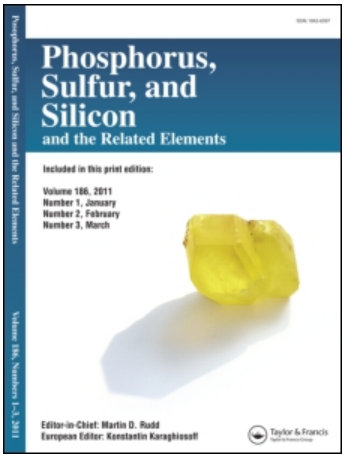

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SYNTHESIS OF NOVEL SULPHONAMIDES AND EVALUATION OF THEIR ANTIBACTERIAL EFFICACY

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SYNTHESIS OF NOVEL SULPHONAMIDES AND EVALUATION OF THEIR ANTIBACTERIAL EFFICACY

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*4-(4′-sulphanilyl)-1-phenyl pipearzine (**2**) has been prepared by ther reaction of N-acetyl sulphanilyl chloride (ASC) with 1-phenyl piperazine followed by the hydrolysis of the product by ethanolic HCl. The hydrolyze product on facile condensation reaction with aromatic aldehydes yields Schiff bases / anils / azomethines (**3a–h**). These anils on cyclo condensation reaction with chloro acetyl chloride and thio glycolic acid (mercapto acetic acid) yields 2-azetidinones and 4-thiazolidinones respectively. Biological screening of the prepared compounds have been screened on some strains of bacteria.*

Keywords: 2-Azetidinones; 4-thiazoidinones; cyclo-condensation reaction; facile condensation; N-acetyl sulphanilyl chloride

The development of sulphonamides is one of the most fascinating and informative fields in medicinal chemistry, highlighting the roles of skillful planning and serendipity in drug research. The discovery of sulphonamide marked the beginning of the chemotherapeutic era by making possible a direct attack on microbial infections.[1] Sulphonamide antibacterials continued to be used because they are effective, inexpensive and free of super infection problems of the broad spectrum antibiotics.[2]

As a part of surge of interest in heterocycles that have been explored for developing pharmaceutically important molecules 4-thiazolidinones[3–5] and 2-azetidinones[6–9] have played an important role in medicinal chemistry. Moreover, they have been studied extensively because of their ready accessibility, diverse chemical reactivity, and broad spectrum of biological activities.

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Also, piperazine derivatives plays pivotal role in medicinal chemistry due to its application in the therapy of functional diseases.[10] During the past years considerable evidence has been accumulated to demonstrate the efficiency of substituted 2-azetidinones, 4-thiazolidinones, piperazine derivatives, and sulphonamides.[11–13]

Keeping in view of biological importance of these groups, we replace them by piperazine moiety at N^4-position of sulphanilamide and 2-azetidinone/4-thiazolidinone at N^1-position in sulphanilamide and our approach clearly shows the biological importance of the coupled products. The research work is scanned in Scheme 1.

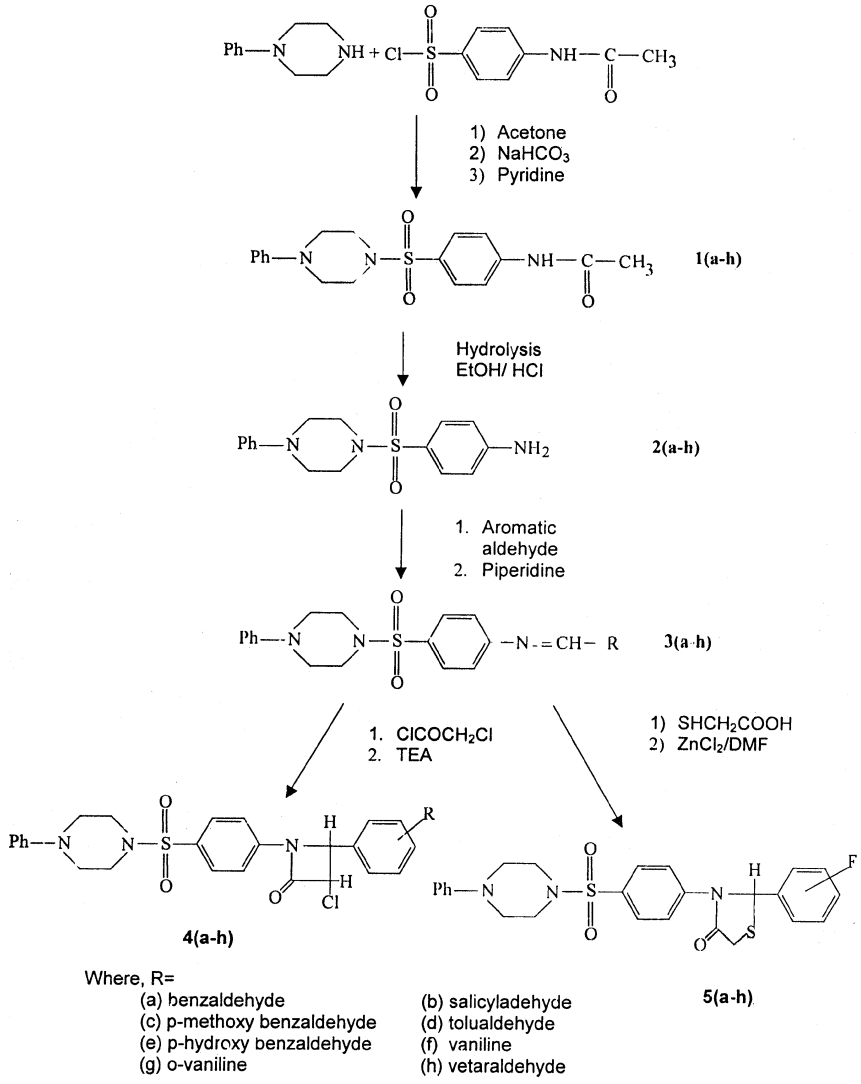
ANTIMICROBIAL ACTIVITY

Antibacterial Activity

Antibacterial activities of all the compounds were studied against Gram positive bacteria (Bacillus subtillis and staphylococcus aureus) and Gram negative bacteria (E. coli and Salmonella typhi) at a concentration of 50 μg/ml by agar cup plate method.[14] Methanol system was used as control in this method. Under similar conditions usinf penicillin and sulphanilamide as a standard comparison carried out control experiment. The area of inhibition of zone is measured in centimeters. Compounds **4c**, **4d**, **4h**, **5b**, **5d**, and **5f** were found more active against the above microbes. Other compounds found to be less or moderate active than the standards (Tables I and II).

TABLE I Antibacterial Activity of Compounds **4a–h**

	Zone of Inhibition			
	Gram +ve		Gram −ve	
Compounds	Bacillus subtillis	Staphyloccous aureus	Salmonella typhi	E.coli.
4a	54	60	43	65
4b	45	67	52	69
4c	70	78	78	62
4d	82	72	68	78
4e	45	65	43	75
4f	65	60	62	49
4g	68	55	68	58
4h	80	70	74	67
Penicillin	85	65	75	73
Sulphanilamide	78	75	82	69



SCHEME 1

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra in $CDCl_3$ on Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. The required N-acetyl

TABLE II Antibacterial Activity of Compounds **5a–h**

	Zone of Inhibition			
	Gram +ve		Gram −ve	
Compounds	Bacillus subtillis	Staphyloccous aureus	Salmonella typhi	E.coli.
5a	55	67	67	54
5b	80	70	75	69
5c	76	56	67	57
5d	68	77	75	78
5e	65	78	80	67
5f	64	70	80	77
5g	55	59	65	70
5h	68	61	70	80
Sulphanilamide	78	75	82	69

sulphanilyl chloride (ASC) was prepared by reported method.[15] All chemicals used were of laboratory grade.

Preparation of 4-(4′-acetylaminobenzene Sulphonyl)-1-phenyl Piperazine (1)

General Procedure

1-Phenyl piperazine (0.05 mmol) was dissolved in mixture of 40 ml anhydrous acetone and 1 ml of dry pyridine in a 250 ml flask, and 11.67 g (0.05 mmol) of pure ASC slowly was added. Sodium bicarbonate was added as an acid acceptor. The reaction mixture was set aside overnight and almost pure 4-(4′-acetylaminobenzene sulphonyl)-1-phenyl piperazine (**1**) was filtered off, washed with cold water, and air dried. It was then recrystallized from methylated spirit to give white product (**1**) in 70% yield.

Preparation of 4-(4′-sulphanilyl)-1-phenyl Piperazine (2)

General Procedure

4-(4′-Acetylaminobenzene sulphonyl)-1-phenyl piperazine (**1**) was hydrolyzed by refluxing with 75 ml of ethanol containing 15 ml of concentrated HCl for 4–5 h. It was then poured into ice-cold water and finally made just alkaline with liq. ammonia. The resultant product 4-(4′-sulphanilyl)-1-phenyl piperazine (**2**) was filtered off, washed with water, and air dried. It was then recrystallizd from ethanol to give product (**2**) in 65% yield.

Preparation of Schiff Bases (3a–h)

General Procedure

A mixture of equimolar amount (0.01 mmol) of 4-(4′-sulphanilyl)-1-phenyl piperazine (**2**) and the substituted benzaldehydes in ethanol (40 ml) and piperidine (0.3 ml) was refluxed for 5 h in a water bath. The reaction mixture was concentrated, cooled, and poured into water; the solid obtained was filtered and recrystallized from ethanol to give white Schiff base (**3a–h**). It was obtained in 60–65% yield.

Preparation of 2-Azetidinones (4a–h)

General Procedure

A mixture of Schiff base (**3a–h**) (0.002 mmol) and triethyl amine (TEA) (0.004 mmol) was dissolved in 1,4-dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution chloro acetyl chloride (0.004 mmol) was added drop wise within a period of 20 min. The reaction mixture was then stirred for an additional 3 h and left at room temperature for 48 h. The resultant mixture was concentrated, cooled, poured into ice cold water, then air dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethyl acetate: 70% benzene as eluent. Recrystallization from ether/n-hexane gave 2-azetidinones (**4a–h**), which were obtained in 55–60% yield.

Preparation of 4-Thiazolidinones (5a–h)

General Procedure

A mixture of Schiff bases (**3a–h**) (0.01 mmol) in THF (30 ml) and mercapto acetic acid (0.01 mmol) with a pinch of anhydrous $ZnCl_2$ was refluxed for 12 h in an oil bath. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using benzene: chloroform (8:2, v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol (50–60% yield).

All the compounds [(**4a–h**) and (**5a–h**)] were characterized by analytical and spectral data (Tables III and IV) of the compounds is assigned in Scheme 1.

RESULTS AND DISCUSSION

N-acetyl sulphanilyl chloride (ASC) was reacted with 1-phenyl piperazine to give 4-(4′-acetylaminobenzene sulphonyl)-1-phenyl piperazine

TABLE III Analytical and Spectral Data of Compounds **4a–h**

Compounds	Molecular formula	Yield (%)	M.P. (°C)	% Analysis found(calcd.) %C	%H	%N	%S	PMR (δ,ppm)
4a	$C_{25}H_{24}N_3O_3SCl$	65	162	62.0 [62.3]	4.95 [4.98]	8.70 [8.72]	6.60 [6.65]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (15H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H)
4b	$C_{25}H_{24}N_3O_4SCl$	53	158	60.0 [60.3]	4.80 [4.82]	8.80 [8.84]	6.40 [6.43]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (14H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H) 3.4(1H,s,OH)
4c	$C_{26}H_{25}N_3O_3SCl$	60	145	62.5 [63.0]	5.20 [5.24]	8.45 [8.48]	6.45 [6.46]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (14H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H) 3.7 (3H, s, OCH_3)
4d	$C_{26}H_{26}N_3O_4SCl$	56	170	60.5 [61.0]	5.05 [5.08]	8.20 [8.27]	6.25 [6.26]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (14H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H) 1.3 (3H, s, CH_3)
4e	$C_{25}H_{24}N_3O_4SCl$	49	185	60.0 [60.3]	4.80 [4.82]	8.40 [8.44]	6.40 [6.43]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (14H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H) 3.5 (1H, s, OH)
4f	$C_{26}H_{26}N_3O_5SCl$	48	135	59.0 [59.2]	4.90 [4.93]	7.95 [7.96]	6.05 [6.07]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (13H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H) 3.7 (3H, s, OCH_3) 4.4 (1H, s, OH)
4g	$C_{26}H_{26}N_3O_5SCl$	56	168	59.0 [59.2]	4.90 [4.93]	7.95 [7.96]	6.05 [6.07]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (13H, m + d,aromatic, C_4H) 9.2 (1H, d, C_3H) 3.7 (3H, s, OCH_3) 4.4 (1H, s, OH)
4h	$C_{27}H_{28}N_3O_5SCl$	52	148	59.5 [59.8]	5.15 [5.17]	7.75 [7.76]	5.90 [5.91]	2.2–3.2 (8H, t, $4CH_2$), 6.2–7.8 (13H, m + d, aromatic, C_4H) 9.2 (1H, d, C_3H) 3.8 (6H, s, $2OCH_3$)

TABLE IV Analytical and Spectral Data of Compounds **5a–h**

Compounds	Molecular formula	Yield (%)	M.P. (°C)	% Analysis found(calcd.) %C	%H	%N	%S	PMR (δ,ppm)
5a	$C_{25}H_{25}N_3O_3S_2$	61	140	62.5 (62.6)	5.20 (5.22)	8.75 (8.77)	13.0 (13.4)	2.2–3.2 (10H, t, $5CH_2$), 6.2–7.8 (14H, m, aromatic) 9.2 (1H, s, CH)
5b	$C_{25}H_{25}N_3O_4S_2$	63	145	60.5 (60.6)	5.00 (5.05)	8.45 (8.48)	12.5 (12.9)	2.2–3.2 (10H, t, $5CH_2$), 6.2–7.8 (13H, m, aromatic) 9.2 (1H, s, CH) 3.4 (1H, s, OH)
5c	$C_{26}H_{27}N_3O_3S_2$	58	154	63.0 (63.3)	5.45 (5.48)	8.50 (8.52)	12.95 (13.0)	2.2–3.2 (10H, t, $5CH_2$), 3.7 (3H, s, OCH_3) 6.2–7.8 (13H, m, aromatic) 9.2 (1H, s, CH)
5d	$C_{26}H_{27}N_3O_4S_2$	70	138	61.0 (61.3)	5.25 (5.30)	8.20 (8.25)	12.5 (12.6)	1.3 (3H, s, CH_3), 2.2–3.3 (10H, t, $5CH_2$), 6.7–8.5 (13H, m, aromatic) 9.2 (1H, s, CH)
5e	$C_{25}H_{25}N_3O_4S_2$	62	168	60.5 (60.6)	5.00 (5.05)	8.45 (8.48)	12.5 (12.9)	2.2–3.2 (10H, t, $5CH_2$), 6.8–8.2 (13H, m, aromatic) 9.2 (1H, s, CH) 3.5 (1H, s, OH)
5f	$C_{26}H_{27}N_3O_5S_2$	49	170	59.5 (59.4)	5.10 (5.14)	8.05 (8.00)	12.0 (12.2)	2.2–3.2(10H, t, $5CH_2$), 6.2–7.8 (12H, m, aromatic) 9.2 (1H, s, CH) 3.7 (3H, s, OCH_3) 4.4 (1H, s, OH)
5g	$C_{26}H_{27}N_3O_5S_2$	53	152	59.0 (59.4)	5.15 (5.14)	7.95 (8.00)	12.0 (12.2)	2.2–3.2 (10H, t, $5CH_2$), 6.2–7.8 (12H, m, aromatic) 9.2 (1H, s, CH) 3.7 (3H, s, OCH_3) 4.4 (1H, s, OH)
5h	$C_{27}H_{29}N_3O_5S_2$	65	166	60.0 (60.1)	5.35 (5.57)	7.75 (7.79)	11.5 (11.9)	2.2–3.2 (10H, t, $5CH_2$), 6.2–7.8 (12H, m, aromatic) 9.2 (1H, s, CH) 3.8 (6H, s, $2OCH_3$)

(**1**) by the reported method.[16] It can be hydrolyzed to 4-(4′-sulphanilyl)-1-phenyl piperazine (**2**) by ethanolic HCl.[17] It was characterized by elemental analysis, IR spectral studies, and NMR spectral studies. The IR spectra of the compound (**2**) show the bands at 3390 and 3410 cm^{-1} for-NH_2 group.

This hydrolyzed product (**2**) was dissolved in ethanol and was reacted with aromatic aldehydes in the presence of piperidine to yield Schiff bases (**3a–h**). These Schiff bases (**3a–h**) were then characterized by the elemental analysis, IR spectral studies, and NMR spectral studies. The IR spectra of Schiff bases show the prominent band at 1630 cm^{-1} for the azomethine group.[18]

These Schiff bases on cyclo-condensation reaction with chloro acetyl chloride afford 2-azetidinone (**4a–h**) and with thio-glycolic acid afford 4-thiazolidinone (**5a–h**) respectively. The structures of both these compounds (**4a–h**) and (**5a–h**), respectively, have been confirmed by elemental analysis, IR spectral studies, and NMR spectral studies. These compounds shows the band at 1690 cm^{-1} for cyclic >C=O group.[18] All the compounds show the NMR signals for different kinds of protons at their respective positions. The data are shown in Tables III and IV.

The antibacterial activity of both the series (**4a–h**) and (**5a–h**), respectively, have been carried out against some strain of bacteria. The results show that the prepared compounds are toxic against the bacteria. The comparison of the antibacterial activity of these compounds with penicillin and sulphanilamide shows that these compounds have almost similar activity.

The C,H,N,S analysis of all the compounds of the series are presented in Tables III and IV. The values are consistent with their predicted structure (Scheme 1).

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