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AN EFFICIENT, MULTI-COMPONENT ONE POT SYNTHESIS OF 2-SUBSTITUTED-4,5-DIHYDRO-6*H*-1,3,4-OXADIAZIN-6-ONE AS POTENT ASPULVINONE DIMETHYLALLYLTRANSFERASE INHIBITOR, PHOBIC DISORDERS TREATMENT AND COMPLEMENT FACTOR D INHIBITOR

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ABSTRACT
Heterocyclic compound containing three heteroatoms in six membered rings shows wide applications in medicinal as well as agricultural field. This work involves multi-component one pot synthesis of 2-Substituted-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one derivatives from various substituted acyl chloride derivatives 1(a-e), hydrazine hydrate 2 and α-halo acetic acid 3 were mixed in ethanol and the reaction mixture was refluxed to obtain products 4(a-e), their structures were confirmed by spectroscopy. These products exhibited antibacterial and antifungal activity. Library of such 2-Substituted-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one derivatives has been generated and screened for anti-bacterial and antifungal activity. Also Biological prediction study of the library was done to find out most active molecules. Computer programme PASS predicted for three activities with top probability for compound 4(a-e) as-
1. Aspulvinone dimethylallyltransferase inhibitor,
2. Phobic disorders treatment,
3. Complement factor D inhibitor.

KEYWORDS
4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one, antibacterial and antifungal activity, PASS.

INTRODUCTION
Heterocyclic compounds containing three heteroatom in six membered ring has superfine applications in medicinal, dye as well as agricultural field[i]. Oxadiazine derivatives containing one oxygen atom and two nitrogen atom in six membered rings, most of oxadiazine derivatives show fine medicinal applications like gamma secretase modulators for treatment of Alzheimer's disease[ii]. A literature search revealed that 1,3,5-oxadiazine derivatives possess quite interesting pharmacological properties. For example, Oxadiazinane-4-thione derivatives are use as promising agent in biliary tract disorders treatment[iii]. Some of oxadiazine cyanine dyes shows photosensitization and antimicrobial activity[iv]. In the field of agriculture oxadiazine

shows bioactivation[v], insecticides and fungicides. Chiral, non-racemic oxadiazines[vi-xi] compound shows good central nervous system activity. Looking to the importance, we intended to synthesize new 1,3,4-oxadiazin-6-one derivatives.

EXPERIMENTAL WORK

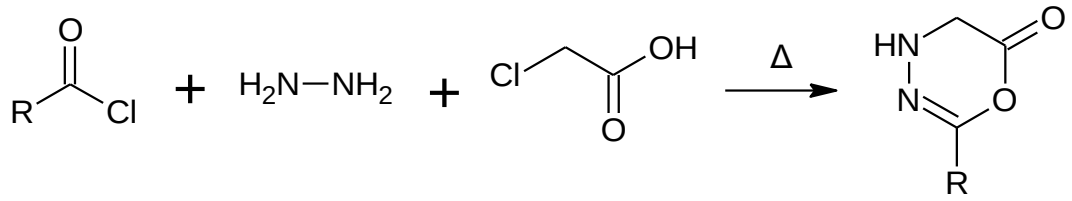
All chemicals and solvents were reagent grade and used as purchased without any further purification. Analytical thin layer chromatography was performed on percolated silica gel 60-F 254 plates. IR spectra on KBr disks were recorded on a Schimazdu IR-470 FT-IR spectrophotometer. The routine nuclear magnetic resonance spectra were taken in DMSO/$CDCl_3$ using a Bruker 300 MHz spectrophotometer with TMS as an internal standard. Chemical shift δ was given in ppm relative to TMS. The data found were in consistent with the proposed structure. Elemental analysis was done using EURO Vector Elemental Analyzer. Melting points are determined in an open capillary tube and are uncorrected.

GENERAL PROCEDURE:

Synthetic procedure for the 2-phenyl-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4) :-

In 100 mL round bottom flask, Benzoyl chloride 1 (2.80 g, 0.02 mol), hydrazine hydrate 2 (0.64 g, 0.02 mol), and monochloro acetic acid 3 (1.90 g, 0.02 mol) were mixed in ethanol (50 mL) and the reaction mixture was slowly heated to 80 ^{0}C and stirred at this temperature for 5 h. The completion of the reaction was confirmed by TLC (Ethyl acetate: Hexane 1:9). The reaction mixture was allowed to cool at room temperature, poured into crushed ice. The solid separated was filtered, washed with little methanol and purified by recrystallization from methanol to get pure products, 4 (1.00g, 71.42%).

(SCHEME 1)



1 (a-e) 2 3 4 (a-e)

SPECTRAL ANALYSIS

2-phenyl-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4a)

Molecular formula: $C_9H_8N_2O_2$

Melting point: 170 °C.

IR, (KBr) ν_{max}, cm^{-1}: 3015, 3250 (Ar-H, CH_2), 1640 (C=N), 1545 (C=C), 1295 (C–O–C).

^{1}H NMR (DMSO, 300MHz), δ, ppm: 3.88 (2H, s, CH_2); 7.05 (1H, s, NH); 7.37-7.74 (5H, m, C_6H_5).

^{13}C NMR (DMSO, 100MHz), δ, ppm: 46.18 (CH_2), 141.10 (C); 127.43, 128.44, 131.61, 133.52 (C6H5); 173 (C=O).

2-(4-chlorophenyl)-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4b)

Molecular formula: $C_9H_7N_2O_2Cl$

Melting point: 178 °C.

IR spectrum, (KBr) ν_{max}, cm^{-1}: 3020, 3220 (Ar-H, CH_2), 1630 (C=N), 700 (C–Cl), 1285 (C–O–C).

^{1}H NMR (DMSO, 300MHz), δ, ppm: 3.96 (2H, s, CH_2); 7.10 (1H, s, NH); 7.80-8.14 (4H, m, C_6H_4).
^{13}C NMR (DMSO, 100MHz), δ, ppm: 44.11 (CH_2), 141.10 (C); 128.40, 129.90, 135.52, 137.52 (C_6H_4); 170 (C=O).

2-(2-chlorophenyl)-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4c)
Molecular formula: $C_9H_7N_2O_2Cl$
Melting point: 160 °C.
IR spectrum, (KBr) ν_{max}, cm^{-1}: 3015, 3250 (Ar-H, CH_2), 1640 (C=N), 710 (C–Cl), 1305 (C–O–C).
^{1}H NMR (DMSO, 300MHz), δ, ppm: 3.88 (2H, s, CH_2); 7.95 (1H, s, NH); 7.80-8.14 (4H, m, C_6H_4).
^{13}C NMR (DMSO, 100MHz), δ, ppm: 43.18 (CH_2), 140.22 (C), 123.99, 125.33, 127.43, 128.44, 131.61, 133.52 (C6H4); 172 (C=O).

2-(4-hydoxyphenyl)-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4d)
Molecular formula: $C_9H_8N_2O_3$
Melting point: 205 °C.
IR spectrum, (KBr) ν_{max}, cm^{-1}: 3020, 3240 (Ar-H, CH_2), 1630 (C=N), 1295 (C–O–C).
^{1}H NMR (DMSO, 300MHz), δ, ppm: 3.88 (2H, s, CH_2); 7.00 (1H, s, NH); 3.96 (1H, bs, OH); 7.10-7.24 (4H, m, C_6H_4).
^{13}C NMR (DMSO, 100MHz), δ, ppm: 44.25 (CH_2), 144.22 (C), 123.99, 125.33, 127.43, 128.44, (C6H4); 170.50 (C=O).

2-methyl-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4e)
Molecular formula: $C_4H_6N_2O_2$
Melting point: 158 °C.
IR spectrum, (KBr) ν_{max}, cm^{-1}: 3015, 3250 (CH_2), 1640 (C=N), 1545 (C=C), 1295 (C–O–C).
^{1}H NMR (DMSO, 300MHz), δ, ppm: 3.70 (2H, s, CH_2); 7.35 (1H, s, NH); 1.3 (3H, s, CH_3).
^{13}C NMR (DMSO, 100MHz), δ, ppm: 18.25(CH_3), 42.60 (CH_2), 145.28 (C), 171.10 (C=O).

Table 1: Analytical data of the compounds 4(a-e)

Product	R	Time (hrs)	Yield %	Found/(Calculated) %			
				C	H	N	O
4(a)	C_6H_5	5	71.42	60.51 (61.36)	3.65 (4.58)	15.37 (15.90)	18.01 (18.16)
4(b)	4-Cl-C_6H_5	3	70.05	50.70 (51.32)	3.29 (3.35)	12.50 (13.30)	15.01 (15.19)
4(c)	2-Cl-C_6H_5	4	72.10	50.71 (51.32)	3.29 (3.35)	12.56 (13.30)	15.10 (15.19)
4(d)	4-OH-C_6H_5	4:30	60.55	55.71 (56.25)	3.89 (4.20)	14.56 (14.58)	24.10 (24.98)
4(e)	CH_3	6	50.42	42.01 (42.10)	5.20 (5.30)	24.11 (24.55)	27.56 (28.04)

RESULT AND DISCUSSION:

Microbial Testing

The literature survey of the antimicrobial activity of oxadiazine derivatives has shown that many of them are useful as the best bactericides and fungicides. Hence, the new compounds synthesized in the present investigation were screened for their antibacterial and antifungal activities. The antimicrobial activity of oxadiazine derivatives was verified using cup-plate agar diffusion method[xi]. The microbial entities used involved together gram positive and gram negative strains like *Escherichia coli*, *S albus*, and *Candida albicans*. Nutrient media plates were seeded with a bacterial inoculum of $1x10^6$ CIU/mL and each well diameter 10 mm was loaded with 0.1 mL of test compound solution 1000 µg/mL. After incubation for 24 hr, the zone of inhibition was recorded using vernier caliper. For comparison, standard drug Streptomycin and Grisco fulvin were subjected to similar conditions as standard reference commercial antibacterial and fungicide respectively.

Antimicrobial activities of 2-substituted -4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one

All derivatives of 2-substituted-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one 4(a-e) were screened for anti-bacterial and antifungal activity and the results are as shown in **Table 2.**

Table 2: Antimicrobial Screening results of compounds 4(a-e)

Comp. No	***E. coli*** in mm	***S. albus*** in mm	***C. albicans*** in mm
Streptomycin	25	26	--
Grisco fulvin	--	--	30
4(a)	10	12	16
4(b)	12	15	18
4(c)	11	11	13
4(d)	17	18	12
4(e)	09	09	10

The confirmed structures were subjected to computer programme PASS for the prediction of their biological activities. Compound 4(a-e) were predicted for three activities with top probability.

1. Aspulvinone dimethylallyltransferase inhibitor, 2. Phobic disorders treatment 3. Complement factor D inhibitor

Table 3: Antimicrobial Screening results of compounds 4(a-e)

Comp. No	Aspulvinone dimethylallyltransferase inhibitor	Phobic disorders treatment	Complement factor D inhibitor
4a	0.791	0.777	0.756
4b	0.624	0.855	0.749
4c	0.622	0.817	0.753
4d	0.843	0.555	0.597
4e	0.745	0.751	0.718

CONCLUSION:

In summary, we have established an effectual method for the synthesis of 2-substituted-4,5-dihydro-6*H*-1,3,4-oxadiazin-6-one 4(a-e) derivatives with excellent yield in an organic medium and **2-(4-hydoxyphenyl)-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one 4(d)** is most active against *E. coli, S. albus and* **2-(4-chlorophenyl)-4, 5-dihydro-6*H*-1,3,4-oxadiazin-6-one (4b)** is most active against ***C. albicans***.

Biological prediction analysis revealed that the 4(d) is predicted to be moderately active as Aspulvinone dimethylallyltransferase inhibitor. 4(b) can be most active in the series as Phobic disorders treatment and 4(a) exhibit promising activity in Complement factor D inhibitor, hence it is recommended for the screening of the same activity.

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