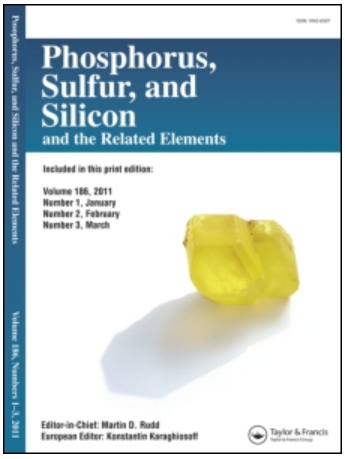

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SYNTHESIS AND PHARMACOLOGICAL USE OF 10*H*-PHENOTHIAZINES, THEIR SULFONES, AND RIBOFURANOSIDES

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This article describes the synthesis of 10*H*-phenothiazines from 2-aminobenzenethiol and o-halonitrobenzenes via Smiles rearrangement. Upon refluxing with hydrogen peroxide in glacial acetic acid, these phenothiazines yield the corresponding 10H-phenothiazine-5,5-dioxides. The phenothiazines have also been used as base to prepare ribofuranosides by the reaction with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate. All the synthesized compounds have been characterized by spectral and elemental analysis and have been examined for antioxidant and antimicrobial activity.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antioxidant and antimicrobial activity; phenothiazines; ribofuranosides; Smiles rearrangement

INTRODUCTION

Phenothiazines, their sulfones, and ribofuranosides have attracted considerable interest due to their widespread use in pharmacology. They have been used, for example, as analgesic,[1] anticancer,[2] and antibacterial[3] agents. A slight change in substitution pattern in the phenothiazine nucleus causes tremendous differences in the biological activity.[4–15] in this article, we report the synthesis and biological (antioxidant and antimicrobial) activity of some new 10*H*-phenothiazines.

RESULTS AND DISCUSSION

10*H*-Phenothiazines **5a**,**b** have been synthesized by Smiles rearrangement of the corresponding substituted 2-formamido-2′-nitrodiphenylsulfides **4a**,**b**. These, in turn, were

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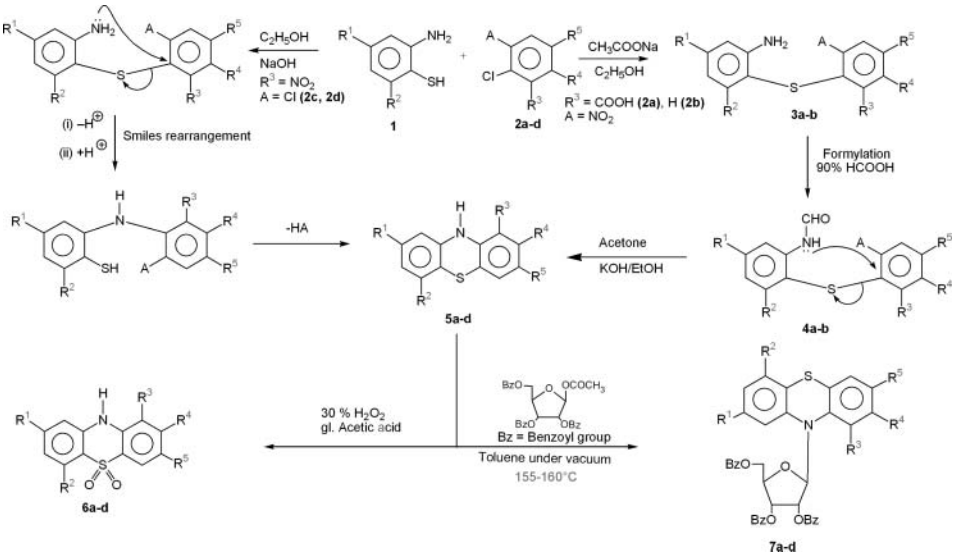
prepared by formylation of 2-amino-2′-nitrodiphenylsulfides **3a**,**b** with 90% formic acid. Compounds **3a**,**b** were obtained by condensation of 2-amino-4,6-dimethylbenzenethiol (**1**) with *o*-halonitrobenzenes **2a**,**b** in ethanolic sodium acetate solution. 1-Nitrophenothiazines **5c**,**d** have been synthesized by refluxing 2-amino-4,6-dimethylbenzenethiol (**1**) with reactive halonitrobenzenes **2c**,**d**, which have either two nitro or one halo and one nitro group *ortho* to the reactive halogen atom, in alcohol in the presence of sodium hydroxide, where Smiles rearrangement occurs in situ. These phenothiazines, upon refluxing with 30% hydrogen peroxide in glacial acetic acid, yield the corresponding sulfones **6a**,**d**, while upon treatment with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate under reduced pressure in toluene, they give the corresponding ribofuranosides **7a**,**d** (Scheme 1).



Scheme 1

The structures proposed for the synthesized compounds are well-supported by elemental analyses and spectroscopic data. All these compounds have also been tested for antioxidant and antimicrobial activities (see the Supplemental Materials, available online, for complete details).

The structures proposed for the synthesized compounds are well supported by elemental analyses (Table I) and spectroscopic data (Table II).

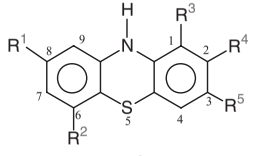
IR Spectra

The IR spectral data of compounds **3a**,**b** show two peaks in the region of 3465–3410 cm^{-1} and 3340–3315 cm^{-1} due to the asymmetric and symmetric vibration of the primary amino group. Two peaks in the region of 1560–1550 cm^{-1} and 1365–1340 cm^{-1} are also observed due to the asymmetric and symmetric vibration of the $-NO_2$ group. The IR spectra of compounds **4a**,**b** resemble those of the parent diphenylsulfide derivatives. A single peak due to N—H stretching is observed in the region of 3350–3310 cm^{-1}, and also a peak due to C=O stretching is observed in the region of 1705–1680 cm^{-1}. In compounds **5a–d**, a single peak due to N—H stretching is observed in the region of 3380–3320 cm^{-1}, and

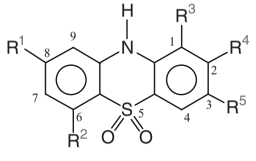
Table I Characterization data of compounds **5a–d**, **6a–d**, and **7a–d**

									% Found (calcd.)		
	R^1	R^2	R^3	R^4	R^5	Molecular formula	Mp	Yield %	C	H	N
5a	CH_3	CH_3	COOH	H	NO_2	$C_{15}H_{12}N_2O_4S$	240	65	57.23 (56.96)	3.72 (3.79)	8.79 (8.86)
5b	CH_3	CH_3	H	H	NO_2	$C_{14}H_{12}N_2O_2S$	140	52	61.98 (61.76)	4.38 (4.41)	10.25 (10.29)
5c	CH_3	CH_3	NO_2	H	H	$C_{14}H_{12}N_2O_2S$	62	83	61.95 (61.76)	4.44 (4.41)	10.33 (10.29)
5d	CH_3	CH_3	NO_2	Cl	Cl	$C_{14}H_{10}N_2O_2SCl_2$	65	50	49.47 (49.26)	2.90 (2.93)	8.16 (8.21)
6a	CH_3	CH_3	COOH	H	NO_2	$C_{15}H_{12}N_2O_6S$	250	56	51.63 (51.72)	3.38 (3.44)	8.10 (8.04)
6b	CH_3	CH_3	H	H	NO_2	$C_{14}H_{12}N_2O_4S$	150	62	55.45 (55.26)	3.90 (3.94)	9.16 (9.21)
6c	CH_3	CH_3	NO_2	H	H	$C_{14}H_{12}N_2O_4S$	55	48	55.47 (55.26)	3.92 (3.94)	9.16 (9.21)
6d	CH_3	CH_3	NO_2	Cl	Cl	$C_{14}H_{10}N_2O_4SCl_2$	250	45	45.28 (45.04)	2.72 (2.68)	7.46 (7.50)
7a	CH_3	CH_3	COOH	H	NO_2	$C_{41}H_{32}N_2O_{11}S$	81	68	64.93 (64.73)	4.17 (4.21)	3.62 (3.68)
7b	CH_3	CH_3	H	H	NO_2	$C_{40}H_{32}N_2O_9S$	108	55	67.22 (67.03)	4.40 (4.46)	3.88 (3.91)
7c	CH_3	CH_3	NO_2	H	H	$C_{40}H_{32}N_2O_9S$	85	71	67.24 (67.03)	4.39 (4.46)	3.87 (3.91)
7d	CH_3	CH_3	NO_2	Cl	Cl	$C_{40}H_{30}N_2O_9SCl_2$	110	41	61.33 (61.14)	3.76 (3.82)	3.51 (3.56)

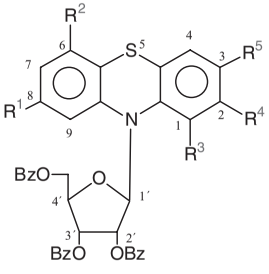
Table II Spectral data of compounds **5a–d**, **6a–d**, and **7a–d**



5a-d



6a-d



7a-d

	IR KBr ν(cm^{-1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	Mass m/z (%)
5a	3320 (>N−H str.), 2910 (−CH_3 str.), 1550, 1380 (−NO_2 str.)	11.20 (s, −COOH), 7.04–6.20 (m, arom-H), 8.52 (s, >NH), 2.05 (s, 6-CH_3), 2.08 (s, 8-CH_3)	119.8 (C-1), 135.2 (C-2), 113.9 (C-3), 131.2 (C-4), 131.8 (C-6), 139.1 (C-7), 132.8 (C–8), 140 (C-9), 21.3 (8-CH_3), 14.0 (6-CH_3)	316 (M^+), 315 (29), 175 (100)
5b	3380 (>N−H str.), 2915 (−CH_3 str.), 1530, 1365 (−NO_2 str.)	7.96–6.73 (m, arom-H), 8.65 (s, >NH), 2.06 (s, 6-CH_3), 2.07 (s, 8-CH_3)	125.2 (C-1), 131.2 (C-2), 149.2 (C-3), 119.2 (C-4), 137.9 (C-6), 131.2 (C-7), 139.2 (C–8), 121.5 (C-9), 22.0 (8-CH_3), 14.8 (6-CH_3)	272 (M^+), 271 (60), 175 (100)
5c	3330 (>N−H str.), 2910 (−CH_3 str.), 1550, 1385 (−NO_2 str.)	7.16–6.39 (m, arom-H), 8.69 (s, >NH), 2.07 (s, 6-CH_3), 2.09 (s, 8-CH_3)	122.7 (C-1), 138.2 (C-2), 114.8 (C-3), 136.1 (C-4), 132.8 (C-6), 137 (C-7), 134.0 (C–8), 140.8 (C-9), 21.2 (8-CH_3), 13.8 (6-CH_3)	272 (M^+), 226 (43), 225 (52), 242 (62), 255 (100)
5d	3320 (>N−H str.), 790 (C−Cl str.), 2940 (−CH_3 str.), 1560, 1370 (−NO_2 str.)	8.05–6.70 (m, arom-H), 9.01(s, >NH), 2.2 (s, 6-CH_3), 2.10 (s, 8-CH_3)	147.2 (C-1), 131.8 (C-2), 132.5 (C-3), 129.2 (C-4), 138.2 (C-6), 132.0 (C-7), 138.9 (C–8), 122.0 (C-9), 21.8 (8-CH_3), 14.9 (6-CH_3)	340 (M^+), 342 (M+2), 310 (43), 293 (52), 94 (62), 323 (100)
6a	3328 (>N−H str.), 2988 (−CH_3 str.), 1570, 1365 (NO_2 str.), 1160, 1156 (SO_2 sym. str.), 1076 (C−S str.)	11.18 (s, −COOH), 8.06–6.38 (m, arom-H), 9.01 (s, >NH), 2.11 (s, 6-CH_3), 2.13 (s, 8-CH_3)	123.1 (C-1), 129.0 (C-2), 119.1 (C-3), 131.2 (C-4), 128.8 (C-6), 140.0 (C-7), 139.2 (C–8), 140.7 (C-9), 22.4 (8-CH_3), 14.2 (6-CH_3)	348 (M^+), 347 (28), 207 (100)

6b	3400 (>N−H str.), 2925 (−CH_3 str.) 1566, 1350 (−NO_2 str.), 1156, 1151 (SO_2 sym. str.), 1070 (C−S str.),	7.8–6.50 (m, arom-H), 9.06 (s, >NH), 2.10 (s, 6-CH_3), 2.12 (s, 8-CH_3)	125.2 (C-1), 122.1 (C-2), 149.2 (C-3), 119.2 (C-4), 137.9 (C-6), 131.2 (C-7), 138.2 (C–8), 121.2 (C-9), 21.1 (8-CH_3), 14.2 (6-CH_3)	304 (M^+), 303 (30), 267 (100)
6c	3335 (>N−H str.), 2910 (-CH_3 str.), 1555, 1380 (−NO_2 str.), 1172, 1156 (SO_2 sym. str.), 1066 (C−S str.)	8.05–6.28 (m, arom-H), 9.07 (s, >NH), 2.16 (s, 6-CH_3), 2.20 (s, 8-CH_3)	129.1 (C-1), 139.9 (C-2), 135.1 (C-3), 142.2 (C-4), 149.0 (C-6), 125.1 (C-7), 147.0 (C–8), 114.2 (C-9), 22.4 (8-CH_3), 13.6 (6-CH_3)	304 (M^+), 287 (100), 274 (61), 258 (41), 257 (51)
6d	3380 (>N−H str.), 2938 (−CH_3 str.) 1545, 1360 (−NO_2 str.), 1170, 1150 (SO_2 sym. str.), 1060 (C−S str.)	7.32–6.40 (m, arom-H), 9.05 (s, >NH), 2.25 (s, 6-CH_3), 2.28 (s, 8-CH_3)	147.1 (C-1), 131.8 (C-2), 132.5 (C-3), 129.2 (C-4), 138.2 (C-6), 132.0 (C-7), 138.9 (C–8), 122.6 (C-9), 22.5 (8-CH_3), 13.6 (6-CH_3)	372 (M^+), 374 (M+2), 325 (38), 326 (50), 342 (28), 355 (100)
7a	1590, 1410 (−NO_2 str.), 1145 (C−O−C str.)	11.25 (s, COOH), 8.08–6.91 (m, arom-H), 2.11 (s, 6-CH_3), 2.18 (s, 8-CH_3)	120.8 (C-1), 135.8 (C-2), 139.8 (C-3), 138.2 (C-4), 132.9 (C-6), 135.2 (C-7), 130.9 (C–8), 141.5 (C-9), 89.8 (C-1′), 94.2 (C-2′), 75.8 (C-3′), 93.4 (C-4′), 21.2 (8-CH_3), 13.4 (6-CH_3)	760 (M^+), 759 (21), 619 (100)
7b	1588, 1420 (−NO_2 str.), 1120 (C−O−C str.)	7.62–6.25 (m, arom-H), 2.18 (s, 6-CH_3), 2.28 (s, 8-CH_3 at C_8)	125.0 (C-1), 123.2 (C-2), 150.0 (C-3), 118.1 (C-4), 137.0 (C-6), 131.8 (C-7), 139.0 (C–8), 120.8 (C-9), 93.6 (C-1′), 94.8 (C-2′), 76.8 (C-3′), 96.5 (C-4′), 20.8 (8-CH_3), 13.2 (6-CH_3)	716 (M^+), 715 (30), 619 (100)
7c	1550, 1390 (−NO_2 str.), 1146 (C−O−C str.)	7.20–6.80 (m, arom-H), 2.15 (s, 6-CH_3), 2.23 (s, 8-CH_3)	128.6 (C-1), 139.8 (C-2), 113.3 (C-3), 131.2 (C-4), 130.6 (C-6), 133.4 (C-7), 135.2 (C–8), 145.8 (C-9), 91.8 (C-1′), 95.6 (C-2′), 74.9 (C-3′), 95.2 (C-4′), 20.9 (8-CH_3), 13.8 (6-CH_3)	716 (M^+), 686 (61), 670 (40), 671 (42), 699 (100)
7d	1558, 1365 (−NO_2 str.), 1180 (C−O−C str.), 800 (C−Cl str.)	8.10–7.25 (m, arom-H), 2.15 (s, 6-CH_3), 2.28 (s, 8-CH_3)	129.2 (C-1), 136.7 (C-2), 113.8 (C-3), 132.8 (C-4), 131.1 (C-6), 132.8 (C-7), 133.8 (C–8), 142.6 (C-9), 90.2 (C-1′), 93.2 (C-2′), 75.8 (C-3′), 93.8 (C-4′), 21.1 (8-CH_3), 14.0 (6-CH_3)	784 (M^+), 786 (M+2), 754 (68), 738 (32), 737 (40), 767 (100)

two peaks in the region of 1560–1530 cm^{-1} and 1385–1365 cm^{-1} are observed due to the asymmetric and symmetric vibration of the $-NO_2$ group. In addition, a peak due to $-CH_3$ stretching is observed in the region of 2940–2910 cm^{-1}. Compounds **6a–d** show a single peak in the region of 3400–3328 cm^{-1} due to N—H stretching and two peaks in the region of 1570–1545 cm^{-1} and 1380–1350 cm^{-1} due to the asymmetric and symmetric stretching of the $-NO_2$ group. Also, a peak due to $-CH_3$ stretching is observed in the region of 2988–2910 cm^{-1}. Compounds **6a–d** also show two peaks in the region of 1365–1345 cm^{-1} and 1172–1150 cm^{-1} due to the asymmetric and symmetric vibration of the sulfonyl group.

In compounds **7a–d**, a peak due to —N—H stretching is absent, indicating its ribosylation. These compounds show two peaks in the region of 1590–1550 cm^{-1} and 1420–1365 cm^{-1} due to the asymmetric and symmetric stretching of the $-NO_2$ group. Also, bands due to —C=O and C—O—C appear at 1750–1745 cm^{-1} and 1180–1120 cm^{-1}, respectively.

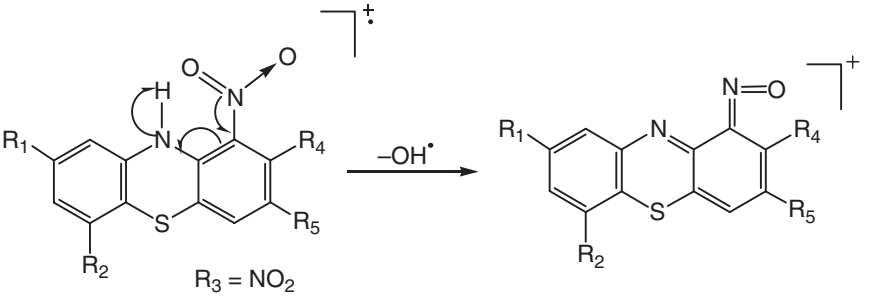
^{1}H NMR Spectra

The ^{1}H NMR spectra of compounds **5a–d** show two main peaks: One singlet is observed in the region δ 8.52–9.01 ppm due to the N—H proton, and a multiplet is observed due to aromatic protons in the region δ 6.20–8.05 ppm. In addition, two singlets are observed in the region δ 2.05–2.2 ppm due to $-CH_3$ protons at C_6 and C_8. In compounds **3a**,**b**, a broad signal due to $-NH_2$ group is observed at δ 4.24–3.68 ppm. In compounds **6a–d**, one singlet due to N—H proton appears in the region δ 9.01–9.07 ppm, and a multiplet due to aromatic protons is observed in the region δ 6.28–8.06 ppm. In addition, two singlets are observed in the region δ 2.10–2.28 ppm due to $-CH_3$ protons.

The ^{1}H NMR spectra of ribofuranosides **7a–d** do not show any peaks due to >N—H, indicating the site of ribosylation, and they show a multiplet at δ 6.25–8.10 due to aromatic protons. C′$_4$—H and CH_2 protons of sugar moiety give a multiplet in the region δ 4.34–4.83, while C′$_2$—H and C′$_3$—H appear as a multiplet at δ 5.71–5.84 ppm. A multiplet at δ 6.48–6.36 ppm is observed for the C′$_1$—H proton.

Mass Spectra

The mass spectra of 10*H*-phenothiazines and 1-nitro-10*H*-phenothiazines display molecular ion peaks in accordance with their molecular weights. 1-Nitro-10*H*-phenothiazines undergo fragmentation due to loss of the OH radical by McLafferty



Scheme 2

rearrangement, yielding M^+–17 peak (Scheme 2). In addition peaks due to loss of NO, NO_2, and HNO_2 appear at M^+–30, M^+–46, and M^+–47, respectively.

EXPERIMENTAL

Melting points of all the synthesized compounds were determined with an electrothermal apparatus (open capillary method) and are uncorrected. The IR spectra were recorded in KBr with a Shimadzu 8400 S FTIR spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL AL-300 spectrometer in DMSO-d_6 and $CDCl_3$, at frequency of 300 MHz, using TMS as internal standard. Mass spectra were obtained with a JEOL SX 102/DA 600 instrument using Xe/Ar as FAB gas. The purity of the compounds was checked by TLC using silica gel "G" as adsorbent and visualizing either by UV light or in an iodine chamber.

Synthesis of 2-Amino-2′-nitrodiphenylsulfides (3a,b): General Procedure

To a solution of 2-amino-4,6-dimethylbenzenethiol (**1**) (0.01 mol) in ethanol (20 mL) containing anhydrous sodium acetate (0.01 mol) in a 50 mL round bottom flask, a solution of halonitrobenzene **2a**,**b** (0.01 mol) in ethanol (10 mL) was added. The reaction mixture was refluxed for 4–5 h, and the resulting solution was cooled and kept overnight in an ice chamber. The separated solid was filtered, washed with ethanol (20 mL), and recrystallized from methanol.

Synthesis of 2-Formamido-2′-nitrodiphenyl Sulfides (4a,b): General Procedure

2-Amino-2′-nitrodiphenylsulfides **3a**,**b** (0.01 mol) were refluxed for 4 h in 90% formic acid (20 mL). The reaction mixture was poured into crushed ice, and the separated solid was filtered, washed with a minimum amount of water, and crystallized from benzene.

Synthesis of 10*H*-Phenothiazines (5a,b): General Procedure

To the formyl derivative **4a**,**b** (0.01 mol), acetone (15 mL) and an alcoholic solution of potassium hydroxide (0.2 g in 5 mL of ethanol) was added, and the resulting mixture was heated at 20°C for about 30 min. Then a second amount of KOH (0.2 g in 5 mL of ethanol) was added, and refluxing was continued for about 4 h. The reaction mixture was poured into crushed ice, and the separated solid was filtered, washed with a minimum amount of cold water and then with ethanol (20 mL), and crystallized from benzene.

Synthesis of 1-Nitro-10*H*-phenothiazines (5c,d): General Procedure

2-Amino-4,6-dimethylbenzenethiol (**1**) (0.01 mol), NaOH (0.01 mol), and absolute alcohol (20 mL) were introduced in a round bottom flask equipped with a reflux condenser, and then an alcoholic solution of reactive halonitrobenzenes **2c**,**d** was added. Refluxing was continued for 2 h. The reaction mixture was concentrated up to half of its volume, cooled,

and filtered. The precipitate was washed with a minimum amount of hot water and then with ethanol (20 mL), and was crystallized from acetone.

Synthesis of Substituted 10*H*-Phenothiazine-5,5-dioxides (6a–d): General Procedure

A mixture of the respective phenothiazine **5a–d** (0.01 mol), glacial acetic acid (20 mL), and 30% H_2O_2 (5 mL) was refluxed for 15 min at 50–60°C and cooled, and then another amount of 30% H_2O_2 (5 mL) was added. The mixture was further refluxed for 4 h and poured into a beaker filled with crushed ice. The resulting precipitate was separated by filtration, washed with a minimum amount of water, and recrystallized from ethanol.

Synthesis of N-(2′,3′,5′-Tri-*O*-benzoyl-β-*D*-ribofuransoyl)phenothiazines (7a–d): General Procedure

β-*D*-Ribofuranose-1-acetate-2,3,5-tribenzoate (0.002 mol) was added to a solution of respective phenothiazine **5c**,**d** in toluene, and the mixture was refluxed in vacuum with stirring in an oil bath at 155–160°C for 15 min. The vacuum was removed, and the reaction mixture was protected by a guard tube from moisture. Stirring was continued for a further 10 h, and vacuum was applied for 10 min after every hour. The obtained viscous mass was then dissolved in 10–15 mL methanol, boiled for 10–15 min, cooled, and filtered. Methanol was removed by distillation under reduced pressure. The residue obtained was dissolved in ether (25 mL), filtered, concentrated to half of the volume, and kept overnight in a refrigerator to yield the crystalline compound.

BIOLOGICAL ACTIVITY

Antioxidant Activity

The synthesized compounds were screened for antioxidant activity by 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay and 2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\bullet+}$) radical cation decolorization assay.

DPPH Radical Scavenging Assay

Radical scavenging activity of all synthesized compounds was determined spectrophotometrically against stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical by Cuendet et al.[16] (See the Supplemental Materials, Tables S1 and S2.)

ABTS Radical Cation Decolorization Assay

The ($ABTS^{\bullet+}$) assay was carried out using the improved assay of Re et al.,[17], which is based on the oxidation of ABTS with potassium persulfate leading to ($ABTS^{\bullet+}$).

Antimicrobial Activity

The paper disc method[18] was used to test the antimicrobial activity by measuring the zone of inhibition on agar plates for different bacteria, such as *Enterobacter*, coagulase

negative *staphylococci*, and coagulase positive *staphylococci* as test organisms and with fungus such as *Candida albicans.* Vancomycin and gatifloxacin were used as standard drugs against bacteria, and flucanazole was used against fungus at a concentration of 100 μg per disc. Results of the antimicrobial activities are shown in Table S3 (Supplemental Materials).

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