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Synthesis and characterization of N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2,6-diphenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide

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ABSTRACT

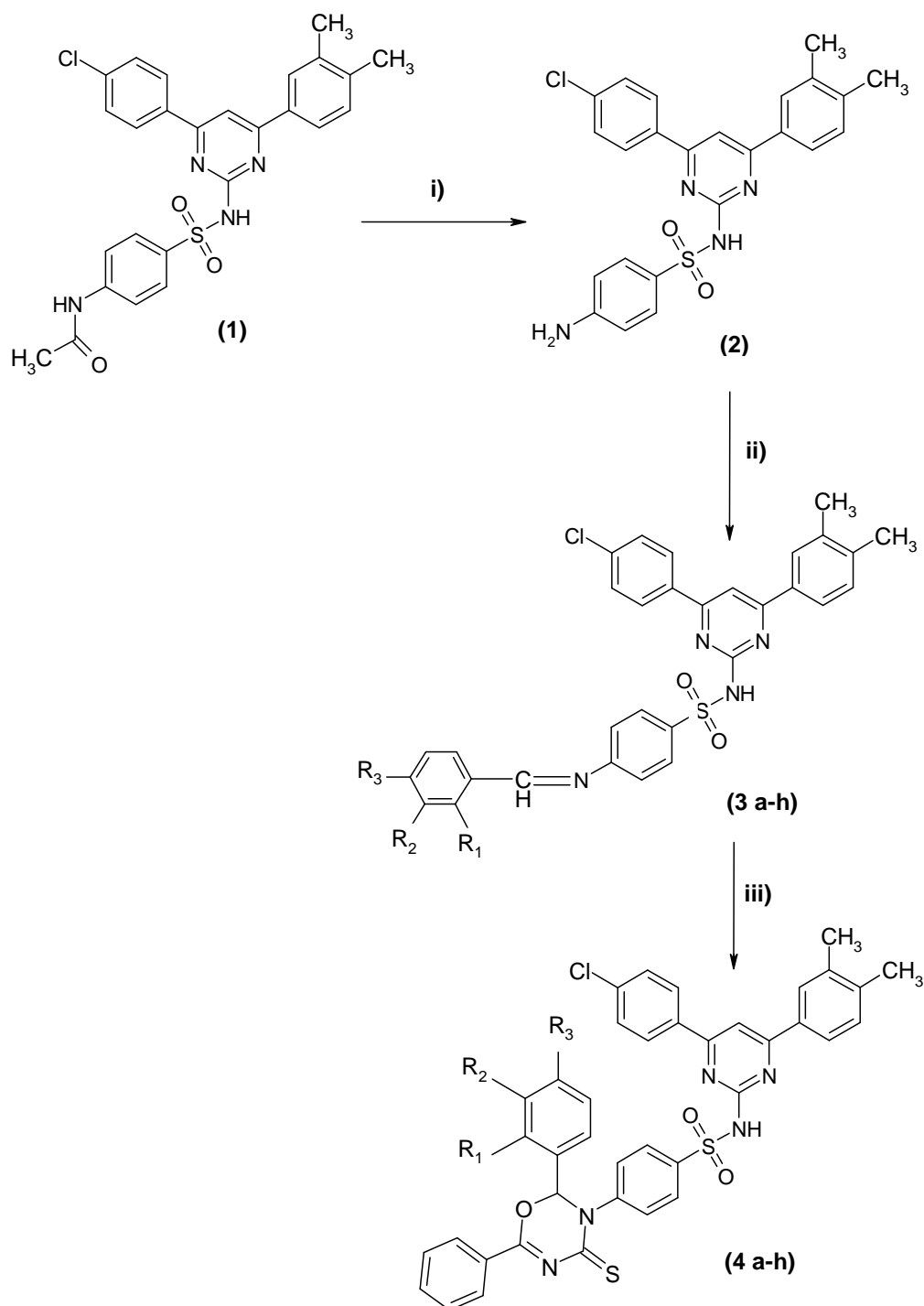
4-Amino-N-[4-(4-chloro-phenyl)-6-(3,4-dimethyl-phenyl)-pyrimidin-2-yl]- benzenesulfonamide (2) was prepared by the hydrolysis of N-{4-[4-Chloro-phenyl]-6-(3,4-dimethyl-phenyl)-pyrimidin-2-ylsulfamoyl]-phenyl}-acetamide (1). It was on-facile condensation reaction with various aromatic aldehydes yields Schiff bases /anils/azomethines (3a-h). These anils on cyclo addition reaction with benzoyl isothiocyanate afforded 1,3,5-Oxadiazine (4a-h). The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: 1,3,5-Oxadiazine, cyclo addition reaction, facile condensation, N-Acetyl Sulphanilyl chloride, Antimicrobial activity.

INTRODUCTION

The development of sulphonamides is one of the most fascinating and informative fields in medicinal chemistry, highlighting the roles of skillful planning and serendipity in drug research. The discovery of sulphonamides marked the beginning of the chemotherapeutic area by making possible a direct attack on microbial infections¹. Sulphonamides antibacterials continued to be used because they are effective, inexpensive and free of super infection problems of the broad-spectrum antibiotic². As a part of surge of interest in heterocyclic that have been explored for developing pharmaceutically important molecule 1,3,5-Oxadiazine³⁻⁵ have played an important role in medicinal chemistry. Moreover, they have been studied extensively because of their ready accessibility, diverse chemical reactivity, and broad spectrum of biological activities.

Pyrimidine derivatives occupy a unique position as leiodynamic agents, both as essential components of nucleic acids and also as therapeutic agents⁶⁻⁷. During the past years considerable evidence has been accumulated to demonstrate the efficiency of substituted 1,3,5-Oxadiazine and sulphonamides.



Scheme 1 Reagents and conditions : i) Hydrolysis/NaOH; ii) Ethanol /Substituted benzaldehyde / 8hr; iii) TEA/1,4-Dioxane / Benzoyl isothiocyanate

(a) $R_1=R_2=R_3=H$; (b) $R_1=R_2=H, R_3=OCH_3$; (c) $R_1=R_2=H, R_3=OH$; (d) $R_1=OH, R_2=R_3=H$; (e) $R_1=R_2=H, R_3=CH_3$; (f) $R_1=R_2=H, R_3=Cl$; (g) $R_1=H, R_2=OCH_3, R_3=OH$; (h) $R_1=H, R_2=OCH_2CH_3, R_3=OCH_2CH_3$;

Scheme 1

Keeping in view of biological importance of this group, we replace them by pyrimidine moiety at N1-position of sulphanilamide and 1,3,5-Oxadiazine at N4-position in sulphanilamide and our approach clearly shows the biological importance of the coupled products. The research work is scanned in scheme.

Antimicrobial Activity**Antibacterial Activity**

Antibacterial activities of all compounds were studied against Gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram negative bacteria (*E. coli* and *Salmonella typhi*) at a concentration of 50 µg/ml by agar cup plate method⁸. Methanol system was used as control in this method. Under similar condition as in of penicillin and sulphanimide as a standard comparison carried out control experiment. The area of inhibition of zone is measured in centimeters. Compounds **4a**, **4e**, **4f** were found more active against the above microbes. Other compounds found to be less or moderate active than the standards (**Table I**).

Antifungal Activity

The compounds (**4a-h**) was tested for in vitro antifungal activity against *Candida albicans* and *Aspergillus niger*. The standard drug used was Griseofulvin. The investigation antifungal screening is reported in **Tables I**. Compounds **4b**, **4g** Shows good activity against *C. albicans* fungal strain.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ¹H NMR spectra in CDCl₃ on Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. The required N-Acetyl Sulphanilyl chlorides (N-ASC) were prepared by reported method⁹. All chemicals used were of laboratory grade.

Preparation of N-{4-[4-Chloro-phenyl]-6-(3,4-dimethyl-phenyl)-pyrimidin-2-ylsulfamoyl]-phenyl}-acetamide (**1**) was prepared according to the reported method¹⁰.

Preparation of 4-Amino-N-[4-(4-chloro-phenyl)-6-(3,4-dimethyl-phenyl)-pyrimidin-2-yl]-benzenesulfonamide (**2**) was prepared according to the reported method¹¹.

Preparation of 4-(Arylidine-amino-N-[4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-pyrimidin-2-yl]-benzenesulfonamide (**3 a-h**) was prepared according to the reported method¹¹.

Preparation of N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2,6-diphenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4a-h)

General procedure

A mixture of Schiff base (**3 a-h**) (0.002 mol) and triethyl amine (TEA) (0.004 mol) was dissolved in 1, 4-dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution benzoyl isothiocyanate (0.004 mol) was added drop wise within a period of 30 min. The reaction mixture refluxed for 6 h in a water bath. The reaction mixture was concentrated, cooled and poured into ice cold water the solid obtained was filtered and recrystallized from absolute ethanol to give white 1,3,5-oxadiazin (**4 a-h**), which were obtained in 55-60% yield.

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2,6-diphenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4a)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 190-192°C; IR: Aromatic stretching 3030, 1350 C=S stretching, SO₂ 1320 cm⁻¹; ¹H NMR: 7.6 (s, 1H, H-5- of the pyrimidine ring), 7.2-8.1 (17H, m, Aromatic), 5.64 (1H, s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N *Anal* Cald.for C₃₉H₀N₅O₃S₂Cl(716.27): C,65.40;H4.22;N,9.78;S,8.95;Cl,4.95 Found: C,65.30;H4.20;N,9.58;S,8.75;Cl,4.75 Yield 55%;

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2-(4-methoxyphenyl)-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4b)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 195-197°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N *Anal* Cald.for C₄₀H₃₂N₅O₄S₂Cl(746.27): C,64.17;H4.22;N,9.78;S,8.59;Cl,4.75 Found: C,64.10;H4.20;N,9.70;S,8.39;Cl,4.55 Yield 65%;

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2-(4-hydroxyphenyl)-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4c)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 189-190°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N *Anal* Cald.for C₃₉H₄₀N₅O₄S₂Cl(732.27): C,63.67;H4.13;N,9.56;S,8.76;Cl,4.84 Found: C,63.47;H4.03;N,9.50;S,8.56;Cl,4.80 Yield 52%;

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2-(2-hydroxyphenyl)-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4d)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 179-180°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N *Anal* Cald.for C₃₉H₄₀N₅O₄S₂Cl(732.27): C,63.67;H4.13;N,9.56;S,8.76;Cl,4.84 Found: C,63.37;H4.01;N,9.30;S,8.46;Cl,4.70 Yield 54%;

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(6-phenyl-4-thioxo-2-p-tolyl-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4e)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 190-192°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N , 21.3 –CH₃ *Anal* Cald.for C₄₀H₃₂N₅O₃S₂Cl(730.0): C,65.79;H4.42;N,9.59;S,8.78;Cl,4.85 Found: C,65.59;H4.22;N,9.49;S,8.71;Cl,4.52 Yield 57%;

4-(2-(benzo[d][1,3]dioxol-5-yl)-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)-N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)benzenesulfonamide (4f)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 193-195°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N , 101.2 –O-CH₂-O- *Anal* Cald.for C₄₀H₃₀N₅O₅S₂Cl(760.28): C,63.19;H3.98;N,9.21;S,8.44;Cl,4.66 Found: C,63.09;H3.90;N,9.20;S,8.04;Cl,4.60 Yield 52%;

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2-(4-hydroxy-3-methoxyphenyl)-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4g)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 190-192°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR:

115-129 Benzene, 156.3 O – C = N , 56 –OCH₃ Anal Cald.for C₄₀H₃₂N₅O₅S₂Cl(762.30): C,63.02;H4.23;N,9.19;S,8.41;Cl,4.65 Found: C,62.92;H4.23;N,9.01;S,8.21;Cl,4.515 Yield 65%;

N-(4-(4-chlorophenyl)-6-(3,4-dimethylphenyl)pyrimidin-2-yl)-4-(2-(3,4-diethoxyphenyl)-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)benzenesulfonamide (4g)

This compounds was obtained as colorless crystals (absolute ethanol), m.p 199-201°C; IR:Aromatic stretching 3030, 1350 C=S stretching, SO₂1320 cm⁻¹; ¹H NMR: 7.6 (s,1H,H-5- of the pyrimidine ring), 7.2-8.1(17H,m,Aromatic), 5.64 (1H , s, 1H for oxadiazine); ¹³CNMR: 115-129 Benzene, 156.3 O – C = N , 14.8 –CH₃ Anal Cald.for C₄₃H₃₈N₅O₅S₂Cl(804.38): C,64.21;H4.76;N,8.71;S,7.97;Cl,4.41 Found: C,64.02;H4.56;N,8.52;S,7.88;Cl,4.21 Yield 55%;

RESULTS AND DISCUSSION

Since the antibacterial effect of sulphanilamide has been attributed to the presence of a sulphonamide groups (-SO₂ NH₂-) and NH₂ group in para position, it is of interest to study the effect of fixation of these groups to the pyrimidine moiety.

The starting material , N-{4-[4-Chloro-phenyl]-6-(3,4-dimethyl-phenyl)-pyrimidin-2-ylsulfamoyl]-phenyl}-acetamide (**1**) was prepared by according to the reported method [18]. It can be hydrolyzed to 4-Amino-N-[4-(4-chloro-phenyl)-6-(3,4-dimethyl-phenyl)-pyrimidin-2-yl]-benzenesulfonamide (**2**) by sodium hydroxide solution. It is characterized by the elemental analysis, IR spectral studies, and NMR spectral studies. The structure of (**2**) was established by spectroscopic evidence.

This hydrolyzed product (**2**) was dissolved in absolute ethanol and was reacted with aromatic aldehyde in the presence of piperidine to yield Schiff bases (**3 a-h**) were then characterized by the elemental analysis, IR spectral studies, and NMR spectral studies. The IR spectra of Schiff bases show the prominent band at 1630 cm⁻¹ for the azomethine group[19]. All the compounds show the NMR signals for different kinds of protons at their respective positions. It is characterized by the elemental analysis, IR spectral studies, and NMR spectral studies. The IR spectra of the compound (**2**) show the bands at 3410 cm⁻¹ for –NH₂ group.

These Schiff bases on cyclo addition reaction with benzoyl isothiocyanate afforded 1,3,5-Oxadiazine (**4a-h**). The structures of these compounds have been confirmed by elemental analysis, IR spectral studies, and NMR spectral studies. These compounds shows the band at 1620, 1350 cm⁻¹ for C=N , C=S group . All the compounds show the NMR signals for different kinds of protons at their respective positions.

The antibacterial activities of both the series (**4 a-h**), have been carried out against some strain of bacteria. The results show that the prepared compounds are toxic against the bacteria. The comparison of the antibacterial activity of these compounds with penicillin and sulphanilamide shows that these compounds have almost similar activity.

TABLE I Antibacterial Activity and Anti fungal activity of compounds (4 a-h)

Compounds	Antibacterial Activity				Anti fungal activity	
	% Zone of Inhibition					
	Gram +ve		Gram -ve			
	<i>B.Subtillis</i>	<i>S.Aureus</i>	<i>E.Coli</i>	<i>Ps.Aeruginosa</i>	<i>C. Albicans</i>	<i>A. Niger</i>
4a	50	43	45	61	43	42
4b	75	67	74	66	41	56
4c	54	40	41	53	50	45
4d	72	68	70	74	54	55
4e	61	49	59	61	65	75
4f	78	68	71	75	38	42
4g	57		55	48	62	71
4h	43	39	59	62	45	67
Penicillin	83	66	77	75	-	-
sulphanilamide	79	71	83	70	-	-
Griseofulvin	-	-	-	-	78	82

CONCLUSION

The clubbing of sulfa pyrimidine and 1,3,5-Oxadiazine has been done successfully into one molecule. Both the moieties have important applications in medicinal use; the produced compounds may be act as good biological compounds.

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