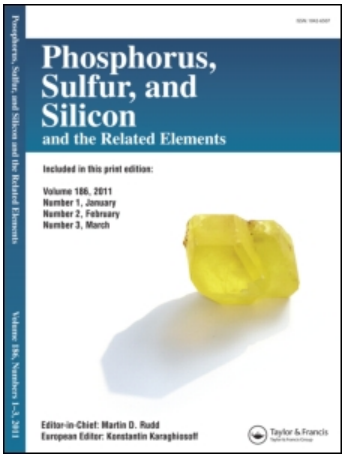

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Synthesis of Some New 4-{2-[(Aryl)amino]-1,3-thiazol4-yl}benzene-1,2-diols as Possible Antibacterial and Antifungal Agents

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Some new 4-{2-[(aryl) amino]-1,3-thiazol-4-yl}benzene-1,2-diols are prepared and characterized by spectral analysis. The newly prepared compounds are studied for their antibacterial and antifungal activity. Interestingly, almost all the compounds are found to possess promising antibacterial and antifungal activity against all tested microorganisms.

Keywords Antibacterial; antifungal; thiazole

Heterocycle containing a thiazole ring system are found to exhibit a wide spectrum of biological activities, including antibacterial and antifungal activities and many thiazole-containing compounds are reported to have herbicidal, fungicidal, antitubercular, antiallergic, antianaphylactic, antiarthritic antibiotic, antiviral, anti-inflammatory, analgesic and psychotropic agents.[1–14] 4-(chloroacetyl)-catechol is an important moiety in broncho-plasmolytic agents such as Adrenaline, Nor-adrenaline, Isoprenaline and Cobefrin.[15,16] As a part of our research program to find potent thiazole-containing antimicrobial agents,[17] we aimed at synthesizing new thiazoles starting from 4-(chloroacetyl) catechol and to study their antimicrobial activity.

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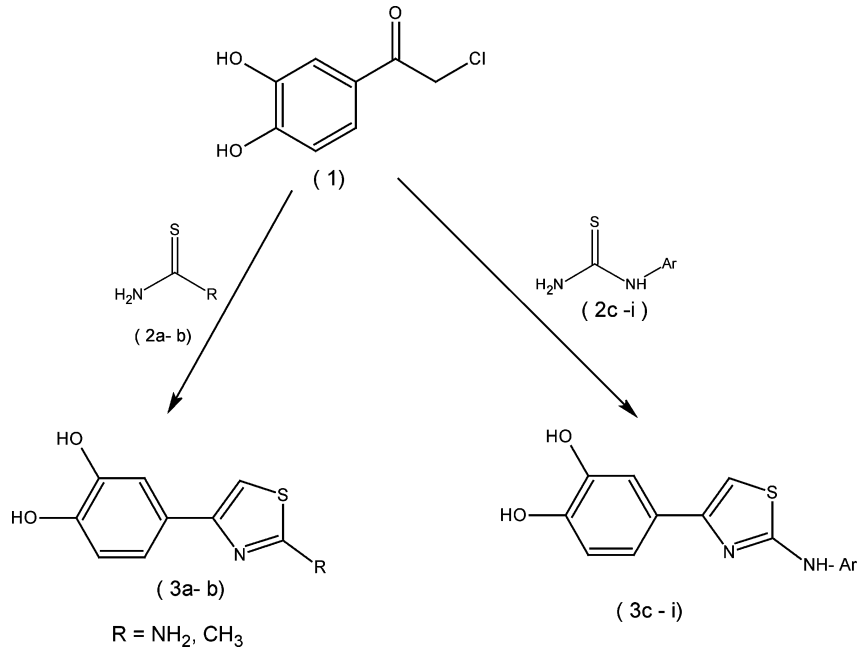
RESULTS AND DISCUSSION

In the present investigation, some new 4-{2-[(aryl) amino]-1,3-thiazol-4-yl}benzene-1,2-diol (**3a–i**) are prepared by reacting 4-(chloroacetyl) catechol (1) with thiourea (**2a**), thioacetamide (**2b**), and various N-aryl substituted thioureas (**2c–i**) by following the classical Hantzsch synthesis (Scheme 1). 4-(chloroacetyl)-catechol (**1**) is prepared by reacting catechol with chloroacetyl chloride.[18] Substituted thioureas are synthesized according to the standard literature procedure.[19] We have attempted to synthesize mono and bis-ethers **3a–i** by reacting with alkyl iodide and dimethylsulphate. In both cases, we ended up with impure products. Mass analysis revealed that along with a hydroxy-protected product, an amino-protected product also formed. We have not further attempted to get pure products. For this reason, this limited our study in the synthesis and antimicrobial evaluation of 4-{2-[(aryl) amino]-1,3-thiazol-4-yl}benzene-1,2-diols only.

The IR spectrum of **3i** exhibited absorption bands at 3757.1 cm^{-1}, and 3679.9 cm^{-1} is due to two phenolic —OH groups. Absorption bands 1604.7 cm^{-1}, 1523.7 cm^{-1}, and 1323.1 cm^{-1} are due to C—O, —C=N-, and —C=S-functional groups, respectively. The ^{1}H-NMR spectrum of



SCHEME 1

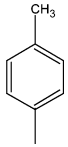
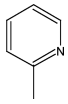
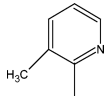
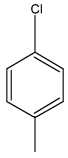
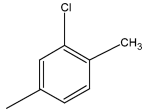
3i showed two singlets at δ 6.8 and δ 6.9 that are due to two phenolic −OH protons, a singlet at δ 8.06 is due to an aromatic proton, and one doublet of a doublet at δ 7.89 is due to an aromatic protons. A multiplet at δ7.41–7.31 due to the aromatic protons on the benzene ring bearing bromine. A singlet at δ 8.16 due to an aromatic proton on the thiazole ring. A singlet at 4.8 is due to a NH-proton. The mass spectrum of **3i** showed m/z 363 in accordance with its molecular formula $C_{15}H_{11}BrN_2O_2$. The ^{13}C NMR (DMSO-d_6) of **3f** showed peaks at 22.41, 103.85, 108.87, 113.43, 115.84, 116.14, 117.21, 124.64, 140.34, 145.42, 145.85, 146.95, 149.75, and 160.16, which accounts for 15 carbon atoms present in the molecule. The experimental data of other compounds are presented in Table I. The spectral data are presented in Table II.

An antibacterial study carried out for **3a–i** reveals that except for **3c** and **3d**, all other compounds possess excellent antibacterial activity against all tested organisms. Even though the observed antibacterial activity cannot be related to the variation in the N-substitution at thiazole moiety, the combination of potential thiaz moiety with catechol may be the reason for the excellent antibacterial activity. However, antifungal study results reveal that compound **3c** is most active amongst all. A known antifungal agent N-[4-(4-chlorophenyl)-2-thiazolyl salicylamide[20] contains the 4-chlorophenyl moiety. The compound **3g** that contains the 4-chlorophenyl moiety has also shown good antifungal activity. Hence, we can conclude that the higher activity of compound **3c** may be attributed to the N- (3-chorophenyl) moiety. The higher antifungal activity of **3e** may be due to the presence of a potent pyridine moiety. The compounds **3a**, **3f**, and **3i** are found to be least active. Other compounds have shown good to moderate antifungal activity.

Antibacterial Activity

We investigated the newly synthesized 4-{2-[(aryl) amino]-1,3-thiazol-5-yl} benzene-1,2-diol (**3a–i**) for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphyllococcus aureus* (ATTC-25923), *Psuedomonus aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (Recultered) bacterial strains by the disc diffusion method.[21–23] The discs measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 discs were dispensed to each screw-capped bottle and sterilized by dry heat at 140°C for an hour. The test compounds were prepared with different concentrations using Dimethylformamide (DMF). One mL containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in a nutrient agar

TABLE I Characterization Data of 4-{2-[(Aryl)amino]-1,3-thiazol-4-yl}benzene-1, 2-diol (3a–i)

Compound no.	R, AR	M.p. (°C)	Yield (%)	Mol. formula	% Nitrogen	
					Found	Calcd.
3a	$R = NH_2$	235–236	78	$C_9H_8N_2O_2S$	13.25	13.45
3b	$R = CH_3$	230–232	82	$C_9H_9NO_2S$	6.68	6.78
3c		200–202	90	$C_{15}H_{11}ClN_2O_2S$	8.81	8.79
3d		248–250	86	$C_{16}H_{14}N_2O_2S$	9.39	9.28
3e		260–262	78	$C_{14}H_{11}N_3O_2S$	14.78	14.73
3f		>260	72	$C_{15}H_{13}N_3O_2S$	14.10	14.04
3g		223–225	80	$C_{15}H_{11}ClN_2O_2S$	8.80	8.79
3h		220–222	80	$C_{16}H_{13}ClN_2O_2S$	8.48	8.42
3i		210–212	52	$C_{15}H_{11}BrN_2O_2S$	7.68	7.71

[a]Compounds showed satisfactory microanalysis.
[b]Reported yields are after recrystallisation.
[c]The compounds were crystallized form ethanol/dimethylformamide.

medium separately seeded with fresh bacteria. The incubation was carried out at 37°C for 24 h. Ampicillin was used as standard drug. Ampicillin has 16–22 mm inhibition length for *Escherichia coli* and 27–35 mm inhibition length for *Staphyllococcus aureus* at the concentration of 10 μg/mL. Solvent and growth controls were kept, and the zones of inhibition and minimum inhibitory Concentrations (MIC) were noted.

TABLE II Spectral Characterization Data of the Compounds

Compound no.	IR (cm^{-1})	^{1}H-NMR (δ, ppm)	^{13}C-NMR (δ, ppm)	Mass (EIMS, m/z)
3a	3757 cm^{-1} (phenolic-OH group), 3456 cm^{-1} (—NH_2), 1647 cm^{-1} (C—O), 1531.4 cm^{-1} (—C=N—), 1377.1 cm^{-1} (—C=S—)	—	—	m/z: 209 (100%, M^1), 193 (42%, M-NH_2), 166 (36%, C $_8H_6O_2S$)
3b	3600–3500 1 cm^{-1} (broad, two phenolic —OH group), 2862.2 cm^{-1} and 2788.9 cm^{-1} (—CH_3), 1612 cm^{-1}(C—O), 1527.5 cm^{-1}(—C=N—), 1373.2 cm^{-1} (—C=S—)	—	—	—
3f	3224.8 cm^{-1} (—NH—), 1608.5 cm^{-1}(C—O), 1531.4 cm^{-1} (—C=N—), 1338.5 cm^{-1} (—C=S—)	δ2.55 (s, 3H, —CH_3), δ7.3 (s, 1H, Ar-OH), δ7.29 (s, 1H, Ar-OH), δ 6.82$_{(J=8.4)}$ (d, 1H, Ar-H), δ 6.97$_{(J=7.5)}$ (d, 1H, Ar-H), δ 7.2$_{(J=7.8)}$ (d, 1H, Ar-H), δ7.17 (s,thiazole-H), δ7.80 (t,1H, Ar-H) 12.5(br s, 1H, —NH—)	22.41, 103.85, 108.87, 113.43, 115.84, 116.14, 117.21, 124.64, 140.34, 145.42, 145.85, 146.95, 149.75, 160.16	m/z: 299 (80%, M^+), 207 (32%, $C_9H_8N_2O_2S$), 230 (6%, $C_7H_7BrN_2S$), 166 (26%, $C_8H_6O_2S$)
3i	3757.1 cm^{-1} and 3679.9 cm^{-1} (two phenolic —OH group), 1604.7 cm^{-1} (C—O), 1523.7 cm^{-1} (—C=N—) nd 1323.1 cm^{-1} (—C=S—)	δ6.8 (s, 1H,Ar-OH), δ 6.9 (s, 1H, Ar-OH), δ 8.06 (s, 1H, Ar-H), δ7.89 (dd, 1H, Ar-H), δ7.41–7.31 (m, 4H, Ar-H), δ8.16 (s, thiazole-H), 10.4 (s, 1H, —NH—)	—	m/z: 363 (100%, M^+, $C_{15}H_{11}BrN_2O_2$), 284 (12%, M-Br), 230 (6%, $C_7H_7BrN_2S$), 166 (36%, $C_8H_6O_2S$)

[a]Recorded using DMSO-d_6 or $CDCl_3$ as solvents.

Results of such studies are given in Table II. All compounds need further evaluation at different concentrations and with different known antifungal agents.

Antifungal Study

Newly prepared compounds 4-{2-[(aryl)amino]-1,3-thiazol-4-yl} benzene-1,2-diol (3a–i) were screened for their antifungal activity against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Candida albicans* (NCIM No. 3100), *Penicillium marneffei* (Recultered) and *Trichophyton mentagrophytes* (Recultered) in DMSO by the serial plate dilution methodm.[21–23] Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and the pH was adjusted to 5.7. Normal saline was use to make a suspension of spores of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL of saline to get a suspension of corresponding species. Agar media of 20 mL was poured into each petridish. An excess of suspension was decanted, and the plates were dried by placing them in an incubator at 37°C for 1 h. Using an agar, punch wells were made on these seeded agar plates, and 10 μg/mL–100 μg/mL of the test compounds in DMSO were added into each well labeled. A control was also prepared for plates in the same way using solvent DMSO. The petridishes were prepared in triplicate and maintained at 37°C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Results of such studies are given in Table III. The activity of each compound was compared with Itraconozole as a standard drug. The MIC for the Itraconazole in DMSO was 0.03–16 μg/mL against the tested species.[21] We found that Itraconazole exhibited maximum inhibition at the concentration $\leq$0.125 μg/mL and no inhibition at the concentration $\leq$1.0 μg/mL which is well in agreement with the literature.[21]

EXPERIMENTAL

Preparation of 4-(Chloroacetyl) Catechol (1)

This compound was prepared as per the literature procedure.[19] Yield 60%, off-white needles, m.p. 173°C dec.

General Procedure for the Synthesis of N-Substituted Thioureas (2c–i)[20]

Benzoylchloride (0.01 mol) was added over 5 min to a freshly prepared solution of ammonium thiocyanate (0.012 mol) in dry acetone, and the

TABLE III Antibacterial Activity of the Newly Synthesized Compounds 3a–i at the Concentration 10 μg/mL–100 μg/mL

Compound no.	*Escherichia coli*	*Staphyllococcus aureus*	*Psuedomonus aeruginosa*	*Klebsiella pneumoniae*
3a	+++	+++	+++	+++
3b	+++	+++	+++	+++
3c	+++	+++	+++	—
3d	+++	+++	+++	—
3e	+++	+++	+++	+++
3f	+++	+++	+++	+++
3g	+++	+++	+++	+++
3h	+++	+++	+++	+++
3i	+++	+++	+++	+++

Standard drug: Ampicillin, which has a 16–22 mm inhibition length for *Escherichia coli* and 27–35 mm inhibition length for *Staphyllococcus aureus* at the concentration of 10 μg/mL.

—, <8 mm, no inhibition (for any concentration).
+, 8–10 mm, minimum inhibition (100 μg/mL).
++, 10–15 mm, moderate inhibition (60 μg/mL).
+++, 15–20 mm, maximum inhibition (10 μg/mL).

mixture was heated under reflux for about 15 min. Heating was stopped, and an appropriate aniline in acetone was added over a period of 15 min. The mixture was heated under reflux for 30 min and then poured to crushed ice. The resulting solid was collected, washed with water and

TABLE IV Antifungal Activity of Newly Synthesized Compounds (3a–i)

Compound no.	*Aspergilus flavus*	*Aspergilus fumigatus*	*Penicillium marneffei*	*Candida albicans*	*Trichophyton mentagrophytes*
3a	—	—	—	+++	—
3b	—	—	+++	—	—
3c	+++	+++	+++	+++	+++
3d	—	—	+++	+++	—
3e	+++	+++	+++	—	+++
3f	—	—	+++	—	—
3g	+++	+++	+++	—	+++
3h	+++	—	+++	+	+++
3i	—	—	+++	—	—
Standard drug, Itraconazole			+++	≤0.125 μg/mL	
			—	≤1.0 μg/mL	

—, <8 mm, no inhibition (for any concentration).
++, 10–15 mm, moderate inhibition (100 μg/mL).
+++, 15–20 mm, maximum inhibition (10 μg/mL).

followed by cold mixture of water and methanol (1:1). Suitably substituted benzoylthioureas were added to a preheated solution of aqueous sodium hydroxide (5%) and stirred. The mixture was then poured into crushed ice containing hydrochloric acid (5%). The benzoic acid separated was removed by treating the reaction mixture with sodium carbonate. The product was collected, washed with water, and then dried. All products were isolated in a yield varying from 80–90% and were taken directly for the next reaction without further purification.

General Procedure for the Synthesis of 4-{2-[(Aryl) amino]-1,3-thiazol-4-yl}benzene-1,2-diol (3a–i)

4-(chloroacetyl) catechol (0.01 mol) and an appropriate alkylthiomide/thiourea/substituted thiourea (0.01 mol) in absolute ethanol was refluxed for 6 h and allowed to stand overnight. The solid separated on cooling was filtered and recrystallized in a mixture of ethanol and dimethylformamide mixture (5–10% of dimethylformamide in ethanol).

CONCLUSION

Some new 4-{2-[(4-aryl) amino]-1,3-thiazol-4-yl} benzene-1,2-diols (**3a–i**) were synthesized and screened for their antibacterial and antifungal activity. Antibacterial study carried out for **3a–i** revealed that for except **3c** and **3d**, all compounds possess excellent antibacterial activity against all tested organisms. However, antifungal study results revealed that compound **3c** is most active amongst all. Compounds **3a**, **3f**, and **3i** are found to be least active. Other compounds have shown good-to-moderate antifungal activity. The combination of potential thiazole moiety with catechol may be the reason for the excellent antibacterial activity. Since we have limited our antimicrobial study in 4-{2-[(4-aryl) amino]-1,3-thiazol-4-yl}benzene-1,2-diol only, there is more scope to investigate antimicrobial activity modifying the structure with mono and bis substitution at hydroxy function.

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