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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF (E)-HYDROXYCHALCONES: 2′-HYDROXY-2-BROMO CHALCONE IS POTENTIALLY ANTIBACTERIAL AGAINST *Staphylococcus aureus* AND *Shigella sonnei*

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ABSTRACT

Fourteen (E)-hydroxychalcones (**3a-3n**) were synthesised through the Claisen-Schmidt condensation. The reaction between arylmethyl ketones and aromatic aldehydes in the presence of NaOH afforded corresponding (E)-hydroxychalcones in good to excellent yields. The synthesised compounds were identified by spectroscopy (UV, IR, ^{1}H NMR and ^{13}C NMR). The antibacterial activity of these (E)-hydroxychalcones was studied against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*, *Salmonella typhi* and *Shigella sonnei*) bacterial strains. (E)-3-(2-Bromophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**3d**) had displayed a high antibacterial activity against *S. aureus* and *S. sonnei* with the MIC value of 0.78 mg/mL. Parent chalcones, viz. (E)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**P1**) and (E)-1,3-diphenylprop-2-en-1-one (**P2**), containing furyl and phenyl B ring, respectively, were also used for a comparative study.

Keywords: Agar Well Diffusion Assay, Antibacterial, Claisen-Schmidt Condensation, Organic Synthesis, MIC.

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INTRODUCTION

Chalcones (1,3-diaryl-2-propene-1-ones or benzylideneacetophenones), a group of molecules within the flavonoid family, comprise two aromatic rings connecting through an α,β-unsaturated carbonyl bridge (Fig.-1). The α,β-unsaturated ketone and hydroxyl substituents present are considered to be responsible for their diverse biological activities.[1–5]

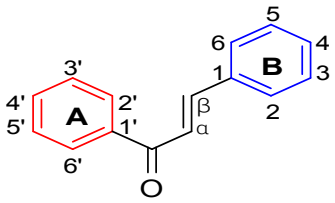

Fig.-1: Chalcone Skeleton

In the recent past, a number of researchers have focused on the synthesis of new chalcones through different synthetic routes. The most common method employed is the Claisen-Schmidt condensation between arylmethyl ketones **1** and aromatic aldehydes **2** in the presence of a base.[6] Other synthetic methods include carbonylative Heck coupling reaction,[7] Sonogashira isomerisation coupling,[8] Suzuki-Miyaura coupling reaction,[9,10] Wittig reaction,[11] Julia-Kocienski olefination,[12] Friedel-Crafts acylation,[13,] etc. Recently, we have reported antibacterial activity of some simple (E)-chalcones.[14] Literature survey on antibacterial activity of chalcones led us to draw some contrary indications: (a) an electron-donating group (e.g. halogen) in A ring displays superior activity,[15] (b) an electron-withdrawing group (e.g. nitro)

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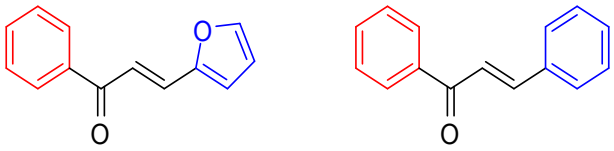
in the same ring is found better,[14] (c) a 4′-OH group enhances the antibacterial property,[16] (d) a 2′-OH is more important than a 4′-OH group,[14] (e) instead of 2′-OH group, 2-OH or 4-OH in B ring is more significant,[17–21] (f) an electron-donating group at B ring is more prominent,[20,22] and (g) a heterocyclic B ring is effective.[21] Structure-activity relationship of complex chalcones and hybrids is also reviewed.[23] However, the structure-activity relationship of chalcones for displaying antibacterial activity is not well understood. Therefore, in this study, readily available (E)-hydroxychalcones (**3a-3n**) were synthesised to evaluate their antibacterial activity.

EXPERIMENTAL

Material and Methods

2′-Hydroxyacetophenone (**1a**) (Aldrich), 3′-hydroxyacetophenone (**1b**) (Sigma), 4′-hydroxyacetophenone (**1c**) (Sigma), acetophenone (**1d**) (Aldrich), 2-furaldehyde (**2a**) (Fischer), benzaldehyde (**2b**) (Qualigens), 4-methoxybenzaldehyde (**2c**) (Aldrich), 2-bromobenzaldehyde (**2d**) (Aldrich), 2-hydroxybenzaldehyde (**2e**) (Loba), 3-hydroxybenzaldehyde (**2f**) (Sigma) and 4-hydroxybenzaldehyde (**2g**) (Sigma) were used as substrates. Gentamicin (10 µg/disc), purchased from Himedia, was used as a standard antibiotic for the antibacterial assay. Parent chalcones, namely (E)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**P1**) and (E)-1,3-diphenylprop-2-en-1-one (**P2**), were previously synthesised in our laboratory and were also used in this study (Fig.-2).[24]



P1 **P2**

Fig.-2: Structures of Parent Chalcone P1 and P2

Detection Method

Pre-coated silica gel 60 F_{254} (Sigma-Aldrich) was used for thin-layer chromatography (TLC). UV spectra were obtained by using a Cary 60 UV-Vis spectrophotometer (Agilent). IR spectra were recorded in a KBr disc using an IRTracer-100 FTIR spectrophotometer (Shimadzu). NMR spectra were recorded in either CD_3OD or $CDCl_3$ on an Avance Neo 400 MHz FT-NMR spectrometer (Bruker). Epoch2 (BioTek Instruments) was used for spectrophotometry.

General Procedure for the Synthesis of (E)-Hydroxychalcones (3a-3n)

Method I: A round-bottomed flask, equipped with a magnetic stirring bar, was cooled to 0 °C. To this, NaOH (1.60 g), distilled water (6 mL) and EtOH (30 mL) were added, and then stirred. Subsequently, arylmethyl ketone (**1**, 12 mmol) and aromatic aldehyde (**2**, 12 mmol) were added to the homogeneous reaction mixture. Stirring of the reaction mixture was continued at room temperature overnight, and the progress of the reaction was monitored by TLC (hexane: EtOAc, 8:1). After completion, the reaction was quenched with 10% HCl (30 mL). The product was extracted with EtOAc (30 mL × 3), washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by recrystallisation with EtOH. (E)-Hydroxychalcones **3a-3c** were synthesised by this method.

Method II: In a round-bottomed flask, arylmethyl ketone (**1**, 25 mmol), aromatic aldehyde (**2**, 25 mmol), and EtOH (25 mL) were added. The reaction mixture was stirred at room temperature to get a homogeneous solution. Subsequently, 40% aq. NaOH (12.5 mL) was added slowly. The mixture was stirred overnight, and the progress of the reaction was monitored by TLC (hexane: EtOAc, 1:1). After completion, the reaction mixture was diluted with H_2O (70 mL) and then acidified with 10% HCl. The solid product formed was collected by filtration and was purified by recrystallisation with EtOH. (E)-Hydroxychalcones **3d-3n** were synthesised by this method.

Analytical Data

(E)-3-(Furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (3a)

Substrates used: 2′-hydroxyacetophenone (**1a**, 1.634 g, 12 mmol) and 2-furaldehyde (**2a**, 1.0 mL, 12 mmol). Yield: 2.188 g, 85.1%.[24] State: yellow crystal. UV (MeOH) λ nm: 359, 247. IR (KBr) ῡ cm^{-1}:

3280, 1640, 1570, 1556, 1161. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 7.95 (d, *J* = 8.0 Hz, 1H), 7.65-7.60 (m, 1H), 7.64 (d, *J* = 14.8 Hz, βH), 7.58 (d, *J* = 15.2 Hz, αH), 7.44 (dd, *J* = 7.6, 8.4 Hz, 1H), 6.92-6.87 (m, 3H), 6.54 (dd, *J* = 1.6, 2.0 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 195.04, 164.52, 153.18, 147.40, 137.54, 132.53, 131.24, 121.55, 120.35, 119.25, 118.90, 118.45, 114.14.

(E)-1-(2-Hydroxyphenyl)-3-phenylprop-2-en-1-one (3b)
Substrates used: 2′-hydroxyacetophenone (**1a**, 1.634 g, 12 mmol) and benzaldehyde (**2b**, 1.22 mL, 12 mmol). Yield: 1.178 g, 43.8%.[24] State: yellow crystal. UV (MeOH) λ nm: 316, 227. IR (KBr) ῡ cm^{-1}: 3280, 1639, 1571, 1508, 1205. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 12.79 (s, OH), 7.92 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.91 (d, *J* = 15.6 Hz, βH), 7.66-7.65 (m, 2H), 7.65 (d, *J* = 15.2 Hz, αH), 7.51-7.47 (m, 1H), 7.43-7.42 (m, 3H), 7.02 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.96-6.91 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 193.98, 163.83, 145.70, 136.64, 134.83, 131.15, 129.88, 129.27, 128.89, 120.36, 120.25, 119.08, 118.88.

(E)-1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3c)
Substrates used: 2′-hydroxyacetophenone (**1a**, 1.634 g, 12 mmol) and 4-methoxybenzaldehyde (**2c**, 1.5 mL, 12 mmol). Yield: 2.136 g, 70.0%.[24] State: yellow crystal. UV (MeOH) λ nm: 365, 241. IR (KBr) ῡ cm^{-1}: 3300, 1641, 1566, 1494, 1211. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 8.03 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.80 (d, *J* = 15.6 Hz, βH), 7.67 (d, *J* = 15.2 Hz, αH), 7.65 (d, *J* = 8.8 Hz, 2H), 7.45-7.40 (m, 1H), 6.93-6.87 (m, 4H), 3.77 (s, OCH_3). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 195.58, 164.54, 163.84, 146.81, 137.37, 132.06, 131.42, 128.94, 121.66, 120.29, 119.19, 119.13, 115.71, 56.09.

(E)-3-(2-Bromophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (3d)
Substrates used: 2′-hydroxyacetophenone (**1a**, 3.404 g, 25 mmol) and 2-bromobenzaldehyde (**2d**, 4.626 g, 25 mmol). Yield: 6.973 g, 92.0%. State: yellow crystal. UV (MeOH) λ nm: 306, 223. IR (KBr) ῡ cm^{-1}: 3217, 1654, 1598, 1573, 1197, 572. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 7.66 (d, *J* = 15.6 Hz, βH), 7.61-7.60 (m, 2H), 7.55 (d, *J* = 15.6 Hz, αH), 7.45 (d, *J* = 7.2 Hz, 1H), 7.35-7.32 (m, 3H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H) (Fig.–3a). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 192.51, 159.21, 146.24, 140.81, 136.32, 131.86, 131.01, 130.19, 129.80, 123.28, 121.51, 121.13, 115.97 (Fig.–3b).

(E)-3-(Furan-2-yl)-1-(3-hydroxyphenyl)prop-2-en-1-one (3e)
Substrates used: 3′-hydroxyacetophenone (**1b**, 3.404 g, 25 mmol) and 2-furaldehyde (**2a**, 2.1 mL, 25 mmol). Yield: 4.997 g, 92.8%. State: yellow crystal. UV (MeOH) λ nm: 335, 243. IR (KBr) ῡ cm^{-1}: 3255, 1647, 1595, 1550, 1240. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.58 (d, *J* = 15.2 Hz, βH), 7.58 (d, *J* = 8.0 Hz, 1H), 7.54-7.53 (m, 1H), 7.52 (d, *J* = 1.2 Hz, 1H), 7.41 (d, *J* = 15.6 Hz, αH), 7.38 (dd, *J* = 0.4, 7.6 Hz, 1H), 7.06 (ddd, *J* = 0.8, 2.4, 8.0 Hz, 1H), 6.71 (d, *J* = 3.2 Hz, 1H), 6.50 (dd, *J* = 1.6, 3.2 Hz, 1H), 5.51 (s, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 189.84, 156.33, 151.85, 145.27, 139.86, 131.15, 130.13, 121.25, 120.35, 119.43, 116.71, 115.19, 112.95.

(E)-1-(3-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3f)
Substrates used: 3′-hydroxyacetophenone (**1b**, 3.404 g, 25 mmol) and 4-methoxybenzaldehyde (**2c**, 3.404 g, 25 mmol). Yield: 5.879 g, 92.5%. State: yellow crystal. UV (MeOH) λ nm: 336, 235, 221. IR (KBr) ῡ cm^{-1}: 3361, 1649, 1598, 1558, 1255. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 7.66-7.55 (m, 2H), 7.61 (d, *J* = 12.8 Hz, βH), 7.43 (d, *J* = 14.8 Hz, αH), 7.43-7.39 (m, 1H), 7.34 (s, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 3.74 (d, *J* = 8.4 Hz, OCH_3). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 192.67, 163.62, 159.21, 146.42, 141.16, 131.73, 130.97, 128.97, 121.30, 121.03, 120.81, 115.92, 115.66, 56.04.

(E)-3-(2-Bromophenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (3g)
Substrates used: 3′-hydroxyacetophenone (**1b**, 3.404 g, 25 mmol) and 2-bromobenzaldehyde (**2d**, 4.626 g, 25 mmol). Yield: 6.961 g, 91.8%. State: yellow crystal. UV (MeOH) λ nm: 305, 236. IR (KBr) ῡ cm^{-1}: 3412, 1637, 1575, 1477, 1199, 630. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 8.18 (d, *J* = 15.2 Hz, βH), 8.04 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 15.2 Hz, αH), 7.61 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 7.2, x Hz, 1H), 7.36 (dd, *J* = 7.2, x Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 8.4 Hz, 1H) (Fig.–3c).

^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 195.24, 164.58, 144.31, 137.81, 135.97, 134.77, 133.18, 131.70, 129.66, 129.36, 127.15, 124.70, 121.52, 120.43, 119.26 (Fig.–3d).

(E)-3-(Furan-2-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3h)
Substrates used: 4′-hydroxyacetophenone (**1c**, 3.404 g, 25 mmol) and 2-furaldehyde (**2a**, 2.1 mL, 25 mmol). Yield: 4.991 g, 93.2%. State: yellow crystal. UV (MeOH) λ nm: 341, 234. IR (KBr) ῡ cm^{-1}: 3124, 1647, 1606, 1570, 1230. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.99 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 15.2 Hz, βH), 7.50 (d, *J* = 1.2 Hz, 1H), 7.44 (d, *J* = 15.2 Hz, αH), 6.91 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 3.2 Hz, 1H), 6.49 (dd, *J* = 1.6, 3.2 Hz, 1H), 5.85 (s, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 188.58, 160.30, 152.01, 145.01, 131.34, 130.47, 119.36, 116.22, 115.70, 112.86.

(E)-1-(4-Hydroxyphenyl)-3-phenylprop-2-en-1-one (3i)
Substrates used: 4′-hydroxyacetophenone (**1c**, 3.404 g, 25 mmol) and benzaldehyde (**2b**, 2.54 mL, 25 mmol). Yield: 5.046 g, 90.0%. State: yellow crystal. UV (MeOH) λ nm: 317, 226. IR (KBr) ῡ cm^{-1}: 3120, 1647, 1606, 1566, 1220. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.99 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 16.0 Hz, βH), 7.63-7.61 (m, 2H), 7.52 (d, *J* = 16.0 Hz, αH), 7.40-7.39 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 189.08, 161.80, 144.46, 135.25, 131.50, 131.39, 130.63, 129.16, 128.61, 122.05, 115.67.

(E)-1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3j)
Substrates used: 4′-hydroxyacetophenone (**1c**, 3.404 g, 25 mmol) and 4-methoxybenzaldehyde (**2c**, 3.404 g, 25 mmol). Yield: 5.868 g, 92.3%. State: yellow crystal. UV (MeOH) λ nm: 318, 227. IR (KBr) ῡ cm^{-1}: 3118, 1647, 1602, 1560, 1166. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 7.92 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 16.8 Hz, βH), 7.62-7.52 (m, 2H), 7.57 (d, *J* = 16.4 Hz, αH), 6.90 (d, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 3.79 (s, OCH_3). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 191.03, 163.98, 163.44, 145.38, 132.42, 131.59, 131.24, 129.21, 120.55, 116.55, 115.61, 56.02.

(E)-3-(2-Bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3k)
Substrates used: 4′-hydroxyacetophenone (**1c**, 3.404 g, 25 mmol) and 2-bromobenzaldehyde (**2d**, 4.626 g, 25 mmol). Yield: 7.069 g, 93.3%. State: brown crystal. UV (MeOH) λ nm: 316, 234. IR (KBr) ῡ cm^{-1}: 3147, 1643, 1589, 1556, 1172, 570. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 8.01 (d, *J* = 15.6 Hz, βH), 7.94 (d, *J* = 6.8 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.63-7.56 (m, 1H), 7.61 (d, *J* = 17.2 Hz, αH), 7.35-7.31 (m, 1H), 7.23-7.19 (m, 1H), 6.81 (d, *J* = 2.0 Hz, 2H) (Fig.–3e). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 190.38, 164.29, 143.03, 136.35, 134.67, 132.75, 132.69, 130.78, 129.41, 129.29, 126.85, 125.93, 116.66 (Fig.–3f).

(E)-3-(2-Hydroxyphenyl)-1-phenylprop-2-en-1-one (3l)
Substrates used: acetophenone (**1d**, 3.004 g, 25 mmol) and 2-hydroxybenzaldehyde (**2e**, 3.053 g, 25 mmol). Yield: 5.258 g, 93.8%. State: yellow crystal. UV (MeOH) λ nm: 349, 297, 256. IR (KBr) ῡ cm^{-1}: 3217, 1639, 1597, 1583, 1230. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 8.02 (d, *J* = 15.6 Hz, βH), 7.93 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 15.6 Hz, αH), 7.56 (d, *J* = 7.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.45-7.41 (m, 2H), 7.17-7.13 (m, 1H), 6.79-6.77 (m, 2H). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 193.43, 159.04, 142.82, 139.82, 134.09, 133.22, 130.63, 129.90, 129.68, 123.24, 122.81, 121.01, 117.25

(E)-3-(3-Hydroxyphenyl)-1-phenylprop-2-en-1-one (3m)
Substrates used: acetophenone (**1d**, 3.004 g, 25 mmol) and 3-hydroxybenzaldehyde (**2f**, 3.053 g, 25 mmol). Yield: 4.992 g, 89.0%. State: yellow crystal. UV (MeOH) λ nm: 304, 252. IR (KBr) ῡ cm^{-1}: 3329, 1653, 1602, 1560, 1274. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 7.97, (d, *J* = 8.0 Hz, 2H), 7.65-7.53 (m, 2H), 7.56 (d, *J* = 16.0 Hz, βH), 7.47-7.43 (m, 1H), 7.45 (d, *J* = 14.8 Hz, αH), 7.19-7.11 (m, 2H), 7.05 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 192.62, 159.28, 146.68, 139.50, 137.65, 134.33, 131.24, 129.99, 129.76, 123.05, 121.45, 119.16, 115.97.

(E)-3-(4-Hydroxyphenyl)-1-phenylprop-2-en-1-one (3n)
Substrates used: acetophenone (**1d**, 3.004 g, 25 mmol) and 4-hydroxybenzaldehyde (**2g**, 3.053 g, 25 mmol). Yield: 4.995 g, 89.1%. State: yellow crystal. UV (MeOH) λ nm: 342, 242. IR (KBr) ῡ cm^{-1}: 3223,

1649, 1598, 1579, 1219. ^{1}H NMR (CD_3OD, 400 MHz) δ ppm: 7.94 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 15.6 Hz, βH), 7.52-7.50 (m, 4H), 7.45 (d, J = 12.8 Hz, αH), 7.42-7.40 (m, 1H), 6.75 (d, J = 8.0 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 192.80, 161.88, 147.11, 139.83, 134.06, 132.04, 129.89, 129.64, 127.80, 119.79, 117.09.

Antibacterial Assay

Staphylococcus aureus (ATCC 25952), *Escherichia coli* (ATCC 25922), *Salmonella typhi* (ATCC 14028) and *Shigella sonnei* (ATCC 25931) were used as the bacterial strains to evaluate antibacterial activity of the synthesised (E)-hydroxychalcones (**3a**-**3n**).[25] Working solutions of (E)-hydroxychalcones were prepared in DMSO with a concentration of 50 mg/mL. Each working solution (50 μL) was loaded in a well of Mueller-Hinton agar (MHA) plate swabbed with the bacterial suspension, in triplicate. Antibiotic gentamycin was used as a positive control. The MHA plates were incubated at 37 °C for 24 hr, and then, zones of inhibition (ZOI) were measured. To determine the Minimum Inhibition Concentration (MIC) value, the standardised bacterial suspension was diluted to 1:10 using normal saline (1.5×10^7 CFU/mL). A mixture of equal volumes of Mueller-Hinton broth (MHB) (1 mL) and each sample solution (1 mL) was then serially diluted in another 14 sterile test tubes that already contained 1 mL of MHB (total volume in each tube = 1 mL). The above bacterial suspension (50 μL) was then inoculated (5×10^5 CFU/mL). Thereafter, the tubes were incubated at 37 °C for 24 hr. The lowest concentration at which no bacterial growth was observed visually was taken as the MIC. Minimum Bactericidal Concentration (MBC) values were subsequently determined through sub-culture of the content from the tubes showing no bacterial growth by direct streaking on sterile MHA plates. After incubation at 37 °C for 24 hr, the plates were examined for the growth of bacteria, and thus MBC values were determined.

RESULTS AND DISCUSSION

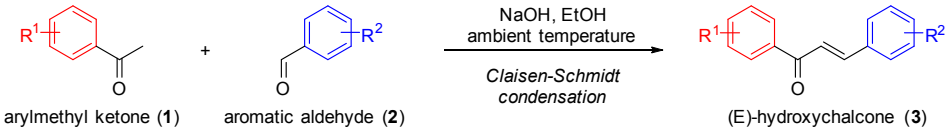
The increase in antibiotic resistance has led to a surge of interest in the identification of new, readily available active molecules. Since chalcones show diverse pharmacological activity, and at the same time, structurally diversified chalcones can be readily synthesised on a gram scale, we are continuously paying efforts on the synthesis of several chalcones, and evaluating their biological activities.[14,24,26] In this work, (E)-hydroxychalcones (**3a**-**3n**) were prepared following a general protocol of classical Claisen-Schmidt condensation. In the presence of NaOH as a base, various arylmethyl ketones **1** and aromatic aldehydes **2** were reacted in EtOH to produce corresponding (E)-hydroxychalcones (**3a**-**3n**) up to 93.8% isolated yield (Table-1).

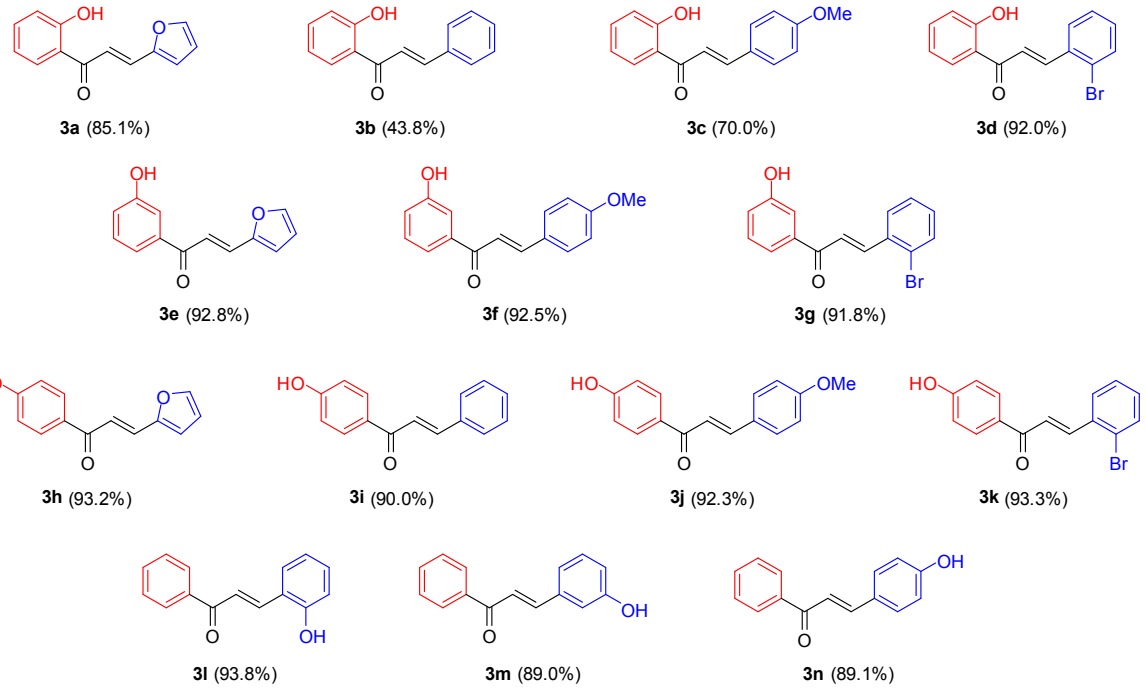
Synthesised (E)-hydroxychalcones (**3a**-**3n**) were characterised by recording of UV-Vis, IR, ^{1}H NMR and ^{13}C NMR spectra (Table–2). All synthesised (E)-hydroxychalcones have displayed the UV-Vis spectral pattern of chalcones. These (E)-hydroxychalcones contained hydroxyl, carbonyl and alkene groups, including aromatic rings. In the FTIR spectra, vibrational stretches of O–H, C=O and C=C appeared at the wave number ranges of 3412–3118, 1662–1637 and 1606–1566 cm^{-1}, respectively. As revealed by the splitting of αH and βH peaks in ^{1}H NMRs, above synthesised (E)-hydroxychalcones were found to be E-configured ($J_{αH–βH}$ = 12.8–17.2 Hz). It is worth mentioning that when ^{1}H NMRs of (E)-hydroxychalcones **3b**, **3e** and **3h** were recorded in $CDCl_3$, peaks for the hydroxyl proton appeared at δ 12.79, 5.51 and 5.85 ppm, respectively. On the other hand, ^{1}H NMRs of the (E)-hydroxychalcones recorded in CD_3OD didn't display hydroxyl proton peaks, perhaps due to deuterium exchange. Interestingly, a doublet at δ 3.74 ppm (J = 8.4 Hz) was observed for OCH_3 in the ^{1}H NMR of compound **3f**, which was due to a long-range spin coupling of the methoxy group.[27] And, the relevant carbon peak was observed at δ 56.04 ppm in the ^{13}C NMR spectrum. In ^{13}C NMRs, the carbon peaks of all (E)-hydroxychalcones were easily traceable. Among 3 hydroxy-bromo chalcones synthesised, (E)-3-(2-bromophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2′-hydroxy-2-bromo chalcone) (**3d**) is commercially available, whereas (E)-3-(2-bromophenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (3′-hydroxy-2-bromo chalcone) (**3g**) and (E)-3-(2-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (4′-hydroxy-2-bromo chalcone) (**3k**) are new compounds. NMR spectra of these hydroxy-bromo chalcones are shown in Fig.-3.

Fluorinated, chlorinated, ferrocenyl, steroidal and other hybrid chalcones have shown potent antibacterial activity;[23] however, synthesis of those chalcone derivatives is a tedious task. Previously, we have

screened the antibacterial activity of some (E)-chalcones that were readily synthesised by the classical protocols of Claisen-Schmidt condensation.[14] In this work, we have synthesised (E)-hydroxychalcones (**3a-3n**) and their antibacterial activity was evaluated.

Table-1: Synthesis of (E)-Hydroxychalcones





As shown in Table-3, the (E)-hydroxychalcones **3d**, **3e**, **3f**, **3l**, and **3m** have displayed notable antibacterial activity, especially against *S. aureus* and *S. sonnei*, with the ZOI range 11–21 mm (entries 6, 7, 8, 14 and 15). Among them, (E)-3-(2-bromophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2′-hydroxy-2-bromo chalcone) (**3d**) was found most effective against those bacterial strains displaying ZOI 21.00±0 and 20.33±0.33 mm, respectively, and the MIC value was found to be 0.78 mg/mL (entry 6).

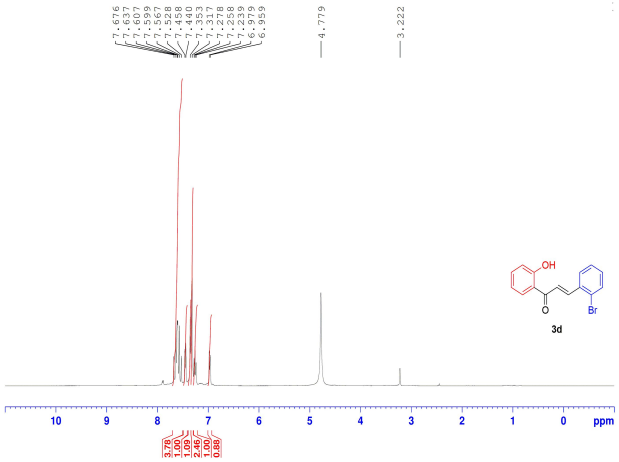
To the best of our knowledge, the antibacterial activity of 2′-hydroxy-2-bromo chalcone (**3d**) has never been reported. When the antibacterial activity of the parent chalcones **P1** and **P2** was compared, replacement of the phenyl B ring with a heteroaromatic furyl ring was found to be inferior (compare entry 1 versus 2). Furthermore, introduction of a hydroxyl substituent in the ortho-, meta- and para-positions in the A ring of furachalcones (compounds **3a**, **3e** and **3h**, respectively) could not enhance the antibacterial activity (compare entry 1 versus 3, 7 and 10). None of the chalcones investigated was found to be effective against *E. coli* and *S. typhi*.

Apparently, no new major class of antibiotics has been discovered after 1962.[28] At the same time, the development of methicillin-resistant *S. aureus* (MRSA) is continuously threatening the world.[29] *S. aureus* is one of the main human pathogens, and it causes external infections. This work has demonstrated that (E)-hydroxychalcones, viz. **3d**, **3e**, **3f**, **3l**, and **3m**, show a significant antibacterial activity against *S. aureus*, and demands a need for aggressive efforts to find a new antibacterial reagent consisting basic framework of (E)-hydroxychalcones, particularly bearing halogen substituent(s).

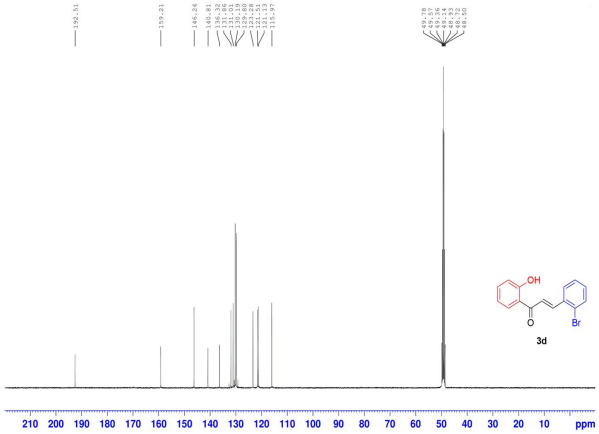
Table–2: Selected UV, IR, ^{1}H NMR, and ^{13}C NMR Data of the Synthesised (E)-Hydroxychalcones

Compound No.	UV (λ nm)	IR ($\bar{\upsilon}$ cm^{-1})	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
3a[a]	359 (n→π*) 247 (π→π*)	3280 (O–H) 1640 (C=O) 1570 (C=C)	7.64 (d, *J* = 14.8 Hz, βH) 7.58 (d, *J* = 15.2 Hz, αH)	195.04 (CO)
3b[b]	316 (n→π*) 227 (π→π*)	3280 (O–H) 1639 (C=O) 1571 (C=C)	12.79 (s, OH) 7.91 (d, *J* = 15.6 Hz, βH) 7.65 (d, *J* = 15.2 Hz, αH)	193.98 (CO)
3c[a]	365 (n→π*) 241 (π→π*)	3300 (O–H) 1641 (C=O) 1566 (C=C)	7.80 (d, *J* = 15.6 Hz, βH) 7.67 (d, *J* = 15.2 Hz, αH) 3.77 (s, OCH_3)	195.58 (CO) 56.09 (OCH_3)
3d[a]	306 (n→π*) 223 (π→π*)	3217 (O–H) 1654 (C=O) 1598 (C=C) 572 (C–Br)	7.66 (d, *J* = 15.6 Hz, βH) 7.55 (d, *J* = 15.6 Hz, αH)	192.51 (CO)
3e[b]	335 (n→π*) 243 (π→π*)	3255 (O–H) 1647 (C=O) 1595 (C=C)	7.58 (d, *J* = 15.2 Hz, βH) 7.41 (d, *J* = 15.6 Hz, αH) 5.51 (s, OH)	189.84 (CO)
3f[a]	336 (n→π*) 235 (π→π*) 221 (π→π*)	3361 (O–H) 1649 (C=O) 1598 (C=C)	7.61 (d, *J* = 12.8 Hz, βH)[c] 7.43 (d, *J* = 14.8 Hz, αH)[c] 3.74 (d, *J* = 8.4 Hz, OCH_3)	192.67 (CO) 56.04 (OCH_3)
3g[a]	305 (n→π*) 236 (π→π*)	3412 (O–H) 1637 (C=O) 1575 (C=C) 630 (C–Br)	8.18 (d, *J* = 15.2 Hz, βH) 7.79 (d, *J* = 15.2 Hz, αH)	195.24 (CO)
3h[b]	341 (n→π*) 234 (π→π*)	3124 (O–H) 1647 (C=O) 1606 (C=C)	7.57 (d, *J* = 15.2 Hz, βH) 7.44 (d, *J* = 15.2 Hz, αH) 5.85 (s, OH)	188.58 (CO)
3i[b]	317 (n→π*) 226 (π→π*)	3120 (O–H) 1647 (C=O) 1606 (C=C)	7.79 (d, *J* = 16.0 Hz, βH) 7.52 (d, *J* = 16.0 Hz, αH)	189.08 (CO)
3j[a]	318 (n→π*) 227 (π→π*)	3118 (O–H) 1647 (C=O) 1602 (C=C)	7.64 (d, *J* = 16.8 Hz, βH)[c] 7.57 (d, *J* = 16.4 Hz, αH) 3.79 (s, OCH_3)	191.03 (CO) 56.02 (OCH_3)
3k[a]	316 (n→π*) 234 (π→π*)	3147 (O–H) 1643 (C=O) 1589 (C=C) 570 (C–Br)	8.01 (d, *J* = 15.6 Hz, βH) 7.61 (d, *J* = 17.2 Hz, αH)[c]	190.38 (CO)
3l[a]	349 (n→π*) 297 (n→π*) 256 (π→π*)	3217 (O–H) 1639 (C=O) 1597 (C=C)	8.02 (d, *J* = 15.6 Hz, βH) 7.70 (d, *J* = 15.6 Hz, αH)	193.43 (CO)
3m[a]	304 (n→π*) 252 (π→π*)	3329 (O–H) 1653 (C=O) 1602 (C=C)	7.56 (d, *J* = 16.0 Hz, βH)[c] 7.45 (d, *J* = 14.8 Hz, αH)[c]	192.62 (CO)
3n[a]	342 (n→π*) 242 (π→π*)	3223 (O–H) 1649 (C=O) 1598 (C=C)	7.65 (d, *J* = 15.6 Hz, βH) 7.45 (d, *J* = 12.8 Hz, αH)	192.80 (CO)

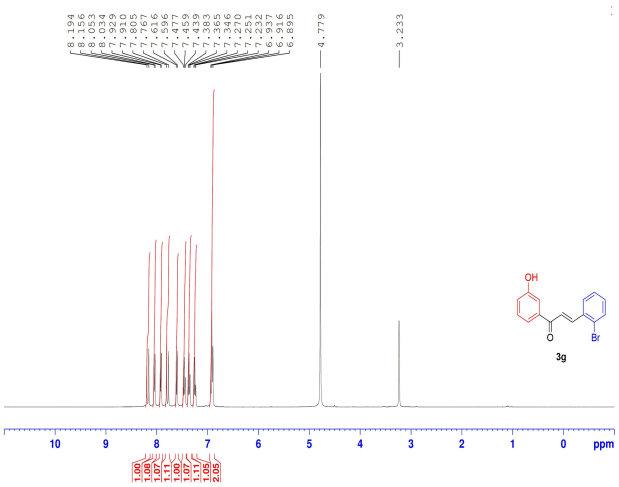
[a] NMRs were recorded in CD_3OD.
[b] NMRs were recorded in $CDCl_3$.
[c] The peak was merged with nearby signals.



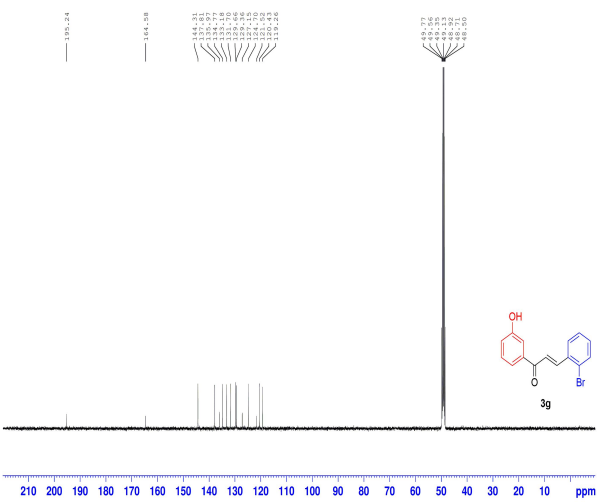
(a) ^{1}H NMR of 2′-hydroxy-2-bromo chalcone (**3d**)



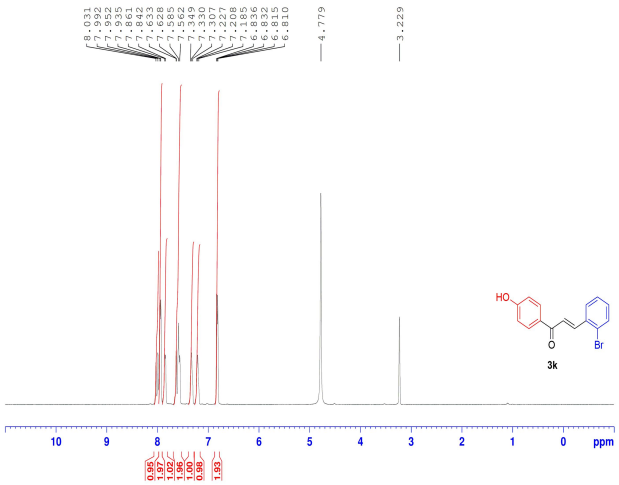
(b) ^{13}C NMR of 2′-hydroxy-2-bromo chalcone (**3d**)



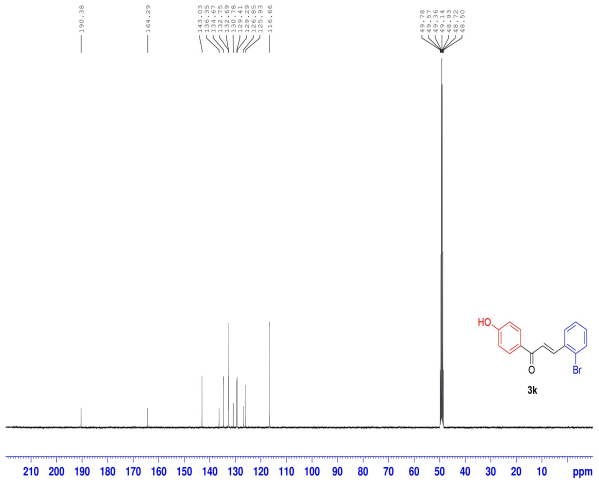
(c) ^{1}H NMR of 3′-hydroxy-2-bromo chalcone (**3g**)



(d) ^{13}C NMR of 3′-hydroxy-2-bromo chalcone (**3g**)



(e) ^{1}H NMR of 4′-hydroxy-2-bromo chalcone (**3k**)



(f) ^{13}C NMR of 4′-hydroxy-2-bromo chalcone (**3k**)

Fig.-3: NMR Spectra of the Synthesised Hydroxy-Bromo Chalcones 3d, 3g, and 3k

Table-3: Antibacterial Activity of the (E)-Hydroxychalcones

S.No.	Compound used	ZOI in mm ± SEM (MIC in mg/mL)			
		S. aureus	*E. coli*	*S. typhi*	*S. sonnei*
1	**P1**	9.67±0.33 (12.50)	–	–	10.00±0 (12.50)
2	**P2**	13.00±1.00 (12.50)	–	–	13.67±0.88 (25.00)
3	**3a**	–	–	–	–
4	**3b**	–	–	–	–
5	**3c**	–	–	–	–
6	**3d**	21.00±0 (0.78)	–	–	20.33±0.33 (0.78)
7	**3e**	11.33±0.33 (12.50)	–	–	11.67±1.20 (25.00)
8	**3f**	11.67+0.33 (25.00)	–	–	11.67±0.67 (25.00)
9	**3g**	–	–	–	–
10	**3h**	–	–	–	–
11	**3i**	–	–	–	–
12	**3j**	–	–	–	–
13	**3k**	–	–	–	10.67±0.67 (25.00)
14	**3l**	20.00±0 (12.50)	–	–	19.33±0.67 (25.00)
15	**3m**	15.00±1.00 (12.50)	–	–	16.33±0.88 (25.00)
16	**3n**	–	–	–	–
17	Gentamicin	23.00±0 (ND)	23.00±0 (ND)	22.67±0.88 (ND)	22.67±0.67 (ND)

(–) = no ZOI, (ND) = not determined

CONCLUSION

(E)-Hydroxychalcones (**3a-3n**) were synthesised in moderate to good isolated yield through the Claisen-Schmidt condensation, and their antibacterial activity was evaluated against 4 bacterial strains. Using 2′-hydroxyacetophenone (**1a**) and 2-bromobenzaldehyde (**2d**) as the substrates, 2′-hydroxy-2-bromo chalcone (**3d**) was synthesised in 92.0% yield, and was found most effective against *S. aureus* and *S. sonnei*. The synthesis of other hydroxy-bromo chalcones, viz. 3′-hydroxy-2-bromo chalcone (**3g**) and 4′-hydroxy-2-bromo chalcone (**3k**) are reported for the first time, but unfortunately, they were either ineffective or weak antibacterial agents.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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