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Research Article

Synthesis, Characterization and Antimicrobial studies of new novel derivatives of 2-amino-6-chlorobenzothiazole

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Abstract: Benzothiazoles and several of their derivatives have been found to be greater interest in view of their varied biological and pharmacological properties. The present work was made an attempt to synthesize some novel compounds comprising benzothiazole moiety and thiazolidinone, azetidinone. Twenty four compounds of 2-(6-chloro-(1,3) benzothial-2-yl)amino)-N-benylidene acetohydrazides(Va-h),2-(6-chloro-benzthiazol-2-yl)amino)-N-(2-aryl-4-oxathiazolidin-3-yl) acetamides VI(a-h) and 2-(6-chlorobenzothiazol-2-yl)amino)-N-(4-aryl-3-chloro-2-oxoazetidene-1-yl)acetamides (VIIa-h) were synthesized. All the synthesized compounds were characterized by TLC, IR and HNMR spectral properties.The synthesized compounds were screened for antimicrobial activity mainly antibacterial and anti-fungal activity. Tested compounds exhibited moderate to good antimicrobial activity against gram +ve and gram –ve bacteria. A few of the compounds exhibited antifungal activity equal to standard drug against *Aspergillus flavus* and weak against *Candida albicans.*
Keywords: Benzothiazoles derivatives, Synthesis, IR, Antimicrobial studies, *Aspergillus flavus*

INTRODUCTION

Benzothiazoles and several of their derivatives have been found to be greater interest in view of their varied biological and pharmacological properties [1]. Literature survey confirms different synthetic derivatives of benzothiazole have various biological activities like anti-tumar [2-3], antimicrobial , antibacterial, anthelmentic [4-7], antiinflammatory and antitubercular activities [8]. In view of biological significance of benzothiazole moiety, it is yet to be explored synthetically and biologically with several other important heterocyclic systems. Benzothiazoles, Azetidinones and Thiazolidinones possess wide range of biological and pharmacological activities.

However very few references are available on the synthesis and evaluation of fluorinated benzothiazoles incorporated with thiazolidinone and azetidinones. In continuation of our work on synthesis and evaluation of benzothiazoles in the present work we have made an attempt to synthesize some novel compounds comprising benzothiazole moiety and thiazolidinone, azetidinone. For the proposed work 2-amino-6-chlorobenzothiazole was selected as a synthon.

MATERIAL AND METHODS

Synthesis and analytical studies of the novel benzylidene derivatives of 2-aminobenothiazoles were carried out by following the **Scheme-I** [9]. and the laboratory grade and analytical grade reagents were supplied by Asian Scientifics Ltd. All the melting points reported in the work are determined by open capillary method expressed in °C and are uncorrected. Standard techniques like TLC (Thin Layer Chromatography) were used to monitor the reactions and the TLC plates (Silica Gel G) in the solvent system chloroform:ethanol (90:10) were used to determine the purity of the synthesized compounds. The spots were observed by exposure to Iodine vapours or in UV chamber. The IR spectra of the compounds were obtained on a Bruker 1720 FT-IR spectrometer (KBr pellets) expressed in cm^{-1}. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AV III 400 spectrometer using TMS as the internal standard in deuterated DMSO.

Step-1: Procedure for the synthesis of 6-chloro-2-Aminobenzothiazole (II):

6-chloro-2-aminobenzothiazole was synthesized by the method described in the literature from 4-Fluoroaniline **(I)**. The compound was prepared in good yield and characterized by the reported method. The melting point of the **II** was found to be 194-196 °C, 90%. The compound **(II)** was recrystallized from ethanol.

Step-2: Synthesis of ethyl [6-chloro-1, 3-benzothiazole-2-yl) amino] acetate (III):

0.01mole of 6-chloro-2-aminobenzothiazole **(II)** was dissolved in 30ml of dry acetone. To this ethylchloroacetate (0.01mole) and 1.38gm of freshly fused potassium carbonate (0.01mole) were added and refluxed on an oil bath at 120-140°C for 20-24 hrs (reaction progress was monitored by TLC using (7:3 chloroform:n-hexane as eluent). The reaction mixture was then poured into the crushed ice; precipitate was filtered and washed with cold water. The product was dried and purified by crystallization from aqueous

alcohol. The melting point of **III** was found to be 167°C.

Step-3: Preparation of 2-[(6-chloro-1,3 benzothiazole-2-yl) amino]aceto hydrazide (IV):

A mixture of ethyl [6-chloro-1,3-benzothiazole-2-yl)amino] acetate **III** (0.01mole) and hydrazine hydrate (99%, 0.015mole) in absolute ethanol (25ml) was heated under reflux on a steam bath for 16-18 hrs. The solvent was removed from the reaction mixture to a possible extent and cooled. The compound that precipitated was filtered, washed with cold water and dried. The product **(IV**) was purified by using alcohol and melting point was found to be 180-190°C.

Step-4: General process for the synthesis of 6-chloro-2-(benzo(d)thiazol-2ylamino)-N-arylidene acetohydrazides V(a-h):

An equimolar (0.01mole) each mixture of 2-[(6-chloro-1,3 benzothiazole-2-yl) amino]aceto hydrazide **IV** and appropriate aromatic aldehydes **(a-h)** in ethanol (25ml) containing 2-3 drops of acetic acid was refluxed on a water bath for 3-4hrs. The solvent was distilled off under reduced pressure and the residue was poured into ice cold water to obtain the product. The compound was filtered and washed with cold water and dried. The crude product was recrystallized from ethanol. Various arylidene derivatives **V (a-h)** were synthesized.

Step-5: General process for the synthesis of 2-[(6-chlorobenzothiazol-2yl)amino]-n-(2-aryl-4-oxothiazolidine-3-yl) acetamide VI(a-h)

A mixture of 6-chloro-2-(benzo(d)thiazol-2ylamino)-N-arylidene acetohydrazides **V(a-h)** (0.001 mole) and mercaptoacetic acid (0.001 mole) was dissolved in dioxane (20 ml) and pinch of anhydrous zinc chloride was added. The reaction mixture was heated under reflux for 12 hrs. and the solvent was removed as far as possible. The residue was cooled triturated with crushed ice (50 gm). The solid separated was filtered, washed with 5% sodium bicarbonate solution until no effervescence were observed and than with portion of a cold water. The crude product was purified by recrystallisation from ethanol to get a crystalline compound. Following the general procedure described above, thiazolidinones **VI(a-h)** were synthesized.

Step-6: General process for the synthesis of 2[(6-chlorobenzothiazole-2-yl)amino]-n-(4-aryl-3-chloro-2-oxoazetidin-1-yl) acetamide VII(a-h)

To a mixture of 6-chloro-2-(benzo(d)thiazol-2ylamino)-N-arylidene acetohydrazides **V(a-h)**, (0.001 mole), triethylamine (0.003 mole) dissolved in dioxane (25 ml) and chloroacetylchloride (0.0012 mole) was added drop wise while cooling and stirring. The reaction mixture was stirred for 14 hrs. at room temperature and solvent was removed under reduced pressure. The residue was cooled and triturated with crushed ice (50 gm). The solid separated was filtered, washed with small portion of cold water and dried. The product was purified by recrystallization from aqueous ethanol to get a pure crystalline compound. Adopting the similar procedure the azetidinones **VII (a-h)** were synthesized.

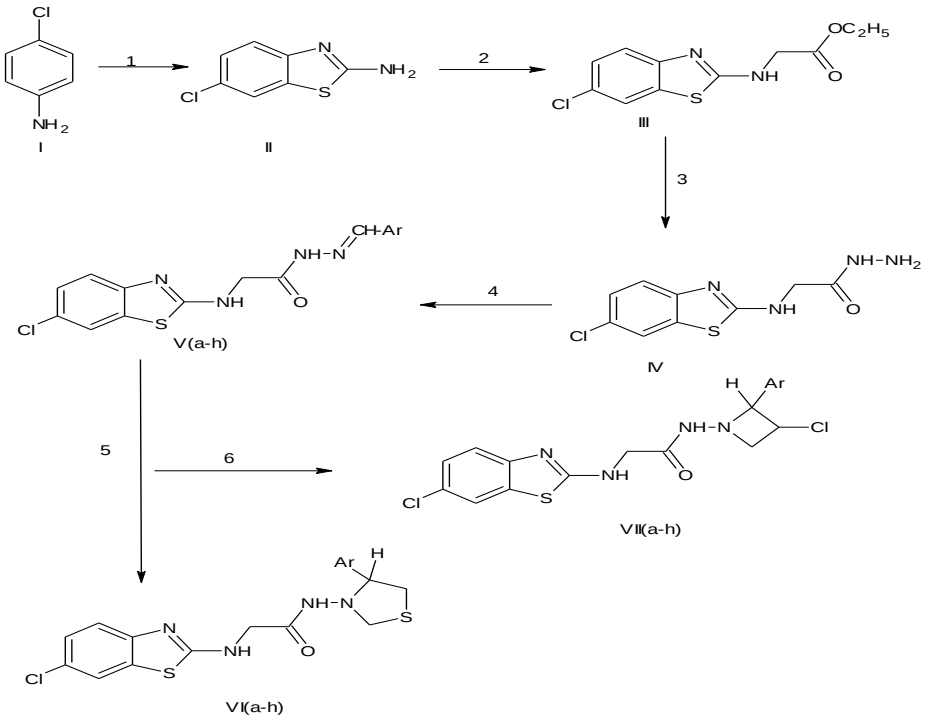


Fig-Synthetic scheme

Antibacterial Studies

The antibacterial studies of synthesized compounds were carried by by cup plate method using nutrient agar medium [10]. The antibacterial studies were carried using *Klebsiella pneumoniae, Proteus vulgaris, Bacillus subtilis, and Staphylococcus epidermidis.*

Antifungal Activity

The synthesized compounds were screened against two selected fungal strains *Candida albicans* and *Aspergillus flavus* by using diffusion method using potato-dextrose agar media (20%) [11].

RESULT AND DISCUSSION

Physical data Melting point, Rf Value, Molecular formula, % yield of synthesized compounds were done. The physical data of 6-chloro-2-(benzo(d)thiazol-2ylamino)-N-arylidene acetohydrazides V(a-h) were given in Table-1, physical and characterization data of 2-[(6-chlorobenzothiazol-2yl)amino]-n- (2-aryl-4-oxothiazolidine-3-yl) acetamide VI(a-h) were given in Table-2 and physical and characterization data of 2[(6-chlorobenzothiazole-2-yl)amino]-N-(4-aryl-3-chloro-2-oxoazetidin-1-yl) acetamide VII(a-h) were given in Table-3.

Spectral Studies of Synthesized compounds

(II) 2-amino-6-chlorobenzothiazole

Mol. Formula : $C_7H_5ClN_2S$, Mol. Weight: 184.64, R_f value: 0.81(Chloroform: Ethyl acetate; 7:3), Yield: 95%, Melting point: 194-196°C, IR (KBr, cm-^{1}) :3069.55(C-H aromatic), 1639.78 (C=C aromatic), 609.12 (C-S), 1463.10 (C-N), 1639.78(C-C aromatic), 3385.94(NH_2), 1463.10 (C-N), 1164.50 (C-F)

(III) Ethyl [(6-chlorobenzothiazol-2-yl) amino] acetate

Mol. Formula: $C_{11}H_{11}ClN_2O_2S$, Mol. Weight: 270, R_f value: 0.76(Chloroform: Ethyl acetate; 7:3), Yield: 82% Melting point: 167°C, IR (KBr, cm-^{1}): 3320 (-NH), 3040 (C – H, aromatic), 2928 (C – H, aliphatic), (C = O, carboethoxy), 1650 (C = N, C = C,aromatic).

(IV) 2[(6-chlorobenzothiazol-2-yl)amino] acetohydrazide

Mol. Formula: $C_9H_{19}ClN_4OS$, Mol. Weight : 256, R_f value: 0.72(Chloroform: Ethyl acetate; 7:3), Yield: 68%, Melting point: 180-190°C , IR (KBr, cm-^{1}) : 3320 (-NH_2); 3440 (-NH), 1675 (C=O), 1605 (C = N).

(Va) 2[(6-chloro-(1,3) benzothiazol-2-yl) amino]-N-benzylidene acetohydrazide

Mol. Formula: $C_{16}H_{13}ClN_4OS$, Mol. Weight: 344, R_f value: 0.63(Chloroform: Ethyl acetate; 7:3), Yield : 70% Melting point: 172, IR (KBr, cm-^{1}) :3320 (CO-NH), 2930 – 2890 (-CH), 1640 (C = O), 1605 (C = N).

(VIa) 2-[(7-chloro-6-fluoro benzothiazol-2-yl) amino]-N-[2-phenyl-4-oxothiazolidinone-3-yl] acetamide

Mol. Formula: $C_{18}H_{15}ClN_4O_2S_2$, Mol. Weight: 418, R_f value: 0.68, Yield: 90%, Melting point: 155, IR (KBr, cm-^{1}) : 3410 (-NH), 3210 (-CO – NH), 2995 – 2810 (C – H str, aromatic & aliphatic), 1625 (C = O), 760 (C – S – C, thiazolidinone)

(VIIa) 2[(6-chlorobenzothiazol-2-yl) amino]-N-[benzylidene-3-chloro-2-oxo azetidene-1-yl] acetamide]

Mol. Formula: $C_{18}H_{14}Cl_2N_4O_2S$, Mol. Weight: 421, R_f value: 0.63, Yield: 70%, Melting point: 190, IR (KBr, cm-^{1}) : 3415 (NH), 3320 (-CO – NH), 3065 – 2850 (-CH, str, aromatic & aliphatic), 1675 (C = O, azetidinone), 1605 (C=N); and 695 (C–Cl,azetidinone)

(Vc) 2[(6-chloro-(1,3) benzothiazol-2-yl) amino]-N-[4-(dimethylamino)benzylidene] acetohydrazide

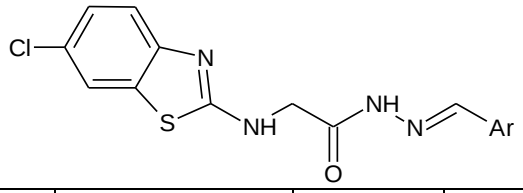
Mol. Formula: $C_{18}H_{18}ClN_5OS$, Mol. Weight: 371, R_f value: 0.71

Yield: 60%, Melting point: 162, IR (KBr, cm-^{1}) : 3415 (NH), 3320 (-CO – NH), 3065 – 2850 (-CH, str, aromatic & aliphatic), 1675 (C = O, azetidinone), 1605 (C=N); and 3290 [-N $(CH_3)_2$], ^{1}H NMR Spectrum (DMSO, δppm): 9.0 (s, NH, amide), 6.6-7.5 (m, 10H, Ar-H), 2.8 (m, 6H, -CH_3).

(VIc) 2-[(6-chloro benzothiazol-2-yl) amino]-N-[2-{4-(dimethylamino) phenyl}-4-oxothiazolidinone-3-yl] acetamide

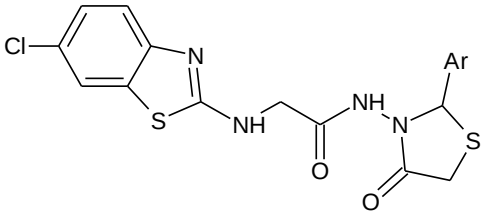
Mol. Formula: $C_{20}H_{20}ClN_5O_2S_2$, Mol. Weight: 461, R_f value: 0.72, Yield: 80%, Melting point: 148, IR (KBr, cm-^{1}) : 3415 (NH), 3320 (-CO – NH), 3065 – 2850 (-CH, str, aromatic & aliphatic), 1675 (C = O, azetidinone), 1605 (C=N); 3290 [-N $(CH_3)_2$]; and 810-830 (C-S). ^{1}H NMR Spectrum (DMSO, δppm): 8.0 (s, -NH, amide), 6.6-7.5 (m, 9H, Ar-H), 3.9 (s, 1H, thiazole), 3.3 (d, 2H, -CH_2).

Table – 1: Physical data of 6-chloro-2-(benzo(d)thiazol-2ylamino)-N-arylidene acetohydrazides V(a-h):



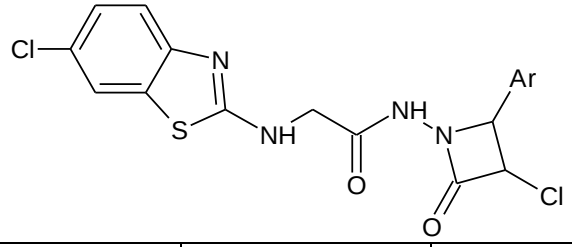
Compound	Ar	Mol. Formula	Mol.wt.	M.P.(°C)	%Yield	Rf
Va	$-C_6H_5$	$C_{16}H_{13}ClN_4OS$	344	172	70	0.63
Vb	$-C_6H_4$-4-OCH_3	$C_{17}H_{15}ClN_4O_2S$	374	196	54	0.78
Vc	$-C_6H_4$-4-$N(CH_3)_2$	$C_{18}H_{18}ClN_5OS$	384	162	60	0.71
Vd	$-C_6H_4$-4-Cl	$C_{16}H_{12}ClFN_4OS$	378	164	68	0.79
Ve	$-C_6H_3$-3,4-di OCH_3	$C_{18}H_{17}ClN_4O_3S$	404	158	45	0.68
Vf	$-C_6H_4$-2-0H	$C_{16}H_{13}ClN_4O_3S$	360	162	78	0.82
Vg	$-C_6H_4$-3-NO_2	$C_{16}H_{12}ClN_5O_3S$	389	150	84	0.85
Vh	-CH=CH-C_6H_4	$C_{18}H_{15}ClN_4OS$	370	174	90	0.78

Table–2: Physical and characterization data of 2-[(6-chlorobenzothiazol-2yl)amino]-n- (2-aryl-4-oxothiazolidine-3-yl) acetamide VI(a-h)



Compound	Ar	Mol. Formula	Mol.wt.	M.P.(°C)	%Yield	Rf
VIa	$-C_6H_5$	$C_{18}H_{15}ClN_4O_2S_2$	418	155	90	0.68
VIb	$-C_6H_4$-4-OCH_3	$C_{19}H_{17}ClN_4O_3S_2$	448	173	76	0.70
VIc	$-C_6H_4$-$N(CH_3)_2$	$C_{20}H_{20}ClN_5O_2S_2$	461	148	80	0.72
VId	$-C_6H_4$-4-Cl	$C_{18}H_{14}ClN_4O_2S_2$	452	144	65	0.58
VIe	$-C_6H_3$-3,4diOCH_3	$C_{20}H_{19}ClN_4O_4S_2$	478	165	80	0.60
VIf	$-C_6H_4$-2-0H	$C_{18}H_{15}ClN_4O_3S_2$	434	146	82	0.61
VIg	$-C_6H_4$-3-NO_2	$C_{18}H_{14}ClN_5O_4S_2$	463	122	68	0.72
VIh	-CH=CH-C_6H_4	$C_{20}H_{17}ClN_4O_2S_2$	444	158	84	0.65

Table – 3: Physical and characterization data of 2[(6-chlorobenzothiazole-2-yl)amino]-N-(4-aryl-3-chloro-2-oxoazetidin-1-yl) acetamide VII(a-h)



Compound	Ar	Mol. Formula	Mol.wt.	M.P.(°C)	%Yield	Rf
VIIa	$-C_6H_5$	$C_{18}H_{14}ClN_4O_2S$	420	190	70	0.63
VIIb	$-C_6H_4$-4-OCH_3	$C_{19}H_{16}ClN_4O_3S$	459	184	34	0.61
VIIc	$-C_6H_4$-4-$N(CH_3)_2$	$C_{20}H_{19}ClN_5O_2S_2$	463	178	88	0.53
VIId	$-C_6H_4$-4-Cl	$C_{18}H_{13}Cl_2N_4O_2S_2$	455	152	64	0.56
VIIe	$-C_6H_3$-3,4-di OCH_3	$C_{20}H_{18}ClN_4O_4S_2$	480	186	69	0.71
VIIf	$-C_6H_4$-2-0H	$C_{18}H_{14}ClN_4O_3S_2$	436	180	78	0.69
VIIg	$-C_6H_4$-3-NO_2	$C_{186}H_{13}ClN_5O4S_2$	465	115	74	0.65
VIIh	-CH=CH-C_6H_4	$C_{20}H_{16}ClN_4O_2S_2$	446	194	64	0.69

Table -4: The anti-bacterial studies of synthesized compunds

Sl. No	Name of the Compounds	Mean of zone inhibition (in mm)			
		Gram -ve		Gram +ve	
		P.vulgaris	K.pneumoniae	S.epidermidis	B.subtilis
01	*1.1.1. Ampicillin*	17	15	17	16
02	Va	10	11	13	11
03	Vb	10	11	14	11
04	Vc	11	10	13	11
05	Vd	9	10	12	11
06	Ve	12	11	14	12
07	Vf	10	12	13	10
08	Vg	9	12	14	10
09	Vh	18	12	12	8
10	Via	10	12	12	12

11	VIb	10	11	10	12
12	VIc	10	12	10	10
13	VId	10	12	11	10
14	VIe	11	13	12	11
15	VIf	13	12	11	12
16	VIg	13	14	12	10
17	Vih	11	10	11	13
18	VIIa	16	17	17	14
19	VIIb	12	12	14	6
20	VIIc	14	13	16	14
21	VIId	15	14	14	16
22	VIIe	17	14	15	14
23	VIIf	17	12	14	19
24	VIIg	15	13	17	16
25	VIIh	12	15	10	10

* All the compounds tested at 100µg/ml concentration.

Table-5: Antifungal Activity of synthesized compunds

Sl. No	**Name of the Compounds**	**Mean of zone inhibition (in mm) (Activity index)**			
		Candida albicans		***Aspergillus flavus***	
		50 µg	**100 µg**	**50 µg**	**100 µg**
01	*1.1.2. Griseofulvin*	20	23	19	26
02	Va	10 (0.5)	13 (0.57)	12 (0.63)	16 (0.62)
03	Vb	11 (0.55)	16 (0.70)	11 (0.58)	21 (0.81)
04	Vc	12 (0.60)	18 (0.78)	15 (0.79)	19 (0.73)
05	Vd	11 (0.55)	16 (0.70)	13 (0.68)	18 (0.69)
06	Ve	10 (0.5)	18 (0.78)	13 (0.68)	21 (0.81)
07	Vf	10 (0.5)	17 (0.74)	12 (0.63)	18 (0.69)
08	Vg	11 (0.55)	19 (0.83)	13 (0.68)	20 (0.77)
09	Vh	11 (0.55)	16 (0.70)	10 (0.53)	21 (0.81)

10	VIa	13 (0.65)	22 (0.96)	15 (0.79)	24 (0.92)
11	VIb	13 (0.65)	16 (0.70)	14 (0.74)	23 (0.88)
12	VIc	11 (0.55)	21 (0.91)	13 (0.63)	22 (0.85)
13	VId	12 (0.60)	21 (0.91)	17 (0.89)	26 (0.10)
14	VIe	10 (0.5)	18 (0.78)	14 (0.74)	22 (0.85)
15	VIf	11 (0.55)	17 (0.74)	15 (0.79)	22 (0.85)
16	VIg	13 (0.65)	18 (0.78)	16 (0.84)	23 (0.88)
17	VIh	12 (0.60)	17 (0.74)	17 (0.89)	24 (0.92)
18	VIIa	10 (0.5)	15 (0.65)	12 (0.63)	18 (0.69)
19	VIIb	13 (0.65)	21 (0.91)	16 (0.84)	26 (0.10)
20	VIIc	11 (0.55)	14 (0.61)	15 (0.79)	24 (0.92)
21	VIId	12 (0.60)	22(0.96)	17 (0.89)	25 (0.96)
22	VIIe	10 (0.5)	16 (0.70)	13 (0.68)	21 (0.81)
23	VIIf	13 (0.65)	18 (0.78)	10 (0.53)	19 (0.73)
24	VIIg	11 (0.55)	16 (0.70)	13 (0.68)	22 (0.85)
25	VIIh	12 (0.60)	18 (0.78)	14 (0.74)	21 (0.81)

Std : Griseofulvin (Grisovin FP). Mean zone of inhibition is including bore diameter, Bore diameter is 8 mm Activity index = Test compound/Standard compound

CONCLUSION

Twenty four compounds of 2-(6-chloro-(1,3) benzothial-2-yl)amino)-N-benylidene acetohydrazides(Va-h),2-(6-chloro-benzthiazol-2-yl)amino)-N-(2-aryl-4-oxathiazolidin-3-yl) acetamides VI(a-h) and 2-(6-chlorobenzothiazol-2-yl)amino)-N-(4-aryl-3-chloro-2-oxoazetidene-1-yl)acetamides (VIIa-h) were synthesized. All the synthesized compounds were characterized by TLC, IR and HNMR spectral properties.The synthesized compounds were screened for antimicrobial activity mainly antibacterial and anti-fungal activity. Tested compounds exhibited moderate to good antimicrobial activity against gram +ve and gram –ve bacteria. A few of the compounds exhibited antifungal activity equal to standard drug against *Aspergillus flavus* and weak against *Candida albicans.*

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