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Synthesis and antifungal activity of [(4-(2-naphthalenyl) thiazol-2-yl)-2-(substituted phenyl)-6-phenyl- 4-thioxo-1,3,5-oxadiazine] derivatives

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ABSTRACT

Novel series of heterocyclic compounds [(4-(2-naphthalenyl) thiazol-2-yl)-2-(substituted phenyl)-6-phenyl- 4-thioxo-1,3,5-oxadiazine (4a-h) have been synthesized by condensation of Schiff bases Arylidine-[4-(2-naphthalenyl)thiazolyl]-2-amines (3a-h) with benzoyl isothiocyanate. Synthesized heterocyclic compounds were characterized by elemental analysis, NMR, CMR and FTIR spectral features. Antifungal activities of all the compounds were studied against various fungi. Compounds 4e and 4h showed good antimicrobial activity. Other compounds showed moderate activity compared to standard drugs against bacterial strains.

INTRODUCTION

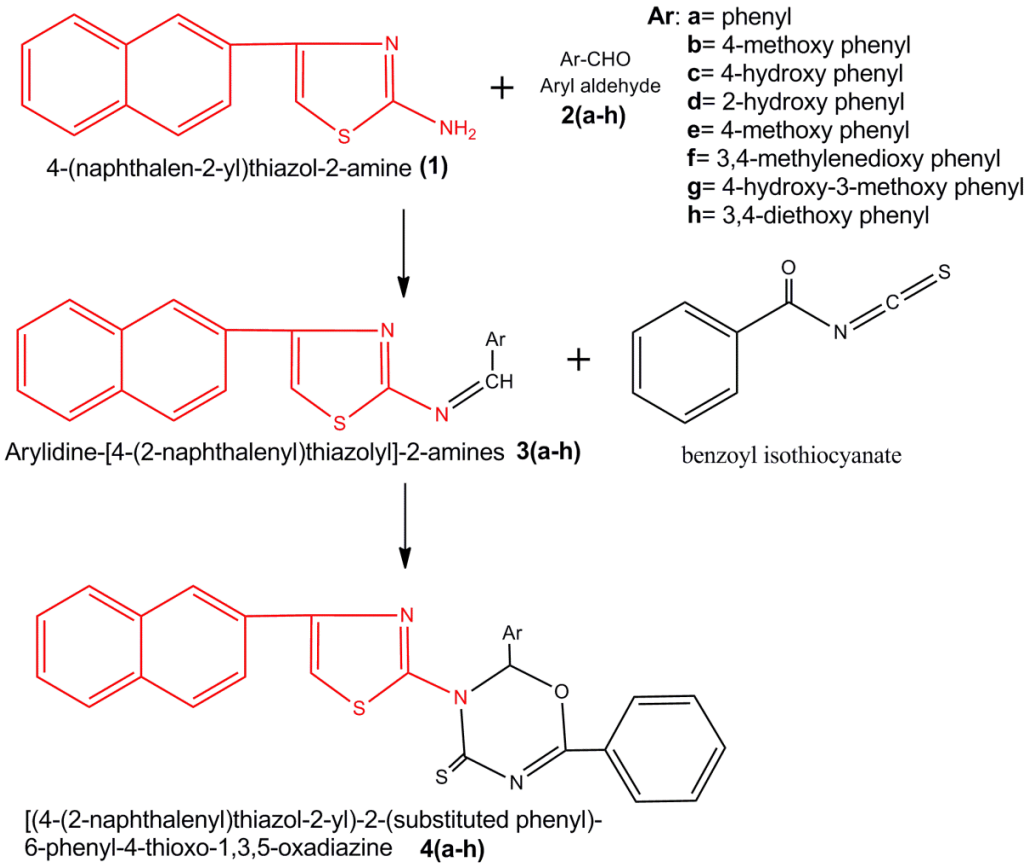
The last few decades have seen a flurry of activity in the synthesis and development of heterocyclic compound because of their important biological properties. 2-Aminothiazoles and their derivatives have long been used as precursors for the synthesis of biologically active molecules [1-4]. Because of their wide spectrum of activity shown by the thiazole moiety, numerous thiazoles substituted with different groups at various positions have been prepared. 2-Aminothiazoles are among the most important compounds in pharmacology. Some of these compounds possess anthelmintic activity, such as thiabedazole.[5] Sulphathiazole [5] possesses antibiotic activity. Nizatidine [5] compound possesses the thiazole moiety, which has clinical use as an antiulcer drug. Farnetiaole [5] has significant immunosuppressant activity, while fentiasac [5] has clinical use as an anti-inflammatory agent. Recent research indicates that some of 2-aminothiazoline derivatives are inhibitors of enzymes such as kinurenine-3-hydroxylase [6] or possess inhibitory activity against the enzyme cyclin-dependent kinase. [7] On the other hand, several coumarin derivatives have pronounced medicinal value as antibacterial and antifungal agents. [8,9] Others display antitubercular activity [10] or show insecticidal properties. [11] The compounds have very important pharmaceutical value because of their anticoagulant and antitumor activities [12-14]. As a part of surge of interest in heterocyclic that have been explored for developing pharmaceutically important molecule 1,3,5-Oxadiazine [15-16] have played an important role in medicinal chemistry. Moreover, they have been studied extensively because of their ready accessibility and broad spectrum of biological activities. Based on this concept, our main concern was to prepare such heterocyclic compounds which possess enhance medicinal properties by introducing thiazole and 1,3,5-Oxadiazine segments together. The present study concerns the synthesis of Schiff bases Arylidine-[4-(2-naphthalenyl)thiazolyl]-2-amines (3a-h) and subsequent reaction with benzoyl isothiocyanate to produced [(4-(2-naphthalenyl) thiazol-2-yl)-2-(substituted phenyl)-6-phenyl-4-thioxo-1,3,5-oxadiazine] (4a-h). Scheme 1 summarizes our synthetic approach to the various phases of this work.

MATERIALS AND METHODS

The aromatic benzadelydes (2a-h) viz; **a:** benzaldehyde, **b:** 4-methoxy benzaldehyde, **c:** 4-hydroxy benzaldehyde, **d:** 2- hydroxyl benzaldehyde, **e:** 4- methoxy benzaldehyde, **f:** 3,4-methylenedioxy benzaldehyde, **g:** 4-hydroxy-3-methoxy benzaldehyde and **h:** 3,4-diethoxy benzaldehyde were obtained from local dealer. All chemicals and solvents used were of laboratory grade. Solvents were dried and distilled before use according to standard procedures. Melting points (^oC) of all the compounds were measured by capillary method and were found uncorrected. The yields of all compounds reported are of crystallized. All solvents used were distilled and dried. The purity of the compounds was checked by TLC. Column chromatography was performed on silica gel (60-120 mesh). C, H, N and S contents of all the compounds were recorded on Thermofinigen 1101 elemental analyzer. IR spectra were recorded in KBr pellets on Nicolet 760D spectrophotometer. PMR and CMR spectra were recorded on Bruker NMR spectrophotometer. PMR ad CMR chemical shifts are recorded in (δ) value using TMS as an internal standard in $CDCl_3/D_6$-DMSO. LC-MS of selected one sample of each series has been carried out on LC-MSD Trap-SL 01046 instrument using CH_3CN solvent. Antibacterial activity of all the compounds was carried out against some gram positive and negative bacterial strains B. Subtillis, S. Aureus, E. coli and Ps. Aeruginosa. Antifungal activities of all the compounds were studied against various fungi e.g. Penicillium Expansum, Botrydepladia Thiobromine, Nigrospora Sp., Trichothesiun Sp. (Tables-2) at a concentration of 100ppm by agar cup method [17]. Methanol system was used as control in the method under similar conditions using penicillin and sulfanilamide as a standard. The comparison carried at control experiment. The area of inhibition of zone is measured as percentage.

Synthesis of Schiff bases Arylidine-[4-(2-naphthalenyl)thiazolyl]-2-amines (3a-h)

Schiff bases (3a-h) were prepared and characterized as per the method reported by us earlier [18,19].



Scheme 1. Synthesis of [(4-(2-naphthalenyl)thiazol-2-yl)-2-(substituted phenyl)-6-phenyl- 4-thioxo-1,3,5-oxadiazine (4a-h)

Synthesis of [(4-(2-naphthalenyl)thiazol-2-yl)-2-(substituted phenyl)-6-phenyl- 4-thioxo-1,3,5-oxadiazine] (4a-h)
A mixture of (3a-h) (0.01 mol), benzoyl isothiocyanate (0.01 mol) and triethyl amine (3 drops) in 1,4-dioxane (30 ml) was refluxed for 3 hrs. The reported solid formed upon dilution with water (20 ml) was filtered, dried and purified.

4a: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2,6-diphenyl-4-thioxo-1,3,5-oxadiazine
Yield was 58%; M. Wt. 477g; Melting Point: 267-268°C (uncorrected); Elemental analysis calculated for $C_{28}H_{19}N_3OS_2$: C 70.44, H 3.99, N 8.8, S 13.41% Found: C 70.3, H 3.8, N 8.7%, S 13.3; ^{1}H NMR (δ ppm): 7.1-8.5(m, 18H, aromatic + CH of thiazole), 5.6 (s, 1H, oxadiazine); ^{13}C NMR (δ ppm): 110-134 (Naphthalene & Benzene), 167,150,102 (thiazole), 169 (O-C=N), 86 (O-C-N), 166 (C=S); IR (KBr, cm^{-1}): 3030,1500, 1600 (Aromatic C-H), 1620 (C=N thiazole ring), 1350 (C=S), 1300 (C-O-C).

4b: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(4-methoxyphenyl)-4-thioxo-1,3,5-oxadiazine
Yield was 56%; M. Wt. 507g; Melting Point: 261-262°C (uncorrected); Elemental analysis calculated for $C_{29}H_{21}N_3OS_2$: C 60.63, H 4.14, N 8.2, S 12.62% Found: C 60.5, H 4.1, N 8.1, S 12.5%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 16H, aromatic + CH of CH=N), 5.6 (s, 1H, oxadiazine), 3.7 (s, 3H, OCH_3); ^{13}C NMR (δ ppm): 112-132 (Naphthalene & Benzene), 165,151,102 (thiazole), 167 (O-C=N), 87 (O-C-N), 164 (C=S); IR (KBr, cm^{-1}): 3032,1505, 1604 (Aromatic C-H), 1625 (C=N thiazole ring), 1351 (C=S), 1303 (C-O-C).

4c: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(4-hydroxyphenyl)-4-thioxo-1,3,5-oxadiazine
Yield was 59%; M. Wt. 493g; Melting Point: 271-273°C (uncorrected); Elemental analysis calculated for $C_{28}H_{19}N_3O_2S_2$: C 68.15, H 3.85, N 8.51, S 12.98% Found: C 68.1, H 3.8, N 8.3, S 12.9%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 16H, aromatic + CH of CH=N), 5.6 (s, 1H, oxadiazine), 3.9 (s, 1H, -OH); ^{13}C NMR (δ ppm): 110-134 (Naphthalene & Benzene), 164,153,101 (thiazole), 164 (O-C=N), 87 (O-C-N), 168 (C=S); IR (KBr, cm^{-1}): 3037,1502, 1609 (Aromatic C-H), 1622 (C=N thiazole ring), 1354 (C=S), 1300 (C-O-C).

4d: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(2-hydroxyphenyl)-4-thioxo-1,3,5-oxadiazine
Yield was 59%; M. Wt. 493g; Melting Point: 274-275°C (uncorrected); Elemental analysis calculated for $C_{28}H_{19}N_3O_2S_2$: C 68.15, H 3.85, N 8.51, S 12.98% Found: C 68.1, H 3.8, N 8.4, S 12.9%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 17H, aromatic + CH of thiazole), 4.3 (s, 1H, oxadiazine), 3.8 (s, 1H, -OH); ^{13}C NMR (δ ppm): 113-134 (Naphthalene & Benzene), 163,154,101 (thiazole), 166 (O-C=N), 84 (O-C-N), 166 (C=S); IR (KBr, cm^{-1}): 3031,1505, 1602 (Aromatic C-H), 1622 (C=N thiazole ring), 1356 (C=S), 1301 (C-O-C).

4e: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(4-methylphenyl)-4-thioxo-1,3,5-oxadiazine
Yield was 55%; M. Wt. 491g; Melting Point: 258-259°C (uncorrected); Elemental analysis calculated for $C_{29}H_{21}N_3OS_2$: C 70.87, H 4.27, N 8.55, S 13.03% Found: C 70.8, H 4.2, N 8.4, S 12.9%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 17H, aromatic + CH of thiazole), 5.6 (s, 1H, oxadiazine), 2.1 (s, 3H, CH_3); ^{13}C NMR (δ ppm): 111-132 (Naphthalene & Benzene), 165,153,100 (thiazole), 169 (O-C=N), 86 (O-C-N), 166 (C=S), 24 (CH_3); IR (KBr, cm^{-1}): 3037,1503, 1609 (Aromatic C-H), 1625 (C=N thiazole ring), 1352 (C=S), 1300 (C-O-C).

4f: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(3,4-methylenedioxyphenyl)-4-thioxo-1,3,5-oxadiazine
Yield was 56%; M. Wt. 521g; Melting Point: 263-264°C (uncorrected); Elemental analysis calculated for $C_{29}H_{19}N_3O_3S_2$: C 66.79, H 3.64, N 8.06, S 12.28% Found: C 66.7, H 3.5, N 7.9, S 12.1%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 18H, aromatic + CH of thiazole), 5.3 (s, 1H, oxadiazine), 5.9 (s, 2H, -O-CH_2-O-); ^{13}C NMR (δ ppm): 112-134 (Naphthalene & Benzene), 168,153,101 (thiazole), 162 (O-C=N), 86 (O-C-N), 166 (C=S), 96 (-CH_2-O); IR (KBr, cm^{-1}): 3038,1504, 1603 (Aromatic C-H), 1626 (C=N thiazole ring), 1358 (C=S), 1304 (C-O-C).

4g: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(4-hydroxy-3-methoxyphenyl) -4-thioxo-1,3,5-oxadiazine
Yield was 60%; M. Wt. 523g; Melting Point: 276-277°C (uncorrected); Elemental analysis calculated for $C_{29}H_{21}N_3O_3S_2$: C 66.53, H 4.01, N 8.03, S 12.23% Found: C 66.4, H 3.9, N 7.9, S 12.1%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 16H, aromatic + CH of thiazole), 5.6 (s, 1H, oxadiazine), 3.8 (s, 1H, -OH), 2.5 (s, 1H, -CH_3); ^{13}C NMR (δ ppm): 112-132 (Naphthalene & Benzene), 165,153,102 (thiazole), 169 (O-C=N), 86 (O-C-N), 166 (C=S), 24 (CH_3); IR (KBr, cm^{-1}): 3039,1504, 1601 (Aromatic C-H), 1626 (C=N thiazole ring), 1358 (C=S), 1303 (C-O-C).

4h: 3-[4-(2-naphthalenyl)thiazol-2-yl)]-2H-2-phenyl-6-(3,4-diethoxyphenyl)-4-thioxo -1,3,5-oxadiazine
Yield was 58%; M. Wt. 565g; Melting Point: 255-256°C (uncorrected); Elemental analysis calculated for $C_{32}H_{27}N_3O_3S_2$: C 67.96, H 4.77, N 7.43, S 11.32% Found: C 67.8, H 4.7, N 7.3, S 11.2%; ^{1}H NMR (δ ppm): 7.2-8.5(m, 16H, aromatic + CH of thiazole), 5.6 (s, 1H, oxadiazine), 2.2 (t, 4H, CH_2), 1.9 (q, 6H, CH_3); ^{13}C NMR (δ ppm): 111-133 (Naphthalene & Benzene), 165,152,102 (thiazole), 169 (O-C=N), 86 (O-C-N), 166 (C=S), 36 (-CH_2-)14 (CH_3); IR (KBr, cm^{-1}): 3032,1505, 1609 (Aromatic C-H), 1624 (C=N thiazole ring), 1353 (C=S), 1306 (C-O-C).

RESULTS AND DISCUSSION

The examination of the C, H, N contents of all the oxadiazine derivatives (4a-h) are consistent with their calculated values for the structures predicted. The typical IR spectra of all the oxadiazine derivatives (4a-h) are shown in Figs. 8.1 to 8.3. The spectra comprise the bands due to aromatic CH including thiazole ring. The thioxo group gave the band around 1350 cm^{-1}. The structures of all the oxadiazine derivatives (4a-h) are confirmed by PMR and CMR spectra of three compounds. The spectra comprise the signals between 7.2-8.5 ppm for aromatic segments while the 5H proton gave the signal around 5.15 ppm. Other signals are appeared at their respective position. This is also supported by CMR. The CMR spectral data are shown under the individual compound. The naphthalene and benzene give the signals between 110 to 134 ppm. Thiazole ring give the signal at 167, 150 and 102 ppm and then O – C = N, O – C – N and C = S signals respectively at 169, 86 and 166 ppm. The LC-MS spectrum of a selected compound gives the peak corresponding to the molecular weight. Thus all these facts confirm the structures of 4(a-h). The antibacterial activity (Table 1) and antifungal activity (Table 2) of (4a-h) has been carried. The results showed that the prepared compounds were toxic against the bacteria. Among [(4-(2-naphthalenyl) thiazol-2-yl)-2-(substitutedphenyl)-6-phenyl-4-thioxo-1,3,5-oxadiazine (4a-h) (Table 1) compounds 4e, 4h shows good antimicrobial activity. Other prepared compounds shows moderate activity compared to standard drugs against all four bacterial strains B. Subtillis, S. Aureus, E. coli and Ps. Aeruginosa.

Table 1. Antibacterial Activity of compounds 4(a-h)

Compound	Zone of Inhibition (in mm)			
	Gram positive		Gram negative	
	B.Subtillis	S.Aureus	E.Coli	Ps.Aeruginosa
4a	13	17	11	10
4b	18	11	15	12
4c	13	11	16	16
4d	15	19	11	17
4e	17	15	20	18
4f	10	16	16	13
4g	12	15	13	13
4h	16	21	18	14
Penicillin	22	24	21	22

Table 2. Antifungal Activity of compounds 4(a-h)

Compound	Zone of inhibition at 1000 ppm (%)			
	Penicillium Expansum	Botrydepladia Thiobromine	Nigrospora Sp.	Trichothesiun Sp.
4a	15	19	13	09
4b	14	13	17	14
4c	16	13	18	18
4d	18	21	12	19
4e	19	22	21	20
4f	13	18	15	14
4g	16	17	12	14
4h	19	23	19	21
Sulphanilamide	23	28	25	27

CONCLUSION

Novel heterocyclic compounds [(4-(2-naphthalenyl) thiazol-2-yl)-2-(substituted phenyl)-6-phenyl- 4-thioxo-1,3,5-oxadiazine (4a-h) have been synthesized successfully and characterized. Antifungal activity has also been carried out; the results obtained were indicated that compounds 4e and 4h showed good antimicrobial activity. Other compounds showed moderate activity compared to standard drugs against bacterial strains.

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