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Research Article

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Synthesis, characterization and biological aspects of novel azetidinone derivatives

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ABSTRACT

*The biologically effective Schiff bases N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **(2a-h)** was prepared by condensation reaction of 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **(1)** aromatic aldehydes. Further reaction of schiff bases with triethyl amine (TEA) and 1,4-dioxane yields 4-(furan-2-yl)-6-methyl-2-oxo-N-(3-chloro-4-oxo-2-arylazetidin-1-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(3a-h)**. Characterization of Schiff bases and novel 2-azetidinone derivatives was carried out by CHN, FT-IR, NMR and LC-MS spectral analysis Also the antimicrobial activity of final compounds was examined against various microorganisms.*

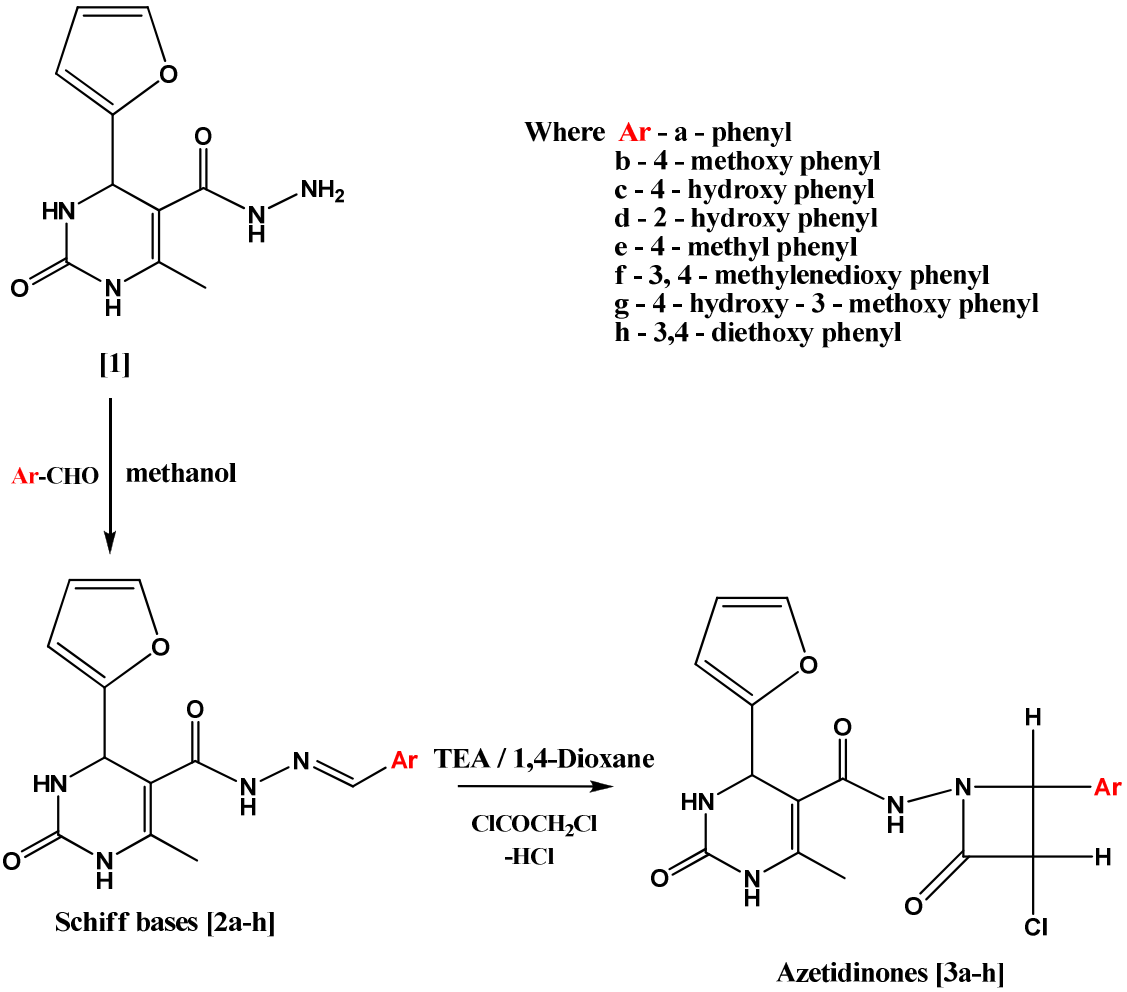
Keywords: Heterocyclic compound, Arylidine derivatives, Azetidinone, Spectroscopic study, Antimicrobial activity.

INTRODUCTION

Acid hydrazide and their derivatives were recently found to be very reactive compounds for the synthesis of various heterocyclic molecules which exhibited biological activities such as antibacterial, antifungal, analgesic, diuretic, cytotoxic, antitubercular and anti-inflammatory [1-5]. Also, acid hydrazide derivatives have increased considerable interest due to their importance as intermediates for the synthesis of the biologically active substances, which play a vital role in medicinal chemistry [6,7].

Azetidinones has played a vital role in the preparation of various biologically active compounds as antimicrobial, antitubercular, antibacterial, anti-inflammatory [8-11]. In addition to these important biological applications, one of the derivative say 2-azetidinone are also of great utility in preparative organic chemistry and studied extensively for number of derivatives [10-11].

Based on above review, our main aim was to build some heterocyclic compounds which contain biological active moieties such as azetidinone, pyrimidone and hydrazide simultaneously in a single molecule. Hence the present communication comprises the synthesis and characterization 4-(furan-2-yl)-6-methyl-2-oxo-N-(3-chloro-4-oxo-2-arylazetidin-1-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(4a-h)**. Furthermore, all compounds **4a–h** were studied for their antibacterial activity and antifungal activity against different Gram–positive, Gram–negative and different fungal strains. The detail procedure is given in **scheme-1** and the results obtained are discussed below.



Scheme-1 Synthesis of compounds Schiff bases (2a-h) and Azetidinones (3a-h)

EXPERIMENTAL SECTION

All common reagents and solvents were used of analytical grade and were used without further purification. Alumina supported pre-coated silica gel 60 F254 thin layer chromatography (TLC) plates were purchased from the E. Merck (India) Limited, Mumbai and were used to check purity of compounds and, to study the progress of the reaction whereby TLC plates were illuminated under Ultraviolet light (254 nm), evaluated in I_2 vapours and visualized by spraying with Draggendorff's reagent. Infrared spectra (FT-IR) were obtained from KBr pellets in the range of 4000–400 cm^{-1} with a Nicolet 400D spectrometer (FT-IR) instrument. ^1H NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO-d_6 as a solvent as well as TMS an internal reference standard. LC-MS of the selected samples were taken on LC-MSD-Trap-SL-01046. Micro analytical (C, N, H) data was obtained by using a Perkin–Elmer 2400 CHN elemental analyzer. Melting points were determined in open capillary tubes and were found uncorrected. 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide was prepared as per the reported method [12]. Schiff bases **(2a-h)** were prepared according to our previous work [13].

Synthesis of N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine -5-carbohydrazide (2a-h)

A mixture of 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbo hydrazide **(1)** (0.25mole) and the aromatic aldehydes (0.25mole) in ethanol (15ml) was refluxed on a water bath for 1.5-3 hrs. The solid separated was collected by filtration, dried and recrystallized from Ethanol: H_2O (1:1). The yields, melting points and other characterization data of these compounds are given in **Table-1**.

Synthesis of 4-(furan-2-yl)-6-methyl-2-oxo-N-(3-chloro-4-oxo-2-arylazetidin-1-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (3a-h)

A mixture of Schiff base **(2a-h)** (0.002 mole) and triethyl amine (TEA) (0.004 mole) was dissolved in 1,4-dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.004 mole) was added drop wise within a period of 30 minutes. The reaction mixture was then stirred for an additional 3 hours and left at room

temperature for 48 hours. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethyl acetate: 70% benzene as eluent. Recrystallization from ether/n-hexane gave desire 2-azetidinone derivatives **(3a-h)**, which were obtained in 65-77% yield. The analytical and spectral data of compounds **(3a-h)** are described. The yields, melting points and other characterization data of these compounds are given in **Table-2**.

BIOLOGICAL SCREENING

Antibacterial activity

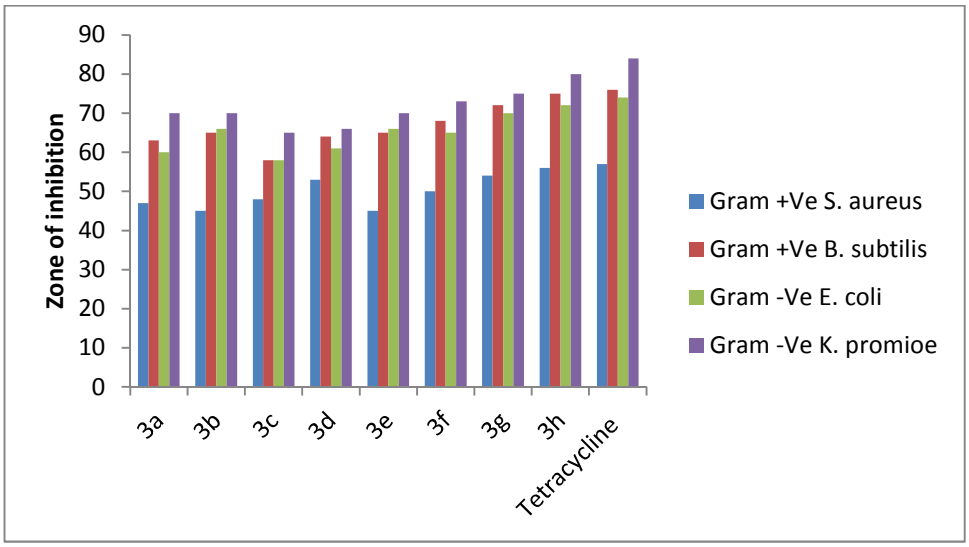
Compounds **3a–h** were screened for *in vitro* antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis* [BS] and *Staphylococcus aureus* [SA]) and Gram-negative bacterial strains (*klebsiella promioe* [KP] and *Escherichia coli* [EC]) utilizing the agar diffusion assay. The wells were dug in the media with the help of a sterile metallic borer. Recommended concentration of the test sample (50µg/mL in DMSO) was introduced in the respective wells. A methanol system was used as control in this method. Reference antibacterial drug, tetracycline was served as positive controls. The plates were incubated immediately at 37 ˚C for 24 hours. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard drug. The comparison of antibacterial activity data of synthesized compounds with standard compound tetracycline is shown in **Figure-1**.

Table-1 Analytical Data and Elemental Analysis of Compounds (2a-h)

Compd.	Molecular formula	M. Wt.	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		%H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{17}H_{16}N_4O_3$	324	82	218-219	62.9	62.95	4.9	4.97	17.2	17.27
2b	$C_{18}H_{18}N_4O_4$	354	75	216-218	60.9	61.01	5.1	5.12	15.8	15.81
2c	$C_{17}H_{16}N_4O_4$	340	80	211-213	59.9	59.99	4.7	4.74	16.4	16.46
2d	$C_{17}H_{16}N_4O_4$	340	79	213-215	59.9	59.99	4.7	4.74	16.4	16.46
2e	$C_{18}H_{18}N_4O_3$	338	77	208-211	63.8	63.89	5.3	5.36	16.5	16.56
2f	$C_{18}H_{16}N_4O_5$	368	72	214-215	58.6	58.69	4.3	4.38	15.2	15.21
2g	$C_{18}H_{18}N_4O_5$	370	80	222-223	58.3	58.37	4.8	4.90	15.1	15.13
2h	$C_{21}H_{24}N_4O_5$	412	81	220-221	61.1	61.15	5.8	5.87	13.5	13.58

***** *Uncorrected*

Figure-1 Antibacterial activity of compounds (3a-h)



Antifungal activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration *in vitro*. Plant pathogenic organisms used were *Nigrospora Sp* [NS], *Aspergillus niger* [AN], *Botrydepladia thiobromine* [BT], *and Rhizopus nigricum* [RN]**,** *Fusarium oxyporium* [FO]. The antifungal activities of all the compounds **(3a-h)** were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^o C for 15 min. at 15atm. pressure. 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:

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

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

Table-2 Analytical Data and Elemental Analysis of Compounds (3a-h)

Compd.	Molecular formula	M. Wt.	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		%H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{19}H_{17}ClN_4O_4$	400	71	225-227	56.9	56.93	4.2	4.28	13.9	13.98
3b	$C_{20}H_{19}ClN_4O_5$	430	68	209-211	55.7	55.75	4.4	4.44	12.9	13.00
3c	$C_{19}H_{17}ClN_4O_5$	416	67	215-218	54.7	54.75	4.0	4.11	13.4	13.44
3d	$C_{19}H_{17}ClN_4O_5$	416	65	228-229	54.7	54.75	4.1	4.11	13.4	13.44
3e	$C_{20}H_{19}ClN_4O_4$	414	77	224-225	57.8	57.90	4.6	4.62	13.4	13.51
3f	$C_{20}H_{17}ClN_4O_6$	444	68	221-223	53.9	54.00	3.8	3.85	12.5	12.60
3g	$C_{20}H_{19}ClN_4O_6$	446	70	213-215	53.7	53.76	4.2	4.29	12.5	12.54
3h	$C_{23}H_{25}ClN_4O_6$	488	72	217-219	56.4	56.50	5.1	5.15	11.4	11.46

***** *Uncorrected*

The antifungal activity data of azetidinone derivatives are given in **Table-3**.

Table-3 Antifungal Activities of Compounds (3a-h)

Compounds	Zone of Inhibition at 1000 ppm (%)				
	Nigrospora Sp.	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Fusarium oxyporium*
3a	62	65	64	61	60
3b	63	65	67	66	62
3c	68	69	68	64	66
3d	62	61	63	69	60
3e	69	66	65	65	61
3f	65	67	68	62	67
3g	72	65	75	68	72
3h	70	73	72	75	70

RESULTS AND DISCUSSION

Schiff bases i.e. N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **(2a-h)** was prepared by condensation reaction of 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **(1)** with different aromatic aldehydes. The structures of synthesized Schiff bases **(2a-h)** were examined for their physical properties and further confirmed by elemental analysis and other spectral studies.

The C, H, N analysis data **(Table-1)** of all schiff bases were in good agreement with proposed structures as per **Scheme-1**. The **IR** spectrum shows an absorption band at 3410-3425 (N-H), 1240-1250 (C-O), 3030-3080 cm^{-1} (C-H of Ar.), 1720, 1690 cm^{-1} (-CO, CONH), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). **^{1}H NMR**: 7.48-7.86 (5H,m,Ar-H), 11.8-11.9 (1H,s,-CONH), 8.43-8.8 (1H,s,-N=CH), 1.92 (s,3H,-CH_3), 7.72-5.25 (d,4H,furan ring), 3b; 3.87 (3H,s,-OCH_3), 3c; 5.19 (1H,s,-OH), 3d; 5.12 (1H,s,-OH), 3e; 2.30 (3H,s,CH_3), 3f; 5.84 (2H,s,CH_2), 3g; 5.15 (1H,s,-OH) and 3.80 (3H,s,O-CH_3), 3h; 1.35 (6H-2CH_3) and 3.98 (4H-2CH_2).

The C, H, N analysis data **(Table-2)** of 4-(furan-2-yl)-6-methyl-2-oxo-N-(3-chloro-4-oxo-2-arylazetidin-1-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide ***(3a-h)*** were in good agreement with proposed structures as per **Scheme-1**. The **IR** spectrum shows an absorption band at 1730 cm^{-1} (-CO of β-lactam), 3350-3410 cm^{-1} (-OH), 3030-3080 cm^{-1} (C-H, of Ar.), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3), 1720, 1690 cm^{-1} (-CO,CONH), 3410-3425 (N-H), 1240-1250 (C-O) for **(3a-h)** compound. **^{1}H NMR:** 5.95-5.97 (1H,s,-CH), 7.18-7.70 (5H,m, Ar-H), 10.7 (3H,s,-CONH), 2.17 (3H,s,-CH_3), 7.72-5.25 (d,4H,furan ring), 3b; 3.87 (3H,s,-OCH_3), 3c; 5.19 (1H,s,-OH), 3d; 5.12 (1H,s,-OH), 3e; 2.30 (3H,s,CH_3), 3f; 5.84 (2H,s,CH_2), 3g; 5.15 (1H,s,-OH) and 3.80 (3H,s,O-CH_3), 3h; 1.35 (6H-2CH_3) and 3.98 (4H-2CH_2).

CONCLUSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structures as shown in **Scheme-1**. The IR data also direct for assignment of the predicted structure. The final

structure of all compounds is also confirmed by LC-MS and NMR spectral data of all compounds. Some compounds shows good antibacterial activity compared to standard Tetracycline.

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