

Synthesis and Antimicrobial Evaluation of Novel Azetidinones

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Abstract: 3-(4-Aminophenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione (**1**) undergoes facile condensation with different aromatic aldehydes to afford the corresponding 3-(4-(substituted benzylideneamino)phenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione (**2a-e**) in good yields. Cyclocondensation of compounds (**2a-e**) with chloroacetyl chloride yields 3-chloro-4- substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2H)-ylsulfonyl)phenyl)azetidin-2-one (**3a-e**). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: 3-(4-Aminophenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione, Schiff base, Azetidinone, Antibacterial activity.

Introduction

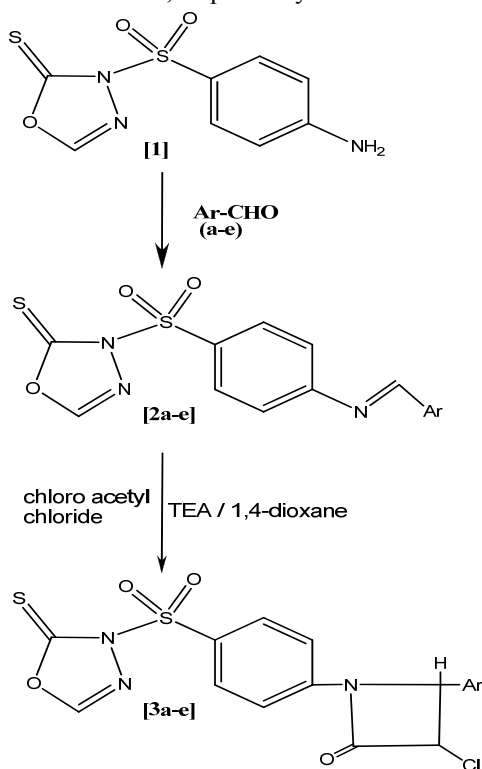
In recent years the Schiff bases have been studied extensively because of their remarkable biological activity^{1,3}. Literature assessment reveals that Schiff bases indicate that they have coordinating behaviors with the transition metal ions. Schiff bases also display biochemical and physiochemical effects⁴⁻⁷. The heterocyclic compounds such as, 4-thiazolidinones, azetidinone, pyrazole and 2-pyrrolidinones, 1,3,5-oxadiazine and tetrazole have prominent role in pharmaceutical⁸⁻¹³. The another moiety dihydrothieno[3,2-c]pyridine also have pharmaceutical activity¹⁴⁻¹⁶. If both these moiety clubbed into one molecule, it will be afford as good bioactive compound. Hence, it was thought of interest to merge both of azetidinone and 3-(4-aminophenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione moieties which may enhance the drug activity of compounds to some extent or they might possess some of the above mentioned biological activities. Hence the present communication comprises the synthesis of 3-chloro-4- substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2H)-ylsulfonyl)phenyl)azetidin-2-one (**3a-e**). The synthetic approach is shown in Scheme 1.

Experimental

All chemicals used were of laboratory grade. 3-(4-Aminophenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione was prepared by reported method¹⁷.

Measurement

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 ^1H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively.



Where Ar=(a)C₆H₅,(b)2-OH-C₆H₄, (c)4-OH-C₆H₄,(d)4-OCH₃-C₆H₄, (e)4-Cl-C₆H₄

Scheme 1. Synthetic approach

Preparation of 3-(4-(substituted benzylideneamino)phenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione (2a-e)

A mixture of 3-(4-aminophenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione (**1**), (0.01 mole) and the aromatic aldehydes (**a-e**) in ethanol (15 mL) was refluxed on a water bath for 2-3 h. 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 Table 1.

Preparation 3-chloro-4- substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2H)-ylsulfonyl)phenyl)azetidin-2-one (3a-e)

A mixture 3-(4-(substituted benzylidene amino) phenyl sulfonyl)-1,3,4-oxadiazole-2(3H)-thione (**2a-e**) (0.01 mole) in THF (30 mL) and triethyl amine (TEA) (0.004 mole) was dissolved in 1,4-dioxane (50 mL), cooled, and stirred. To this well stirred cooled solution of 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

48 h. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air dried. Recrystallization from ether/n-hexane gave 3-chloro-4- substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2*H*)-ylsulfonyl)phenyl)azetidin-2-one (**3a-e**), which were obtained in good yield. The yields, melting points and other characterization data of these compounds are given in Table 2.

Table 1. Analytical data and elemental analysis of compounds (**2a-e**)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* °C	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	C ₁₅ H ₁₁ N ₃ O ₃ S ₂ (345)	79	212-214	52.14	52.16	3.20	3.21	12.14	12.17	18.54	18.57
2b	C ₁₅ H ₁₁ N ₃ O ₄ S ₂ (361)	76	223-224	49.83	49.85	3.05	3.07	11.60	11.63	17.70	17.75
2c	C ₁₅ H ₁₁ N ₃ O ₄ S ₂ (361)	78	217-219	49.82	49.85	3.06	3.07	11.62	11.63	17.72	17.75
2d	C ₁₆ H ₁₃ N ₃ O ₄ S ₂ (375)	75	202-203	51.17	51.19	3.46	3.49	11.16	11.19	17.04	17.08
2e	C ₁₅ H ₁₀ N ₃ O ₃ S ₂ Cl (379.5)	76	214-216	47.42	47.43	2.62	2.65	11.04	11.06	16.86	16.88

*Uncorrected

Table 2. Analytical data and elemental analysis of compounds (**3a-e**)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* °C	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	C ₁₇ H ₁₂ N ₃ O ₄ S ₂ Cl (421)	72	212-214	48.38	48.40	2.85	2.87	9.94	9.96	15.18	15.20
3b	C ₁₇ H ₁₂ N ₃ O ₅ S ₂ Cl (436)	70	205-207	46.62	46.63	2.74	2.76	9.58	9.60	14.64	14.65
3c	C ₁₇ H ₁₂ N ₃ O ₅ S ₂ Cl (436)	69	211-213	46.61	46.63	2.75	2.76	9.59	9.60	14.64	14.65
3d	C ₁₈ H ₁₄ N ₃ O ₅ S ₂ Cl (451)	71	216-218	47.82	47.84	3.11	3.12	9.28	9.30	14.17	14.19
3e	C ₁₇ H ₁₁ N ₃ O ₄ S ₂ Cl 2 (454.5)	71	217-219	44.74	44.75	2.42	2.43	9.20	9.21	14.03	14.05

*Uncorrected

Biological Screening

Antibacterial activities

The 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. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 3e and 3d were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables 3.

Table 3. Antibacterial activity of compounds (**3a-e**)

Compounds	Gram +ve		Gram -ve	
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>E.coli</i>	<i>Klebsiella promioe</i>
3a	44	61	60	65
3b	45	62	61	67
3c	47	66	63	71
3d	51	72	70	78
3e	49	70	67	75
Tetracycline	55	79	74	84

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*. The antifungal activities of all the compounds (**3a-e**) were 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 1 mL. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120° C for 15 min at 15 atm pressure. These media 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:

$$\text{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate, Y = Area of colony in test plate. The fungicidal activity displayed by various compounds (**3a-e**) is shown in Table 4.

Table 4. Antifungal Activity of Compounds (**3a-e**)

Compounds	<i>Nigrospora Sp.</i>	<i>Aspergillus Niger</i>	<i>Botrydepladia Thiobromine</i>	<i>Rhizopus Nigricum</i>
3a	57	50	61	55
3b	59	52	62	59
3c	65	62	61	57
3d	71	66	72	63
3e	68	71	67	61

Results and Discussion

It was observed that 3-(4-aminophenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione (**1**) undergoes facile condensation with aromatic aldehydes to afford the corresponding 3-(4-(substituted benzylideneamino)phenylsulfonyl)-1,3,4-oxadiazole-2(3H)-thione (**2a-e**). The structures of **2a-e** were confirmed by elemental analysis and IR spectra showing an absorption band at 1630-1670 cm⁻¹ (C=N), 3030-3080 cm⁻¹ (C-H, of Ar.), 2815-2850cm⁻¹ (-OCH₃). ¹H NMR: 7.52 – 7.86 (8H, m) (Ar - H), 8.43-8.80 (1H, s) (-N=CH), 7.52-7.56(1H,s)(oxadiazole ring N=CH), 2d; 3.90 (3H, s) (-OCH₃). ¹³C NMR: 155.6-122.8 (Ar-12C), 190.4(-CS), 150.8 (oxadiazole ring), 160.3(-N=CH);2b: 55.5-56.7 (-OCH₃). The C, H, N analysis data of all compounds are presented in Table 1.

The structures assigned to 3-chloro-4- substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2H)-ylsulfonyl)phenyl)azetid-2-one (**3a-e**) were supported by the elemental

analysis and IR spectra showing an absorption bands at 1750-1760 (C=O of azetidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.). $^1\text{H NMR}$: 7.95–7.47(9H,m)(Ar - H), 7.52-7.56(1H,s) (oxadiazole ring N=CH), 5.19(1H,s)(N-C₂H), 5.49(1H,d)(C₃H), 3d; 3.90 (3H,s)(-OCH₃). $^{13}\text{C NMR}$: 122.5-142.9 (Ar-12C), 162.6(-CO), 190.3(-CS), 151.3 (oxadiazole ring), 67.6(C₂), 64.3 (C₃H), 3d; 55.5-56.7 (-OCH₃). The C, H, N, S analysis data of all compounds are presented in Table 2.

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.

Conclusion

We have developed novel and efficient synthesis of 3-chloro-4- substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2H)-ylsulfonyl)phenyl)azetidin-2-one (**3a-e**). All the newly synthesized compounds were shoe moderate antibacterial and antifungal activities.

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