

SYNTHESIS AND INVITRO ANTIBACTERIAL SCREENING OF SOME NEW AZOMETHINES DERIVED FROM SULPHONAMIDES

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ABSTRACT

Objective: The purpose of research was to synthesize the better antimicrobial compounds using different substituted aromatic aldehydes containing allyl and allyl oxy group are chosen as the starting material for synthesis of imines with sulphonamides helps to formation in presence of alcohol and acidic reagent.

Methods: Reagents used in the present study were of analytical grade and solvents were used after distillation. All the melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using pre coated TLC plates (MERCK) using n-hexane: ethyl acetate (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254 nm. IR spectra were recorded using KBr on Perkin Elmer spectrophotometer. ¹H NMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard and chemical shift values were expressed in ppm. Elemental analysis (CHN) was performed on Carlo Erba 1108.

Results: A new series of azomethines was synthesized by condensation of different sulphonamide derivatives with substituted aromatic aldehydes containing allyl and allyloxy group. The structures of these products were confirmed by physical and spectral analysis. The compounds were assayed for antibacterial activity against different human pathogens such as *E. coli*, *P. aeruginosa*, *S. aureus*, *B. subtilis*. All the compounds exhibited considerable inhibition against the bacteria tested.

Conclusion: Antibacterial activity observed for the synthesized azomethine compounds through the disc diffusion assay. The reference antibacterial drug was Streptomycin and Penicillin-G for *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis*. Synthesized imines show good biological activity and have the good yield.

Keywords: Antibacterial screening, Azomethines, Disc diffusion, *P. aeruginosa*, *S. aureus*, *B. subtilis*.

INTRODUCTION

The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistance to antibiotics. The lack of effective treatments is the main cause of this problem [1-2]. The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need [3]. Azomethine are some of the most widely used organic compounds. Sulphonamide derivatives have been subject to intensive studies, where a wide variety of those derivatives have been prepared and used in various biological and pharmacological fields. Azomethines are among the most studied sulphonamide derivatives which have been used for numerous biological application [4-5]. These types of derivatives are very important because of their varied structures and biological activities [6-7]. They are the important compound owing to their wide range of biological activities and industrial application. They have been found to possess the pharmacological activities such as antimicrobial [8-13], antipathogenic [14-15], antidepressant [16], antiviral [17-18], anticancer [19-20], Fungicide [21-22], bactericide [23-24], Cytotoxicity [25], herbicide [26], insecticide [27-28], antioxidant agent [29-30], antiproliferative [31-32].

The development of bacterial resistance to existing drugs is a major problem in antibacterial therapy and necessitates continuing research into new classes of antibacterials. It is evident that in azomethine derivatives the C=N linkage is an essential structural requirement for biological activity. These compounds are readily hydrolyzed under acidic conditions leading to active aldehydes which can act as alkylating agents. Many attempts have been made to synthesize characterize and to study biological activity of azomethine. In view of the conclusions drawn from the previous work and looking to the antimicrobial efficacy of sulphonamides like sulphanilimide, sulphamethoxazole, sulphathiazole & sulphadimidine moieties attached to aryl ring it seems logical to combine all these moieties together in a parent molecule. This study was aimed at exploring the

potential antimicrobial compounds containing an azomethine group (-CH=N).

MATERIALS AND METHODS

Chemistry

All chemicals and solvents, reagents used in the present study were of analytical grade and solvents were used after distillation. All the melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using pre-coated TLC plates (MERCK) using n-hexane: ethyl acetate (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254 nm. IR spectra were recorded using KBr on Perkin Elmer spectrophotometer. ¹H NMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard and chemical shift values were expressed in ppm. Elemental analysis (CHN) was performed on Carlo Erba 1108. Our general synthetic route leading to new azomethines involved the reaction between aromatic aldehydes containing allyl and allyloxy group with different sulphonamide derivatives is shown in scheme 1.

General procedure for the synthesis of azomethines

A solution of substituted aromatic aldehydes (0.01M: in 5 mL ethanol) was taken in a flask and sulphonamide derivatives (0.01M: : 5 mL ethanol) was slowly added with continuous stirring. The contents of the flask were refluxed for three hours and left over night. The reaction mixture was cooled in an ice bath and a drop of sulfuric acid was added to it. The azomethines base separated out, collected and further purified by recrystallization from ethanol.

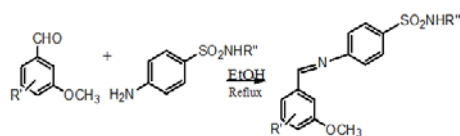
RESULTS

1(a) 4-[[[E)-(4-hydroxy-3-methoxyphenyl) methyldene] amino] benzenesulfonamide

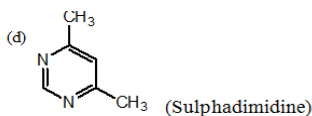
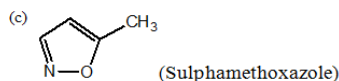
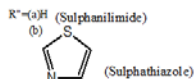
Recrystallization from ethanol: C₁₄H₁₄N₂O₄S; M. wt 306; Yield 58%; m. p. 200°C; colour-whitish yellow; IR (KBr) cm⁻¹ 3400 cm⁻¹ (O-H),

1670 cm^{-1} (CH=N), 1139 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,3H,Ar-H), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 2.2 (s,2H,SO₂NH₂). Anal. Calcd.(%):C=54.90, H=4.60, N=9.12, O=20.91, S=10.47.

1. General Scheme of the reaction



Where R' = (1) p-OH,
(2) p-CH₂=CH-OCH₂-NO₂,
(3) p-OH, m-CH₂-CH-CH₂.



Scheme

1(b) 4-[[4-hydroxy-3-methoxybenzylidene]amino]-N-(1,3 thiazol-2-yl) benzenesulfonamide

Recrystallization from ethanol: C₁₇H₁₅N₃O₄S₂; M. wt 389; Yield 72%; m. p.150°C; colour-yellow; IR (KBr) cm^{-1} 1620 (O-H), 1650 cm^{-1} (CH=N), 1115 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,3H,Ar-H), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 6.5-7.5 (m,2H,CH). Anal. Calcd.(%):C=52.40, H=3.91, N=10.70, O=16.52, S=16.47.

1(c) 4-[[4-hydroxy-3-methoxybenzylidene]amino]-N-(5-methylisoxazol-2-yl)benzenesulfonamide

Recrystallization from ethanol: C₁₈H₁₇N₃O₅S; M. wt 387; yield 98%; m. p.190°C; colour-pale yellow; IR (KBr) cm^{-1} 1640 (O-H), 1670 cm^{-1} (CH=N), 1149 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,3H,Ar-H), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 5.2 (s,1H,CH), 2.5 (s,3H,CH₃). Anal. Calcd.(%):C=52.30, H=4.01, N=10.70, O=16.52, S=16.47.

1(d) N-(4,6-dimethylpyrimidin-2-yl)-4-[[E)-(4-hydroxy-3-methoxyphenyl)methylidene] amino] benzene sulfonamide

Recrystallization from ethanol: C₂₀H₂₀N₄O₄S; M. wt 412; Yield 50%; m. p.110°C; colour-yellow; IR (KBr) cm^{-1} 1640 (O-H), 1660 cm^{-1} (CH=N), 1153 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,3H,Ar-H), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 5.2 (s,1H,CH), 2.5 (s,3H,CH₃). Anal. Calcd.(%):C=58.20, H=4.93, N=13.50, O=15.60, S=7.77.

2(a) 4-[[5-Methoxy-2-nitro-4-vinyloxymethyl-benzylidene)-amino]-benzenesulfonamide:

Recrystallization from ethanol: C₁₇H₁₇N₃O₆S; M. wt 391; Yield 66%; m. p.120°C; colour-yellow; IR (KBr) cm^{-1} 1617 (CH=N), 1598 cm^{-1} (NO₂), 1139 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 5.2-7.2 (m,2H,Ar-H), 5.4 (s,2H,CH), 6.5 (t,1H,CH), 4.2 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,2H,SO₂NH₂). Anal. Calcd.(%): C=52, H=4.55, N=10.70, O=24.57, S=8.19.

2(b) 4-[[5-Methoxy-2-nitro-4-vinyloxymethyl-benzylidene)-amino]-N-thiazol-2-yl-benzene sulfonamide

Recrystallization from ethanol: C₂₀H₁₈N₄O₆S₂; M. wt 474; Yield 70%; m. p.110°C; colour- brown yellow; IR (KBr) cm^{-1} 1627 cm^{-1}

(CH=N), 1588 cm^{-1} (NO₂), 1190 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 5.2-7.2 (m,2H,Ar-H), 5.4 (s,2H,CH), 6.5 (t,1H,CH), 4.2 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 6.5-7.5 (m,2H,CH). Anal. Calcd.(%): C=50.30%, H=3.82, N=11.81, O=20.55, S=13.51.

2(c) N-(4,6-Dimethyl-pyrimidin-2-yl)-4-[[5-methoxy-2-nitro-4-vinyloxymethyl-benzylidene)-amino]-benzenesulfonamide

Recrystallization from ethanol: C₂₃H₂₃N₅O₆S; M. wt 520; yield 60%; m. p.130°C; colour- brown yellow; IR (KBr) cm^{-1} 1620 cm^{-1} (CH=N), 1542 cm^{-1} (NO₂), 1139 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 5.2-7.2 (m,3H,ArH), 5.4 (s,2H,CH), 6.5 (t,1H,CH), 2 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 3.8 (s,1H,CH), 2.8-3 (s, 6H, CH₃). Anal. Calcd. (%):C=55.50, H=4.68, N=14, O=19.37, S=6.44.

2(d) 4-[[4-Allyloxy-5-methoxy-2-nitro-benzylidene)-amino]-N-(5-methyl-isoxazol-3-yl)-benzene sulfonamide

Recrystallization from ethanol: C₂₁H₂₀N₄O₇S; M. wt 472; Yield 70%; m. p.120°C; colour- brown yellow; IR (KBr) cm^{-1} 1640 cm^{-1} (CH=N), 1540 cm^{-1} (NO₂), 1120 cm^{-1} (S=O); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 5.2-7.2 (m,2H,Ar-H), 5.4 (s,2H,CH), 6.5 (t,1H,CH), 4.2 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 5.2 (s,1H,CH), 2.5 (s,3H,CH₃). Anal. Calcd.: C=53.30, H= 4.35, N=11.80, O= 23.76, S= 6.79.

3(a) 4-[[3-Allyl-4-hydroxy-5-methoxy-benzylidene)-amino]-benzenesulfonamide

Recrystallization from ethanol: C₁₇H₁₈N₂O₄S; M. wt 346; Yield 72%; m. p.75°C; colour- yellow; IR (KBr) cm^{-1} 3430 (O-H), 1630 cm^{-1} (CH=N); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,2H,Ar-H), 4.96 (d,2H,CH), 6.4 (p,1H,CH), 3.5 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 2.2 (s,2H,SO₂NH₂). Anal. Calcd.(%):C=58.90, H=5.28, N=8.09, O=18.47, S=9.27.

3(b) 4-[[3-Allyl-4-hydroxy-5-methoxy-benzylidene)-amino]-N-thiazol-2-yl-benzenesulfonamide

Recrystallization from ethanol: C₂₀H₁₉N₃O₄S; M. wt 429; Yield 80%; m. p.65°C; colour- creamish white; IR (KBr) cm^{-1} 3410 (O-H), 1650 cm^{-1} (CH=N); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,2H,Ar-H), 4.96 (d,2H,CH), 6.4 (p,1H,CH), 3.5 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 6.5-7.5 (m,2H,CH). Anal. Calcd.(%): C=55.90, H=4.49, N=9.70, O=14.98, S=14.93.

3(c) 4-[[3-Allyl-4-hydroxy-5-methoxy-benzylidene)-amino]-N-(5-methyl-isoxazol-3-yl)-benzene sulfonamide

Recrystallization from ethanol: C₂₁H₂₁N₃O₅S; M. wt 427; Yield 95%; m. p.70°C; colour- creamish white; IR (KBr) cm^{-1} 3400 (O-H), 1670 cm^{-1} (CH=N); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,2H,Ar-H), 4.96 (d,2H,CH), 6.4 (p,1H,CH), 3.5 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 5.2 (s,1H,CH), 2.5 (s,3H,CH₃). Anal. Calcd.(%): C=59.00, H=4.98%, N=9.80, O=18.70, S=7.51.

3(d) 4-[[3-Allyl-4-hydroxy-5-methoxy-benzylidene)-amino]-N-(4,6-dimethyl-pyrimidin-2-yl)-benzene sulfonamide

Recrystallization from ethanol: C₂₃H₂₄N₄O₄S; M. wt 452; Yield 80%; m. p.72°C; colour- creamish white; IR (KBr) cm^{-1} 3450 (O-H), 1640 cm^{-1} (CH=N); ^1H NMR(DMSO d_6) δ ,ppm: 3.75 (s,3H,CH), 3.0 (s,1H,OH), 5.2-7.2 (m,2H,Ar-H), 4.96 (d,2H,CH), 6.4 (p,1H,CH), 3.5 (d,2H,CH), 8.4 (s,1H,CH=N), 7.6 (t,2H,CH), 7.9 (t,2H,CH), 4.2 (s,1H,SO₂NH), 3.8 (s,1H,CH), 2.8-3 (s,6H,CH₃). Anal. Calcd.(%):C, C=61.10, H=5.30, N=12.38, O=14.14, S=7.09.

DISCUSSION

All the compounds were screened for their in vitro antibacterial activity at Birla Institute of Medical Research and College of Life Sciences, Gwalior, against 24h old cultures of bacterial pathogens. Antibacterial activity was determined against Gram-ve bacteria i. e. *Escherichia coli* & *Pseudomonas aeruginosa* and Gram+ve bacteria i. e. *Staphylococcus aureus* & *Bacillus subtilis*, bacterial strains using

disc diffusion assay. For this sterile filter paper disc (8 mm) impregnated with fixed doses (500 µg/mL, 1000 µg/mL) of synthesized compounds under investigation were placed upon the seeded petri dishes. Similar plates were prepared for the standard drugs, the reference antibacterial drug was Streptomycin for Gram – ve bacteria and Penicillin-G was used for Gram+ve bacteria.

Dimethyl formamide is used as control solvent. The plates were allowed to stay for 24h at 37°C for bacterial strains. The zone of inhibition, observed around the disc after incubation were measured. The compounds show less activity at 500 µg/disc concentrations and exhibited promising activities at 1000 µg/disc concentration, are presented in table 1.

Table 1: Results of *in-vitro* antibacterial activity observed for the synthesized imine compounds through disc diffusion assay

S. No.	Compound	Zone of Inhibition	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>
1.	1(a)	1	-	-	-	-
		2	16	-	12	14
2.	1(b)	1	-	-	-	-
		2	10	-	14	10
3.	1(c)	1	10	-	14	12
		2	20	12	28	14
4.	1(d)	1	-	-	-	-
		2	16	-	16	16
5.	2(a)	1	-	-	-	-
		2	10	-	12	-
6.	2(b)	1	-	-	-	-
		2	16	-	16	16
7.	2(c)	1	11	-	-	10
		2	22	16	16	16
8.	2(d)	1	-	-	-	-
		2	16	-	16	16
9.	3(a)	1	10	-	16	-
		2	16	14	22	12
10.	3(b)	1	-	-	14	-
		2	10	14	20	12
11.	3(c)	1	12	10	14	12
		2	24	20	28	24
12.	3(d)	1	-	-	-	-
		2	15	14	14	12
	Control (Std-Streptomycin)		28	24		
	Penicillin-G				38	32
	Blank(DMF)		-	-	-	-

1= 500µg/mL, 2=1000 µg/mL, (-)= No effect

CONCLUSION

In the present work, 12 new compounds were synthesized. The synthetic route for the compounds is outlined in scheme-1. Equimolar quantities of these aromatic amines and sulphonamides derivatives was reacted for the first time in presence of mild acidic condition give azomethine in good to excellent yield. All the synthesized compounds were purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FTIR, ¹HNMR data and elemental analyzer. The IR spectra of the synthesized compounds showed the presence azomethine group of C=N stretching bands at 1600-1690 cm⁻¹. In ¹HNMR spectra, all the compounds were characterized by the presence of imino proton (CH=N) at 8.1-8.5 ppm. All compounds gave satisfactory elemental analysis.

In table 1 show result of *in-vitro* antibacterial activity observed for the synthesized azomethine compounds through disc diffusion assay. The reference antibacterial drug was Streptomycin for Gram – ve bacteria i. e. *E. coli*, and *P. aeruginosa*. Penicillin-G was used as reference antibacterial drug for Gram+ve bacteria i. e. *S. aureus* and *B. subtilis*. The inhibition depends on type of bacterial strain, solvent as well as the structure of compound. All the azomethine compounds contain the same central moiety with different side chains. So in a particular solvent, for a particular effect side chains play important role in inhibition. Azomethines containing sulphamethoxazole as moiety in (1c,2c,3c) show excellent yield and exhibited remarkable inhibition in all bacterial strains. The presence of electron withdrawing substitution on aromatic ring increases the antibacterial activity of different derivatives. Azomethines containing sulphathiazole (1b,2b,3b) and sulphanilimide (1a,2a,3a) as moiety show average yield and moderate inhibition activity while

azomethines containing sulphadimidine (1d,2d,3d) as moiety show minimum yield and less inhibition activity.

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