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Synthesis, Characterization And Antibacterial Activity Of Azitidinone Containing Compounds

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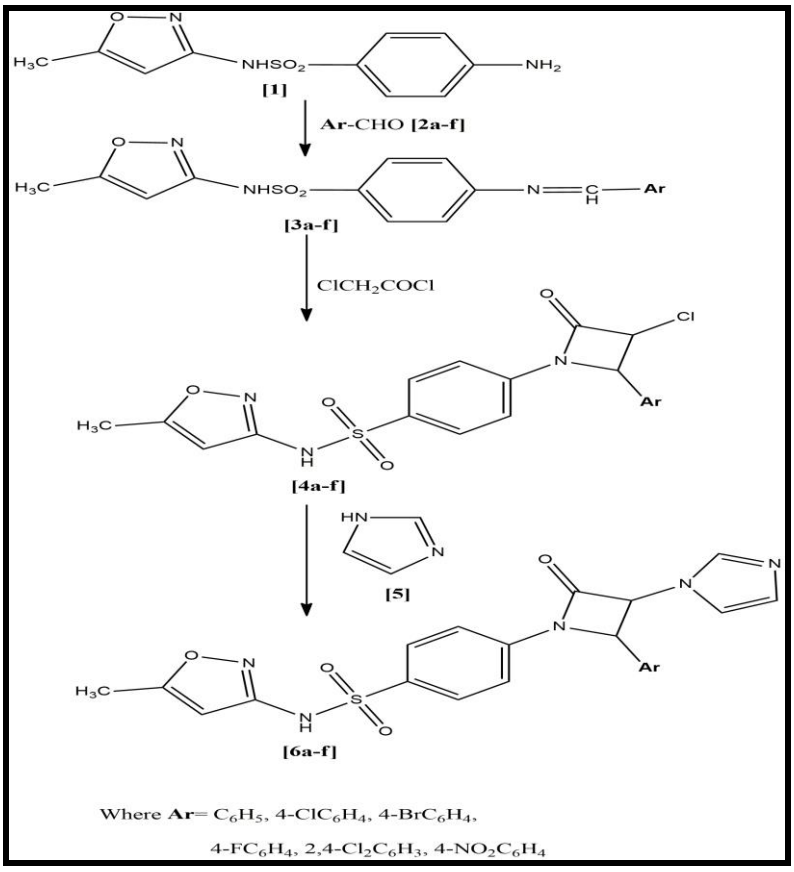
Abstract
The Schiff's bases, 4-(substituted benzylidene amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (3a-f) were papered from Sulphamethoxazole (1) and aromatic aldehydes (2a-f), then it were condensed with chloro acetyl chloride to yields 2-azitidinone derivatives, namely 4-(3-chloro-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (4a-f). The (4a-f) were further treated with 1H-imidazole to 4-(3-(1H-imidazol-1-yl)-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide(6a-f). The derivatives (3a-f),(4a-f) and (6a-f) were characterized by elemental content and spectral features. Their antibacterial activity has also been monitored against common microbes.

Keywords: *Sulphamethoxazole, Schiff's bases, 2-azitidinone, 1H-imidazole, elemental analysis, spectroscopy analysis and antibacterial activity.*

Introduction

Due to different pharmaceutical and biological applications heterocyclic compound are one of very most significant class of organic molecules [1–4]. β-lactam or 2-azetidinone compounds have been the building blocks for the synthesis of essential biological compounds [5]. 2-azetidinone derivatives occupy an important role in medicinal chemistry and this is confirmed by the literature [6,7]. β-lactams possess powerful activities, including antibacterial, antifungal, anti-inflammatory, anticonvulsant, anti-HIV, anti-parkinsonian, antidiabetic, and antitubercular activities [8-13]. Hence, the present authors thought to synthesis 2-azetidinone derivatives from Schiff's base. The work is screened as follows.



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EXPERIMENTAL

Material and Methods

All the chemicals were used of pure grade. Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Synthesis of 4-(substituted benzylidene amino)-N-(5-methylisoxazol-3-yl)benzene sulfonamide (3a-f) :

A mixture of (1) (0.01mole) and aromatic aldehydes (2a-f) in R-spirit (20ML) was refluxed for 2 to 2.5 hrs. The solid separated was collected by filtration, dried and recrystallized from R-spirit [14]. The yields, melting points and other characterization data of these compounds are given in Table -1.

Table-1: Analytical Data and Elemental Analysis of Compounds (3a-f)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{17}H_{15}N_3O_3S$ (341)	79	128-129	59.81	59.8	4.43	4.4	12.31	12.3	9.39	9.3
3b	$C_{17}H_{14}N_3O_3SCl$ (375.5)	75	132-133	54.33	54.3	3.75	3.7	11.18	11.1	8.53	8.5
3c	$C_{17}H_{14}N_3O_3SBr$ (420)	73	136-137	48.58	48.5	3.36	3.3	10.00	9.9	7.63	7.6
3d	$C_{17}H_{14}N_3O_3SF$ (359)	70	115-116	56.82	56.8	3.93	3.9	11.69	11.6	8.92	8.9
3e	$C_{17}H_{13}N_3O_3SCl_2$ (410)	76	131-132	49.77	49.7	3.19	3.1	10.24	10.2	7.82	7.8
3f	$C_{17}H_{14}N_4O_5S$ (386)	77	122-123	52.84	52.8	3.65	3.6	14.50	14.4	8.30	8.2

***** Uncorrected LC-MS data of 3a-342.6,3e-411.8

Synthesis of 4-(3-chloro-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (4a-f) :

The mixture of Schiff's bases, 4-(substituted benzylidene amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (3a-f) and TEA) was dissolved in 1,4-dioxane, cooled it, and stirred it well. To this well-stirred cooled reaction solutions chloro acetyl chloride was added drop wise within a period of 45 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 n-hexane/ petroleum ether gave 4-(3-chloro-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (4a-f). The yields, melting points and other characterization data of these compounds are given in Table -2.

Table-2: Analytical Data and Elemental Analysis of Compounds (4a-f)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	$C_{19}H_{16}N_3O_4SCl$ (417)	72	185-186	54.61	54.6	3.86	3.8	10.06	10.0	7.67	7.67
4b	$C_{19}H_{15}N_3O_4SCl_2$ (452.5)	69	187-188	50.45	50.4	3.34	3.3	9.29	9.2	7.09	7.0
4c	$C_{19}H_{15}N_3O_4SCl$ Br (496)	66	180-181	45.94	45.9	3.04	3.0	8.46	8.4	6.45	6.4
4d	$C_{19}H_{15}N_3O_4SCl$ F (435)	72	193-14	52.36	52.3	3.47	3.4	9.64	9.6	7.36	7.3
4e	$C_{19}H_{14}N_3O_4SCl_3$ (486.5)	71	186-187	46.88	46.8	2.90	2.8	8.63	8.6	6.59	6.5
4f	$C_{19}H_{15}N_4O_6SCl$ (463)	70	191-192	49.30	49.2	3.27	3.2	12.10	12.0	6.93	6.9

***** Uncorrected LC-MS data of 4a-419.3,4e-489.1

Synthesis of 4-(3-(1H-imidazol-1-yl)-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (6a-f):

An equimolar mixture of 4-(3-chloro-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (4a-f) and 1H -imidazole in ethyl acetate was refluxed in presence of K_2CO_3 for 2-3hrs., then cooled, poured into ice-cold water and then air-dried. Recrystallization from petroleum ether gave 4-(3-(1H-imidazol-1-yl)-2-oxo-4-arylazetidin-1-

yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (6a-f). The yields, melting points and other characterization data of these compounds are given in Table -3.

Table-3: Analytical Data and Elemental Analysis of Compounds (6a-f)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
6a	$C_{22}H_{19}N_5O_4S$ (449)	65	217-218	58.79	58.7	4.26	4.2	15.58	15.5	7.13	7.1
6b	$C_{22}H_{18}N_5O_4SCl$ (483.5)	63	221-222	54.60	54.5	3.75	3.7	14.47	14.4	6.63	6.6
6c	$C_{22}H_{18}N_5O_4SBr$ (528)	65	227-228	50.01	50.0	3.43	3.4	13.25	13.2	6.07	6.0
6d	$C_{22}H_{18}N_5O_4SF$ (467)	60	235-236	56.52	56.5	3.88	3.8	14.98	14.9	6.86	6.8
6e	$C_{22}H_{17}N_5O_4SCl_2$ (518)	63	218-219	50.97	50.9	3.31	3.3	13.51	13.5	6.19	6.1
6f	$C_{22}H_{18}N_6O_6S$ (494)	61	213-214	53.44	53.4	3.67	3.6	17.00	16.9	6.48	6.4

***** Uncorrected LC-MS data of 6a-450.3,6e-519.7

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria and gram-negative bacteria by agar cup plate method.[15,16] A methanol system was used as control in this method. The percentage area of inhibition of zone measured. Compounds 3e,4e and 6e were found more toxic for microbes.

Table-4: Antibacterial Activity of Compounds (3a-f)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	*Staphylococcus aureus*	*Klebsiella promioe*	*E.coli*
3a	08	06	07	08
3b	13	11	10	13
3c	09	10	08	10
3d	11	09	09	12
3e	14	12	11	14
3f	13	10	09	12
Tetracycline	20	19	18	22

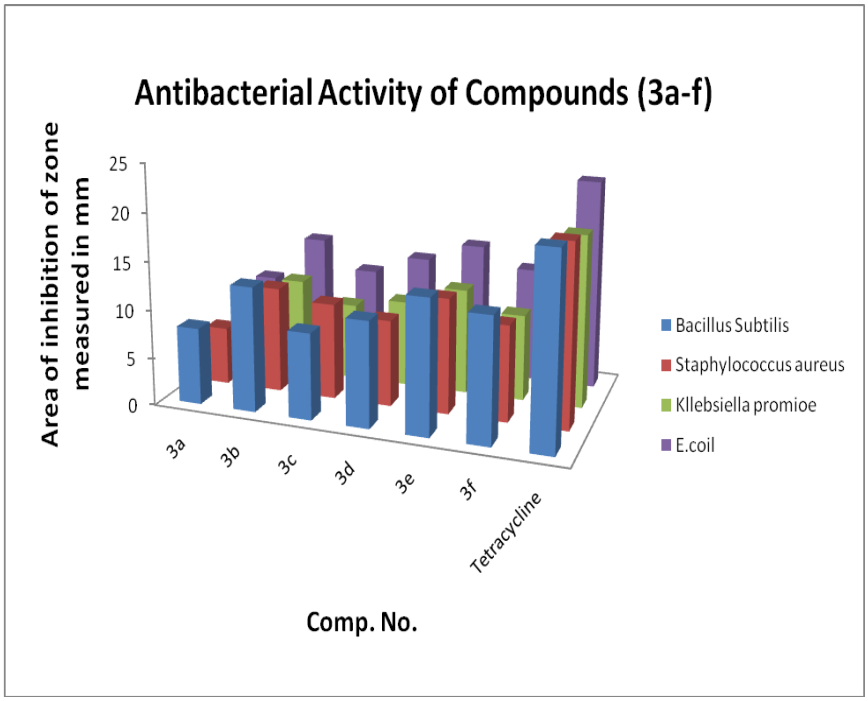


Table-5: Antibacterial Activity of Compounds (4a-f)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
4a	11	08	10	09
4b	16	12	13	14
4c	12	11	11	13
4d	14	10	12	14
4e	17	13	13	15
4f	16	11	12	13
Tetracycline	20	19	18	22

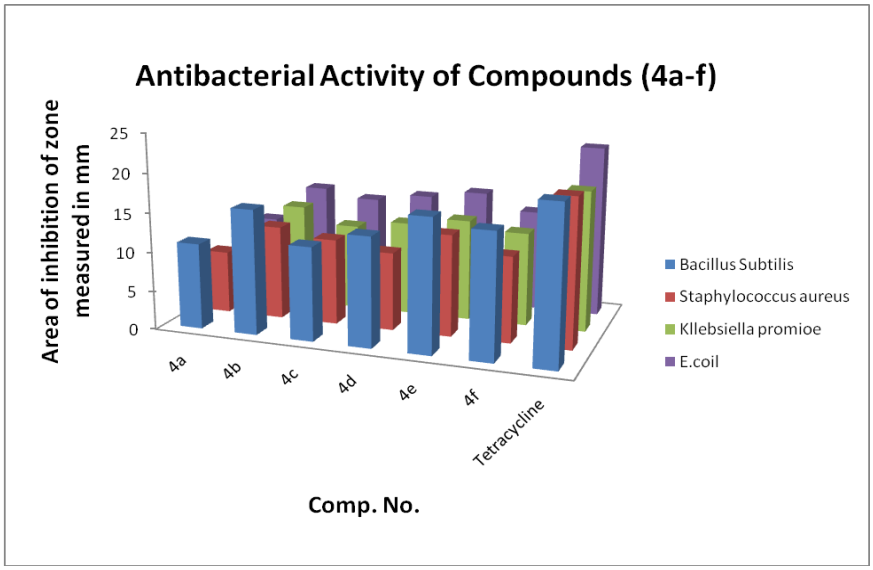
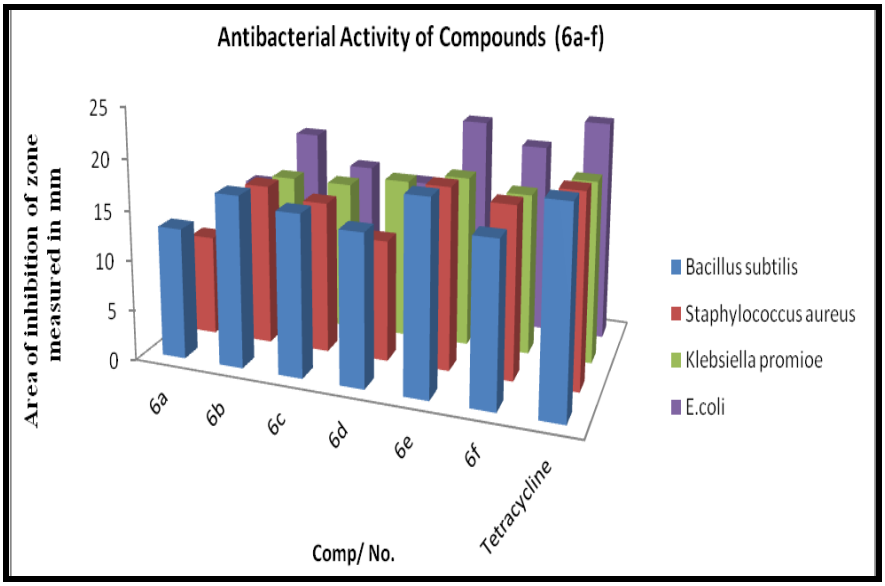


Table-6: Antibacterial Activity of Compounds (6a-f)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
6a	13	10	12	12
6b	17	16	15	18
6c	16	15	15	15
6d	15	12	16	14
6e	19	18	17	21
6f	16	17	16	19
Tetracycline	20	19	18	22



RESULTS AND DISCUSSION

The structures of 4-(substituted benzylidene amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (3a-f) were confirmed by elemental analysis and IR spectra showing an absorption band at 3240,3150(-NH), 3058-3040(-C-H of Ar),2920,2850(-C-H of Ali.),1632(-C=N),1332,1150(-SO_2), 1232(-C-O),1080,755(-C-Cl), 1525,1321 (-C-NO_2), 560(-C-Br), 1270(-C-F). ^{1}H NMR : 6.10-7.90 (10H,m, Ar-H),2.45(3H,s,CH_3),8.35(1H,s,N=CH) and 8.40 (1H,s,NH). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 4-(3-chloro-2-oxo-4-arylazetidin-1-yl)-N-(5-methyl isoxazol-3-yl) benzene sulfonamide (4a-f) were supported by the elemental analysis and IR spectra showing an absorption bands at 3242,3150(-NH), 3075-3040(-C-H of Ar),2975,2840(-C-H of Ali.),1630(-C=N),1330,1150(-SO_2), 1232(-C-O), 1675 (C=O stretching of Azetidinone), 1080,755(-C-Cl), 1525,1321 (-C-NO_2), 560(-C-Br), 1270(-C-F). ^{1}H NMR : 6.10-7.95 (10H,m, Ar-H),2.45(3H,s,CH_3), 8.40 (1H,s,NH),5.30(d, 1H,C_4-H), 5.72 (d,1H,C_3-H).The C, H, N, S analysis data of all compounds are presented in Table-2.

The structures assigned to 4-(3-(1H-imidazol-1-yl)-2-oxo-4-arylazetidin-1-yl)-N-(5-methyl isoxazol-3-yl) benzenesulfon amide (6a-f) were supported by the elemental analysis and IR spectra showing an absorption bands at 3245,3155(-NH), 3075-3045(-C-H of Ar),2970,2845(-C-H of Ali.),1630(-C=N),1332,1150(-SO_2), 1232(-C-O), 1675 (C=O stretching of Azetidinone), 1080,755(-C-Cl), 1525,1321 (-C-NO_2), 560(-C-Br), 1270(-C-F). ^{1}H NMR : 6.10-8.10 (13H,m, Ar-H),2.45(3H,s,CH_3), 8.40 (1H,s,NH),5.20(d, 1H,C_4-H), 5.75 (d,1H,C_3-H). The C, H, N analysis data of all compounds are presented in Table-3.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. The final structure of selected compounds is confirmed by LC-MS which is consistent with predicted structure.

Conclusion

The reaction between Sulphamethoxazole (1) and aromatic aldehydes (2a-f) yields Schiff's bases, 4-(substituted benzylidene amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (3a-f). The reaction of (3a-f) with chloro acetyl chloride, yields 4-(3-chloro-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (4a-f), which on reaction with 1H -imidazole yields 4-(3-(1H-imidazol-1-yl)-2-oxo-4-arylazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzene sulfonamide (6a-f) , their structured were predicated by the elemental and spectral analysis. Newly prepared compounds were shows moderate to good antibacterial and antifungal activities.

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