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SYNTHESIS AND EVALUATION OF SOME NOVEL 4-PHENYL-6-METHYL-5-[(2'-SUBSTITUTED-PHENYL) 1,3,4-OXADIAZOLE)]-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE DERIVATIVES FOR ITS ANTIDEPRESSANT ACTIVITY IN EXPERIMENTAL ANIMALS

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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.

KEYWORDS: 3,4 dihydropyrimidin 2 (1H) one, oxadiazole, Forced S wim Test, Depression, Desipramine.

1.0 INTRODUCTION

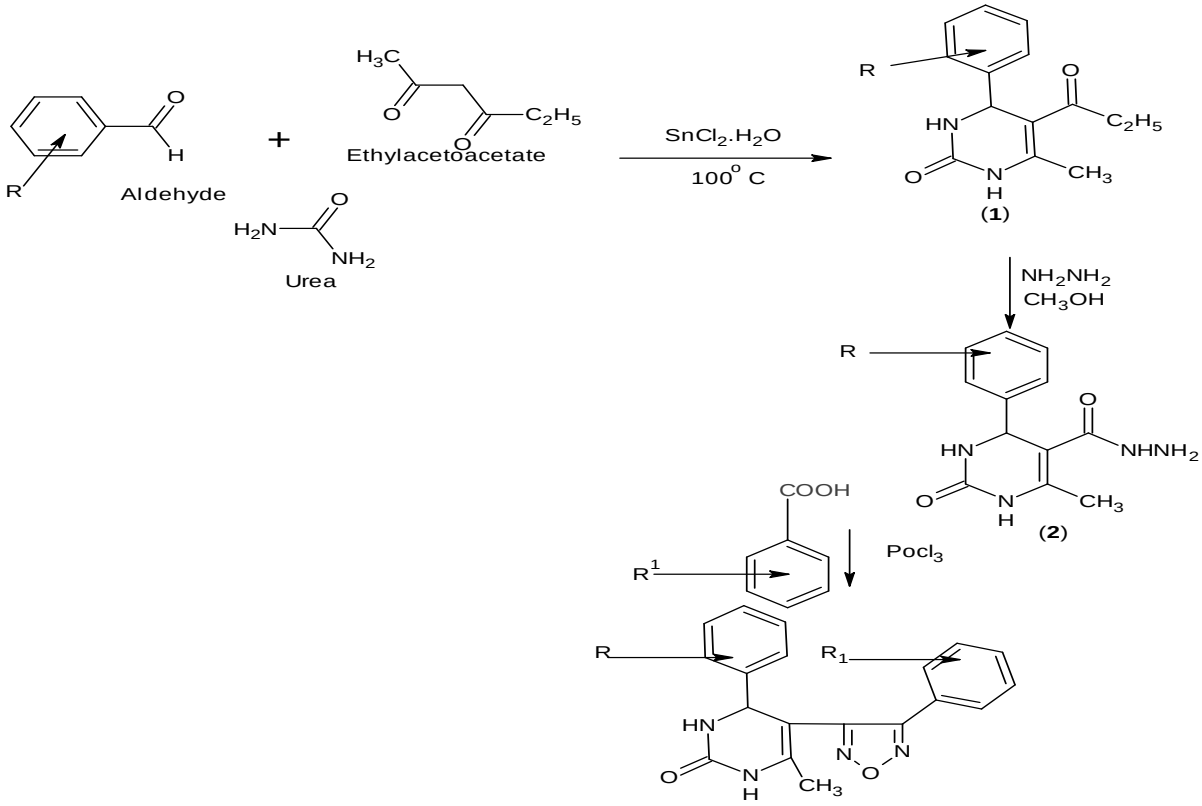
The presence of pyrimidine ring in cytosine, thymine and urea, which are the essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity[1] Additionally, the structurally related marine alkaloids batzelladine A and B were shown to be the first low molecular weight 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.[3-6]

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**

Scheme



3.0 Experimental

The title compounds can be synthesized by Bignelli condensation in which 0.01 mole of an ethyl acetoacetate is allowed to react with 0.01 mole of urea and 0.01 mole of aldehyde to offer tetrahydropyrimidine-2-one. This on further treatment with 0.01 mole Hydrazine hydrate and 0.01 mole aldehyde gives corresponding oxadiazole derivatives.(a-i).[7-9]

4.0 Spectral Data

a: 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);

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

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

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

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

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

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

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

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

5.0 Evaluation of Antidepressant Activity

The synthesized compounds a-I are evaluated for antidepressant activity by forced swim test (FST) in mice at dose of 100 mg/kg and compared with the standard drugs Desipramine (20 mg/kg). There were no mortality and noticeable behavioral changes in acute oral toxicity for all the groups tested. The synthesized compounds were found to be safe up to 1500 mg/kg body weight. Initially, dose-dependent study of compound a at different doses (25, 50, 100, and 200 mg/kg, i.p.) were performed to ensure the maximum effective dose for new synthesized compounds as antidepressant in FST. From this study, we found that 100 mg/kg is the maximum effective dose and therefore was selected for further pilot study of antidepressant-like effects of compounds b-i in FST. Antidepressant activity was assessed as mean immobility time in seconds, and data has been presented as mean ± S.E.M as shown in (Table 2).[10-12]

6.0 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 (%)
a	H	2-Cl	$C_{18}H_{15}N_4O_2Cl$	354.5	128-120	70.25
b	H	H	$C_{18}H_{16}N_4O_2$	320	120-122	74.33
c	H	4-NH_2	$C_{18}H_{17}N_5O_2$	335	228-230	82.85
d	4-Cl	2-Cl	$C_{18}H_{14}N_4O_2Cl_2$	389	180-182	78.71
e	4-Cl	H	$C_{18}H_{15}N_4O_2Cl$	354.5	158-160	90.23
f	4-Cl	4-NH_2	$C_{18}H_{16}N_5O_2Cl$	369.5	212-214	90.0
g	3-NO_2	2-Cl	$C_{18}H_{14}N_5O_4Cl$	399.5	166-168	78.18
h	3-NO_2	H	$C_{18}H_{15}N_5O_4$	365	156-158	70.83
i	3-NO_2	4-NH_2	$C_{18}H_{16}N_6O_4$	380	122-124	65.82

Table. 2: Anti-depressant activity of synthesized compounds.

Sr. No.	Compound code	Duration of immobility Sec. (mean ± SEM)	% decrease in immobility	Locomotor activity scores for 10 minutes (sec.) (mean ± SEM)
1	**a**	33.6 ± 4.1***	**68.3**	423 ± 14.0^{ns}
2	**b**	49.7 ± 2.6***	**39.76**	434 ± 9.0^{ns}
3	**c**	16.4 ± 3.1***	**69.45**	421 ± 16.0^{ns}
4	**d**	10.89 ± 0.7***	**86.45**	425 ± 14.0^{ns}
5	**e**	26.78 ± 1.6***	**71.57**	445 ±14.0^{ns}
6	**f**	38.5 ± 3.85***	**56.34**	439 ± 13.0^{ns}
7	**g**	49.67 ± 3.98***	**44.79**	426 ± 28.0^{ns}
8	**h**	23.45 ± 1.3***	**69.45**	402 ± 27.0^{ns}
9	**i**	67.8 ± 4.3***	**31.07**	448 ± 19.0^{ns}
10	**Control**	**90.6±3.2**	**0.0**	**508±12**
11	**Desipramine**	**21.6±1.5**	**79.27**	**470±19**

Data analyzed by one-way ANOVA followed by Dunnett's test. n = 6; dose = 100 mg/kg. Values are represented as mean ± S.E.M. Values are significant at ***P < 0.001, compared with control group. ns: not significant (P < 0.05) as compared to vehicle-treated group.

7.0 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. The synthesized compounds shows antidepressant activity due to the presence of 1,3,4-oxadiazole nucleus.

8.0 REFERENCES

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