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SYNTHESIS AND ANALGESIC ACTIVITY OF SOME NOVEL 4-PHENYL-6-METHYL-5-[(2'-SUBSTITUTED-PHENYL) 1,3,4-OXADIAZOLE)]-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE DERIVATIVES

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ABSTRACT

The reaction of substituted aromatic aldehydes with ethylacetoacetate in presence of urea yielded **5**-Ethoxy carbonyl-6- methyl-4-phenyl-3, 4-dihydropyrimidin-2 (1H)-one.(**1**), which on treatment with hydrazine hydrate produced 4-phenyl-6-methyl-2-pyrimidinone 5-carbohydrazide.**(2)**, cyclization with substituted benzoic acids in presence of phosphorous oxychloride produced 4-phenyl-6-methyl-5-[(2'- substituted-phenyl) 1,3,4-oxadiazole)] - 3, 4-dihydropyrimidin-2(1*H*)-one. 3**(a-i)**. Purity was checked by TLC and the chemical structures of synthesized compounds were elucidated by their IR, ^{1}H NMR analysis data. The synthesized compounds were screened for Analgesic activity.

KEYWORDS: *3 4-dihydropyrimidin-2 (1H)-one, oxadiazole, Analgesic activity.*

1.0 INTRODUCTION

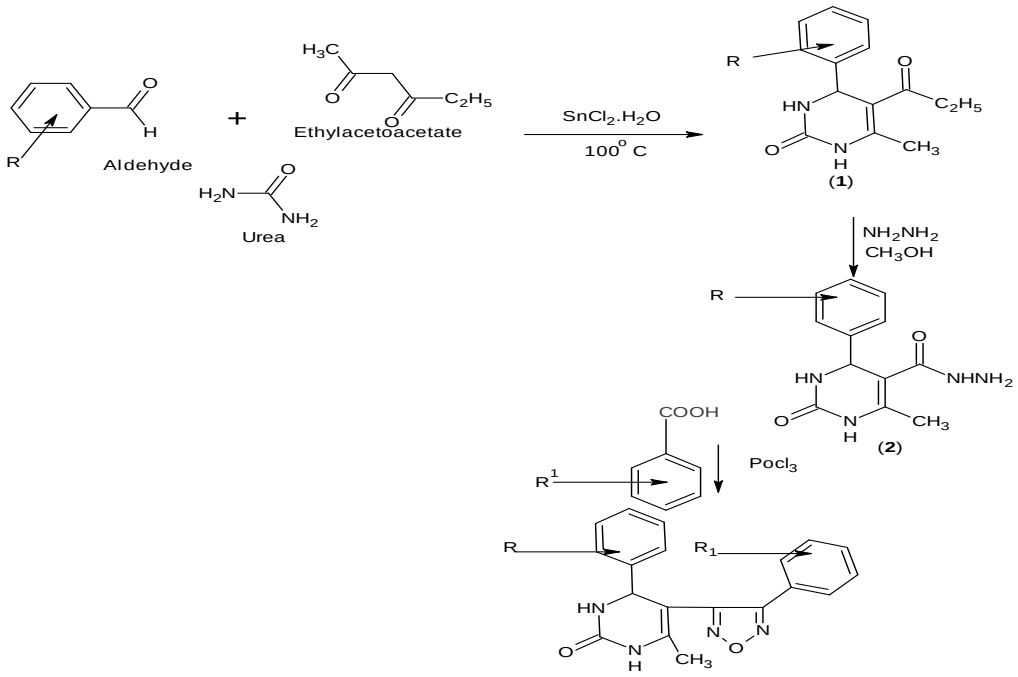
The presence of pyrimidine ring in cytosine, thymine and urea, which are the essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity[1] Additionally, the structurally related marine alkaloids batzelladine A and B were shown to be the first low molecular weight natural products to inhibit the binding of HIV gp-120 to CD-4

cells, so disclosing new vistas towards the development of AIDS therapy.[2] These ring systems are often incorporated into drugs designed as anticancer, antiviral, antihypertensive, analgesic, antipyretic, anti-inflammatory, antipsoriasis agents. Some of them are active on the blood circulatory system and can stimulate the skin preparative regeneration and increase the efficacy of antibiotic therapy.[3]

2.0 MATERIALS AND METHODS

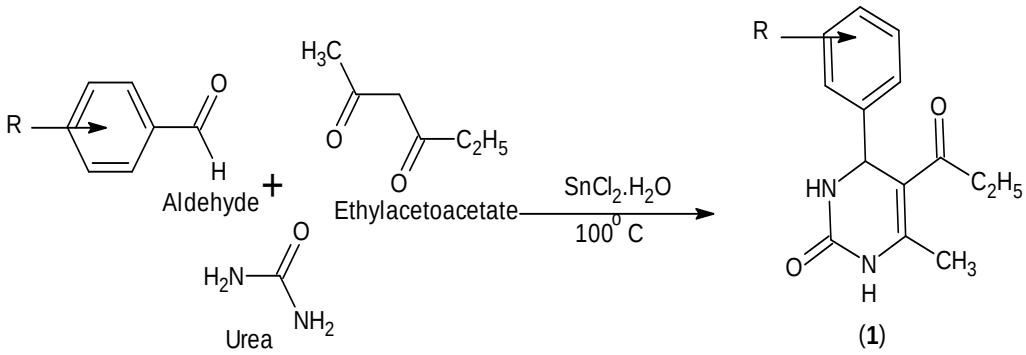
Melting points of all the synthesized compounds were determined by open capillary tubes using paraffin bath and are uncorrected. ^{1}H NMR spectra were recorded on a Varian-NMR-mercury 300 MHz spectrophotometer in $CDCl_3$ using TMS as an internal standard.

Scheme of synthesis



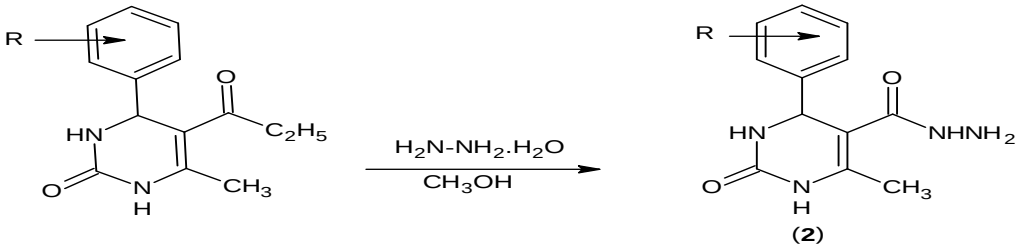
Experimental

(1) **Synthesis of 5-Ethoxy carbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one.**



1a IR (KBr): 3349(N-H), 3044 (aromatic CH stretching), 1720 (C=O ester), 1468 (unsaturated aromatic C-N) and 2875cm^{-1} (CH_3).

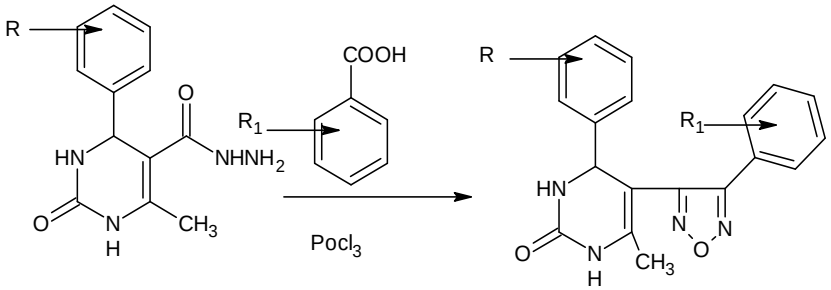
(2) **Synthesis of 4-phenyl-6-methyl-2-pyrimidinone 5-carbohydrazide**.



(2)

2a. IR (KBr): 3354(N-H), 3134 (unsaturated aromatic C=C), 1600(C=O amide), 2855 (CH_3 Asymmetric), 1455(C-N).

(3) Synthesis of **4-phenyl-6-methyl-5-[(2'-substituted-phenyl)1,3,4-oxadiazole)]-3,4-dihydropyrimidin-2(1*H*)-one.** ***3(a-i).***



3a: IR (KBr): 3345 (N-H), 3160 (unsaturated aromatic C=C), 1647 (C=N), 1133cm^{-1} (C-O-C), and 740 cm^{-1} (C-Cl).

^{1}H NMR: δ 5.4-5.54 **(**m,8H,Pyrimidine ring); 7.26-7.31(m,5H,Chloro phenyl), and 2.01(d, 6H,methy).

3b: IR (KBr): 3422 (N-H), 3345 (unsaturated aromatic C=C), 1149 (C-O-C).

3c: IR (KBr): 3348 (N-H), 3167cm^{-1} (unsaturated aromatic C=C), 1600(N=C stretching), 1592 (C=N), and 1109 (C-O-C).

3d: IR (KBr): 3380(N-H), 3160 (unsaturated aromatic C=C), 1680 (C=N), 1197 (C-O-C), 850 (C-Cl).

3e: IR (KBr): 3343 (N-H stretching), 3215 (unsaturated aromatic C=C), 1181 (C-O-C), 1599 (C-N), 774 (C-Cl).

3f: IR (KBr): 3343cm^{-1} (N-H), 2989 (unsaturated aromatic C=C), 1545 (C-O-C), 695(C-Cl).

3g: IR (KBr): 3243cm^{-1} (N-H), 3193 (unsaturated aromatic C=C), 1149 (C-O-C), 730 (C-Cl), 1684 (C=N).

3h: IR (KBr): 3167(unsaturated aromatic C=C), 1232 (C-O-C), 1545 (NO_2), 1690 (C=N).

3l: IR (KBr): 3275 (N-H), 3089 (unsaturated aromatic C=C), 1109 (C-O-C), 1535 (NO_2), 1700 (C=N).

3.0 *Analgesic activity*

The experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) and was conducted according to the guidelines prescribed by CPCSEA for use and care of experimental animals. Adult, healthy male albino mice, weighing between 20-25 gm were used for the study. They were housed comfortably in a group of six in clean plastic cage under standard environmental conditions of temperature (24±2°C), relative humidity of 30-70 % and 12 hrs light/dark cycle. All animals had free access to water and standard pelletized laboratory animal diet *ad libitum*. Test compounds were administered orally at a dose of 10mg/ kg body weight suspended in sterile water for injection. Standard group received diclofenac at a dose of 5mg/kg body weight intraperitoneally prior to acetic acid administration. The mice were placed individually into glass beakers and after 30 minutes administration of acetic acid, the mice are then observed for a period of 10 minutes and the number of writhes is recorded for each animal.

4.0 RESULTS AND DISCUSSION

Table. 1: Physical data of synthesized *3 4-dihydropyrimidin-2 (1H)-one* compounds.

Compound Code	R	R^1	Molecular formula	Molecular weight	Melting point	Yield (%)
3a	H	2-Cl	$C_{18}H_{15}N_4O_2Cl$	354.5	128-120	70.25
3b	H	H	$C_{18}H_{16}N_4O_2$	320	120-122	74.33
3c	H	4-NH_2	$C_{18}H_{17}N_5O_2$	335	228-230	82.85
3d	4-Cl	2-Cl	$C_{18}H_{14}N_4O_2Cl_2$	389	180-182	78.71
3e	4-Cl	H	$C_{18}H_{15}N_4O_2Cl$	354.5	158-160	90.23
3f	4-Cl	4-NH_2	$C_{18}H_{16}N_5O_2Cl$	369.5	212-214	90.0
3g	3-NO_2	2-Cl	$C_{18}H_{14}N_5O_4Cl$	399.5	166-168	78.18
3h	3-NO_2	H	$C_{18}H_{15}N_5O_4$	365	156-158	70.83
3i	3-NO_2	4-NH_2	$C_{18}H_{16}N_6O_4$	380	122-124	65.82

Statistical analysis

Data obtained is expressed as mean ± S.E.M (Standard Error Mean), test groups were compared with control and were tested for its significance using ANOVA followed by Dunnett's test. Values of $P < 0.05$ or lower were regarded as significant.

Table. 2: Analgesic activity of the synthesized compounds.

Group	No. of writhis	Percentage protection
Control	61.33±1.202	-
Standard	17.00±0.5774**	72.28
3a	19.33 ±0.222*	69.11
3b	18.00±1.155**	70.00
3c	23.00±1.528**	62.49
3d	19.66±0.8333**	68.00
3e	20.00±1.000**	67.38
3f	22.23±1.453**	63.59
3g	19.33±0.6667**	68.48
3h	20.33±0.8819**	66.85
3i	19.50±1.155**	70.66

5.0 CONCLUSION

The 3 4-dihydropyrimidin-2 (1H)-one was synthesized by solvent free Biginelli reaction using stannous chloride as catalyst. The synthesized pyrimidinone was reacted with hydrazine hydrate to yield carbohydrazide which on further reaction with various substituted benzoic acid yielded the final 4-phenyl-6-methyl-5-[(2'- substituted-phenyl) 1,3,4-oxadiazole)] - 3, 4-dihydropyrimidin-2(1*H*)-one. All the synthesized compounds were screened for Analgesic. The Analgesic activity was carried out were found to be more potent as analgesic agents.

- The compounds 3b and 3i have shown good activity.

6.0 ACKNOWLEDGEMENT

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