Piperidine Mediated Synthesis of *N*-Heterocyclic Chalcones and Their Antibacterial Activity

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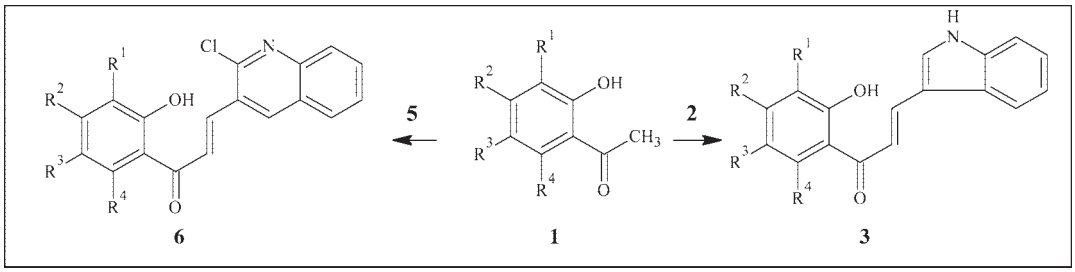

The chalcones 1-(2′-hydroxy-aryl)-3-(1-indol-3-yl)-prop-2-en-1-one **(3)** and 1-(2′-hydroxy-aryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one **(6)** were synthesised by piperidine mediated condensation of an ethanolic solution of an *o*-hydroxyacetophenone **(1)** with corresponding heteroaryl-3-carboxaldehyde. The structures have been established on the basis of elemental (C, H, N) analysis, UV, IR, ^{1}H NMR spectral data. The compounds **3** and **6** were screened for antimicrobial activities against a variety of bacterial agents.

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INTRODUCTION

Chalcones are well known naturally occurring pigments which serve as valuable intermediate in organic synthesis of flavonoid compounds [1]. It has found significant role in pharmaceutical effects [2] including antioncogenic, antiinflammatory, antiulcerative, analgesic, antiviral, antimalarial and antibacterial activities. Chloroquinoline [3] and indole [4] compounds are known to exhibit variety of antimicrobial activity. Also, it has been reported that chalcone having quinoline moiety is an intermediate for the synthesis of chloroquinoline cyanopyridines and cyanopyrans derivatives [5].

In the Claisen-Schemidt condensation of Chalcone synthesis, 2′-hydroxy functional group may cyclise to the corresponding flavanones under higher concentration of alkali. Also, side reactions such as multiple condensations, polymerizations, and rearrangements are common. These undesirable side reaction decreases the yields of the target adduct and render their purification difficult [6]. So, it was planned to use a weaker base like piperidine instead of using strong base to enhance the better yields.

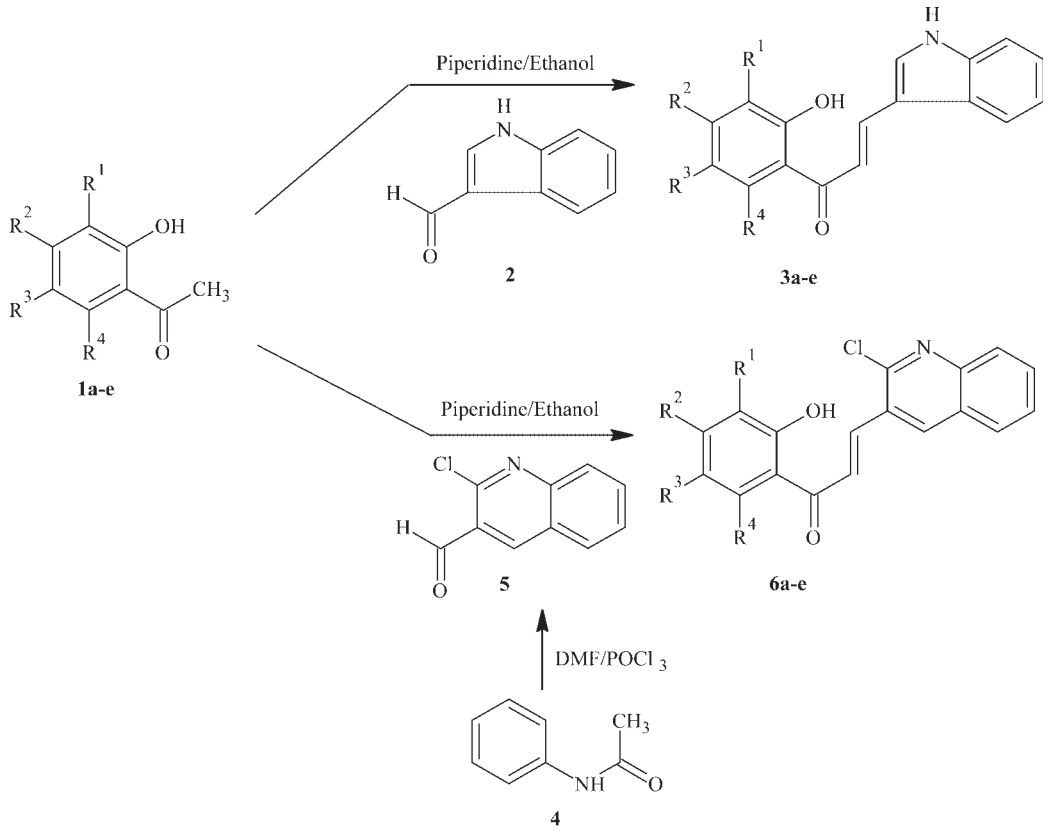
In present communication, we report piperidine mediated synthesis of N-heterocyclic chalcones **3** and **6** from indole-3-carboxaldehyde and 2-chloroquinoline-3-carboxaldehyde respectively. The structures of the compound **3** and **6** have been established on the basis of elemental (C, H, N) analysis, UV, IR, ^{1}H NMR spectral data and they were screened for antibacterial activities.

RESULTS AND DISCUSSION

The syntheses of 1-(2′-hydroxy-aryl)-3-(1-indol-3-yl)-prop-2-en-1-one **(3)** and 1-(2′-hydroxyaryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one **(6)** was carried out by condensation of an ethanolic solution of an *o*-hydroxyacetophenone **(1)** in the presence of piperidine with indole-3-carboxaldehyde **(2)** and with 2-chloroquinolin-3-carboxaldehyde **(5)** as shown in Scheme 1.

The compounds **3** and **6** gave violet colouration with alcoholic $FeCl_3$ test indicating the presence of chelated hydroxyl group in it. Also, gave positive test for presence of elements such as N and Cl in corresponding chalcone by sodium fusion extraction test. When using $AlCl_3$-HCl as shift reagents, bathochromic shift about 40 nm at band-I was observed in UV spectral studies of products **3** and **6** due to presence of chelated hydroxyl group. IR spectra of compounds **3** revealed the presence of —NH absorption bands in the region of 3228–3098 cm^{-1}, in addition to two characteristic signals about 1630 cm^{-1} for the unsaturated keto group and 3043–3444 cm^{-1} for hydroxyl groups. Similarly, IR spectrum of compounds **6** showed absorption at 3436–3431 cm^{-1}, 1654–1621 cm^{-1}, 1446–1432 cm^{-1} and 744–756 cm^{-1} for presence of —OH, —C=O, —C=N—, —Cl groups, respectively. The ^{1}H NMR spectra gave two doublet centred about δ 7.6 and δ 8.2 with coupling constant about $J = 15$ Hz were assigned to the trans olefinic proton at C_α and C_β position. The entire ^{1}H NMR spectral data were given in the experimental part and the values were in accordance with the title compounds **3** and **6**.

Scheme 1



Antibacterial activities. The antibacterial activity of the compounds **3** and **6** have been evaluated using filter paper disc diffusion method [7] at a concentration of 100 μg/disc against human pathogenic bacteria such as *Staphylococcus aureus* (G^+), *Shigella dysenteriae* (G^-) and *Salmonella typhi* (G^-). Kanamycin (30 μg/disc) was used as standard for comparing the activity. Each sample was used in triplicates for the determination of antibacterial activity. The diameter of observed inhibition zone of **3** and **6** were measured (in mm) and they are given in Table 1.

By visualizing the antibacterial data, it could be observed that most of the compound shows significant activity. The compound **3e**, **6a**, **6e** showed excellent activity for all the three test microorganisms. However, compounds **3d, 6c** are inactive against *S. aureus* and compounds **3d, 6b** are inactive for *S. dysenteriae*. Similarly compounds **3b, 6d** are inactive against *S. typhi*. The preliminary result confirms the importance of chloroquinone nucleus and indole nucleus with respect to antibacterial activity.

EXPERIMENTAL

Melting point determinations were made in open capillaries and were uncorrected. TLC was carried out using Merck brand Silica Gel-G and spotting was done using iodine or UV light. UV spectra were taken in Perkin-Elmer 402 UV-Vis spectrophotometer. IR spectra were recorded in Perkin-Elmer 577 IR spectrophotometer. ^{1}H NMR spectra were conducted on Bruker (300 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The chemical shifts are reported in ppm scale. The compound **(2)** was obtained from SISCO research laboratories and used as such. The compound **(5)** was prepared adopting the published procedure with the same melting point at 150°C [8].

General procedure for synthesis of 1-(2′-hydroxy-aryl)-3-(1-indol-3-yl)-prop-2-en-1-one (3). To a mixture of *o*-hydroxyacetophenone (0.01 mol) and indole-3-carboxaldehyde (0.01 mol) in ethanol (50 mL), piperidine (1 mL) was added and refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcone **3**.

Synthesis of 1-(2′-hydroxy-4′-methoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3a). Yellow solid (0.75 g, 25.6%); mp. 196°C; λ_{max} ($CHCl_3$, nm): 274, 396; ir (KBr, cm^{-1}): 3374(ν_{OH}), 3225($\nu_{>NH}$), 1625($\nu_{C=O}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.90 (s, 1H, 2′-OH), 6.54 (d, 1H, 3′-H), 3.87 (s, 3H, 4′-OCH_3), 6.44 (d, 1H, 5′-H), 7.96 (d, 1H, 6′-H), 7.81 (d, 1H, C_αH, J = 15.3 Hz), 8.18 (d, 1H, C_βH, J = 15.3 Hz), 8.61 (s, 1H, > NH), 7.66 (d, 1H, 2-H), 8.04 (d, 1H, 4-H), 7.33 (m, 2H, 5- and 6-H), 7.46 (m, 1H, 7-H); *Anal*. Calcd for

Table 1

Antibacterial activity of compound **3** and **6**.

R	Compound	Diameter of zone inhibition (mm)		
		S. aureus	*S. dysenteriae*	*S. typhi*
	3a	18 ± 0.7	19 ± 1.1	21 ± 0.6
	3b	12 ± 0.9	18 ± 0.8	–
	3c	10 ± 0.7	16 ± 0.9	15 ± 0.7
a: $R^2 = OCH_3$; R^1, R^3, $R^4 = H$	**3d**	–	–	12 ± 1.1
b: $R^3 = OCH_3$; R^1, R^2, $R^4 = H$	**3e**	28 ± 1.2	27 ± 1.1	24 ± 2.1
c: R^1, $R^2 = OCH_3$; R^3, $R^4 = H$	**6a**	26 ± 2.3	26 ± 1.2	22 ± 0.5
d: R^1, R^2, $R^4 = OCH_3$; $R^3 = H$	**6b**	23 ± 1.8	–	14 ± 0.7
e: R^2, $R^4 = OCH_3$; R^1, $R^3 = H$	**6c**	–	13 ± 0.5	11 ± 0.7
	6d	20 ± 1.3	22 ± 0.9	–
	6e	22 ± 0.9	24 ± 0.5	22 ± 0.8
	Kanamycin	29 ± 2.1	31 ± 1.8	28 ± 1.6

$C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.52; H, 5.14; N, 4.71.

Synthesis of 1-(2′-hydroxy-5′-methoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3b). Yellow solid (0.9 g, 30.7%); mp. 120°C; λ_{max} ($CHCl_3$, nm): 258, 344; ir (KBr, cm^{-1}): 3444(ν_{OH}), 3166($\nu_{>NH}$), 1633($\nu_{C=O}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.80 (s, 1H, 2′-OH), 6.97 (d, 1H, 3′-H), 7.11 (d, 1H, 4′-H), 3.87 (s, 3H, 5′-OCH_3), 7.97 (s, 1H, 6′-H), 7.85 (d, 1H, C_αH, J = 15.3 Hz), 8.22 (d, 1H, C_βH, J = 15.3 Hz), 8.61 (s, 1H, > NH), 7.54 (d, 1H, 2-H), 8.04 (d, 1H, 4-H), 7.34 (m, 2H, 5- and 6-H), 7.46 (m, 1H, 7-H); *Anal*. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.73; H, 5.16; N, 4.72.

Synthesis of 1-(2′-hydroxy-3′,4′-dimethoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3c). Yellow solid (1.32 g, 40.8%); mp. 124°C; λ_{max} ($CHCl_3$, nm): 268, 345; ir (KBr, cm^{-1}): 3438(ν_{OH}), 3228($\nu_{>NH}$), 1627($\nu_{C=O}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.6 (s, 1H, 2′-OH), 3.94 (s, 3H, 3′-OCH_3), 3.96 (s, 3H, 4′-OCH_3), 6.57 (d, 1H, 5′-H), 7.98 (d, H, 6′-H), 7.82 (d, 1H, C_αH, J = 15.3 Hz), 8.15 (d, 1H, C_βH, J = 15.3 Hz), 8.70 (s, 1H, > NH), 7.61 (s, 1H, 2-H), 8.04 (d, 1H, 4-H), 8.34 (m, 2H, 5- and 6-H), 7.49 (d, 1H, 7 H); Anal. Calcd for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.36; H, 5.28; N, 4.35.

Synthesis of 1-(2-hydroxy-3′,4′,6′-trimethoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3d). Yellow solid (0.84 g, 23.8%); mp. 202°C; λ_{max} ($CHCl_3$, nm): 296, 402; ir (KBr, cm^{-1}): 3143(ν_{OH}), 3098($\nu_{>NH}$), 1637($\nu_{C=O}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.2 (s, 1H, 2′-OH), 3.8 (s, 9H, 3′-, 4′- and 6′-OCH_3), 7.19 (s, 1H, 5′-H), 7.89 (d, 1H, C_αH, J = 15.3 Hz), 8.19 (d, 1H, C_βH, J = 15.3 Hz), 9.9 (s, 1H, > NH), 7.61 (s, 1H, 2-H), 7.99 (s, 1H, 4-H), 7.29 (m, 2H, 5- and 6-H), 7.47 (d, 1H, 7-H); *Anal*. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.91; H, 5.41; N, 3.89.

Synthesis of 1-(2-hydroxy-4′,6′-dimethoxyphenyl)-3-(1-indol-3-yl)-prop-2-en-1-one (3e). Yellow solid (1.46 g, 45.2%); mp. 198°C; λ_{max} ($CHCl_3$, nm): 281, 396; ir (KBr, cm^{-1}): 3410(ν_{OH}), 3230($\nu_{>NH}$), 1610($\nu_{C=O}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.05 (s, 1H, 2′-OH), 6.01 (d, 1H, 3′-H), 3.82 (s, 3H, 4′-OCH_3), 6.13 (s, 1H, 5′-H), 3.88 (s, 3H, 6′-OCH_3), 7.74 (d, 1H, C_αH, J = 15.3 Hz), 8.15 (d, 1H, C_βH, J = 15.3 Hz), 8.99 (s, 1H, > NH), 7.48 (d, 1H, 2-H), 8.12 (m, 1H, 4-H), 7.33 (m, 2H, 5- and 6-H), 7.40 (d, 1H, 7-H); Anal. Calcd for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.41; H, 5.29; N, 4.29.

General procedure for synthesis of 1-(2′-hydroxy-aryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6). To a mixture of *o*-hydroxyacetophenone (0.01 mol) and 2-chloroquinoline-3-carboxaldehyde (0.01 mol) in ethanol (50 mL), piperidine (1 mL) was added and refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcone **6**.

Synthesis of 1-(2′-hydroxy-4′-methoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6a). Yellow solid (1.32 g, 38.9%); mp. 226°C; λ_{max} ($CHCl_3$, nm): 269, 361; ir (KBr, cm^{-1}): 3432(ν_{OH}), 1633($\nu_{C=O}$), 1432($\nu_{-C=N-}$), 748(ν_{Cl}); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.10 (s, 1H, 2′-OH), 6.48 (s, 1H, 3′-H), 3.75 (s, 3H, 4′-OCH_3), 6.42 (d, 1H, 5′-H), 7.92 (d, 1H, 6′-H), 7.56 (d, 1H, CαH, J = 15.2 Hz), 7.83 (d, 1H, C_βH, J = 15.2 Hz), 8.06 (s, 1H, 4-H), 7.72 (d, 1H, 5-H), 7.48 (m, 2H, 6- and 7-H), 7.61 (m, 1H, 8-H); Anal. Calcd for $C_{19}H_{14}ClNO_3$ (339.77): C, 67.16; H, 4.15; N, 4.12. Found: C, 67.27; H, 4.12; N, 4.17.

Synthesis of 1-(2′-hydroxy-5′-methoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6b). Yellow solid (0.83 g, 24.5%); mp. 216°C; λ_{max} ($CHCl_3$, nm): 258, 331; ir (KBr, cm^{-1}): 3434(ν_{OH}), 1654($\nu_{C=O}$), 1434($\nu_{-C=N-}$), 750(ν_{Cl}); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.80 (s, 1H, 2′-OH), 6.97 (d, 1H, 3′-H), 7.18 (d, 1H, 4′-H), 3.76 (s, 3H, 5′-OCH_3), 7.98 (s, 1H, 6′-H), 7.66 (d, 1H, C_αH, J = 15.1 Hz), 8.11 (d, 1H, C_βH, J = 15.1 Hz), 8.06 (s, 1H, 4-H), 7.74 (d, 1H, 5-H), 7.58 (m, 2H, 6- and 7-H), 7.90 (m, 1H, 8-H); Anal. Calcd for $C_{19}H_{14}ClNO_3$ (339.77): C, 67.16; H, 4.15; N, 4.12. Found: C, 66.99; H, 4.16; N, 4.11.

Synthesis of 1-(2′-hydroxy-3′,4′-dimethoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6c). Yellow solid (1.48 g, 40%); mp. 216°C; λ_{max} ($CHCl_3$, nm): 267, 349; ir (KBr, cm^{-1}): 3434(ν_{OH}), 1654($\nu_{C=O}$), 1446($\nu_{-C=N-}$), 750(ν_{Cl}); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.6 (s, 1H, 2′-OH), 3.86 (s, 3H, 3′-OCH_3), 3.82 (s, 3H, 4′-OCH_3), 6.61 (d, 1H, 5′-H), 7.52 (d, 1H, 6′-H), 7.88 (d, 1H, C_αH, J = 15.2 Hz), 8.18 (d, 1H, C_βH, J = 15.2 Hz), 8.10 (s, 1H, 4-H), 7.68 (d, 1H, 5-H), 7.62 (m, 2H, 6- and 7-H), 7.94 (d, 1H, 8-H); Anal. Calcd for

$C_{20}H_{16}ClNO_4$ (369.79): C, 64.96; H, 4.36; N, 3.79. Found: C, 64.79; H, 4.35; N, 3.75.

Synthesis of 1-(2-hydroxy-3′,4′,6′-trimethoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6d). Yellow solid (0.86 g, 21.5%); mp. 216°C; λ_{max} ($CHCl_3$, nm): 265, 383; ir (KBr, cm^{-1}): 3432(ν_{OH}), 1633($\nu_{C=O}$), 1432($\nu_{-C=N-}$), 746(ν_{Cl}); ^1H NMR (300 MHz, $CDCl_3$): δ 12.2 (s, 1H, 2′-OH), 3.86 (s, 9H, 3′-, 4′- and 6′-OCH_3), 7.12 (s, 1H, 5′-H), 7.69 (d, 1H, $C_\alpha H$, J = 15.3 Hz), 8.18 (d, 1H, $C_\beta H$, J = 15.3 Hz), 8.09 (s, 1H, 4-H), 7.32 (d, 1H, 5-H), 7.44 (m, 2H, 6- and 7-H), 7.92 (d, 1H, 8-H); *Anal*. Calcd for $C_{21}H_{18}ClNO_5$ (399.82): C, 63.08; H, 4.54; N, 3.50. Found: C, 62.88; H, 4.56; N, 3.51.

Synthesis of 1-(2-hydroxy-4′,6′-dimethoxyphenyl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (6e). Yellow solid (1.36 g, 36.8%); mp. 216°C; λ_{max} ($CHCl_3$, nm): 270, 345; ir (KBr, cm^{-1}): 3431(ν_{OH}), 1621($\nu_{C=O}$), 1436($\nu_{-C=N-}$), 756(ν_{Cl}); ^1H NMR (300 MHz, $CDCl_3$): δ 14.05 (s, 1H, 2′-OH), 6.54 (s, 1H, 3′-H), 3.76 (s, 3H, 4′-OCH_3), 6.18 (d, 1H, 5′-H), 3.82 (s, 3H, 6′-OCH_3), 7.72 (d, 1H, $C_\alpha H$, J = 15.2 Hz), 8.21 (d, 1H, $C_\beta H$, J = 15.2 Hz), 8.09 (s, 1H, 4-H), 7.58 (d, 1H, 5-H), 7.42 (m, 2H, 6- and 7-H), 7.86 (m, 1H, 8-H); Anal. Calcd for $C_{20}H_{16}ClNO_4$ (369.79): C, 64.96; H, 4.36; N, 3.79. Found: C, 64.76; H, 4.34; N, 3.75.

Antibacterial activities. The antibacterial activity of the compounds **3** and **6** have been evaluated using filter paper disc diffusion method [7] at a concentration of 100 μg/disc against human pathogenic bacteria such as *Staphylococcus aureus* (G^+), *Shigella dysenteriae* (G^-), and *Salmonella typhi* (G^-). Kanamycin (30 μg/disc) was used as standard for comparing the activity. Each sample was prepared with dimethyl sulfoxide (DMSO) to the concentration of 100 μg/mL. Dried and sterilized filter paper discs (6 mm in diameter) were impregnated with test solution using micropipette and the residual solvents were completely evaporated. Discs containing the test materials were placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard disc of kanamycin (30 μg/disc) and blank discs were used as positive and negative control, respectively. These plates were then kept at low temperature (4°C) for 24 h to allow maximum diffusion of test materials and kanamycin. The plates were then incubated at 37°C for 18 h to allow maximum growth of the organisms. Then, the antimicrobial activity of the test agents was determined by measuring the diameter of zone of inhibition expressed in mm. The experiment was carried out in triplicate.

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