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^{1}H, ^{13}C, 2D NMR and GCMS characterization of diol derivatives

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Sodium borohydride (SBH) reduction of isocoumarins has been effected in presence of methanol to their respective diols. Diols have been isolated, purified and characterized by GCMS, proton, carbon and two-dimensional NMR spectroscopy analysis. Complete NMR assignments of diols are made using H–H COSY, as well as HSQC, HMQC and HMBC heteronuclear correlation techniques.

Keywords: Isocoumarins, diols, $NaBH_4$, 2D NMR, GCMS

Sodium borohydride have been extensively used in the reduction of ketones and aldehydes. It was superior to LAH and LBH as it was easier to manipulate and have lower sensitivity towards moisture[1-3]. Previously reduction of various esters and lactones by SBH was performed either in mixed solvent of *t*-BuOH-MeOH or THF-methanol to give the corresponding alcohols and diols in good yields[4]. Based on above facts, reduction of isocoumarins, **1a-1h** with SBH was effected to produce the corresponding diols, (**Table I**). Assignments of protons and carbons of diols were made by two-dimensional heteronuclear-correlated experiments (HMQC, using delay values which corresponded to 1*J* (C, H), HMBC using delay values which corresponded to long range correlations 2*J* (C,H) or 3*J* (C,H) even 4*J* (C,H) between the carbons and protons., and H–H correlation spectroscopy which corresponded to 2*J* (H,H) of CH_2 group and 3*J* (H,H) between the proton-carbon-protons.

Results and Discussion

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 C_6H_4-CO respectively along with other fragmentation peaks. IR spectra of diols showed peak values at 3400-3070 (due to OH), 3000- 3080 (due to Arom CH) 1500 - 1420 (due to C=CH), 1019 cm^{-1}(due to C-O).

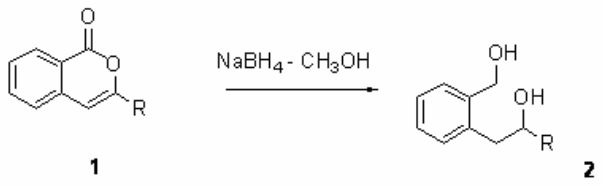
IR spectra of compound **2b** (**Figure 1**) showed peak values at 3238 (due to OH), 3024, 3011 (due to arom CH) 1474, 1424 (due to C=CH), 1057 cm^{-1}(due to C-O). The mass spectra of **2a-h** showed the peaks at 77, 91, 104 (100 %), and M-18.

For reliable interpretation, especially in ^{13}C spectra, bidimensional correlation spectra (in DMSO) were registered: COSY, HSQC, HMQC, and HMBC heteronuclear correlation techniques were used. It is possible to identify all protons of the compounds basing on COSY spectrum. The reference of signals in carbon spectrum is based on cross peaks in HMQC and HMBC spectra. Correlations in HMQC spectrum correspond to the presence of spin-spin interaction between protons and nucleus ^{13}C through one chemical bond. They allow attributing signals of all protonate carbon atoms reliably.

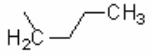
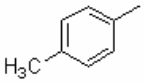
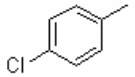
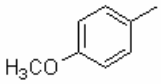
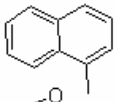
In the NMR spectra of compound **2b** (**Figure 2**), the H–H COSY spectrum of **2b** (**Figure 3**), shows that δ 5.38 and δ 5.10 protons are not interrelated each other but interrelated with δ 4.75 and 4.55 protons respectively, however, δ 4.75 and δ 2.90 protons are not only interrelated each other but also interrelated with δ 5.39 protons. δ 5.39 (1 H, d), 5.10 (1H, t) which have proton-proton correlative signal in H–H COSY spectrum with 4.75 (1H, dd) and 4.55 (1H, m) respectively and no proton-carbon signal in HSQC spectrum (**Figure 4**), is assigned to the proton of hydroxyl groups H-17 and H-16 respectively.

Protons at δ 2.90 (2H, m) have correlation with 4.75 (1H, dd) and assigned to H-8. HSQC shows the

Table I – Sodium borhydride reduction of isocoumarins[a]



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

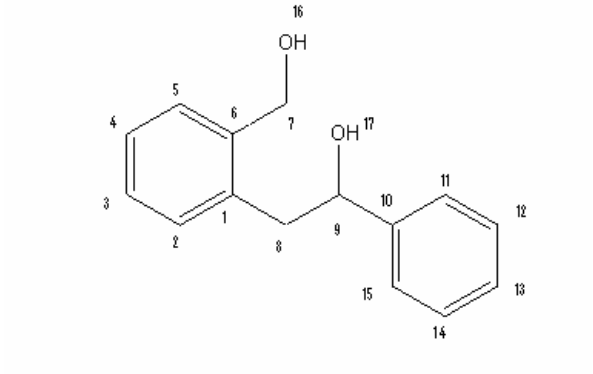


Figure 1 — Structure of compound **2b**

protons at δ 4.7 (1H, dd) and 4.55 (1H, m) corresponds to 73.44 carbon (C-9) and 61.01 carbon (C-7). Also shows that proton at δ 2.9 corresponds to 42.07(C-8). By HMBC spectrum (**Figure 5**) specific assignments of protons and carbons are made as following. The δ 146.040 carbon is correlative with δ 2.9 of H-8 and 5.39 of H-17 proton is assigned to C-10. The H-7, H-8 and H-16 protons are correlative in HMBC with δ 140.348 carbon C-6. The H-7, H-8 is correlative in HMBC with *δ* 136.84 carbon but not with H-17 and H-16 protons is assigned to C-1. Long range coupling of δ 130.282 was observed in HMBC spectrum with H-8 and was assigned as C-2. Further, the δ 4.55 and 4.75 protons are correlative with δ 127.822 and 125.77 carbons in HMBC, being C-5 and C-11, 15.

Similarly IR spectra of the compound **2d** (**Figure 6**) showed peak values at 3244 (due to OH), 3033, 3018 (due to Arm CH) 1490, 1422 (due to C=CH), 1061 cm^{-1} (due to C-O).

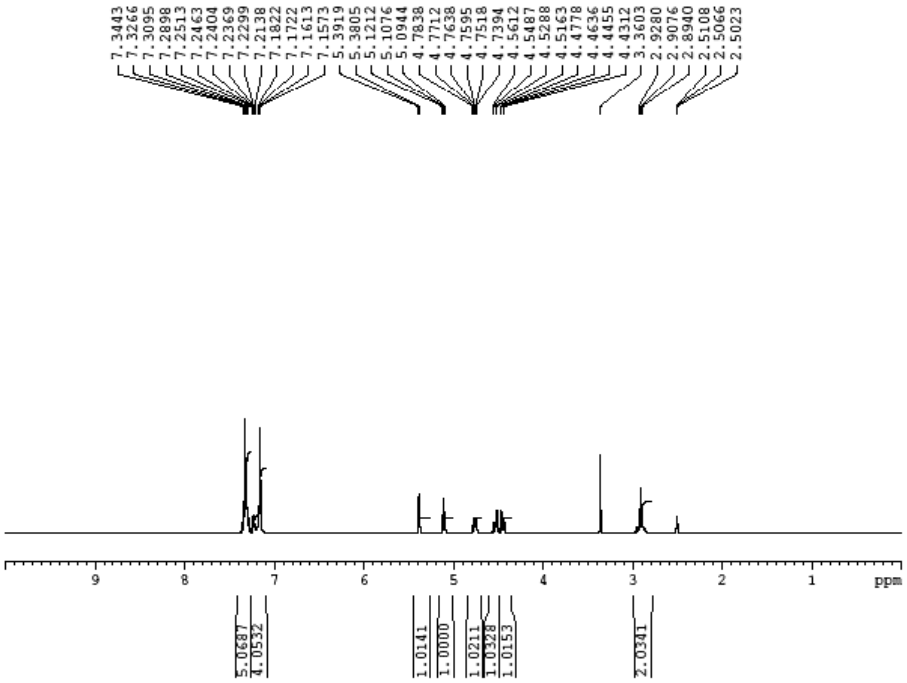


Figure 2—^{1}H NMR of compound **2b**

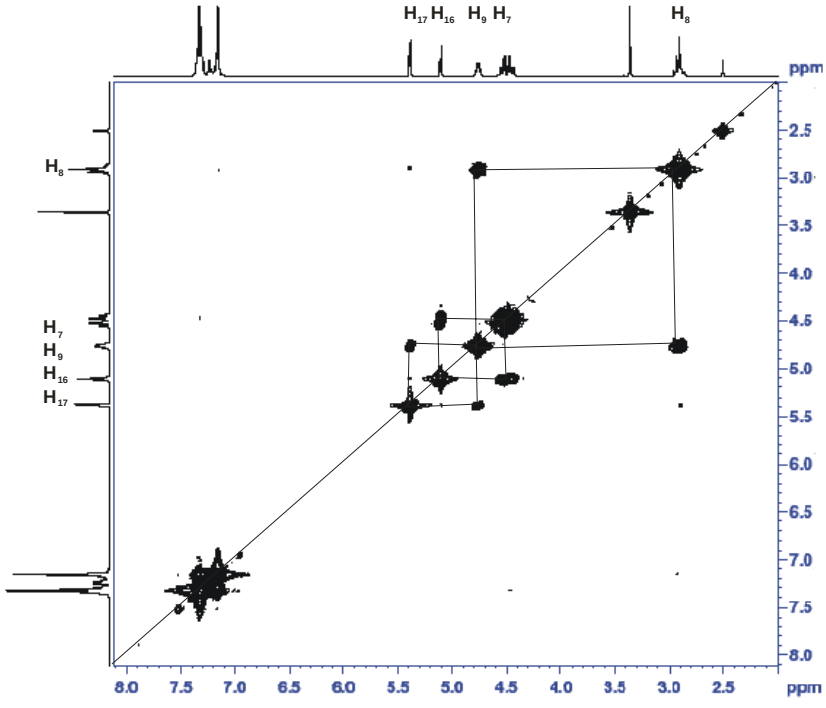


Figure 3 — ^{1}H - ^{1}H COSY NMR of compound **2b**

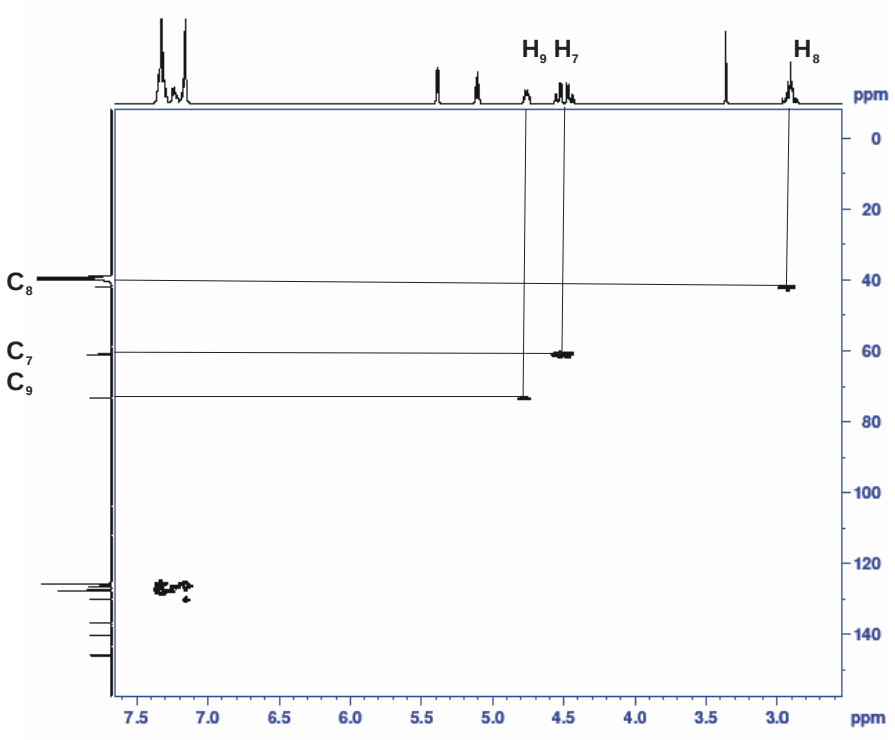


Figure 4 — HSQC NMR of compound **2d**

Figure 7 shows the NMR spectra of compound **2d**. H–H COSY spectrum of **2d** (**Figure 8**), shows that δ 5.49 and δ 5.13 protons are not interrelated each other but interrelated with δ 4.78 and 4.52 protons respectively, however, δ 4.75 and δ 2.91 protons are not only interrelated each other but also interrelated with δ 5.39 protons. δ 5.49 (1 H, d), 5.13 (1H, t) which have proton-proton correlative signal in H–H COSY spectrum with 4.78 (1H, dd) and 4.52 (1H, m) respectively and no proton-carbon signal in HSQC spectrum, is assigned to the proton of hydroxyl groups H-11 and H-8 respectively.

The protons at δ 2.90 (2H, m) have correlation with 4.75 (1H, dd) and assigned to H-9. HSQC spectra (**Figure 9**), shows the protons at δ 4.7 (1H, dd) and 4.55 (1H, m) corresponds to 72.69 carbon (C-9) and 61.01 carbon (C-7). Also shows that proton at δ 2.9 corresponds to 41.93(C-10). By HMBC spectrum (**Figure 10**), specific assignments of protons and carbons are made as following. The δ 146.040 carbon is correlative with δ 2.9 of H-9 and 5.39 of H-11 protons is assigned to C-12. The H-7, H-8 and H-9 protons are correlative in HMBC with *δ* 140.348 carbon C-6. The H-7, H -9 are correlative in HMBC with δ 136.84 carbon but not with H-11 and H-8 protons is assigned to C-1. Long range coupling of δ 130.282 was observed in HMBC spectrum with H-9 and was assigned as C-2. Further, the δ 4.55 and 4.75 protons are correlative with δ 127.822 and 125.77 carbons in HMBC, being C-5 and C-13, 17.

Experimental Section

Melting points were taken in open capillary tubes and are corrected with reference to benzoic acid. IR spectra in KBr pellets were recorded on a Nucon Infrared spectrophotometer. NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. LC-MS analyses were performed with LCMS-Agilent-1100 series Ion Trap. GCMS analyses were performed with Agilent GCMS-5973 Inert MSD series.

Typical Procedure

Isocoumarins, **1a-h** needed were prepared by the reported procedures,[5-7] and are purified, characterized for further reaction. Typical procedures used for the conversion of isocoumarins to corresponding diols were as follows (**Table I**).

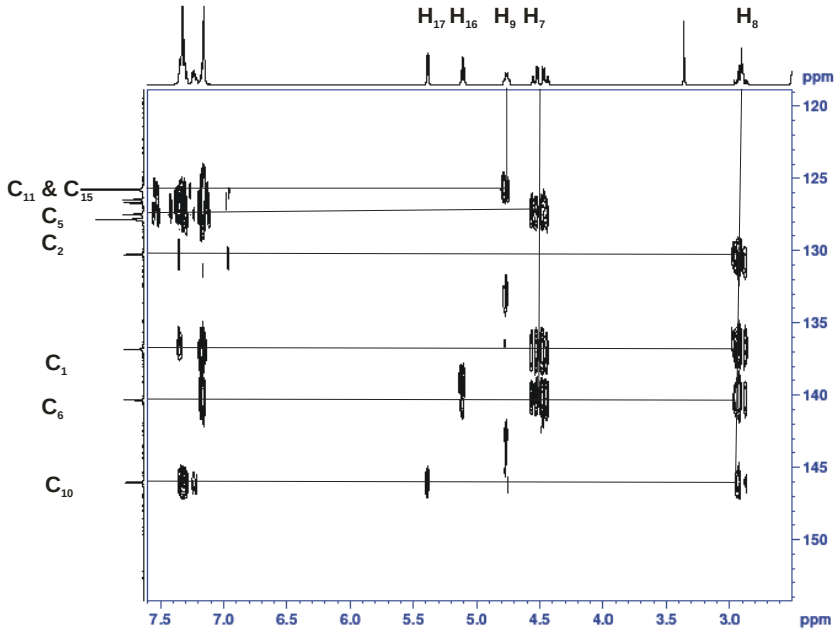


Figure 5 — HMBC NMR of compound **2b**

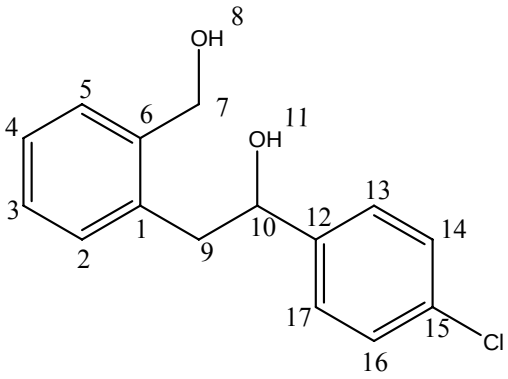


Figure 6 — Structure of compound **2d**

1-(2-(Hydroxymethyl)phenyl)hexan-2-ol, 2a

3-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 hr, then two more equivalents of $NaBH_4$ was further added and left overnight at 50ºC for completion of reaction. After TLC anlaysis, solvent methanol was removed, extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried with anhy. 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 and GCMS techniques.

Similar procedure was followed for conversion of isocoumarins, **1b-1h** to the corresponding diols, **2b-2h**. All the compounds have been purified and characterized, however three of the compounds **2a, 2b** and **2d** are presented herewith.

1-[2-(Hydroxymethyl)phenyl]hexan-2-ol, 2a

Gummy solid, (IR, cm^{-1}): 3323, 3064, 3020, 2850, 1455, 1424, 1011; ^{1}H NMR (DMSO): 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 (DMSO): δ 140.70, 137.92, 130.55, 127.89, 127.01 126.09, 71.29, 61.37, 37.37, 28.01, 22.72, 14.50; GCMS:- 190 (M-18), $C_{13}H_{20}O_2$ Mol. Wt.: 208.3, Calcd. 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, m.p. 90°C, (IR, cm^{-1}): 3238, 3024, 2850, 1474, 1424, 1325, 1201, 1057, 950, 758, 702, 552, 486; ^{1}H NMR (DMSO): 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 (DMSO): δ 146.55, 140.84, 137.37, 130.80, 128.37, 128.01, 127.22, 127.01, 126.31, 126.28, 73.94, 61.55, 42.60; GCMS:- 210 (M-18),

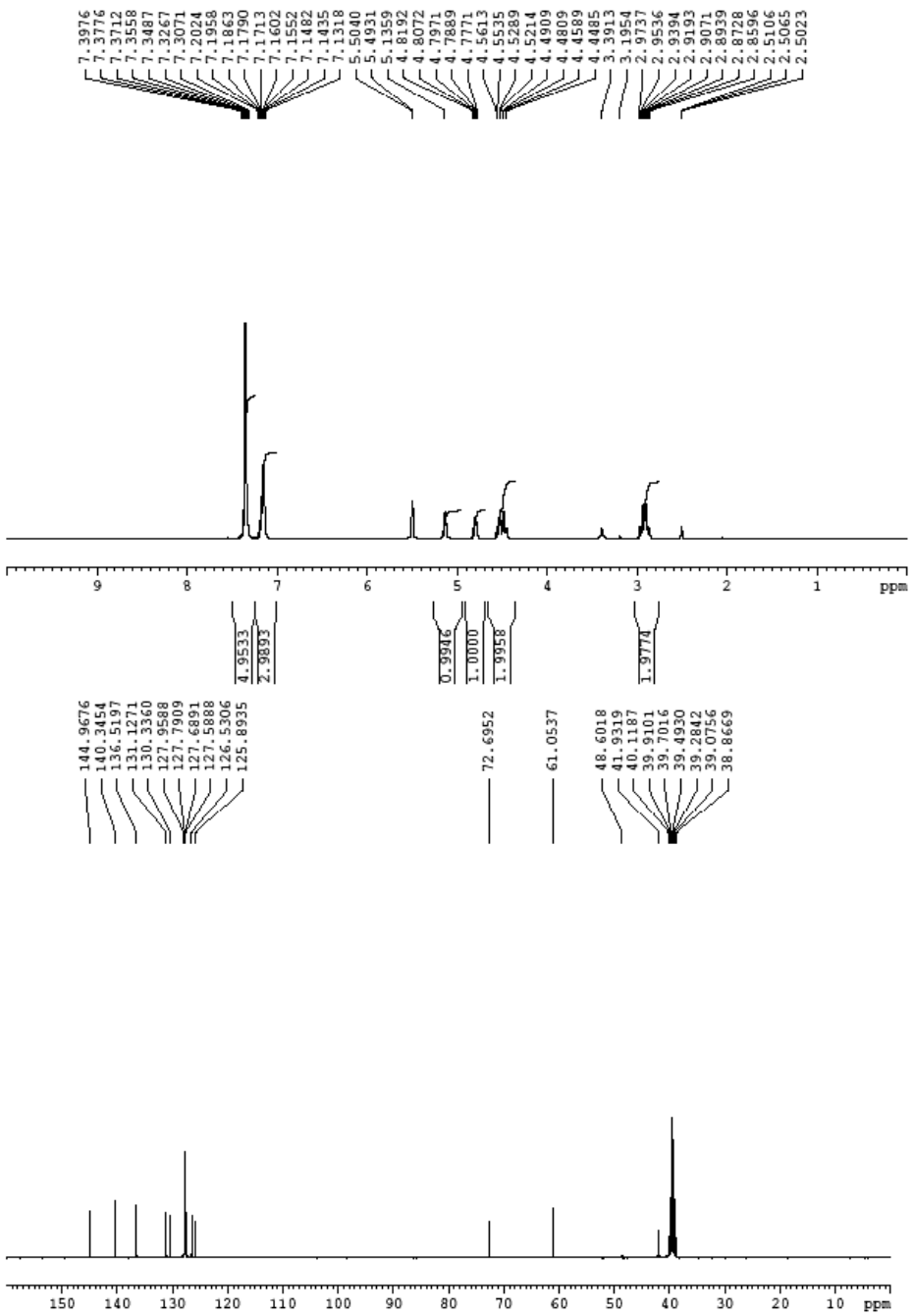


Figure 7 — ^{1}H and ^{13}C NMR of compound **2d**

$C_{15}H_{16}O_2$ Mol. Wt.: 228.29, Calcd,. C, 78.92; H, 7.06; O, 14.02. Found C, 78.65; H, 6.92; O, 13.98%.

1-(4-Chlorophenyl)-2-[2-(hydroxymethyl)phenyl]-ethanol, 2d

Colourless solid, m.p. 104°C, (IR, cm^{-1}): 3244, 3018, 2853, 1490, 1422, 1325, 1212, 1061, 1000, 772, 742, 554, 487; ^{1}H NMR (DMSO): 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 (DMSO): δ 145.47, 140.83, 136.99, 131.59, 130.82, 128.28, 128.18, 128.04, 127.01, 126.38, 73.16, 61.51, 42.41; GCMS:- 244 (M-18), $C_{15}H_{15}ClO_2$, Mol. Wt.: 262.73, Calcd. C, 68.57; H, 5.75; O, 12.18, Found: C, 68.23; H, 5.64; O, 12.12%.

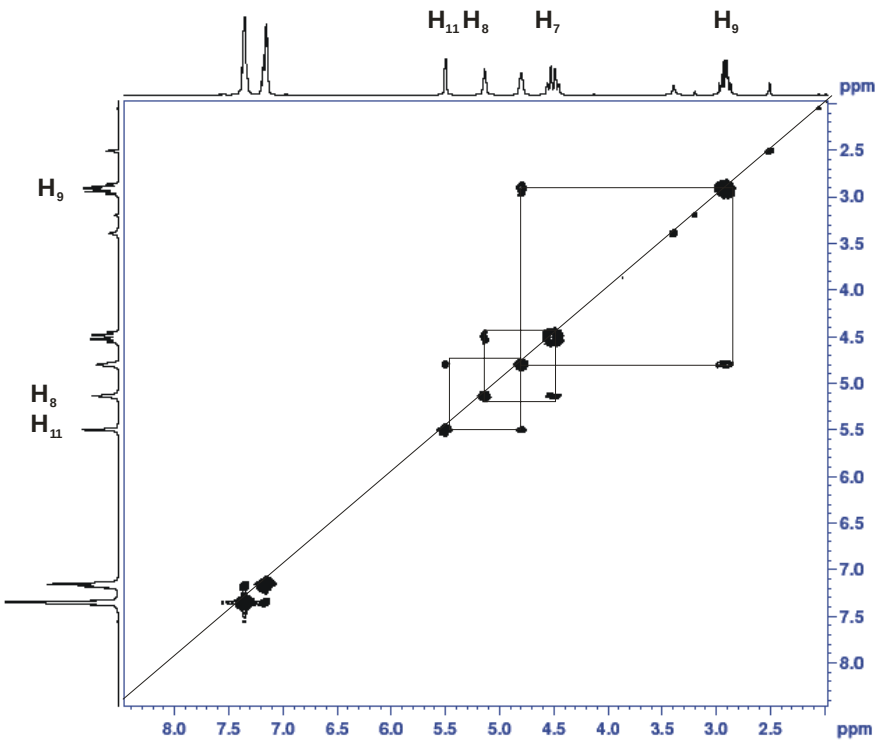


Figure 8 — ^{1}H - ^{1}H COSY NMR of compound **2d**

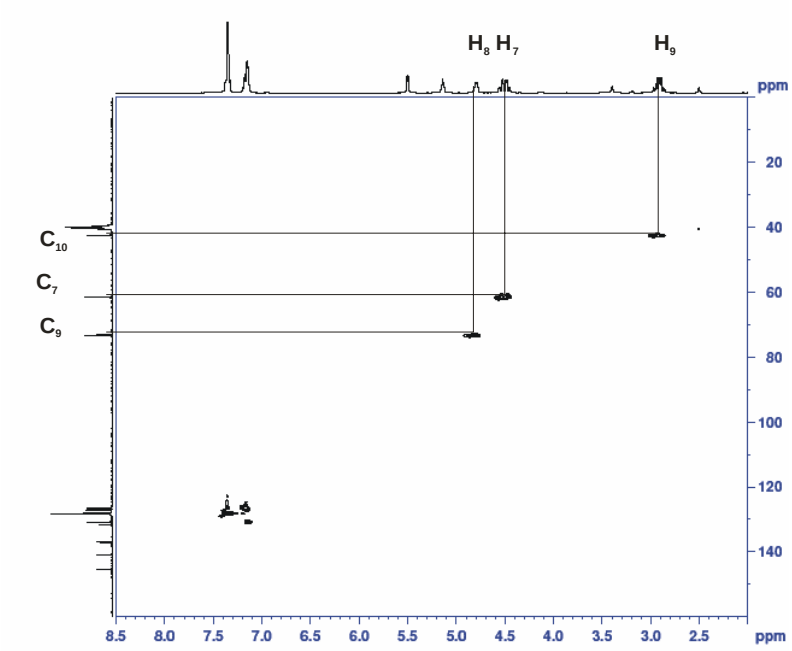


Figure 9 — HSQC NMR of compound **2d**

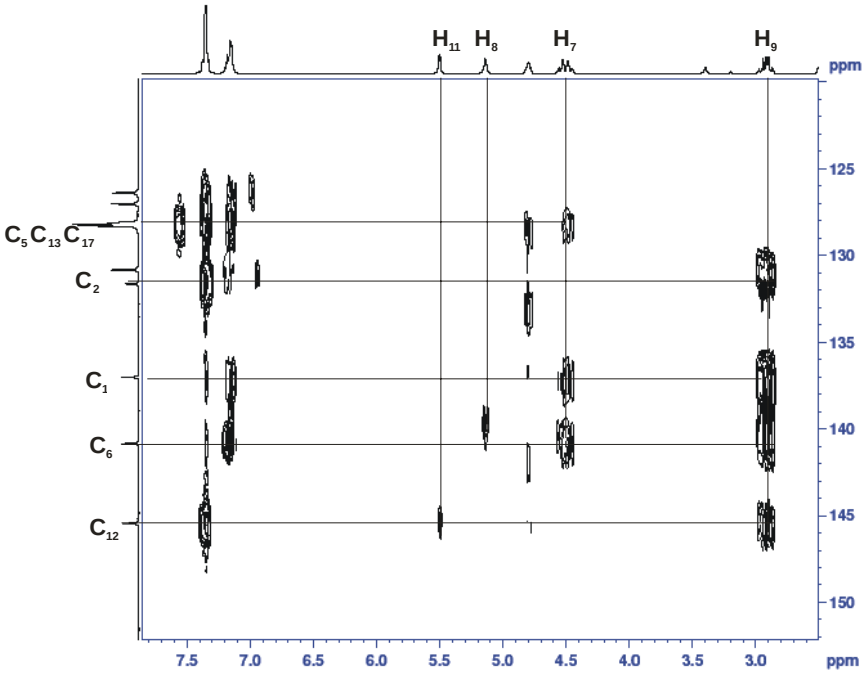


Figure 10 — HMBC NMR of compound **2d**

Conclusion

A simple and efficient conversion of isocoumarins into the corresponding diols is reported (**Table I**). The reaction was quiet useful for direct conversion and for the isocoumarins with different substituents.

Acknowledgements

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