SYNTHESIS OF NEWER OXADIAZOLE SUBSTITUTED AZETIDINONE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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Abstract:
A new series of 2-({[5-(3-chloro-2-oxo-4-substituted-phenylazetidin-1-yl)-1,3,4-oxadiazol-2-yl]methyl} amino)benzoic acid (13-20) have been synthesized from 2-[({5-[(substituted-benzylideneamino]-1,3,4-oxadiazol-2-yl}methyl)amino]-benzoic acid (5-12). All these synthesized compounds have been screened for their antimicrobial activity. The structures of all these newly synthesized compounds have been established by IR, ^{1}H-NMR spectroscopic data and elemental analyses.

Keywords: Oxadiazole, Azetidinone, Antimicrobial activity, Benzoic acid.

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INTRODUCTION :

The 1,3,4-oxadiazole derivatives are well known in medicinal chemistry due to their diverse biological activities like anticancer[1-3], antitumor[4-5], antimicrobial[6-7,17-21], anti-diabetic[8], antiinflammatory[9,22,23] analgesic[24], anticonvulsant[25], and antioxidant[26].1,3,4-Oxadiazole moiety containing drugs such as furamizole, raltegravir and nesapidil (Fig. 1) are also commercially available. The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocyclicsc. Furthermore, azetidin-2-one (β-lactam) ring is present in several widely used families of antibiotics. It has also been found that the azetidinone[10-12] bearing compounds show varied biological properties. Moreover, certain azetidinone congeners have also found to be associated with antimicrobial[13-14] activity. Considering the bio potency of different heterocyclic nuclei having azetidinone rings prompted us to synthesize azetidinyloxadiazoles and screened them for antimicrobial activity.

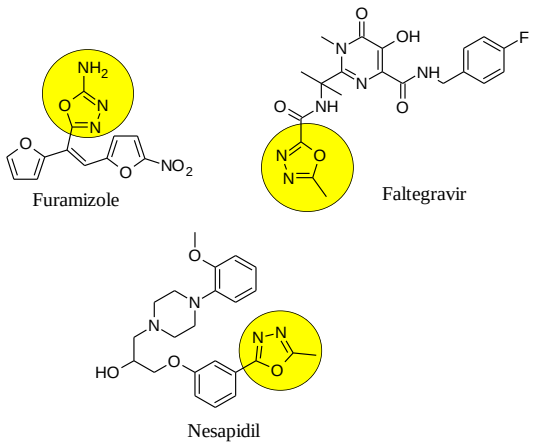


Fig.1- 1, 3, 4-Oxadiazole moiety containing commercially available drugs.

MATERIALS AND METHODS:

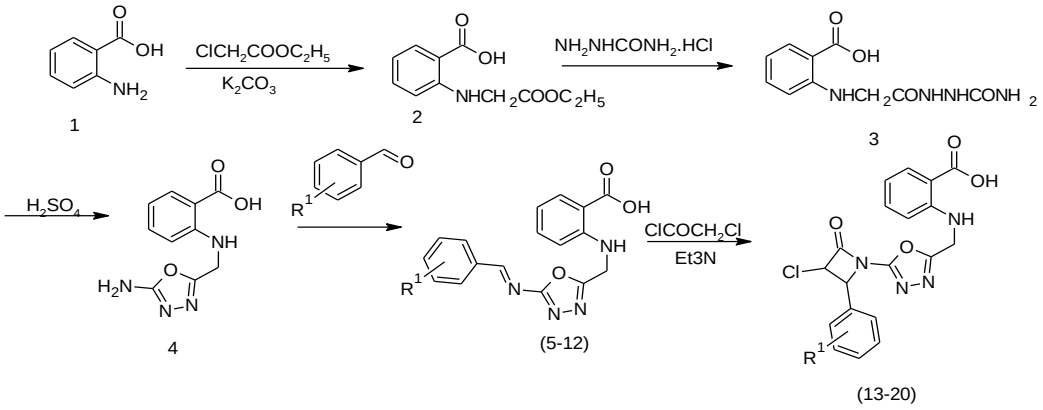
Chemistry

Antharnilic acid was reacted with ethyl chloroacetate to give 2-[(2-ethoxy-2-oxoethyl) amino]benzoic acid (2), which was further reacted with semicarbazide hydrochloride to yield 2-{[2-(2-carbamoylhydrazinyl)-2- oxoethyl] amino} benzoic acid (3) (Scheme-1). The compound (3) on dehydration with conc. H_2SO_4 afforded 2-{[(5-amino-1,3 ,4 -oxadiazol -2-yl)methyl]amino}-benzoic acid (4). This compound further reacted with substituted benzaldehyde to give 2-[({5-[(substituted-benzylideneamino]-1,3,4-oxadiazol-

2-yl}methyl) amino]-benzoic acid (5-12), which on cyclization with chloroacetyl chloride to give 2-({[5-(3-chloro-2-oxo-4-substituted-phenylazetidin-1-yl)-1,3,4-oxadiazol-2-yl] methyl} amino) benzoic acid (13-20).

Materials

All chemicals and reagents were purchased from Sigma Aldrich and Spectrochem, used as such without further purification. Melting points of newly synthesized compounds were taken in open capillaries with help of thermionic melting point apparatus and are uncorrected. The purity of the compounds was checked by thin layer chromatography on silica gel-G, eluent was a mixture of methanol-DCM and spots were located by iodine. The structure of these compounds was elucidated by IR, ^{1}H-NMR and elemental analyses. The IR (KBr) spectra were recorded on FTIR Paragon 500 (Perkin–Elmer), max in cm^{-1}. The ^{1}H-NMR spectra were recorded In DMSO-d_6 on Brucker-300 FT instrument, chemical shift (δ) in ppm. Tetramethylsilane (TMS) was used as internal reference standard. The carbon, hydrogen and nitrogen analyses were found within 0.4% of the theoretical value.



Scheme-1

2-[(2-Ethoxy-2-oxoethyl)amino]benzoic acid (2)

A mixture of anthranilic acid (1) (0.1 mol), ethyl chloroacetate (0.1 mol) and anhydrous K_2CO_3 (0.30 mol) in acetone (100 mL) was refluxed for about 16 h. The progress reaction was monitored by TLC. The reaction mixture was filtered and the excess of solvent was distilled off under reduced pressure. The resulting solid mass was poured into ice water, filtered and the separated solid was recrystallised from methanol–water to give compound **2**, Compound 2: m.p. 126-127 °C, yield 72%, IR (KBr) in cm^{-1} : 3485 (OH); 3130 (NH); 3038 (CH aromatic); 2928 (CH_2); 1715 (CO); 1585 (C···C of aromatic ring). ^{1}H-NMR (DMSO-d_6) in ppm: 11.5 (s, 1H, COOH,), 7.62–7.43 (m, 4H, ArH), 5.82 (s, 1H, NH), 4.54 (s, 2H, NCH_2), 4.24 (q, 2H, J=7.2 Hz, $COOCH_2CH_3$), 1.22 (t, 3H, J=7.2 Hz, $COOCH_2CH_3$). $C_{11}H_{13}NO_4$: Calc. C(43.73%), H(4.00%), N(4.64%) ; Found C(43.79%), H(4.05%), N(4.68%).

2-{[2-(2-Carbamoylhydrazinyl)-2-oxoethyl]amino}benzoic acid (3)

A solution of 2-[(2-ethoxy-2-oxoethyl) amino] benzoic acid (2) (0.06 mol) and semicarbazide hydrochloride (0.06 mol) in methanol (100 mL) was added anhydrous NaOH (0.12 mol) and the reaction mixture was refluxed for 16 h. The progress reaction was monitored by TLC. The excess of solvent removed under reduced pressure and the viscous mass recrystallised from methanol–water to afford compound 3. Compound 3: m.p. 143-145 °C, yield 66%, IR (KBr) in cm^{-1} : 3474 (OH); 3133 (NH); 3025 (CH aromatic); 2923 (CH_2); 1717 (CO); 1570 (C···C of aromatic ring). ^{1}H-NMR (DMSO-d_6) in ppm: 11.31 (s, 1H, COOH), 8.42 (m, 4H, NHNHC ON H_2), 7.66–7.42 (m, 4H, ArH), 5.73 (s, 1H, NH), 4.72 (s, 2H, NCH_2). $C_{10}H_{12}N_4O_4$: Calc. C(36.2 7%), H(3.35%), N(16.92%); Found C(36.20%), H(3.31%), N(16.85%).

2-{[(5-Amino-1,3,4-oxadiazol-2-yl)methyl]amino}-benzoic acid (4)

A mixture of compound 3 (0.06 mol) and conc. H_2SO_4 (25 mL) was kept 18 h at room temperature. The progress reaction was monitored by TLC. The reaction mixture was poured into ice cold water, neutralized with liquid ammonia and solid was filtered. The product obtained was recrystallised from ethanol–water. Compound 4: m.p. 154-155°C, yield, 52%, IR (KBr) in cm^{-1} : 3480 (OH), 3142 (NH), 3335 (NH2), 3020 (CH aromatic), 2924 (CH_2), 1720(CO), 1585 (C···C of aromatic ring), 1605 (CN), 1210 (CN), 1050 (NN), 652 (CBr); ^{1}H-NMR (DMSO-d_6) in ppm;

11.30 (s, 1H, COOH), 7.65-7.40 (m, 4H, ArH), 6.20 (bs, 2H, NH_2), 5.90 (s, 1H, NH), 4.75 (s, 2H, NCH_2). $C_{10}H_{10}N_4O_3$: Calc. C(38.36%), H(2.90%), N(17.89%); Found C(38.40%) H(2.87%), N(17.95%).

2-[({5-[(Substituted-benzylideneamino]-1,3,4-oxadiazol-2-yl}methyl)amino]-benzoic acid (5-12)

A solution of compound 4 (0.025 mol) in absolute ethanol (50 mL) with substituted aromatic aldehydes (0.025 mol) in the presence of acetic acid was refluxed for 16 h. The progress reaction was monitored by TLC. The reaction mixture was distilled off. The solid thus obtained was recrystallised from the appropriate solvent as given in Table-1. By this procedure, compounds (5-12) were obtained starting from benzaldehyde, 4-methylbenzaldehyde 4-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-dimeihylaminobenzaldehyde, 4-nitrobenzaldehyde and 2-chlorobenzaldehyde, respectively. Their physical and elemental analyses are given in Table 1. Compound 7: m.p. 168-170 °C, yield 60%, IR (KBr) in cm^{-1} : 3480 (OH); 3159 (NH); 3068 (CH aromatic); 2925 (CH2), 1715(CO); 1585 (C···C of aromatic ring), 1605 (CN), 1210 (CN), 1134 (COC), 1045 (NN). ^{1}H-NMR (DMSO-d_6) in ppm: 11.43 (s, 1H, COOH), 8.1 (s, 1H, N=CH), 7.65–6.81 (m, 8H, ArH), 5.65 (s, 1H, NH), 4.50 (s, 2H, NCH_2), 3.72 (s, 3H, $ArOCH_3$).7004 $C_{18}H_{16}N_4O_4$:Calc. C(50.13%), H(3.51%), N(12.99 %); Found C(50.20%), H(3.58%), N(13.02%).

2-({[5-(3-Chloro-2-oxo-4-substituted-phenylazetidin-1-yl)-1,3,4-oxadiazol-2-yl]methyl} amino)-benzoic acid (13-20)

A solution of compound 7 (0.02 mol) and triethylamine (0.04 mol) in 1,4-dioxane (80 mL) was added chloroacetyl chloride (0.02 mol) at 0 ^oC drop wise. The reaction mixture was refluxed for 6h. The progress reaction was monitored by TLC. The reaction mixture was filtered and filtrate was concentrated, the solid was recrystallised from methanol–water to give compound 15. By this procedure compounds (13-20) were obtained starting from (5-12), respectively. The physical and elemental analyses of compounds (13-20) are given in Table 1. Compound 15: m.p. 185-187 °C, yield 55%, IR (KBr) in cm^{-1}: 3480 (OH); 3159 (NH); 3060 (CH aromatic); 2923 (CH_2), 1710(CO); 1580 (C···C of aromatic ring), 1608 (CN), 1215 (CN), 1130 (COC), 1050 (NN). ^{1}H-NMR (DMSO-d_6) in ppm: 11.43 (s, 1H, COOH), 7.82–6.83 (m, 8H, ArH), 5.62 (s, 1H, NH), 5.42 (d, J=7.2 Hz, 1H, CHCl) 4.88 (d, J=7.2 Hz, 1H, N-CH), 4.54 (s, 2H, NCH_2), 3.73 (s, 3H, $ArOCH_3$). $C_{20}H_{17}ClN_4O_5$: Calc. C(47.31%), H(3.18%), N(11.03%); Found . C(47.37%), H(3.21%), N(11.10%).

Table-I: Physical and Elemental analysis of compounds (5-20)

Com p No.	R^1	M.P. (^oC)	Yield (%)	Recrysta-llization solvent	Mol. Formula	Elemental analysis %					
						C		H		N	
						Calc.	Found	Calc.	Found	Calc.	Found
5	H	145-146	62	Methanol-Water	$C_{17}H_{14}N_4O_3$	63.35	63.39	4.38	3.40	17.38	17.42
6	4-CH_3	155-157	65	Methanol-Water	$C_{18}H_{16}N_4O_3$	64.28	64.32	4.79	4.80	16.66	16.68
7	4-OCH_3	168-170	60	Ethanol-Water	$C_{18}H_{16}N_4O_4$	61.36	61.38	4.58	4.49	15.90	15.94
8	4-Cl	177-179	68	Ethanol-Water	$C_{17}H_{13}ClN_4O_3$	57.23	57.29	3.67	3.66	15.70	15.74
9	4-Br	154-156	70	Methanol-Water	$C_{17}H_{13}BrN_4O_3$	50.89	50.93	3.27	3.29	13.96	14.01
10	4-N(CH_3)$_2$	144-146	65	Ethanol-Water	$C_{19}H_{19}N_5O_3$	62.46	62.48	5.24	5.25	19.17	19.23
11	4-NO_2	175-178	60	Ethanol-Water	$C_{17}H_{13}N_5O_5$	55.59	55.65	3.57	3.56	19.07	19.11
12	2-Cl	159-161	58	Methanol-Water	$C_{17}H_{13}ClN_4O_3$	57.23	57.29	3.67	3.67	15.70	15.72
13	H	174-176	58	Ethanol-Water	$C_{19}H_{15}ClN_4O_4$	57.22	57.26	3.79	3.80	14.05	14.08
14	4-CH_3	182-184	62	Methanol-Water	$C_{20}H_{17}ClN_4O_4$	58.19	58.23	4.15	4.17	13.57	13.59
15	4-OCH_3	185-187	55	Ethanol-Water	$C_{20}H_{17}ClN_4O_5$	56.02	56.04	4.00	4.02	13.07	13.11
16	4-Cl	166-168	65	Ethanol-Water	$C_{19}H_{14}Cl_2N_4O_4$	52.67	52.69	3.26	3.27	12.93	12.97
17	4-Br	160-162	60	Methanol-Water	$C_{19}H_{14}BrClN_4O_4$	47.77	47.81	2.95	2.96	11.73	11.76
18	4-N(CH_3)$_2$	173-175	58	Ethanol-Water	$C_{21}H_{20}ClN_5O_4$	57.08	57.11	4.56	4.59	15.85	15.89
19	4-NO_2	183-185	61	Methanol-Water	$C_{19}H_{14}ClN_5O_6$	51.42	51.45	3.18	3.19	15.78	15.79
20	2-Cl	182-183	54	Ethanol-Water	$C_{19}H_{14}Cl_2N_4O_4$	52.67	52.69	3.26	3.39	12.93	12.96

RESULTS AND DISCUSSION:

All new compounds (**5-12**, and **13-20**) were tested their pharmacological activity i.e. antifungal and antibacterial and the results are given in Table II. The characteristic feature is that 5-bromoanthranilic acid was substituted at N-position with five member ring structure oxadiazolyl. Furthermore, these compounds were converted in their corresponding substituted benzylidene derivatives, which were finally cyclized into azetidinone derivatives.

Antibacterial activity

The antibacterial activity of compounds **5-20** and standard chloramphenicol was done by filter paper disc method (Gould and Bowie, 1952)[15] against *Staphyloccous aureus 209 p* and *Eschericia coli ESS 2231*, at a concentration of 250 mg/mL. Media with 10% DMSO in methanol was set up as control. The presence of methanol caused no visible change in the bacterial growth.The filter paper disc method was used to evaluate the antibacterial activity of the synthesized compounds. The results of the bactericidal study of the synthesized compounds are displayed in Table II. From the bactericidal activity, it is apparent that compounds **5-12** showed the moderate activity. The zones of inhibition (ZOI) values obtained indicate that compounds 5, 6 and 7 inactive against both the bacteria, while compounds **8, 9 10 11** and **12** have moderate activity. Cyclization of arylidene derivatives (**5-12**) into their corresponding azetidinon **(13-20)** has increased the antibacterial activity. However, it is indicated from the results that compounds **15** and **16** are associated with good antibacterial activity. In addition to this, the screening data of antibacterial activities indicated that some compounds exhibited antibacterial activity against one or more bacteria tested. Compound **16** exhibited excellent activity against *Eschericia coli ESS 2231*. Futhermore it has been found that compound **15** showed better antibacterial activities with standard Chloramphenicol.

Antifungal Activity

The standard agar disc diffusion method (Pai and Platt, 1995)[16] was performed to evaluate the antifungal property of compounds **5-20** and standard fluconazole. *Candida albicans ATCC 10231, Aspergillus fumigatus2091, Candida glabrata HO5,, Candida Krusei GO3* and *Candida albicans ATCC* were used in this study. All cultures were routinely maintained on SDA (A 2) and incubated at 30 ºC. The fungal pellet was homogenized in a sterile hand–held homogenizer. This suspension was then plated onto SDA using a bacterial spreader to obtain a uniform growth field. Sterile 6 mm what man filter paper discs (A 3) were impregnated with 250 mg/mL concentration of various test compounds and standard drug, fluconazole, the results are given in Table II. It was observed that compounds **5-12** displayed antifungal activity against few strains of fungi. However, compound **10** and **11** possessed good antifungal activity than rest of the compounds **5, 6, 7, 8, 9** and **12**. Furthermore, introduction of azetidinone ring in compounds **13-20** enhances the antifungal activities. It is interesting to note from the results that compound **20** exhibited almost same antifungal activity like fluconazole. It is significant to mention that compounds **15** having methoxy group at p-position, seems to be more efficacious than rest of the compounds **13, 14, 16, 17, 18, 19** and **20**. Cyclization of arylidene derivatives **(5-12)** into their corresponding azetidinones **(13-20)**, in addition, the screening data of antifungal activity indicated that compounds **13-20** exhibited moderate to good antifungal activity against one or more fungus tested.

Table II. Antifungal and antibacterial activities of compounds 5-20 by agar diffusion and filter paper disc methods, respectively.

Compounds	Antifungal activity# **[Diameter of the inhibition zone (mm)]**					Antibacterial activity# **[Diameter of the inhibition zone (mm)]**	
	Aspergillus fumigatus	*Candida albicans ATCC 2091*	*Candida albicans ATCC 0231*	*Candida krusei G03*	*Candida glabrata H05*	*Staphylococcus aureus 209p*	*Eschericia coli ESS 2231*
*Control	0	0	0	0	0	0	0
Fluconazole	0	29	25	20	16	-	-
Chloramphenicol	-	-	-	-	-	20	20
5	12	14	10	08	0	0	0
6	10	08	07	06	0	0	0
7	12	11	06	09	0	0	0
8	0	10	08	08	0	10	08
9	0	12	10	10	0	12	09
10	0	08	12	12	0	13	12
11	10	12	12	12	0	10	10
12	8	10	10	11	10	11	13
13	10	12	14	12	08	11	12
14	11	14	16	14	10	14	14
15	13	16	18	16	12	21	20
16	10	14	16	15	10	16	18
17	12	10	14	12	10	14	14
18	14	11	16	11	08	14	12
19	0	09	10	12	09	15	11
20	16	12	14	10	11	14	10

CONCLUSION:

All the newel synthesized compounds were tested for their antifungal and antibacterial activities. From the above results and discussion it's shown that substituted arylidene derivatives **(5-12)** exhibited moderate antifungal and antibacterial activities. The presence of azetidinone moiety in compounds **(13-20)** introduces antifungal and antibacterial activities. Appearance of methoxy group of phenyl ring may play a significant role in the modulation of antibacterial.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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