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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL HETEROCYCLIC COMPOUNDS

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ABSTRACT

2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide **(1)** undergoes simplistic condensation with various substituted benzaldehyde to afford the subsequent 2-(5-benzoyl-1H-benzo[d] [1,2,3]triazol-1-yl)-N'-arylideneacetohydrazide **(2a-h)** in excellent yield. Cyclo condensation of compounds **(2a-h)** with chloro acetyl chloride yields 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-chloro-2-oxo-4-arylazetidin-1-yl)acetamide **(3a-h)**. The structures of these compounds were established on basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Key words: Acetohydrazide, Azetidinone, Antibacterial activity, Spectral studies.

INTRODUCTION

Hydrazide and their heterocyclised products exhibit miscellaneous biological activity, as well as antibacterial, antifungicidal, analgesic, anti-inflammatory activity[1-15]. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the hydrazide i.e. 2-hydroxy benzoic acid hydrazide (salicylhydrazide) and their condensed products play a vital role in medicinal chemistry[16-18]. A large number of azetidinones containing β-lactam rings[19-23] are known to exhibit various biological activities like antibacterial, antifungal[24] and antibiotic[25] activities. More particularly and recently these types of compounds have been found in the treatment of T.B. and other chemotherapeutic diseases. Hence, it was thought of interest in merging of both azetidinone and benzimidazole hydrazide moieties may enhance the drug activity of compounds upto some extent or might posses some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of benzimidazole hydrazide containing an azetidinone moiety. Hence the current communication comprises the synthesis of 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-chloro-2-oxo-4-arylazetidin-1-yl) acetamide **(3a-h)**. The research work is presented in Scheme.

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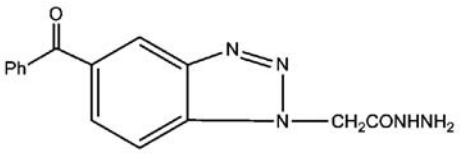
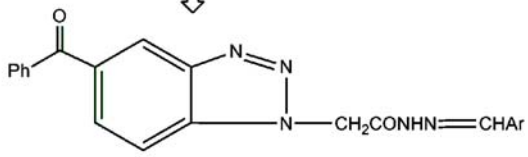


2-(5-benzoyl-1*H*-benzo[d][1,2,3]triazol-1-yl) aceto hydrazide

(1)

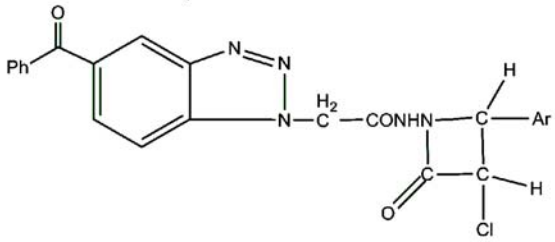
Ar-CHO/EtOH



2-(5-benzoyl-1*H*-benzo[d][1,2,3]triazol-1-yl)-*N′*-arylideneaceto hydrazide

(2a-h)

(i) ClCOCH$_2$Cl
(ii) TEA / 1,4-dioxane



2-(5-benzoyl-1*H*-benzo[d][1,2,3]triazol-1-yl)-*N*-(3-chloro-2-oxo-4-arylazetidin-1-yl) acetamide

(3a-h)

Where, Ar = (a) C_6H_5 (b) 4-OCH_3-C_6H_4 (c) 4-OH-C_6H_4
(d) 2-OH-C_6H_4 (e) 4-CH_3-C_6H_4 (f) 3,4-CH_2O_2-C_6H_4
(g) 4-OH-3-OCH_3-C_6H_3 (h) 3,4-$(C_2H_5)_2$-C_6H_4

Scheme

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400 D spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Brucker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Preparation of 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)-N'-arylideneaceto hydrazide (2a-h)

An equimolecular mixture of 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)aceto hydrazide **(1)** and the various substituted benzaldehyde **(a-h)** in ethanol (15 mL) was refluxed on a water bath for 1-2 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Tables 1 and 2.

Table 1: Analytical data and elemental analysis of compounds (2a-h)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P. (^{0}C)	Elemental analysis					
				% C		% H		% N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{22}H_{17}N_5O_2$ (383)	89	239	68.9	68.92	4.4	4.47	18.2	18.27
2b	$C_{23}H_{19}N_5O_3$ (413)	82	245	66.8	66.82	4.6	4.63	16.9	16.94
2c	$C_{22}H_{17}N_5O_3$ (399)	79	242	66.1	66.16	4.2	4.29	17.5	17.53
2d	$C_{22}H_{17}N_5O_3$ (399)	85	239	66.1	66.16	4.2	4.29	17.5	17.53
2e	$C_{23}H_{20}N_5O_2$ (397)	81	243	69.5	69.51	4.8	4.82	17.6	17.62
2f	$C_{23}H_{17}N_5O_4$ (427)	83	247	64.6	64.63	3.9	4.01	16.3	16.39
2g	$C_{23}H_{19}N_5O_4$ (429)	80	249	64.3	64.33	4.4	4.46	16.3	16.31
2h	$C_{26}H_{25}N_5O_2$ (439)	77	261	71.0	71.05	5.7	5.73	15.9	15.93

Table 2: Spectral data of compounds (2a-h)

	^{1}H NMR (δ, ppm)							
Compd.	**Ar-H**	**-CONH**	**-N=CH**	**-CH_3**	**-OCH_3**	**-OH**	**-OC_2H_5**	**-OCH_2O-cyclic**
2a	6.5–7.9 (m, 14H)	11.80(s)	8.4(s)	-	-	-	-	-
2b	6.5–7.9 (m, 13H)	11.80(s)	8.4(s)	-	3.9(s)	-	-	-
2c	6.5–7.9 (m, 13H)	11.80(s)	8.4(s)	-	-	11.20(s)	-	-
2d	6.5–7.9 (m, 13H)	11.80(s)	8.8(s)	-	-	11.20(s)	-	-
2e	6.5–7.9 (m, 13H)	11.80(s)	8.4(s)	2.4(s)	-	-	-	-
2f	6.5–7.9 (m, 12H)	11.80(s)	8.4(s)	-	-	-	-	6.09 2H (s)
2g	6.5–7.9 (m, 12H)	11.80(s)	8.4(s)	-	3.9(s)	11.20(s)	-	-
2h	6.5–7.9 (m, 12H)	11.80(s)	8.4(s)	-	-	-	4.0,4H,(q) (CH_2)1.33, 6H,(t)(CH_3)	-

Preparation of 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-chloro-2-oxo-4-aryl azetidin-1-yl) acetamide (3a-h):

A mixture 2-(5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)-N'-arylideneaceto hydrazide **(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 chloro acetyl 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 2 days. The resultant mixture was concentrated, cooled, poured into ice-cold water and then air-dried. Recrystallization from ether/n-hexane gave white powered of 2-(5-benzoyl-1H-benzo[d] [1,2,3] triazol-1-yl)-N-(3-chloro-2-oxo-4-aryl azetidin-1-yl) acetamide **(3a-h)**, which was obtained in 62-78% yield. All the compounds were characterized by analytical and spectral data (Table 3 and 4) of the compounds is assigned in Scheme.

Table 3: Analytical data and elemental analysis of Compounds (3a-h)

Compd.	Molecular formula (Mol. wt.)	Yield	M.P. (^{0}C)	Elemental analysis					
				% C		% H		% N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{24}H_{18}N_5O_3Cl$ (459.50)	63	243	62.6	62.68	3.9	3.95	15.23	15.23
3b	$C_{25}H_{20}N_5O_4Cl$ (489.50)	59	255	61.2	61.29	4.1	4.11	14.30	14.30
3c	$C_{24}H_{18}N_5O_4Cl$ (475.50)	58	247	60.5	60.57	3.8	3.81	14.72	14.72
3d	$C_{24}H_{18}N_5O_4Cl$ (475.50)	57	246	60.5	60.57	3.8	3.81	14.72	14.72
3e	$C_{25}H_{20}N_5O_3Cl$ (473.50)	50	249	63.3	63.36	4.2	4.25	14.78	14.78
3f	$C_{25}H_{18}N_5O_5Cl$ (503.50)	52	255	59.5	59.59	3.6	3.60	13.90	13.90
3g	$C_{25}H_{20}N_5O_5Cl$ (505.50)	56	256	59.3	59.35	3.9	3.98	13.84	13.84
3h	$C_{28}H_{26}N_5O_3Cl$ (515.50)	48	265	65.1	65.18	5.0	5.08	13.57	13.57

Table 4: Spectral data of compounds (3a-h)

	^{1}H NMR (δ, ppm)								
Compd.	**C_2-H**	**C_3-H**	**Ar-H**	**-CH_3**	**-OCH_3**	**-OH**	**-OC_2H_5**	**-CONH**	**-OCH_2O -cyclic**
3a	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 14H)	-	-	-		7.8(s)	-
3b	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 13H)	-	3.9(s)	-		7.8(s)	-
3c	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 13H)	-	-	11.20(s)		7.8(s)	-
3d	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 13H)	-	-	11.20(s)		7.8(s)	-
3e	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 13H)	2.4(s)	-	-	-	7.8(s)	-
3f	5.0 (d, 1H)	5.5 (d,1H)	6.9-7.9 (m,12H)	-	-	-	-	7.8(s)	6.09 2H (s)
3g	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 12H)	-	3.9(s)	11.20(s)	-	7.8(s)	-
3h	5.0 (d, 1H)	5.5 (d, 1H)	6.9-7.9 (m, 12H)	-	-	-	4.0, 4H, (q) (CH_2) 1.33, 6H, (t) (CH_3)	7.8(s)	-

Biological screening

Antibacterial activities

Antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and gram-negative bacteria (*E. coli*, and *klebsiella promioe*) at

a concentration of 50 µg/mL by agar cup plate method. Methanol system was used as control in this method. Under similar condition using tetracycline as a standard for comparison carried out control experiment. The area of inhibition of zone measured in mm. Compound **3c**, **3f** and **3g** were found more active against the above microbes. Other compounds found to be less or moderate active than tetracycline (Table 5).

Table 5: Antibacterial activities of Compounds (3a-h)

Compounds	Gram +ve		Gram –ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E. coli***
3a	59	63	54	69
3b	64	64	66	58
3c	73	69	57	72
3d	63	60	64	63
3e	54	57	68	69
3f	75	73	61	65
3g	69	74	65	63
3h	67	71	47	64
Tetracycline	78	66	85	76

Antifungal activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration *in vitro*. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus Niger, Botrydepladia thiobromine,* and *Rhizopus nigricum*, *Fusarium oxyporium*. The antifungal activity of all the compounds **(3a-h)** was 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 one liter. 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 15 atm. pressure. These medium 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:

Percentage of inhibition = 100 (X-Y) / X

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds **(3a-h)** is shown in Table 6.

Table 6: Antifungal activities of Compounds (3a-h)

	Zone of Inhibition at 1000 ppm (%)				
Compounds	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Fusarium oxyporium***	***Nigrospora Sp.***	***Rhizopus Nigricum***
3a	63	64	71	63	53
3b	59	65	69	60	68

Cont…

Compounds	Zone of Inhibition at 1000 ppm (%)				
	Aspergillus Niger	*Botrydepladia Thiobromine*	*Fusarium oxyporium*	*Nigrospora Sp.*	*Rhizopus Nigricum*
3c	61	68	72	59	63
3d	50	66	67	68	75
3e	67	66	63	63	72
3f	56	67	66	67	63
3g	62	74	61	60	57
3h	68	72	68	67	73

RESULTS AND DISCUSSION

It was observed that 2-(5-benzoyl-1H-benzo[d] [1,2,3] triazol-1-yl) aceto hydrazide **(1)** on condensation with various subsituted benzaldehyde to yield 2-(5-benzoyl-1H-benzo[d][1,2,3] triazol-1-yl)-N'-arylideneaceto hydrazide **(2a-h)**. The structures of **(2a-h)** were confirmed by elemental analysis and IR spectra showing absorption band at 1631-1647 (C=N), 3025-3087 cm^{-1} (C-H, of Ar.), 1715-1760 cm^{-1} (-CO), 2818-2850 cm^{-1} (-OCH3), 3450-3485 cm^{-1} (-OH), 2950, 1370 cm^{-1} (-CH3). The C, H, N analysis and ^{1}H NMR data of all compounds are presented in Table 1 and 2.

The cyclocondensation of **(2a-h)** with chloroacetylchloride resulted in formation of yields 2-(5-benzoyl-1H-benzo[d] [1,2,3] triazol-1-yl)-N-(3-chloro-2-oxo-4-arylazetidin-1-yl) acetamide **(3a-h)**. The structures assigned to **(3a-h)** were supported by the elemental analysis and IR spectra showing absorption bands at 1750-1760 (C=O of monocyclic β-lactam), 3035-3090 cm^{-1} (C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 2820-2850 cm^{-1} ($-OCH_3$), 2950, 1370 cm^{-1} ($-CH_3$). The C, H, N analysis and ^{1}H NMR data of all compounds are presented in Table 3 and 4.

The examination of data reveals that the elemental contents are consistence with the predicted structure shown in Scheme. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS data of selected samples. The LC-MS of samples **3b** and **3e** gave the molecular ion peak (m/z) at 491 and 475, respectively. These values are corresponds to their molecular weight.

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