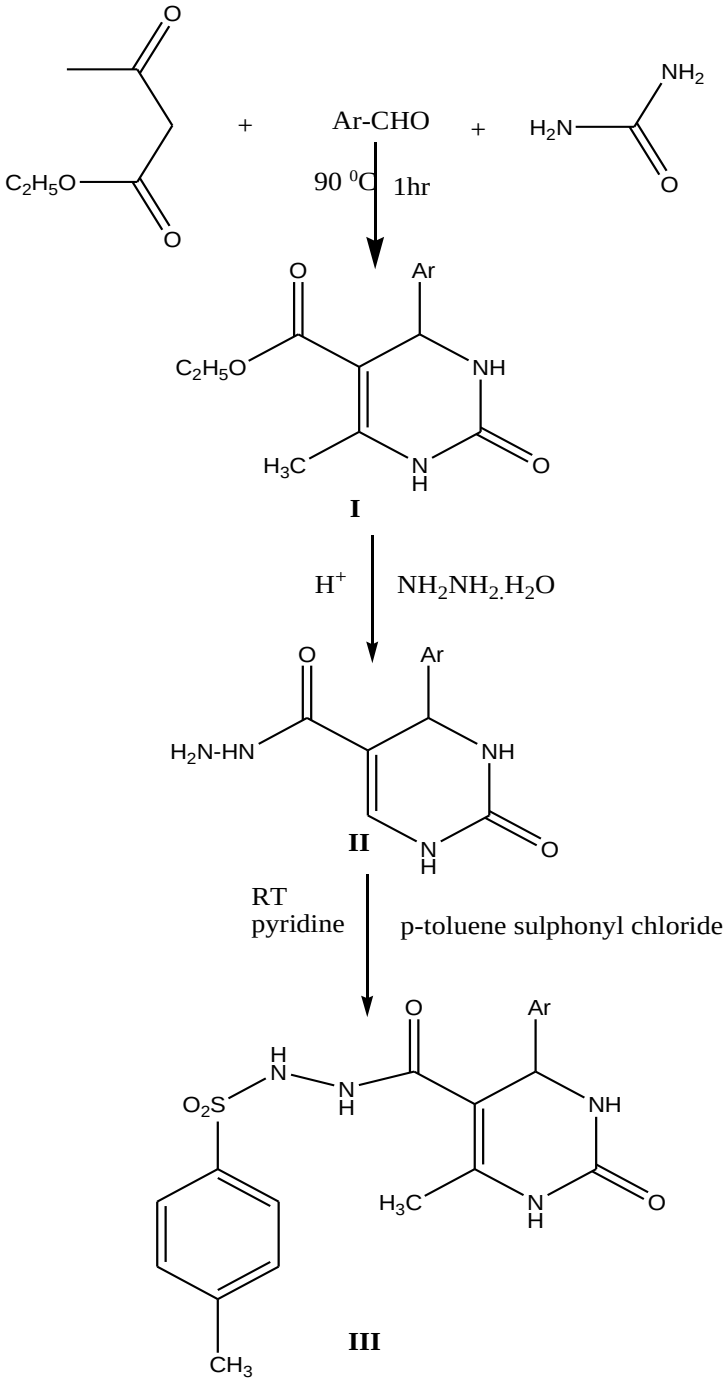
The titled compounds were expected to possess better activities due to incorporation of Mannich base at N_3 position of dihydropyrimidine. To synthesize the substituted dihydropyrimidine derivatives by utilizing appropriate synthetic method. To purify the intermediates and final compounds by recrystallisation and/or chromatographic techniques using suitable solvents .To characterize the synthesized compounds by the help of physical (MP, R_f values) and spectral data (IR, H^1NMR and Mass).To screen the synthesized compounds for their possible analgesic activity.

KEY WORDS

INTRODUCTION

Pyrimidines are 6-membered heterocyclic ring compounds composed of nitrogen and carbon. Pyrimidines are first isolated by Gabriel and Colman in 1899. It can be regarded as a cyclic amine, also known as *m*-diazine (or) 1, 3-diazine. Pyrimidine is weakly basic (*pKa* 1.3) as compared to pyridine (*pKa* 5.2) or imidazole (*p*Ka 7.2). Pyrimidine is symmetrical about the line passing C_2 & C_5, the positions of C_4 and C_6 are equivalent and so are N-1 and N-3. Fused pyrimidines are well known as anti-cancer, antimicrobial, antihypertensive, anti- mycobacterial, antiviral agents and etc. Dihydropyrimidinones, the products of the biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers and alpha-1 antagonists.

SCHEME:



Ar-CHO: benzaldehyde, P-Chlorobenzaldehyde, p-methoxybenzaldehyde, p-hydroxybenzaldehyde, p-nitrobenzaldehyde, 4-hydroxy-3-methoxy benzaldehyde.

EXPERIMENTAL

Chemistry:

All the chemicals were purchased from Sd fine chemicals ltd, Ranbaxy chemicals ltd and Qualigens chemicals ltd. All the solvents for the use are of laboratory grade. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh); spots were visualized with UV light. Merck silica gel (100–200 mesh; Merck, Germany) was used for

chromatography. All the synthesized compounds were purified by recrystallization. Melting points were determined on open capillary method and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics (Perkin-Elmer. USA). ^{1}H-NMR spectra were recorded on Gemini Varian (Varian, USA) 200 MHz, Bruker (Bruker Bioscience, USA) AV 300 MHz, and Unity (Varian) 400 MHz spectrometer in DMSO-d6 or CDCl3 using TMS as an internal standard. Electron impact (EI) and chemical ionization mass spectra were recorded on a VG 7070 H instrument (Micromass, UK) at 70 eV.

Synthesis of 5- (Ethoxycarbonyl)-6-methyl-4-substitutedaryl -3, 4-dihydropyrimidin-2(1H)-ones:-

STEP: I: - In the first step a mixture of three component reaction involving ethylacetoacetate, urea, substituted benzaldehydes as equimolar quantities were taken in round bottom flask. It was stirred for 2minutes, vigorously by hand and then heated in water bath at 90^{0}C for 1hour. With the progress of reaction a solid started to deposit and after 1hour the flask is full of solid. The solid was taken out carefully with a spatchula into a conical flask. The yellow solid was washed with cold water and then recrystallised from rectified spirit to give a colour less solid.

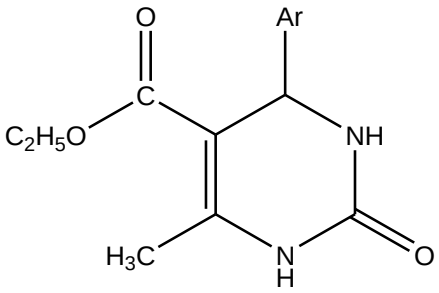


Table-1: physical data of 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl -3,4-dihydropyrimidin-2(1H)-ones (A1-A6):

Code	Ar	M.F	M.W(g)	M.P(^{0}C)	%yield	R_f^*
A1	C_6H_5	$C_{14}H_{16}O_3N_2$	260	205-209	85	0.46
A2	$C_6H_4OCH_3$	$C_{15}H_{18}O_4N_2$	290	198-201	84.4	0.43
A3	C_6H_4OH	$C_{14}H_{16}O_4N_2$	276	226-229	81.6	0.63
A4	C_6H_4Cl	$C_{14}H_{15}O_3N_2$	294	209-211	76	0.56
A5	$C_6H_3OCH_3OH$	$C_{15}H_{18}O_5N_2$	306	235-238	79	0.53
A 6	$C_6H_4NO_2$	$C_{14}H_{15}O_5N_3$	305	208-210	80	0.46

Solvent system: ethylacetate: toluene (3:2)

Spectral information (IR Spectrum, cm^{-1}) of 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl -3, 4-dihydropyrimidin-2(1H) - ones:

A_1:- 5-(Ethoxycarbonyl)-6-methyl-4-phenyl -3,4-dihydropyrimidin-2(1H)- ones:-

3360(N-H Stretch), 3026(Ar-H), 1703(C= O), 1690(C=O), Ar-H(781-790)

A_2:-5-(Ethoxycarbonyl)-6-methyl-4-methoxyphenyl-3,4-dihydropyrimidin-2(1H)- ones:-

2956-3242(N-H), 1704(C=O), 1681(C=O), 1224(-OCH_3), 750-827(Ar-H)

Synthesis of 4-substitutedaryl -6-methyl-2-pyrimidinone-5- carbhydrazides:-

STEP:II:-(stepI) product dihydropyrimidinone (0.01mole) in 20ml ethanol, hydrazine hydrate(0.01mole) was added followed by the addition of a catalytic amount of conc.H_2SO_4 and allowed to stir for 3hrs at 75^0 C. Yellow precipitate were obtained during reflux. A progress of reaction was monitored TLC. After completion of reaction, crude mass allowed to cool and poured on crushed ice. Product obtained as yellowish precipitate was filtered and dried. Purification was done by recrystallization using ethanol.

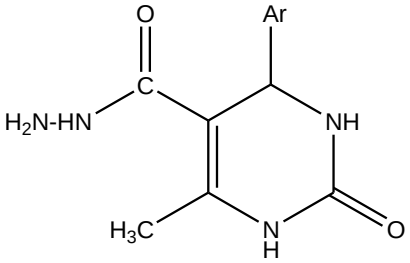


Table-2: physical data of 4-substitutedaryl-6-methyl-2-pyrimidinone-5-carbohydrazides (B1-B6):

Code	Ar	M.F	M.W(g)	M.P(^{0}C)	%yield	R_f^*
B1	C_6H_5	$C_{19}H_{20}O_4N_4$	246	190-193	74	0.56
B2	$C_6H_4OCH_3$	$C_{13}H_{16}O_3N_4$	276	167-170	78	0.55
B3	C_6H_4OH	$C_{12}H_{14}O_3N_4$	262	178-181	76	0.45
B4	C_6H_4Cl	$C_{12}H_{12}O_2N_4Cl$	280.5	215-221	69	0.7
B5	$C_6H_3OCH_3OH$	$C_{13}H_{16}O_4N_4$	292	230-232	78	0.65
B6	$C_6H_4NO_2$	$C_{12}H_{12}O_4N_5$	291	224-226	70	0.62

Solvent system: Ethylacetate: toluene (3:2)

Spectral information (IR Spectrum, cm^{-1}) of 4-substitutedaryl -6-methyl-2-pyrimidinone-5 carbohydrazides:

B_1:- 4-phenyl-6-methyl-2-pyrimidinone-5-carbohydrazides:-

3360(N-H Stretch), 3015(Ar-H), 1695(C=O), 1643(C= O), Ar-H (781-790)

B_2:- 4-methoxyphenyl-6-methyl-2-pyrimidinone-5-carbohydrazides:-

3116(-aromatic), 2954-3242(-NH-NH_2), 1703(C=O), 1681(C=O), 1236(-OCH_3), 750-827(Ar-H)

4.2.4. Synthesis of 4-substitutedaryl -6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbhydrazides:-

STEP: III:-To (step-II) hydrazine compound (5mmole) p-toluene sulphonyl chloride (5m.mole) was added in presence of alcohol and pyridine (6m.mole) and refluxed for 2hrs. A progress of reaction was monitored by using TLC. After completion of reaction the crude mass was separated out and dried.

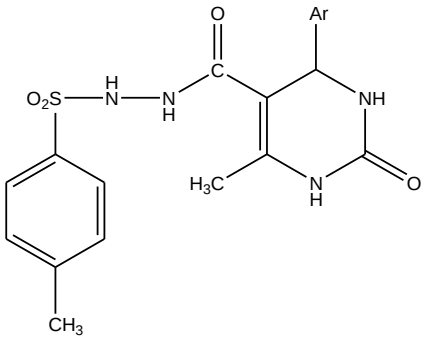


Table-3: physical data of 4-substitutedaryl -6-methyl-2-pyrimidinone-5-(N-p-tosyl)carbohydrazides (C1-C6):

Code	Ar	M.F	M.W(g)	M.P(^{0}C)	%yield	R_f^*
C1	C_6H_5	$C_{19}H_{20}O_4N_4S$	400	192-195	72	0.65
C2	$C_6H_4OCH_3$	$C_{20}H_{22}O_5N_4S$	430	229-231	68	0.46
C3	C_6H_4OH	$C_{18}H_{20}O_4N_4S$	416	229-235	71	0.41
C4	C_6H_4Cl	$C_{19}H_{19}O_4N_4SCl$	434.5	220-222	78	0.53
C5	$C_6H_3OCH_3OH$	$C_{20}H_{22}O_6N_4S$	446	229-231	67	0.46
C6	$C_6H_4NO_2$	$C_{19}H_{18}O_6N_4S$	445	230-233	69	0.67

Solvent system: ethylacetate: toluene (3:2)

Spectral information (IR Spectrum, cm^{-1}) of 4-substitutedaryl-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazides:

C_1:- 4-phenyl-6-methyl-2-pyrimidinone-5-(N-p-tosyl)carbohydrazides :-

3360(N-H Stretch), 3015(Ar-H), 1663(C= O), 1605(C=O), Ar-H (781-790)

C_2:-4-(4-methoxyphenyl)-6-methyl-2-pyridinone-5-(N-p-tosyl) carbohydrazide:-

3116(-aromatic), 2954-3242(N-H), 1703(C=O), 1681(C=O), 1320(-S=O), 1236(-OCH_3), 779-790(Ar-H)

C_4:-4-(4-chlorophenyl)-6-methyl-2-pyridinone-5-(N-p-tosyl) carbohydrazide:-

^{1}H NMR:- δ 8.0(1H,N-H), 7.81(d,1H,arom.), 7.34(d,1H, arom.), 7.0(d,1H,armo.ring Cl^-), 7.15(d,1H,armo.ringCl^-), 6.0(-NH arom.), 5.56(s,1H, arom.), 5.0(1H-OH), 3.73(s,3H,- OCH_3), 2.35(s,3H,-CH_3 arom.), 2.0(1H-NH,-S=O), 1.71(s,3H, arom.).

C_5:-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-pyridinone-5-(N-p-tosyl) carbohydrazide:-

^{1}H NMR:- δ 8.0(1H,N-H), 7.81(d,1H,arom.), 7.34(d,1H, arom.), 6.40(s),645(d),650(d)(1H, arom.), 6.0(-NH arom.), 5.56(s,1H, arom.), 5.0(1H-OH), 3.73(s,3H,- OCH_3), 2.35(s,3H,-CH_3 arom.), 2.0(1H-NH,-S=O), 1.71(s,3H, arom.).

PHARMACOLOGICAL SCREENING:-

The dihydropyrimidinone derivatives were evaluated for their analgesic activity. The animals used were swiss albino mice weighing about 22-25g.Diclofenac sodium (20mg/kg) as standard drug.

HOT PLATE METHOD:-

PROCEDURE: The experiment was carried out using analgesimeter Eddy's hot plate. The mice were divided into 7 groups of three animals each. The temperature was maintained at 55±1^{0}C. The reaction time was measured prior to administration of synthesised compounds and drug administration (0minute). Group 1 was kept as normal (control).The synthesised compounds

were injected orally to mice of group served as standard and were treated with diclofenacsodium 20mg/kg body weight. The reaction time was again measured at 0, 30, 60, 90, 120 minutes after the treatment, the increase in the reaction time against control was calculated.

STATISTICAL ANALYSIS:

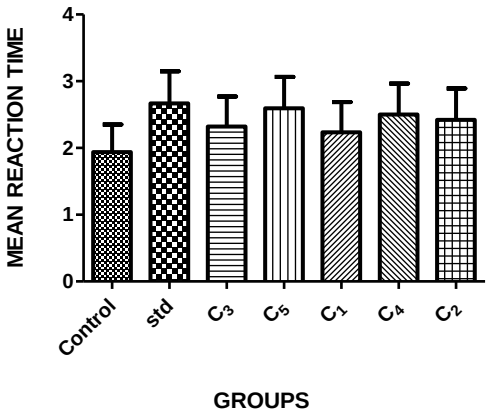
The statisticalanalysis was performed by ANOVA followed by Dunnett's test for multiple comparision of test compound as compared to control.

Hot plate method

GROUP	DOSE (mg/kg)	0minute	30minute	60minute	90minute	120minute
control	0	0.75±0.08	1.23±0.05	2.26±0.05	2.45±0.05	2.99±0.05
standard	20	1.20±0.05	2.04±0.05*	2.90±0.05*	3.22±0.05*	3.98±0.05*
C_3 (PHB)	20	0.98±0,04	1.67±0.06*	2.57±0.05*	2.85±0.05*	3.58±0.05*
C_5 (MHB)	20	1.16±0.04	1.98±0.05*	2.85±0.05*	3.09±0.05*	3.87±0.05*
C_1 (BNZ)	20	0.92±0.05	1.54±0.05*	2.43±0.05*	2.78±0.05*	3.48±0.05*
C_2 (PMB)	20	1.09±0.05	1.87±0.05*	2.76±0.05*	3.00±0.05*	3.76±0.05*
C_4 (PClB)	20	1.00±0.05	1.78±0.05*	2.66±0.05*	298±0.005*	3.67±0.05*

Standard=20mg/kg body weight, values represent mean±SD of 6mice each group; significant at *p<0.0001(Dunnett's test); Dose of test drug=20mg/kgb.w.

Repeated measures one-way ANOVA data

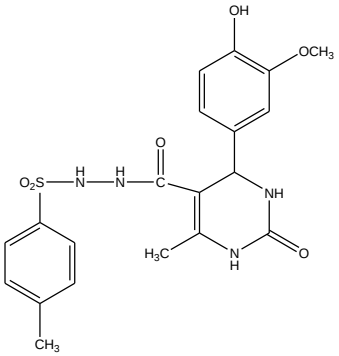


Standard: - Diclofenacsodium
C_3:- p- hydroxybenzaldehyde derivative.
C_5:- (vanillin) 4- hydroxyl-3-methoxybenzaldehyde derivative.
C_1:- Benzaldehyde derivative.
C_4:- p- chlorobenzaldehyde derivative.
C_2:- p- methoxybenzaldehyde derivative.

CONCLUSION

The dihydropyrimidinone derivatives have been synthesized and screened for analgesic activity by Hot plate method.

From the results of Hot plate method it is concluded that the compound (C_5) i.e; 4-hydroxy-3-methoxy benzaldehyde (vanillin) derivative was found to be a good analgesic agent.



4- (4 -hydroxy-3-methoxyphenyl)-6-methyl-2-pyridinone-5-(N-p-tosyl) carbohydrazide.

The compound (C_4) i.e; p-chloro benzaldehyde and p-methoxybenzaldehyde (C_2), derivatives were found to be a moderate analgesic agents. p-hydroxybenzaldehyde (C_3) and benzaldehyde (C_1) derivatives were found to be mild analgesic agents.

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