# SYNTHESIS OF 2-(2-(HYDROXYMETHYL)PHENYL)ETHANOL DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

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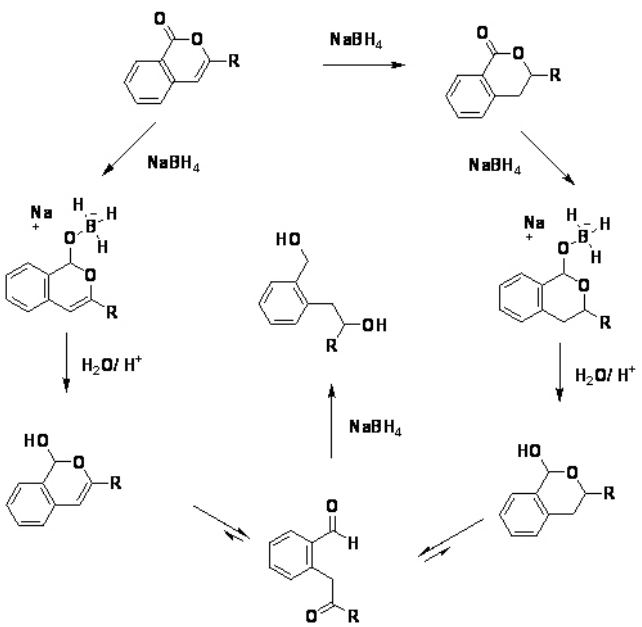
## ABSTRACT

Reaction of 3-substituted isocoumarins **(1a-h)** with excess of sodium borohydride in methanol gave the corresponding 2-(2-(hydroxymethyl)phenyl)ethanol derivatives **(2a-h).** Antimicrobial activities of synthesized compounds were measured, using Gram-negative (Escherichia coli, Salmonella typhi, Proteus mirabilis) and Gram-positive bacteria (Bacillus cereus, Staphylococcus aureus).

**Key words:** Isocoumarin, sodium borohydride, diol, antimicrobial properties.

## INTRODUCTION

Synthesis of variety of compounds like carbocyclic, heterocyclic compounds and various aromatic compounds can be effected from isocoumarins intermediates.[1] The hydroxyl structural moiety was found in numerous pharmaceutically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry.[2] In particular phenylethanol derivatives have good antifungal properties.[3, 4] An increasing number of new isocoumarins in nature and increasing importance of diol derivatives have stimulated our researcher group a continued interest for synthesis of 2-(2-(hydroxymethyl)phenyl)ethanols from the precursor isocoumarins. Recently, several methods have been reported for the synthesis of diols such as palladium catalyzed reactions, electrophilic aromatic substitution, cyclization of 2-allyl- and alkenyl benzoic acid, etc.[5-9] In continuous of research interests,[10-20] present investigation aimed at simplified reaction of isocoumarins and sodium borohydride to the corresponding 2-(2-(hydroxymethyl)phenyl) ethanol derivatives without isolation of intermediate dihydroisocoumarins. (Scheme 1)



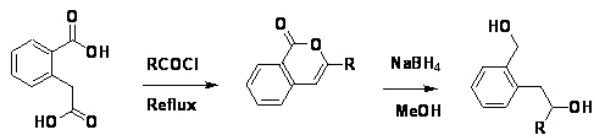

**Scheme 1.** Mechanism of readuction of isocou arins by sodium borohydride

## EXPERIMENTAL

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. All reactions were monitored by thin layer chromatography (TLC) on gel F254 plates. The silica gel (230–400 meshes) for column chromatography was purchased from Spectrochem Pvt. Ltd., India. Melting points were taken in open capillary tubes and are corrected with reference to benzoic acid. IR spectra were recorded on Nucon Infrared spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-*d6* (with TMS for $^1$HNMR and DMSO for $^{13}$CNMR as internal references). Elemental analyses of all compounds were performed on Elementar Vario Micro CHNS analyzer. GCMS analyses were performed with Agilent GCMS- 5973 Inert MSD series.

**General procedure for synthesis of 2-(2-(hydroxymethyl)phenyl) ethanol derivatives from isocoumarins**

Isocoumarins used in our reactions were obtained from homophthalic acid and different acid chloride.[10]




**Homophthalic acid** **1** **2**

The 2-(2-(hydroxymethyl)phenyl)ethanol **(2a-h)** derivatives were prepared from methanolic solution of 3-substituted isocoumarins **(1a-h)** (10 mmol) by addition of sodium borohydride (40 mmol), refluxing for 4 hours at 50°C under nitrogen atmosphere for 4 hrs. Then added further 20 mmol sodium borohydride and continued the process overnight. The completions of reactions were monitored by TLC using pet.ether and ethyl acetate 9:1. Crude mixtures were purified by column chromatography and structures were identified by FTIR, $^1$HNMR, $^{13}$CNMR and GCMS spectroscopic analysis.

**Synthesis of 1-(2-(hydroxymethyl)phenyl)hexan-2-ol (2a) from 3-n-Butyl isocoumarin (1a)**

3-n-Butylisocoumarin, **1a** (1 eq.) was dissolved in 10 volumes of methanol, sodium borohydride (4 eq.) was added to it and stirred at 50°C under nitrogen atmosphere for 4 hrs, then two more equivalents of $NaBH_4$ was further added and left overnight at 50° C for completion of reaction. After TLC analysis, solvent methanol was removed, residue added to water and extracted with ethyl acetate. Ethyl acetate layer was washed with water, dried with anhydrous $Na_2SO_4$, evaporated to yield the product diol, **2a**, which was further purified by washing with petroleum ether. The product was characterized by NMR, GCMS techniques.

Similar procedures were followed for the synthesis of other phenylethanol derivatives **2b-h** and the results have been tabulated as Table 1.

## RESULTS AND DISCUSSION

In this work we report synthesis of potential antibacterial diol derivatives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containing the phenylethanol structural moiety. Thus, the reaction between the isocoumarins **(1)** and sodiumborohydride in methanol at 50°C gave a single product **(2)**. The structure of **2** was confirmed on the basis of IR spectrum which showed the absence of any C=O and C=C stretching of starting material isocoumarin, IR spectra of diols showed peak values at 3400-3070 (due to OH), 3000- 3080 (due to Arm CH) 1500 - 1420 (due to C=CH), 1019 (due to C-O). GCMS analysis of diols formed in the reduction of isocoumarins have shown mass peaks at m/e $M^+$- 18 peaks, base peak at m/e 104 for all compounds, **2a-2h** corresponding to the water elimination and C6H4-CO respectively along with other fragmentation peaks. The present paper also included NMR characterization of these compounds, **2a-2h**.

**Analysis Data**

**1-(2-(hydroxymethyl)phenyl)hexan-2-ol, 2a,** Gummy solid, IR (KBr) ν 3323 (OH), 3064, 3020, 2850, 1455, 1424 (C=C), 1011 $cm^{-1}$ (C-O); $^1$H NMR (400 MHz, DMSO – $d_6$) : δ 7.33 (q, J= 2.98 Hz, 1H), 7.15 (d, J= 2.60 Hz, 3H), 5.07 (t, J= 5.42 Hz, 1H), 4.59- 4.46 (m, 3H), 3.59 -3.56 (m, 1H), 2.64 (t, J= 3.64 Hz, 2H), 1.36 (m, J= 4.63 Hz, 2H) 1.23 (m, J= 6.74 Hz, 4H), 0.84 (t, J= 7.06 Hz, 3H); $^{13}$C NMR (100 MHz, DMSO– $d_6$) δ 140.70, 137.92, 130.55, 127.89, 127.01 126.09 (Aromatic carbons), 71.29, 61.37, 2 X37.37, 28.01, 22.72 (Aliphatic carbons), 14.50; GCMS- 190 (M-18); $C_{13}H_{20}O_2$ Mol. Wt.: 208.3, Calculated C, 74.96; H, 9.68; O, 15.36 Found C, 74.92; H, 9.17; O, 15.34 %.

**2-(2-(hydroxymethyl)phenyl)-1-phenylethanol, 2b** Colourless solid, mp 90°C, IR (KBr) ν 3238 (OH), 3024, 2850, 1474, 1424 (C=C), 1325, 1201, 1057 (C-O), 950, 758, 702 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO - $d_6$) : δ 7.32- 7.22 (m, 5H), 7.15 (d, J= 5.64 Hz, 4H), 5.37 (d, J= 4.52 Hz, 1H), 5.09 (t, J= 5.34 Hz, 1H), 4.74 (m, J= 4.42 Hz, 1H), 4.44 (m, J= 7.43 Hz, 2H), 2.89 (t, J= 6.76 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO – $d_6$) δ 146.55, 140.84, 137.37, 130.80, 128.37, 2X128.01, 2X127.22, 127.01, 126.31, 126.28 (Aromatic carbons), 73.94, 61.55, 42.60 (Aliphatic carbons). GCMS- 210 (M-18), $C_{15}H_{16}O_2$ Mol. Wt.: 228.29, Calcuated C, 78.92; H, 7.06; O, 14.02, Found C, 78.65; H, 6.92; O, 13.98% (OH), (C=C), (C-O)

**2-(2-(hydroxymethyl)phenyl)-1-p-tolylethanol, 2c** Colourless solid, mp 76°C, IR (KBr) ν 3187 (OH), , 3016, 2917, 1934, 1475, 1451(C=C), 1308, 1204, 1062 (C-O), 814, 767, 712 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO – $d_6$) : δ 7.31 (d, J= 5.36 Hz, 1H), 7.20- 7.08 (m, 7H), 5.29 (d, J= 4.32 Hz, 1H), 5.08 (t, J= 5.18 Hz, 1H), 4.69 (d, J= 6.04 Hz, 1H), 4.51 (q, J= 5.90 Hz, 1H), 4.42 (q, J= 6.18 Hz, 1H), 2.85 (q, J= 8.16 Hz, 2H), 2.27 (s, 3H). $^{13}$C (100 MHz, DMSO – $d_6$) δ 143.54, 140.79, 2X137.38, 136.08, 130.73, 2X128.88, 127.92, 2X126.95, 126.23 (Aromatic carbons), 73.71, 61.45, 42.57, 21.17 (Aliphatic carbons). GCMS- 224 (M-18), $C_{16}H_{18}O_2$, Mol. Wt.: 242.31, Calculated C, 79.31; H, 7.49; O, 13.21, Found C, 78.70; H, 7.19; O, 13.11.

**1-(4-chlorophenyl)-2-(2-(hydroxymethyl)phenyl)ethanol, 2d** Colorless solid, mp 104°C, IR (KBr) ν 3244 (OH), 3018, 2853, 1490, 1422 (C=C), 1325, 1212, 1061 (C-O), 1000, 772, 742 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO – $d_6$) : δ 7.35- 7.11 (m, 8H), 5-47- 5.45(d, J= 4.5 Hz 1H), 5.11- 5.08 (t, J= 5.1 Hz 1H), 4.78- 4.72 (m 1H), 4.53- 4.41 (m, 2H), 2.94 -2.82 (m, 2H). $^{13}$C NMR (100 MHz, DMSO – $d_6$) δ 145.47, 140.83, 136.99, 131.59, 130.82, 2X128.28, 2X128.18, 128.04, 127.01, 126.38 (Aromatic carbons), 73.16, 61.51, 42.41 (Aliphatic carbons). GCMS- 244 (M-18), $C_{15}H_{15}ClO_2$, Mol. Wt.: 262.73, Calculated C, 68.57; H, 5.75; O, 12.18, Found C, 68.23; H, 5.64; O, 12.12.

**2-(2-(hydroxymethyl)phenyl)-1-(4-methoxyphenyl)ethanol, 2e** Colourless solid, mp 68°C, IR (KBr) ν 3245 . (OH), 3006, 2852, 1511, 1424 (C=C), 1325, 1243, 1061 (C-O), 1005, 827, 760 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO – $d_6$) : δ 7.30 (d, J= 5.12 Hz, 1H), 7.20 (d, J= 8.32 Hz, 2H), 7.12 (m, 3H), 6.84 (d, J= 8.08 Hz, 2H), 5.25 (d, J= 4.44 Hz, 1H), 5.07 (t, J= 5.32 Hz, 1H), 4.68 (m, J= 4.36 Hz, 1H), 4.50 (q, J= 5.96 Hz, 1H), 4.41 (q, J= 6.22 Hz, 1H), 3.71 (s, 3H), 2.86 (m, J= 7.24 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO – $d_6$) δ 158.55, 140.79, 138.52, 137.36, 130.72, 2X127.89, 127.38, 126.93, 126.21, 2X113.70 (Aromatic carbons), 73.46, 61.44, 42.59 (Aliphatic carbons), 55.45 (O*CH*$_3$),. GCMS-240 (M-18), $C_{16}H_{18}O_3$, Mol. Wt.: 258.31, Calculated C, 74.39; H, 7.02; O, 18.58, Found C,73.97; H, 7.03; O, 18.54.

**2-(2-(hydroxymethyl)phenyl)-1-(naphthalen-1-yl)ethanol, 2f** Colourless solid, mp 142°C, IR (KBr) ν 3229 . (OH), 3061, 2852, 1469, 1448 (C=C), 1331, 1229, 1061 (C-O), 994, 791, 747 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO – $d_6$) : δ 8.27 (d, J= 8.16 Hz, 1H), 7.93 (t, J= 4.66 Hz, 1H), 7.81(d, J= 8.08 Hz, 1H), 7.63 (t, J= 3.54 Hz, 1H), 7.47 (m, 3H), 7.34- 7.33 (m 1H), 7.26- 7.15 (m, 3H), 5.53 (d, J= 4.88 Hz, 2H), 5.12 (t, J= 5.36 Hz, 1H), 4.51 (m, J= 5.94 Hz, 2H), 3.05 (q, J= 3.45 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO – $d_6$) δ 142.23, 140.91, 137.58, 133.73, 130.67, 130.47, 129.07, 128.12, 127.64, 127.08, 126.32, 126.29,125.85, 125.82, 123.89, 123.78 (Aromatic carbons), 70.90, 61.63, 41.43 (Aliphatic carbons). GCMS- 260 (M-18), $C_{19}H_{18}O_2$, Mol. Wt.: 278.35, Calculated C, 81.99; H, 6.52; O, 11.50, Found C, 81.56; H, 6.45; O, 11.46.

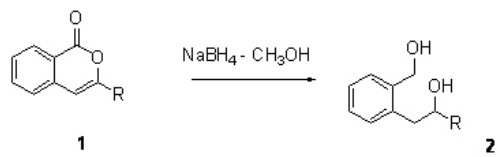
**1-(furan-2-yl)-2-(2-(hydroxymethyl)phenyl)ethanol, 2g** Gummy solid, IR (KBr) ν 3368 (OH), 3064, 2852, 1492, 1451 (C=C), 1010 (C-O) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO – $d_6$) : δ 7.56 (s, 1H), 7.56 (t, J= 0.90 Hz, 1H), 7.33 (t, J= 4.22 Hz, H), 7.12 (m, 3H), 6.35 (q, J= 1.62 Hz, 1H), 6.20 (d, J= 3.12 Hz, 1H), 5.43 (d, J= 5.48 Hz, 1H), 5.07 (t, J= 5.32 Hz, 1H), 4.71 (m, J= 3.88 Hz, 1H), 4.51 (m, J= 5.75 Hz, 2H), 3.01 (m, J= 6.56 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO – $d_6$) δ 158.11, 142.02, 140.85, 136.64, 130.54, 127.95, 127.00, 126.39, 110.60, 106.01 (Aromatic carbons), 67.44, 61.37, 38.73 (Aliphatic carbons). GCMS-200 (M-18), $C_{13}H_{18}O_3$, Mol. Wt.: 218.25, Calculated C, 71.54; H, 6.47; O, 21.99, Found C, 71.00; H, 6.39; O, 21.88.

**2-(2-(hydroxymethyl)phenyl)-1-(thiophen-2-yl)ethanol, 2h** Gummy solid, IR (KBr) ν 3342 (OH),, 3054, 2872, 1492, 1451 (C=C), 1034 (C-O), 748, 699 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO – $d_6$): δ 7.37- 7.32 (m, 2H), 7.15 (d, J= 6.32 Hz, 3H), 6.92 (m, 1H), - 6.84 (d, J= 3.12 Hz, 1H), 5.74 (t, J= 3.28 Hz, 1H), 5.08 (t, J= 5.32 Hz, 1H), 4.98 (m, J= 4.57 Hz, 1H), 4.52 (q, J= 6.02 Hz, 1H), 4.45 (q, J= 6.20 Hz, 1H), 2.98 (d, J= 6.68 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO – $d_6$) δ 143.54, 140.79, 137.38, 136.08, 130.73, 128.88, 127.92, 2X126.95, 126.23 (Aromatic carbons), 73.71, 61.45, 42.57 (Aliphatic carbons). GCMS-216(M-18), $C_{13}H_{18}O_3$, Mol. Wt.: 234.31, Calculated C, 66.64; H, 6.02; O, 13.66; S, 13.68, Found C, 66.52; H, 5.89; O, 13.54.

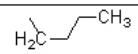
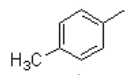
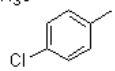
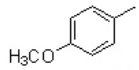
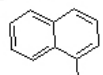
**Antibacterial activity**

The *in vitro* antibacterial screening of synthesized compounds **2a-h** were evaluated against selected Gram-positive organisms viz. *Bacillus cereus, Staphylococcus aureus* and Gram-negative organisms viz. *Escherichia coli, Salmonella typhi, Proteus mirabilis* by Agar well diffusion method.[21] Cultures of bacteria were grown on nutrient broth (HiMedia) at 37$^0$C for 12 – 14 hr and were maintained on respective agar slants at 4$^0$C. Nutrient agar was poured onto a plate and allowed to solidify. Test compounds (DMSO solutions) of 4mg/ml concentration were used as stock solution from this 50 or 100 µl was loaded to each well of 10 mm diameter. The plates were then kept at 5$^O$C for 1 h then transferred to an incubator maintained at 36$^O$C. The width of the growth inhibition zone was measured after 24 h incubation. The activity studies have been carried out with two different concentration and triplicate measurements (Table 2).

**Table 1.-** Reduction of isocoumarins[a] using Sodium borohydride.




**1** **2**

| Entry | Substrate **1** and Product **2** | R | Yield[b] % |
|---|---|---|---|
| 1 | **2a** |  | 84 |
| 2 | **2b** |  | 85 |
| 3 | **2c** |  | 81 |
| 4 | **2d** |  | 74 |
| 5 | **2e** |  | 77 |
| 6 | **2f** |  | 72 |
| 7 | **2g** |  | 79 |
| 8 | **2h** |  | 73 |

[a]All products were identified by $^1$H, $^{13}$C NMR, GCMS
[b]Isolated Yields

**Table 2.-** Antimicrobial activity of synthesized compounds (Zones of inhibition in mm).

| Bacterial Strains | Synthesized Compounds | | | | | | | | | | | | Streptomycin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2a (μL) | | 2b(μL) | | 2c (μL) | | 2d (μL) | | 2e (μL) | | 2f (μL) | | 100 μL |
| | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | |
| | Zone of inhibition in mm | | | | | | | | | | | | |
| *Proteus mirabilis* | - | - | 10 | 22 | - | 15 | - | - | - | - | 13 | 14 | 31 |
| *Bacillus cerus* | - | - | 13 | 18 | 15 | 17 | 13 | 15 | 10 | 16 | 11 | 17 | 29 |
| *Staphylococcus aureus* | 12 | 17 | 17 | 22 | - | 14 | - | 12 | 15 | 21 | 14 | 18 | 28 |
| *Salmonella typhi* | - | - | - | - | - | - | - | - | - | 16 | - | - | 38 |
| *Escherichia coli* | 17 | 20 | 18 | 23 | 16 | 18 | - | 14 | - | - | 12 | 18 | 28 |

## CONCLUSION

In conclusion, we have presented a facile route to diol derivatives **2a-h** starting from isocoumarin derivatives, **1**. The synthesized diol derivatives showed good antibacterial activity against *Staphylococcus aureus*.

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