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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF ARYLIDENE AND HETEROARYLIDENE OF 2-((4-(5-MERCAPTO-1,3,4-OXADIAZOL-2YL) PHENYL) AMINO) THIAZOL-4(5H)-ONE DERIVATIVES

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ABSTRACT

A new series of amido linked heterocycles arylidine/heteroarylidine were prepared by introducing oxadiazole and thiazolidine moieties. The respective arylidine derivatives were assessed for their anti microbial activity against four bacterial strains and three fungal strains. Throughout the synthesis of heterocyclic compounds it was observed that 2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) amino)thiazol-4(5H)-one was worked as versatile intermediate, this intermediate was then condensed with various substituted aromatic aldehydes to obtain a novel series of compounds. Some of those compounds were found potent against the two gram positive, two gram negative and three fungal stains. The newly synthesized compounds were characterized by most acceptable analytical techniques i.e. IR, Mass, ^{1}H NMR, ^{13}C NMR. Broth dilution method was used to perform anti microbial activity.

Keywords: Oxadiazoles, Thiazolidine, Aldehydes, Chalcones, Antimicrobial activity

1. INTRODUCTION

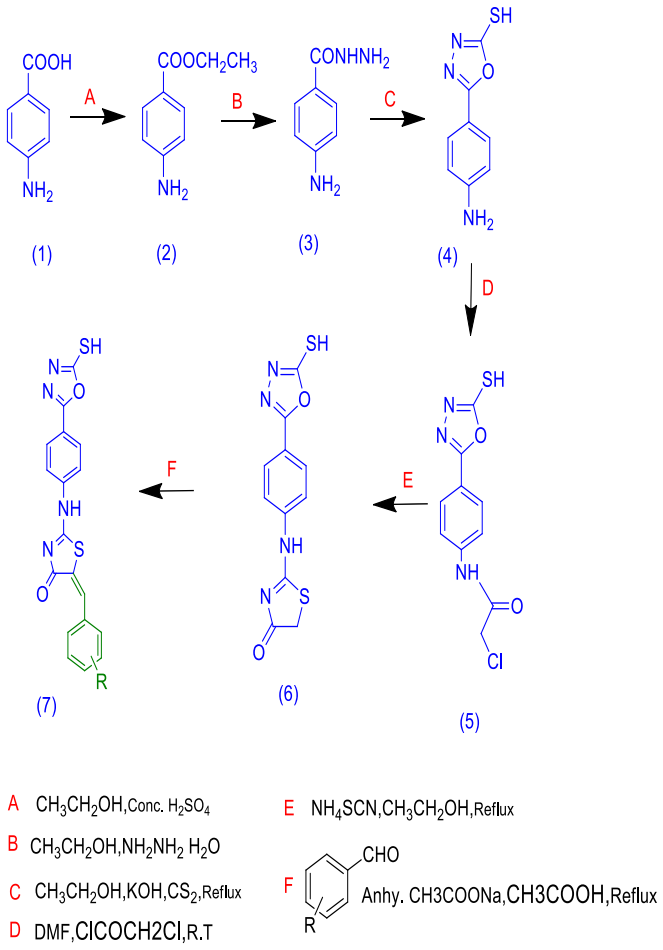
Medicinal or pharmaceutical chemistry is a scientific discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing medicinal drugs [1]. The five-membered heterocyclic ring containing nitrogen and sulfur, the 4-thiazolinone is a class of compounds which merit special attraction because it belongs to an important group of substances, as the reference of an active pharmacological properties this nucleus is associated with various biological activities such as anti diabetic [2], anti-inflammatory [3], antimicrobial [4, 5], anti hyperglycemic [6, 7] anti oxidant [8] and antibacterial [9, 10]. Various methodologies have been described for the synthesis of thiazolidin-4-one.On the other hand oxadiazole is one such molecule which has gained attention in recent times due to its increasing importance in the field of medicinal chemistry. Oxadiazole is a 5-membered ring having one oxygen atom at position 1 and two nitrogen atoms at position 3 and 4 respectively separated by a carbon in-between. Oxadiazole are a class of heterocyclic chemistry which has attracted significant interest in medicinal chemistry and they have been shown a broad range of important biological activities including antimicrobial [11] antibacterial [12], anti-cancer [13] and anti-oxidant [14] properties. The recent antifungal drugs are highly toxic even so they are very less effective. Moreover, invasive microbial epidemic induced by multi-drug-resistant microbes are difficult to determine and handle. To overcome these complications, the design and development of new and safely effective antimicrobial agents are required. In the present studies a novel series of thiazolidine was synthesized by the linkage of oxadiazole to design a novel moiety which possesses unique physico-chemical properties. All the novel compounds were screened for their antimicrobial activities. The newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy.

2. MATERIAL AND METHODS

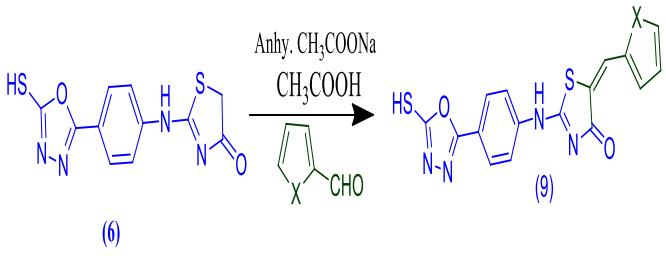
2.1. General information

All the A grade chemical and solvents used in the synthetic work were purchased from lobachemie, sigma-aldrich and specctrochem. Thin-layer chromatography resourced from sigma-aldrich was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with Ultraviolet light (254 and

365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H (400 MHz), ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$ and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal reference standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu) instrument. Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.



Scheme 1: Route of synthesis of compounds 7(a-g).



Scheme 2: Route of synthesis of compounds 9(a-b).

2.2. Synthesis of 5-(4-aminophenyl)-1,3,4-oxadiazole -2-thiol (4)

A mixture of 4-amino benzoic acid (1 mmol) and ethanol (3 mmol) were refluxed at 60°C for 4 hours. Reaction mixture was cooled and poured into ice cold water. Thus the Synthesized solid mass of ethyl 4-aminobenzoate (2) separated out and dried. Further a mixture of ethyl 4-aminobenzoate (1 mmol) and hydrazine hydrate (2 mmol) were refluxed in ethanol for 7 hours. The resultant mixture was concentrated, cooled and poured into crushed ice. The Synthesized solid mass of 4-amino benzohydrazide (3) was seperated out and dried. 4-amino benzohydrazide (1 mmol) was added with CS_2 (1.5 mmol) in a basic alcohol solution and refluxed it for 2-3 hours followed by acidification to prepare 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol (4).

2.3. Synthetic procedure of 2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino) thiazol-4(5H)-one (6)

5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol (3.65 ml, 0.04 mol) was added in 2N aqueous sodium hydroxide (150 ml) at room temperature and it was treated with chloroacetylchloride (3.18 ml, 0.04 mol) where dichloromethane (100 ml) was taken as a solvent. After 1 hour, the layers were separated and the aqueous phase extracted with additional portion of dichloromethane (100 ml). The organic phase was washed with an aqueous solution of 1N HCl, saturated $NaHCO_3$, dried with Na_2SO_4, and concentrated to afford Yield. A mixture of (5) (2.48 g, 0.01mol) and ammonium thiocyanate (0.76 g, 0.01mol) in ethanol (10 mL) was refluxed for 1 hour. The obtained solid was filtered crystallized from dioxane to give **2-**((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) amino)thiazol-4(5H)-one (6).

2.4. General Synthetic procedure of arylidine / Heteroarylidine of 2-((4-(5-mercapto-1,3,4-oxadiazol-2yl)phenyl) amino) thiazol-4(5H)-one derivatives.(7a-g,9a-b)

2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl) phenyl) amino) thiazol-4(5H)-one (6) and various substituted aldehydes were refluxed in acetic acid in presence of sodium acetate for 24 hours. Reaction mixture was poured in ice cold water to separate the product and recrystallized from ethanol.

2.5. Biological activity

To know the biological importance of novel series of arylidene derivatives, the synthesized compounds were screened against their antimicrobial activity at College of

Computer, Science and Information Technology (CCSIT), Junagadh. The compounds were screened against two gram-negative bacteria, namely *Escherichiacoli* (MTCC (Microbial Type Culture Collection) No. 443), *Pseudomonas aeruginosa* (MTCC No. 1688), two gram-positive bacteria namely *Staphylococcus aureus* (MTCC No. 96) and *Strptococcus pyogenus*,(MTCC No. 442) and three fungal stains, namely *Candida albicans*, (MTCC No. 227), *Aspergillus niger* (MTCC No. 282) and *Aspergillus clavatus* (MTCC No.5341). The strains were inoculated in nutrient broth, and kept for 24 hours culture at 34°C. *Ampicilin and greseofulvin* used as standard drugs in MIC to compare all the activity carried out. The MIC is known as the minimum inhibitory concentration able to inhibit any visible growth of micro organisms. Antimicrobial activity was determined by Broth dilution method [15] performed in 64 well micro plate, using 2,3,5-triphenyl tetrazolium chloride (TTC) as an indicator for microbial growth, by dissolving 5 mg of sample in 1 mL DMF as a diluents.

3. RESULTS & DISCUSSION

The series of compounds 7a-g, 9a-b was synthesized by condensation of (6) and substituted aldehydes by using glacial acetic acid in presence of anhydrous sodium acetate at refluxed temperature. The structures of 7a-g, 9a-bwere established on the basis of their spectral data (mass, IR, ^{1}H NMR and ^{13}C NMR).Various substituted aldehydes used are listed in Table 1 with isolated yield and MP.

3.1. Spectral data of the synthesized compounds

3.1.1. (Z)-5-benzylidene-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino)thiazol-4(5H)-one (7a)

White solid, yield: 83%.; **M.P.** 172°C; Chemical Formula: $C_{18}H_{12}N_4O_2S_2$; **IR** (KBr, cm^{-1}): 3300, 3100, 2900, 1720, 2200, 1600, 1550, 1500, 1490, 710, 690. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.59 - 7.47 (m, 3H), 7.44 - 7.33 (m, 5H), 6.78 - 6.64 (m, 2H), 4.29 (s, 1H), 2.06 (s, 1H). **^{13}CNMR** (100 MHz) δ 179(s), 173(s), 168(s), 158(s), 146(s), 134(s), 132(s), 130 (s), 129(m), 128(m), 126(m), 118(s), 118(m), 112(s). **m/z**: 380.

3.1.2. (Z)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino)-5-(4-methylbenzylidene) thiazol-4(5H)-one(7b)

White solid, yield: 79%; **M.P.** 172°C; Chemical Formula:$C_{19}H_{14}N_4O_2S_2$; **IR** (KBr, cm^{-1}): 3300, 3200, 2880, 1735, 2180, 1650, 1580, 1540, 1500, 720, 690. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.50 - 7.48 (m, 2H), 7.48 - 7.33 (m, 3H), 7.33 -7.19 (m, 2H), 6.78 - 6.64 (m, 2H), 4.30 (s, 1H), 2.36 - 2.32 (m, 3H), 2.06 (s, 1H). **^{13}CNMR** (100 MHz) δ 179(s), 173(s), 168(s), 158(s), 146(s), 140(s), 134(s), 131(s), 129(m), 128(m), 126(m), 118(s), 118(m), 112(s), 21(s). **Mass m/z**: 394.

3.1.3. (Z)-5-(4-chlorobenzylidene)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) amino) thiazol-4(5H)-one(7c)

White solid, yield: 74%; **M.P.** 221°C; Chemical Formula: $C_{18}H_{11}ClN_4O_2S_2$; **IR** (KBr, cm-1): 3300, 3100, 2900, 2200, 1720, 1600, 1550, 1500, 1490, 710, 690. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.5-7.4 (m, 2H), 7.4-7.3 (m, 2H), 6.80-6.69 (m, 2H), 6.7-6.6 (m-3H) 4.29(s, 1H), 2.06 (s, 1H) **^{13}CNMR** (100 MHz) δ 177(s), 172(s), 168(s), 158(s), 149(s), 144(s), 143(s), 126(m), 118(s), 117(m), 112(s). **Mass m/z**: 414.

3.1.4. (Z)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino)-5-(4-methoxybenzylidene) thiazol-4(5H)-one(7d)

White solid, yield: 89%; **M.P.** 215°C.; Chemical Formula: $C_{19}H_{14}N_4O_3S_2$; **IR** (KBr, cm-1): 3300, 3280, 3100, 1740, 2190, 1600, 1500, 1480, 740, 690. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.51 - 7.47 (m, 2H), 7.47 - 7.32 (m, 3H), 7.32 - 7.18 (m, 2H), 6.77 - 6.65 (m, 2H), 4.3 (s, 1H), 3.4 (s, 3H), 2.1 (s, 1H). **^{13}CNMR** (100 MHz) δ 180(s), 172(s), 168(s), 158(s), 145(s), 141(s), 133(s), 131(s), 129(s), 128(s), 125(m), 29(s). **Mass m/z**: 410.10.

3.1.5. (Z)-5-(2,4-dimethoxybenzylidene)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) amino)thiazol-4(5H)-one(7e)

White solid, yield: 86%; **M.P.** 209°C; Chemical Formula: $C_{20}H_{16}N_4O_4S_2$; **IR** (KBr, cm-1): 3290, 3150, 2120, 1730, 1600, 1550, 1300, 1490, 740, 690. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.4-7.3 (m, 2H), 7.2 - 7.1 (m, 3H),7.0-6.9(m, 4H), 4.4(s, 3H), 4.2(s, 1H) 4.1(s, 3H) **^{13}CNMR** (100 MHz) δ 180(s), 173(s), 168(s), 158(s), 146(s), 140(s), 134(s), 129(s), 128(s), 126(m), 40(s), 25(s). **Mass m/z**: 440.50.

3.1.6. (Z)-5-(4-fluorobenzylidene)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) amino) thiazol-4(5H)-one(7f)

White solid, yield: 82%; **M.P.** 213°C.; Chemical Formula: $C_{18}H_{11}FN_4O_2S_2$; **IR** (KBr, cm^{-1}): 3190, 3080,

3000, 2190, 1710, 1600, 1500, 1490, 1400, 1710, 1600, 1500, 1490, 1400, 710, 690, 620. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.6(m, 4H), 7.4(m-4H), 6.78(s, 1H), 4.29(s, 1H), 2.06(s, 1H). **^{13}CNMR** (100 MHz) δ 183(s), 171(s), 169(s), 155(s), 148(s), 141(s), 133(s), 129(s), 126(s). **Mass m/z**: 398.08.

3.1.7. (Z)-5-(2-fluorobenzylidene)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) amino) thiazol-4(5H)-one(7g)

White solid, yield: 74%.; **M.P.** 217°C.; Chemical Formula: $C_{18}H_{11}FN_4O_2S_2$; **IR** (KBr, cm^{-1}) 3300, 3120, 3010,2170, 1700,1600, 1550, 1510, 1690, 710, 680, 500. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.9(m, 4H), 7.3(m-4H), 6.7(s, 1H), 4.3(s, 1H), 2.2(s, 1H). **^{13}CNMR** (100 MHz) δ 185(s), 175(s), 173(s), 158(s), 149(s), 133(s), 128(m), 123(m). **Mass m/z**: 398.10.

3.1.8. (Z)-5-(furan-2-ylmethylene)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino) thiazol-4(5H)-one (9a)

White solid, yield: 79%.; **M.P.** 212°C; Chemical Formula: $C_{16}H_{10}N_4O_2S_3$; **IR** (KBr, cm^{-1}) 3280, 3120, 3080, 2890, 1710, 2180, 1520, 1500, 1480, 710, 690. **^{1}HNMR** (400MHz, CDCl3-d)δ 7.62 (s, 1H), 7.50 - 7.35 (m, 2H), 7.22 (s, 1H), 6.90 (s, 1H), 6.80 - 6.66 (m, 2H), 6.51 (s, 1H), 4.38 (s, 1H), 2.07 (s, 1H). **^{13}CNMR** (100 MHz) δ, 178(s), 173(s), 168 (s), 158(s), 150(s), 146(s), 143(s), 126(s), 125(m), 118(s), 118(s), 118(m), 116(s), 112(s), 110(s). **Mass m/z**: 386.47.

3.1.9. (Z)-5-(furan-2-ylmethylene)-2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino) thiazol-4(5H)-one (9b)

White solid, yield: 83%.; **M.P.** 219°C; Chemical Formula: $C_{16}H_{10}N_4O_3S_2$; **IR** (KBr, cm^{-1}): 3260, 3180, 3090, 2835,2170, 1700, 1600,1520, 1490,1400, 710, 690. **^{1}HNMR** (400MHz, $CDCl_3$-d)δ 7.5 (s, 1H), 7.35 (m, 2H), 7.1 (s, 1H), 6.80 (s, 1H), 6.66 (m, 2H), 6.51 (s, 1H), 4.3 (s, 1H), 2.1 (s, 1H). **^{13}CNMR** (100 MHz) δ 180(s), 174(s), 168(s), 158(s), 150(s), 146(s), 143(s), 126(m), 118(m), 116(s), 110(s). **Mass m/z**: 370.12

The structure of the synthesized arylidene derivatives (7a-g & 9a-b) were determined by ^{1}H & ^{13}C NMR, IR and mass spectral analysis. IR spectrum of all the final arylidene derivatives showed characteristic peaks for -C=O stretching in the range of 1700-1720 cm^{-1}, -C=C- in the range of 1560-1575cm^{-1} and -N-H stretching in the range of 3402-3415cm^{-1} was shown in experimental data. ^{1}H NMR showed characteristic peak in the range of 10.91-10.95 δ ppm to confirm the presence of -NH proton of arylidene derivatives. This huge deshielding effect on -NH proton was associated to the presence of electron withdrawing carbonyl groups. Arylidene derivatives (7a-g and 9a-b) showed a characteristic peak of benzylidene proton (=CH) between 7.12-8.15 δ ppm. The molecular weights of synthesized compounds were confirmed by mass spectrometry. The observed molecular weights of particular compounds were showing (M+1) molecular ion peak which were summarized in.

Table 1: List of substituted aryidines with yield and melting point

Sr. No.	Code	R	Yield %	mp °C
1	7a	H	83	212
2	7b	4-CH3	79	207
3	7c	4-Cl	74	221
4	7d	4-OCH3	89	215
5	7e	2,4-OCH3	86	209
6	7f	4-F	82	213
7	7g	2-F	74	217
8	9a	Thiophene-2-carbaldehyde	79	212
9	9b	Furan-2-carbaldehyde	83	219

3.2. Antimicrobial activity

In the current study, all prepared compounds were screened for their anti-microbial activities against two gram negative and two gram positive bacterial strains and three fungal strains. As standard drugs *Ampicilin* and *Griseofulvin* were used in Minimum-bacterial Inhibitory Concentration (MIC). Broth dilution technique was used to resolve all the obtained values, where as a diluents DMSO was used. MIC values of all the compounds are reported in (Table 2). Derivative 9b was exhibited moderate activity against *E. Coli (MTCC 443)* 7e possess moderate activity against *P. Aeruginosa (MTCC 1688)*. Compounds 7a, 7c and 7d posses moderate activity against *S. Aureus (MTCC 96)*. 7f showed moderate activity against *S. pyogenus (MTCC 442)* by comparing *ampicilin*. While 7e was found to posses moderate activity against *C. albicans (MTCC 227)*, 9a and 9b showed activity against *A. niger (MTCC-282)* by comparing *griseofulvin* as a standard drug and none of them showed activity against *A. clavatus* (MTCC No.5341). They are helpful as active pharmaceutical agents. In future further work on these compounds may be helpful for discover lead molecule.

Table 2: Antimicrobial Sensitivity Assay

Code	MIC (µg/mL)						
	antibacterial activity				antifungal activity		
	E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenus*	*C.albicans*	*A.niger*	*A.clavatus*
7a	500	500	200	500	1000	>1000	>1000
7b	500	250	250	500	1000	500	500
7c	1000	1000	62.5	500	500	500	500
7d	250	500	200	500	1000	1000	1000
7e	1000	62.5	250	250	200	>1000	>1000
7f	250	1000	500	62.5	500	500	500
7g	200	500	250	500	500	500	500
9a	1000	500	1000	500	>1000	100	500
9b	100	500	500	250	1000	100	1000
Ampicilin	100	100	250	100	-	-	-
Greseofulvin	-	-	-	-	500	100	100

E. coli: Escherichiacoli, P.aeruginosa: Pseudomonas aeruginosa, S.pyogenus: Strptococcus pyogenus, S. aureus: Staphpyococcusaureus, C.albicans: Candida.albicans, A.niger: Aspergillus niger, A.clavatus: Aspergillus clavatus.

4. CONCLUSION

We have synthesized novel derivatives of arylidine and hetroarylidine 2-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)amino)thiazol-4(5H)-one derivatives successfully in moderate yield. Structures of novel compounds were identified by ^{1}HNMR, ^{13}CNMR, Mass & IR analysis. All the synthesized compounds were evaluated for their antimicrobial activity containing two gram positive and two gram negative bacterial strains and three fungal strains by broth dilution method. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate activity. The best microbial activity was shown by 7a, 7c, 7d, 7e, 7f, 9a and 9b compounds.

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