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Synthesis and Antimicrobial Activity of Novel 1, 3, 5-oxadiazine Derivatives

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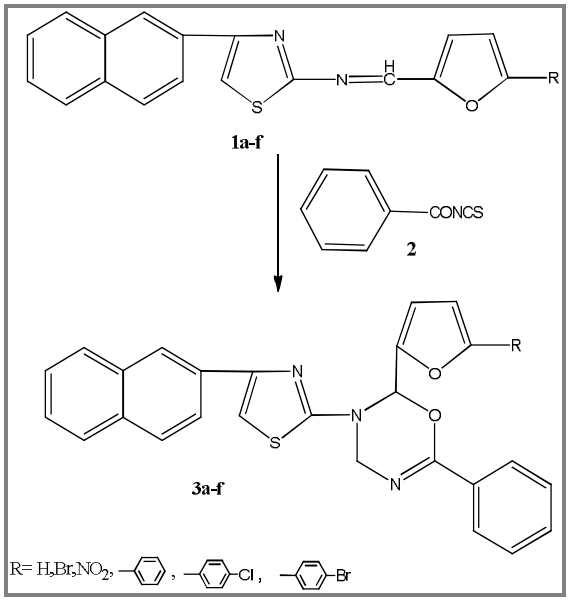
ABSTRACT

Various Schiff base of 2-amino-4-(2-naphthalenyl)thaizole (1a-f) on condensation with benzoyl isothiocyanate (2) afford 3-[4-(2-naphthalenyl)-2-thiazolyl]-2-furanyl-6-phenyl-1,3,5-oxadiazine(3a-f) derivatives. All the derivatives (3a-f) characterized by elemental content and spectral features. The antifungal activity of (3a-f) has also been monitored.

Graphical Abstract



Synthetic route for the synthesis of targeted molecules

Keywords: Schiff base, Thiazole, Benzoyl isothiocyanate, Spectral studies and Antifungal activity.

INTRODUCTION

Nitrogen and Oxygen containing heterocycles have expected considerable interest as of the exclusive physical and chemical characteristics of different heterocyclic compounds [**1, 2**]. Oxadiazines contains oxygen and two nitrogen atoms and were considered as interesting heterocycles for their varied biological activities. A diversity of biological effects is associated with hetero atoms at 1,2,4 or 1,3,4 positions, since they are oxa-analogues of nucleosides-6-oxadihydro uracil, among these 1,3,4-oxadiazines were the most important frameworks for a variety of bioactive molecules [**3**].

Oxadiazine compounds reported for number of therapeutically and antimicrobial activities like cardiovascular, anticonvulsant, antitumor, antibacterial, insecticidal, anti-proliferative and anti-inflammatory agents, anticancer and antitubercular activity [**4-14**]. In continuous of our earlier work here we present research on the Synthesis and antimicrobial activity of novel 1,3,5-oxadiazine derivatives, which are shown in above Reaction scheme.

MATERIALS AND METHODS

Schiff bases of 2-amino-4-(2-naphthalenyl) thaizole (1a-f) was synthesis by reported method [**14**]. All other reagents were used laboratory grade.

^{1}HNMR spectra were recorded on a Bruker (400 MHz) spectrometer. Deutorated DMSO was used as a solvent. The IR spectra of all compounds were taken in KBr pellets on a Nicolet 400D spectrometer. LC-MS of selected samples taken on LC-MSD-Trap-SL 01046. All the compounds were checked for their purity by TLC. The characterization data of all these compounds are given in table 1.

The antifungal activity of both the series of compounds (3a-f) was measured at 1000ppm concentration in vitro Plant pathogen shown in table 2 have been selected for study [**15, 16**].

Synthesis of 3-[4-(2-naphthalenyl)-2-thiazolyl]-2-subsituted furanyl-6-phenyl-1,3,5-oxadiazine (3a-f): A solution of Schiff base of 2-amino-4-(2-naphthalenyl)thaizole (1a-f) in glacial acetic acid was stirred with benzoyl isothiocyanate (2) for 7-8 h at 75-80°C. The solvent was removed under reduced pressure, and the residue was diluted with water. It was extracted with ether, washed with saturated bicarbonate solution, water, brine solution and dried. The solvent was removed and the crude product was purified by recrystallization from ethanol. The yields, melting points and other characterization data of these compounds are given in table 1.

Table 1. Physical and Analytical Data of the Compounds Synthesized (3a-f)

Comp.	Molecular Formula	M.P.* °C	Elemental Analysis			
			C%	H%	N%	S%
			Found Calcd.	Found Calcd.	Found Calcd.	Found Calcd.
3a	$C_{26}H_{19}N_3O_2S$ (437)	182-183	71.38 71.3	4.38 4.3	9.60 9.5	7.33 7.3
3b	$C_{26}H_{18}N_3O_2SBr$ (515)	194-195	60.47 60.4	3.51 3.4	8.14 8.1	6.21 6.2
3c	$C_{26}H_{18}N_4O_4S$ (482)	200-201	64.72 64.7	3.76 3.7	11.61 11.5	6.65 6.6
3d	$C_{32}H_{23}N_3O_2S$ (513)	219-220	74.83 74.8	4.51 4.5	8.18 8.1	6.24 6.2
3e	$C_{32}H_{22}N_3O_2S_2Cl$ (547)	233-234	70.13 70.1	4.05 4.0	7.67 7.6	5.85 5.8
3f	$C_{32}H_{22}N_3O_2S_2Br$ (592)	216-217	64.87 64.8	3.74 3.7	7.09 7.0	5.41 5.4

***Uncorrected* LC-MS data for 3a:438, 3e: 548.5

Antifungal Activities: The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Botrydepladia thiobromine, Nigrosspora Sp., Penicillium expansum and Rhizopus nigricuns*. The antifungal activities of all the compounds (3a-f) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 g, dextrose 20 g, agar 20 g and water 250 mL. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120^{o}C for 15 min. at 15atm. Pressure [**17**]. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\text{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate
Y = Area of colony in test plate

T he Fungicidal activity displayed by various compounds (3a-f) is shown in table-2 and figure 1.

Table 2. Antifungal Activity of Compounds (3a-f)

Comp.	Zone of Inhibition at 1000 ppm (%)			
	Botrydepladia thiobromine	*Nigrosspora Sp*	*Penicillium expansum*	*Rhizopus nigricuns*
3a	55	68	60	61
3b	56	70	62	63
3c	58	71	64	71
3d	57	67	61	65
3e	64	76	68	67
3f	56	70	62	63

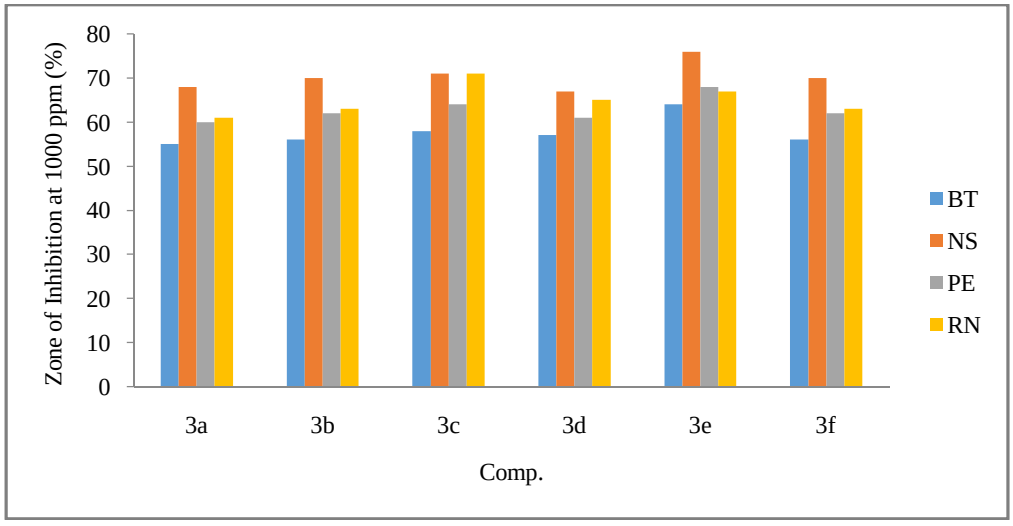


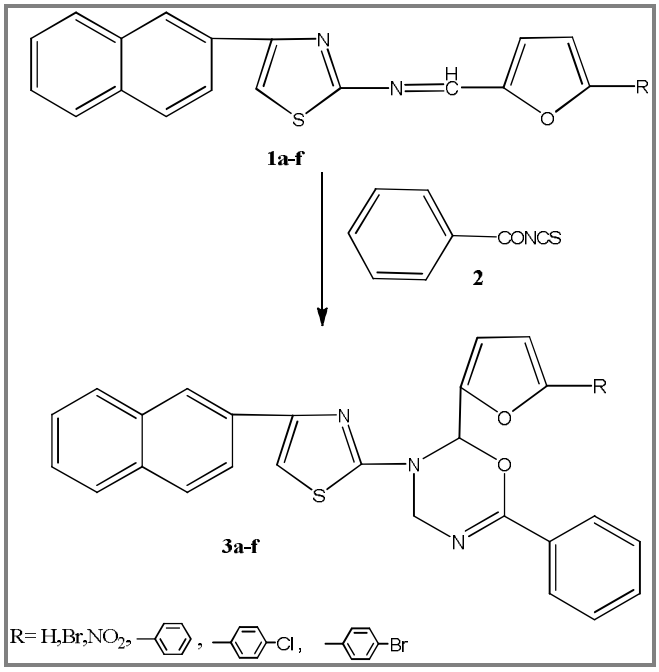
Figure 1. Antifungal Activity of Compounds (3a-f)

RESULTS AND DISCUSSION

The 3-[4-(2-naphthalenyl)-2-thiazolyl]-2-furanyl-6-phenyl-1,3,5-oxadiazine(3a-f) derivatives synthesized from Various Schiff base of 2-amino-4-(2-naphthalenyl)thaizole (1a-f).

The structures of **(3a-f)** were confirmed by elemental analysis and IR spectra showing an absorption bands at 3030-3080 cm^{-1} (C-H of Ar), 710 cm^{-1} (C-S), 1620-1640 cm^{-1} (C=N), 1273

(C=S), 1120 cm^{-1} (C-O), 1080 cm^{-1} (C-Cl), 690cm^{-1} (C-Br) and 1555,1375(-NO_2). ^{1}H NMR (400MHz, DMSO- d_6 ,δ/*ppm*): 7.55-8.40 (m,13H,Ar-H),6.00 (s,1H, CH), 5.25-5.40 (s,2H,CH_2) **(3a)**: 7.70-6.40 (m, 3H,furan-H); **(3b)**: 6.80-6.38 (m,2H,furan-H); **(3c)**: 7.55-6.98 (m,2H,furan-H); **(3d)**: 7.10-6.40 (m, 2H, furan-H),8.14-7.40 (m,5H,Ar-H);**(3e)**:7.10-6.40(m,2H,furan-H), 7.85-7.60 (m, 4H, Ar-H); and **(3f)**: 7.10- 6.40 (m,2H,furan-H),7.72-7.70 (m, 4H, Ar-H). The C, H, N analysis data of all compounds are presented in table 1.



Scheme 1. Synthetic route for the synthesis of targeted molecules.

All the elemental and spectral features suggest that the data are consistent with the predicted structure shown in scheme 1. The LC-MS of selected compounds shows the peak of M^+ ion which is consistent of their molecular weight. All these facts confirm the structures (3a-f).

The examination of antifungal activity data reveals that all compounds exhibited moderate to good antifungal activity and the compounds **3e** and **3c** found more active.

APPLICATION

These compounds may be applicable as Garden fungicides.

CONCLUSION

A novel thiazole-triazine containing heterocyclic compounds are synthesized from thaizole containing schiff's base with phenyl isocyanate. All the synthesized compounds structure was confirmed by elemental as well as spectral studies. All these compounds are shows moderate to good antifungal activity.

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