Journal of Chemistry

Supporting Information

Synthesis of 1,4-Dihydropyridines Bearing a Carbamate Moiety at the 4-Position

Davood Habibi,* Mohammad Ali Zolfigol, Maliheh Safaee

Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran

davood.habibi@gmail.com

TABLE OF CONTENTS

Instrumentation, Analysis and Starting Materials:

Experimental:

General: All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterized by spectroscopy data (FT-IR, ^{1}H NMR spectra). The NMR spectra were recorded in acetone and DMSO. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 90 MHz instruments. The chemical shifts (δ) are reported in ppm relative to the TMS as internal standard. *J* values are given in Hz. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. The elemental analysis was performed using Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel polygram SIL G/UV 254 plates.

Genaral Procedure for the synthesis of carbamates (1a-f):

A mixture of hydroxylbezaldehydes (1.0 mM) and phenyl isocyanate derivatives (1.0 mM) was stirred in ethyl acetate or solvent free at 70 ^{o}C in an appropriate time and progress of the reaction was monitored by TLC (Scheme 1, Table 1). After completion, the suspension was cooled, ethyl acetate evaporated and the carbamate residue dissolved in ethanol (10 mL) and filtered. The obtained crystal was pure and characterized by ^{1}H NMR and IR.

Typical procedure for the synthesis of 1,4-dihydropyridines (2a-f):

A mixture of carbamate (1.0 mM), methyl acetoacetate (2.0 mM) and ammonium fluoride (2.0 mM) was stirred in ethyl acetate at 80 ^{o}C for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the suspension was cooled, EtOAc was evaporated and the dihydropyridine residue dissolved in ethanol (10 mL) and filtered. The obtained crystal was pure and characterized by ^{1}H NMR and IR.

Characterization data of products

4-Formylphenyl phenylcarbamate (1a)

White crystal; mp 135-139 °C; ^{1}H NMR (FT-90 MHz, $CDCl_3$/TMS): δ_{ppm} = 7.23-8.16 (m, 10H); IR (KBr), ν (cm^{-1}): 658, 833, 1201, 1539, 1750, 3324; Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.50; N, 5.80; Found: C, 69.70; H, 4.55; N, 5.84.

3-Formylphenyl phenylcarbamate (1b)

White crystal; mp 164-166 °C; ^{1}H NMR (FT-90 MHz, $CDCl_3$/TMS): δ_{ppm} = 6.59 (br, 1H), 7.1-7.72 (m, 9H), 9.9 (s, 1H); IR (KBr), ν (cm^{-1}): 679, 756, 1207, 1542, 1746, 3324.

4-Formyl-3-methoxyphenyl phenylcarbamate (1c)

White crystal; mp 125-129 °C; ^{1}H NMR (FT-90 MHz, $CDCl_3$/TMS): δ_{ppm} = 3.8 (s, 3H), 6.92-7.6 (m, 8H), 9.24 (br, 1H), 9.94 (s, 1H); IR (KBr), ν (cm^{-1}): 653, 834, 1007, 1276, 1502, 1726, 3324; Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.00; H, 4.70; N, 5.10; Found: C, 66.04; H, 4.81; N, 5.48.

4-Formyl-3-ethoxyphenyl phenylcarbamate (1d)

White crystal; mp 109-112 °C; ^{1}H NMR (FT-90 MHz, acetone-d_6/TMS): δ_{ppm} = 1.30 (t, 3H), 4.10 (q, 2H), 7.01-7.53 (m, 8H), 9.24 (b, 1H), 9.93 (s, 1H); IR (KBr), ν (cm^{-1}): 651, 741, 1012, 1150, 1278, 1725, 3303; Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.30; H, 5.20; N, 4.90; Found: C, 67.31; H, 5.38; N, 4.99.

4-Formylphenyl-3,4-dichloro phenylcarbamate (1e)

White crystal; mp 190-193 °C; ^{1}H NMR (FT-90 MHz, acetone-d_6/TMS): δ_{ppm} = 6.95-7.80 (m, 7H), 9.09 (s, 1H), 10.57 (s, 1H); IR (KBr), ν (cm^{-1}): 641, 812, 1221, 1592, 1682, 1756, 3338; Anal. Calcd for $C_{14}H_9NO_3Cl_2$: C, 52.90; H, 2.90; N, 4.51; Found: C, 53.59; H, 2.90; N, 4.72.

3-Formylphenyl-3,4-dichloro phenylcarbamate (1f)

White crystal; mp 191-194 °C; ^{1}H NMR (FT-90 MHz, acetone-d_6/TMS): δ_{ppm} = 7.40-7.82 (m, 7H), 9.06 (b, 1H), 10.65 (s, 1H); IR (KBr), ν (cm^{-1}): 744, 1204, 1228, 1500, 1679, 1719, 3277; Anal. Calcd for $C_{14}H_9NO_3Cl_2$: C, 52.90; H, 2.90; N, 4.51; Found: C, 52.75; H, 2.77; N, 5.37.

Dimethyl 2,6-dimethyl-4-(4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2a**)

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δ_{ppm} = 2.29 (s, 6H), 3.57 (s, 6H), 4.9 (s, 1H), 7.09-7.50 (m, 9H), 8.94 (s, 1H), 10.17 (s, 1H). IR (KBr); ν (cm^{-1}): 746, 1117, 1204, 1499, 1679, 1719, 3278.

Dimethyl 2,6-dimethyl-4-(3-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2b**)

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δ_{ppm} = 2.28 (s, 6H), 3.42 (s, 3H), 3.59 (s, 3H), 4.93 (s, 1H), 7.04-7.49 (m, 9H), 8.93 (s, 1H), 10.14 (s, 1H); IR (KBr), ν (cm^{-1}): 690, 1017, 1219, 1477, 1660, 1701, 3336; Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.05; H, 5.50; N, 6.42; Found: C, 66.79; H, 5.73; N, 6.81.

Dimethyl 2,6-dimethyl-4-(2-methoxy-4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2c)

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δ_{ppm} = 2.29 (s, 6H), 3.38 (s, 3H), 3.59 (s, 3H), 3.72 (s, 3H), 4.92 (s, 1H), 6.80-7.47 (m, 8H), 8.94 (s, 1H), 10.15 (s, 1H); IR (KBr), ν (cm^{-1}): 750, 1012, 1199, 1276, 1507, 1700, 3278.

Dimethyl 2,6-dimethyl-4-(2-ethoxy-4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2d)

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δppm = 1.3 (t, 3H), 2.29 (s, 6H), 3.5 (s, 6H), 3.9 (q, 2H), 4.92 (s, 1H), 6.8-7.4 (m, 8H), 8.9 (s, 1H), 10.1 (s, 1H); IR (KBr), ν (cm^{-1}): 750, 1012, 1199, 1276, 1507, 1700, 3271.

Dimethyl 2,6-dimethyl-4-(4-(3,4-dichlorophenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2e)

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δ_{ppm} = 2.31 (s, 6H), 3.40 (s, 3H), 3.59 (s, 3H), 4.94 (s, 1H), 7.15-7.48 (m, 7H), 8.95 (s, 1H), 10.19 (s, 1H); IR (KBr), ν (cm^{-1}): 744, 1203, 1227, 1500, 1680, 1719, 3277; Anal. Calcd for $C_{24}H_{22}N_2O_6$: C, 57.00; H, 4.35; N, 5.50; Found: C, 56.66; H, 5.04; N, 6.45.

Dimethyl 2,6-dimethyl-4-(3-(3,4-dichlorophenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2f)

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δ_{ppm} = 1.74 (s, 6H), 2.89 (s, 3H), 3.03 (s, 3H), 4.39 (s, 1H), 6.42-7.24 (m, 7H), 8.38 (s, 1H), 9.94 (s, 1H); IR (KBr), ν (cm^{-1}): 1022, 1151, 1211, 1491, 1682, 1745, 3327; Anal. Calcd for $C_{24}H_{22}N_2O_6$: C, 57.00; H, 4.35; N, 5.50; Found: C, 54.03; H, 4.37; N, 6.20.

Dimethyl 2,6-dimethyl-4-(4-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystal; ^{1}H NMR (FT-90 MHz, DMSO-d_6/TMS): δ_{ppm} = 2.24 (s, 6H), 3.54 (s, 6H), 4.76 (s, 1H), 6.60 (d, 2H), 6.88 (d, 2H), 8.76 (s, 1H), 9.07 (s, 1H). IR (KBr), ν (cm^{-1}): 683, 1125, 1226, 1648, 1673, 3341.

Phenylcarbamic acid

White crystal; ^{1}H NMR (FT-90 MHz, aceton-d_6/TMS): δ_{ppm} = 5.34 (br, 1H), 6.70-7.30 (m, 5H), 7.93 (br, 1H); IR (KBr), ν (cm^{-1}): 696, 1553, 1655, 3315, 3429.

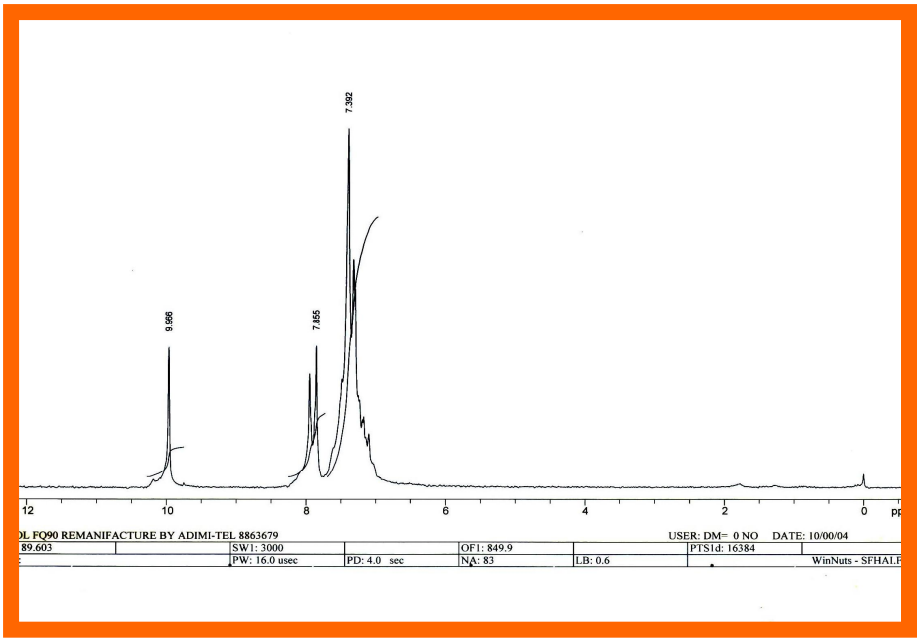

Figure 1. ^{1}H NMR spectrum (90 MHz, $CDCl_3$, d_6) of 4-formylphenyl phenylcarbamate (**1a**)

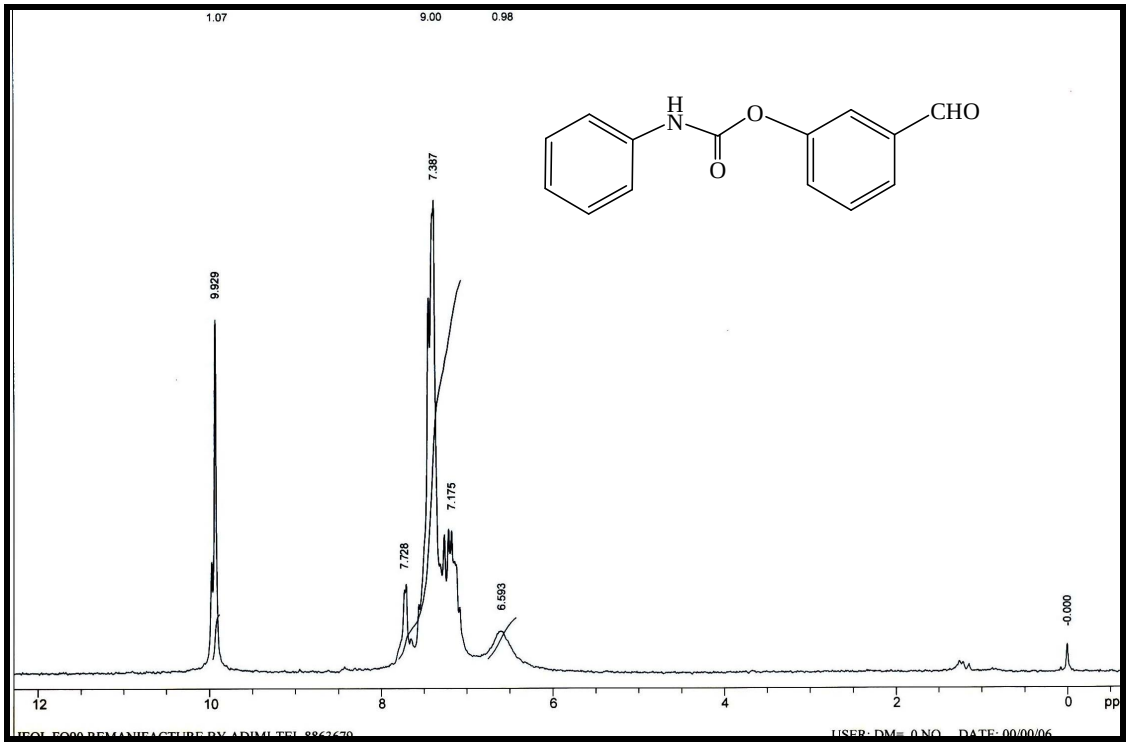

Figure 2. ^{1}H NMR spectrum (90 MHz, $CDCl_3$, d_6) of 3-formylphenyl phenylcarbamate (**1b**)

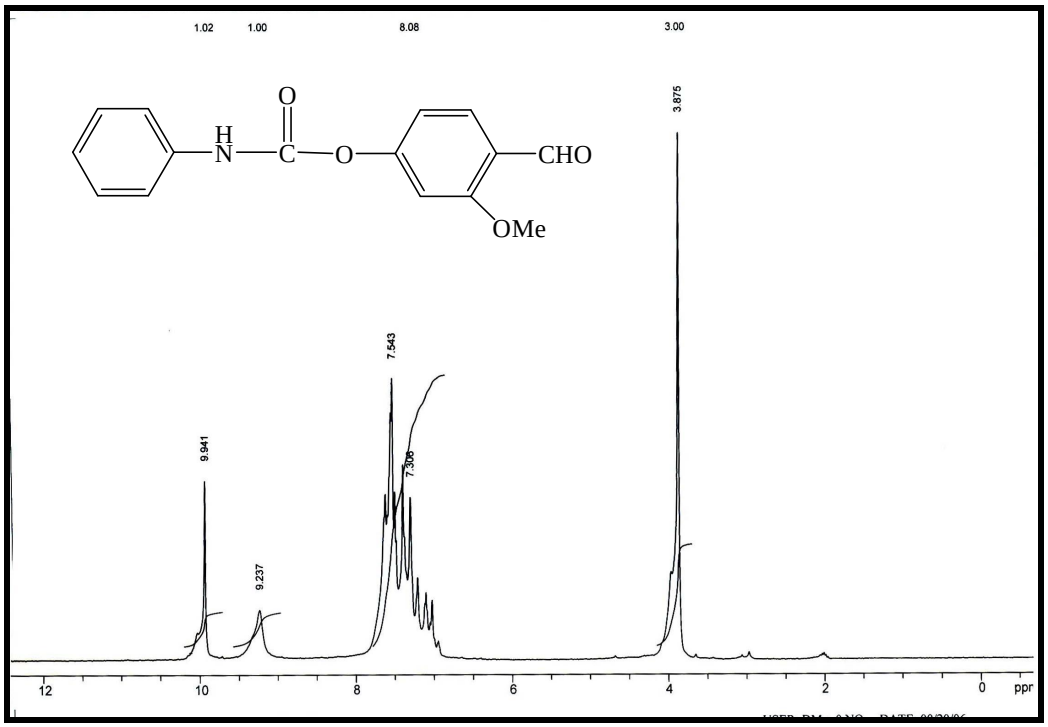

Figure 3. ^{1}H NMR spectrum (90 MHz, acetone-d_6) of 4-formyl-3-methoxyphenyl phenylcarbamate (**1c**)

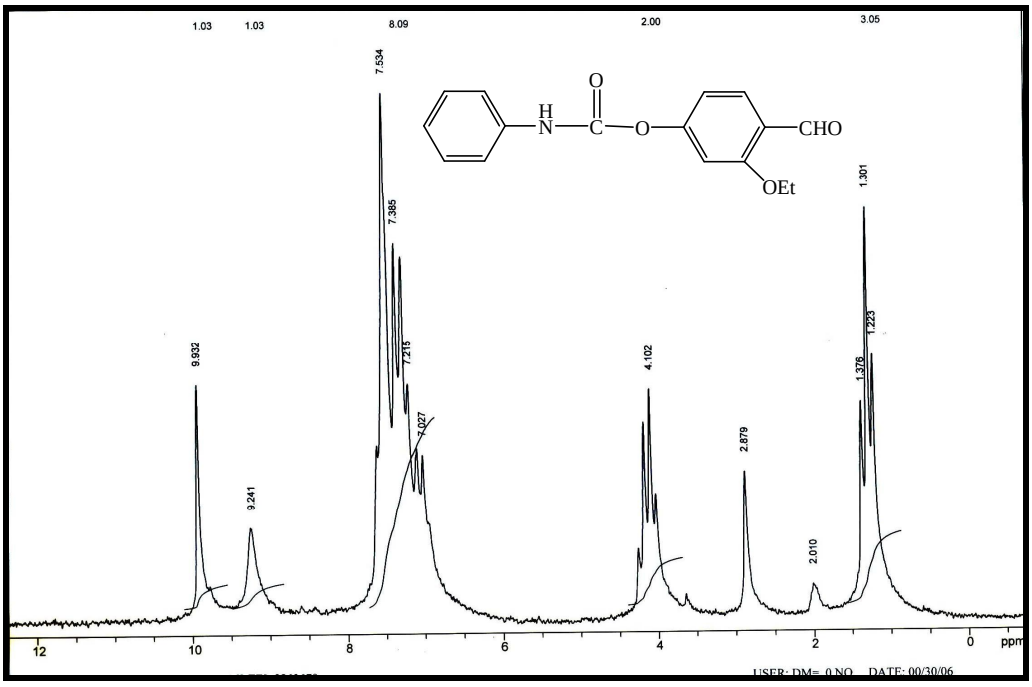

Figure 4. ^{1}H NMR spectrum (90 MHz, acetone-d_6) of 4-formyl-3-ethoxyphenyl phenylcarbamat (**1d**)

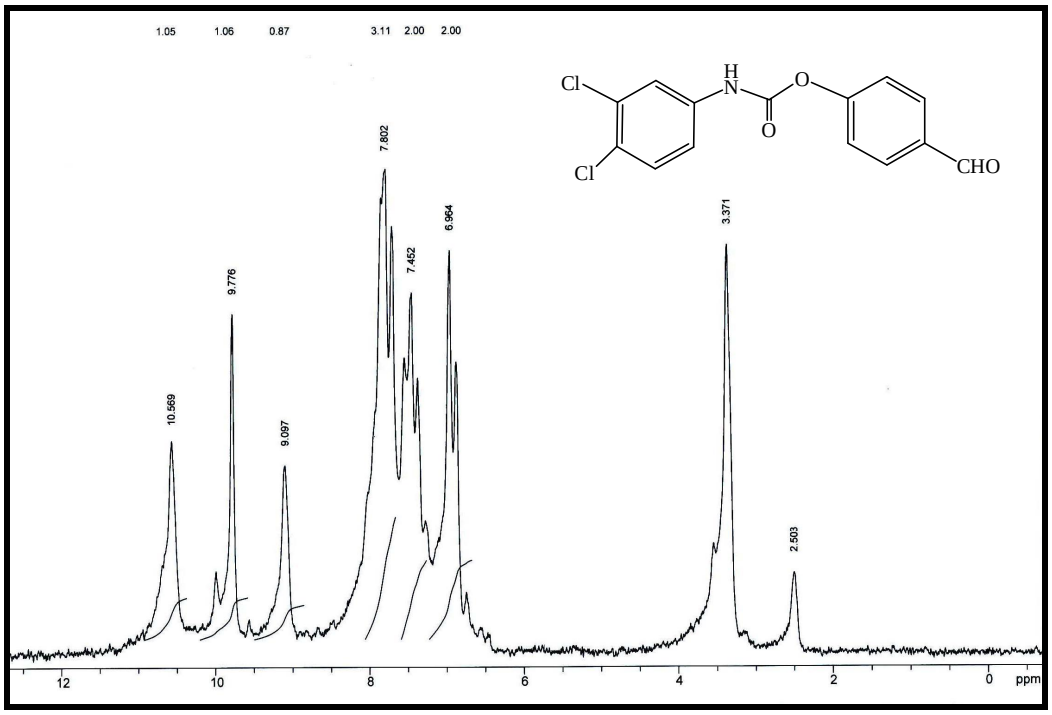

Figure 5. [1]H NMR spectrum (90 MHz, DMSO-d_6) of 4-formylphenyl-3,4-dichlorophenylcarbamate (**1e**)

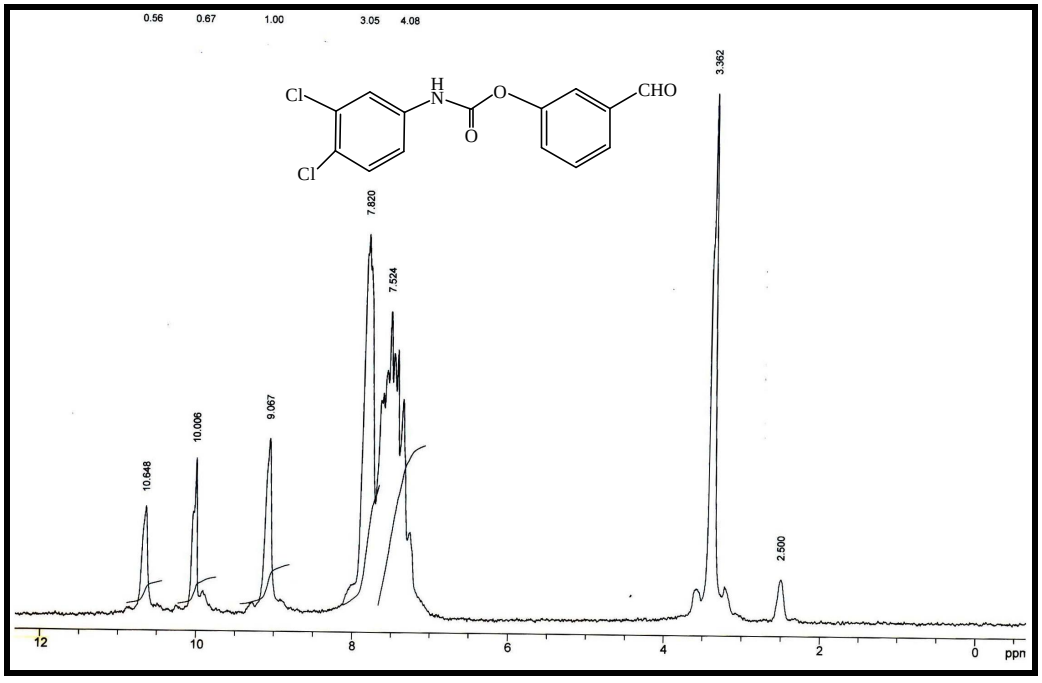

Figure 6. [1]H NMR spectrum (90 MHz, DMSO-d_6) of 3-formylphenyl-3,4-dichlorophenylcarbamate (**1f**)

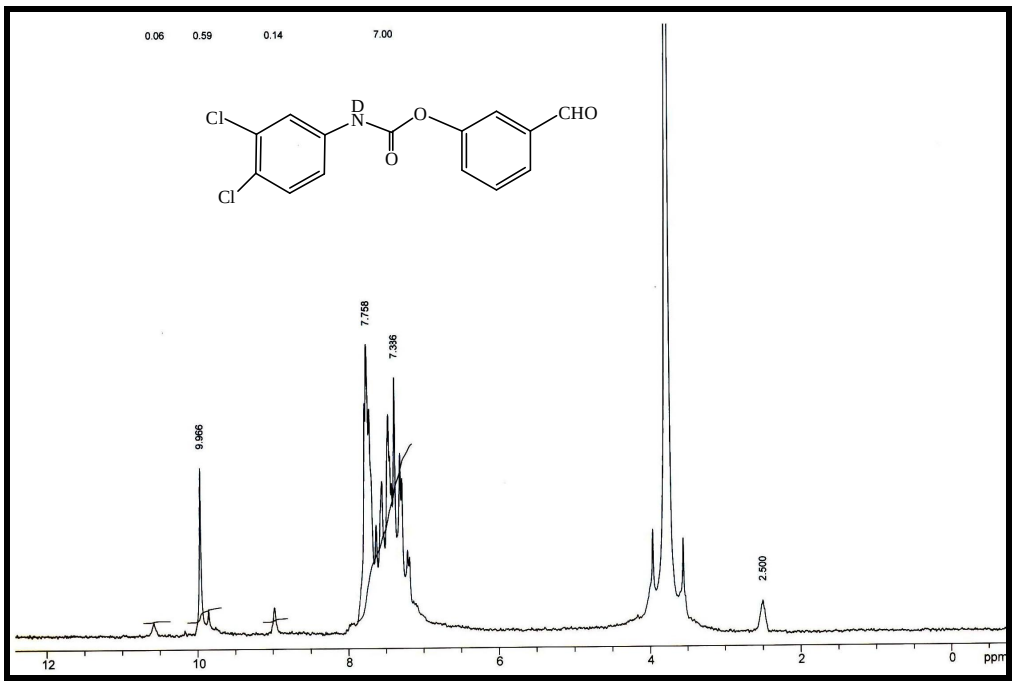

Figure 7. ^{1}H NMR spectrum (90 MHz, DMSO-d_6) of 3-formylphenyl-3,4-dichlorophenylcarbamate (**1f**) in D_2O

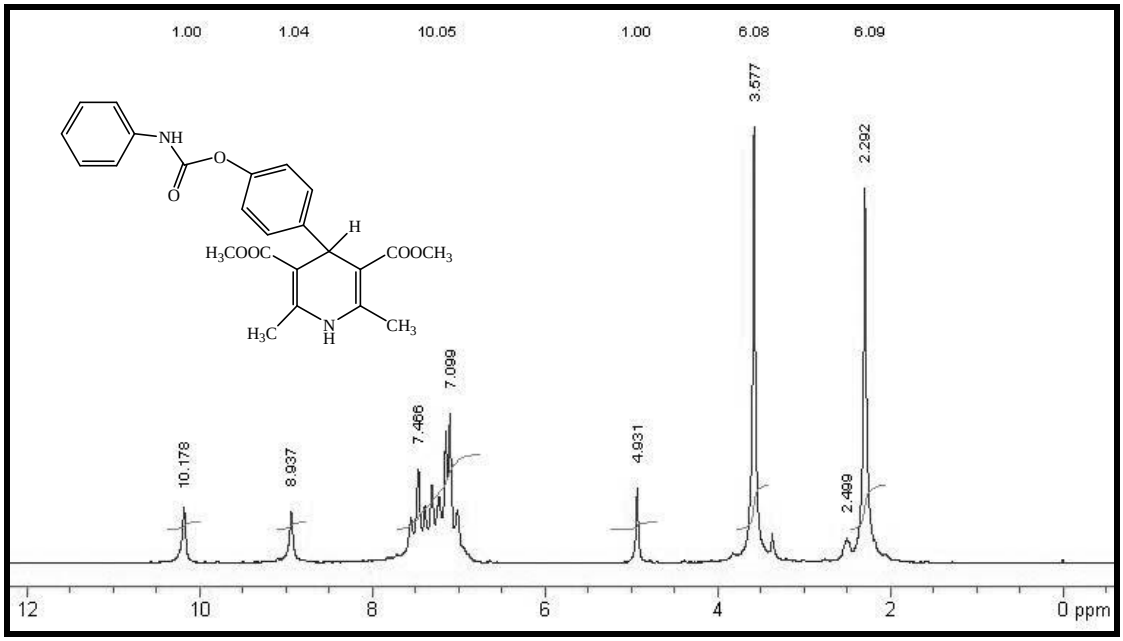

Figure 8. ^{1}H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl-4-(4-(phenylcarbamoyloxy)-phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2a**)

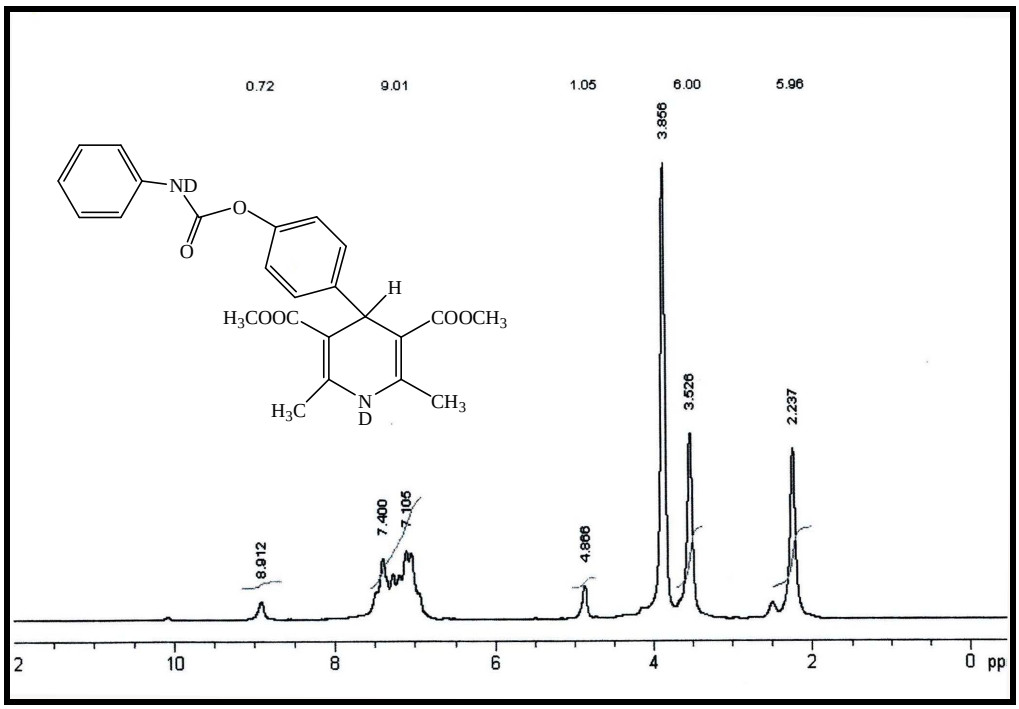

Figure 9. [1]H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl-4-(4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2a**) in D_2O

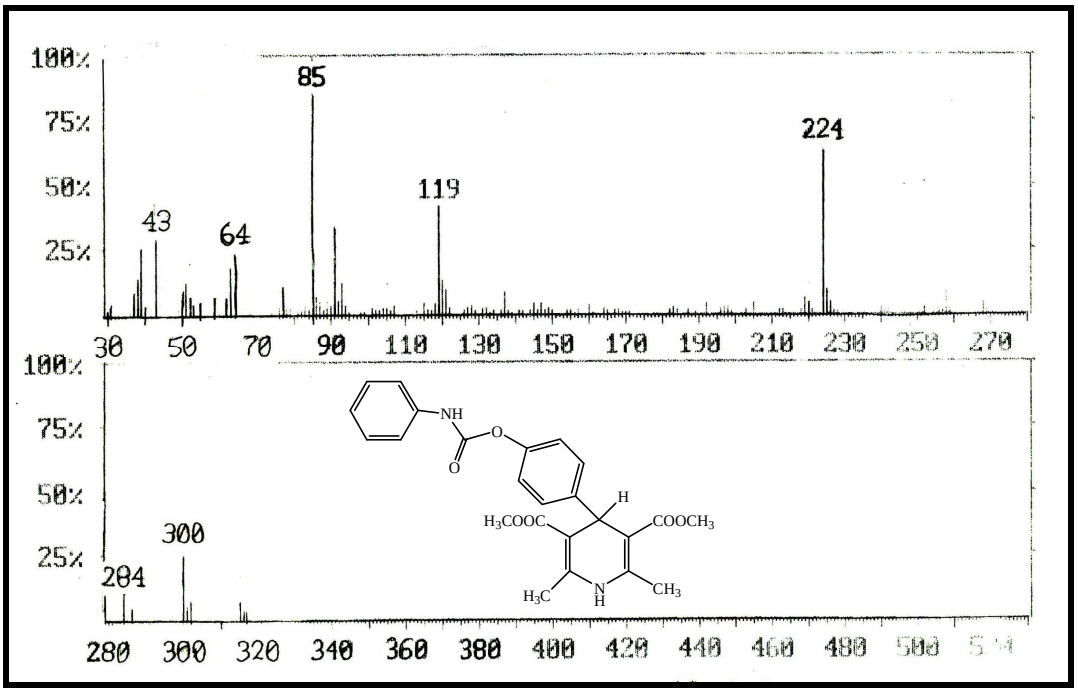

Figure 10. Mass spectrum of dimethyl 2,6-dimethyl-4-(4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2a**)

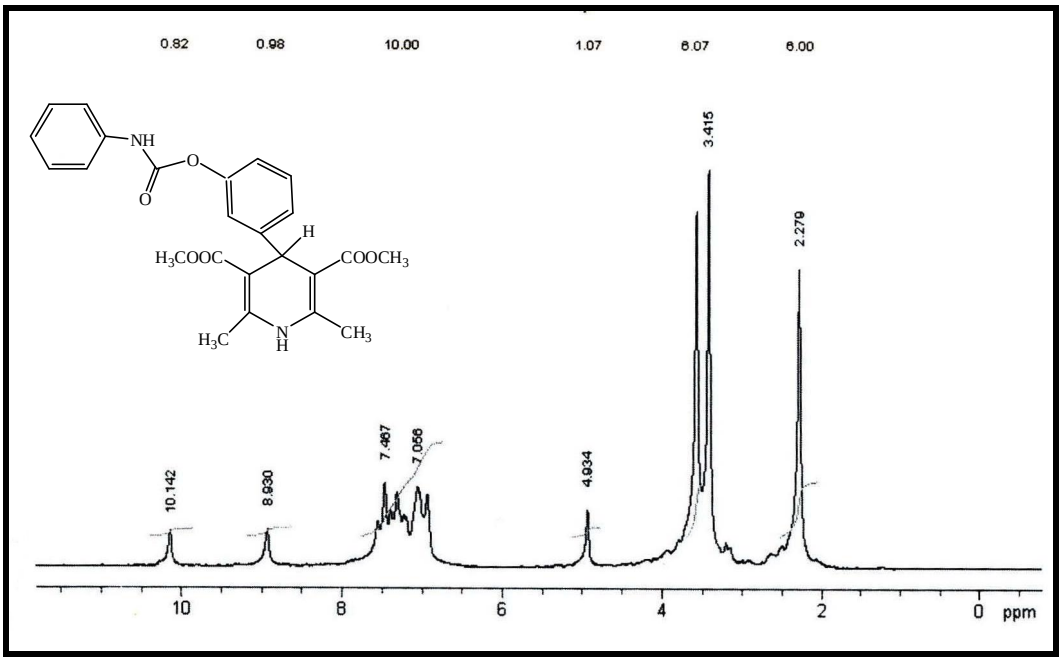

Figure 11. [1]H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl-4-(3-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2b**)

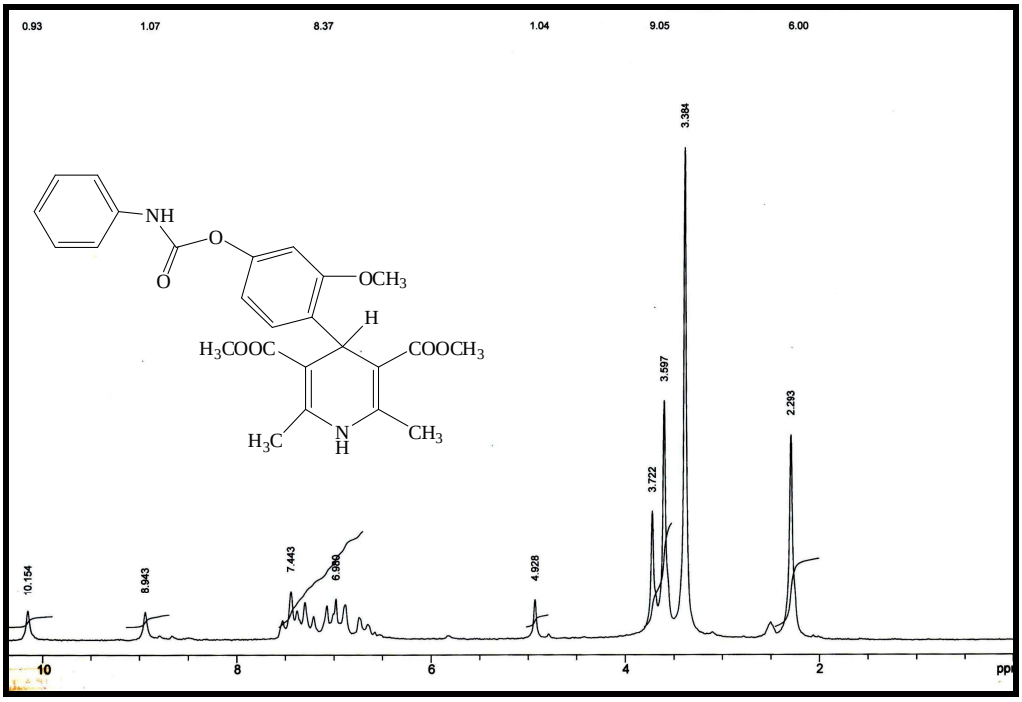

Figure 12. [1]H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl-4-(2-methoxy-4-(phenyl-carbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2c**)

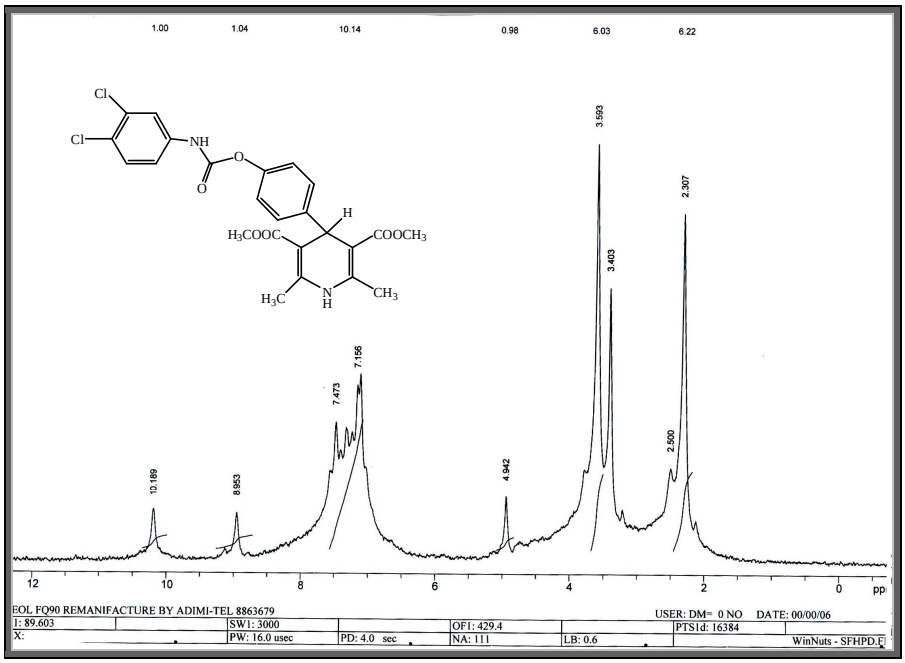

Figure 13. ^{1}H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl 4-(4-(3,4-dichlorophenyl-carbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2e**)

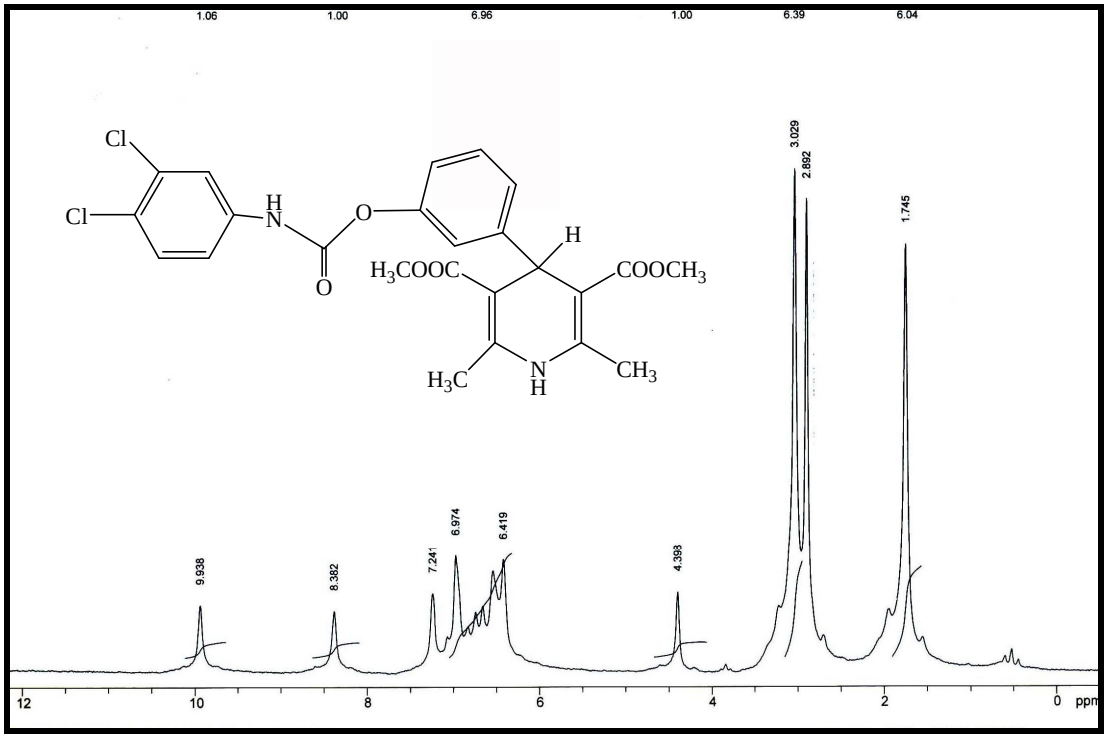

Figure 14. ^{1}H NMR spectrum (90 MHz, acetone-d_6) of dimethyl 2,6-dimethyl 4-(3-(3,4-dichlorophenyl-carbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2f**)

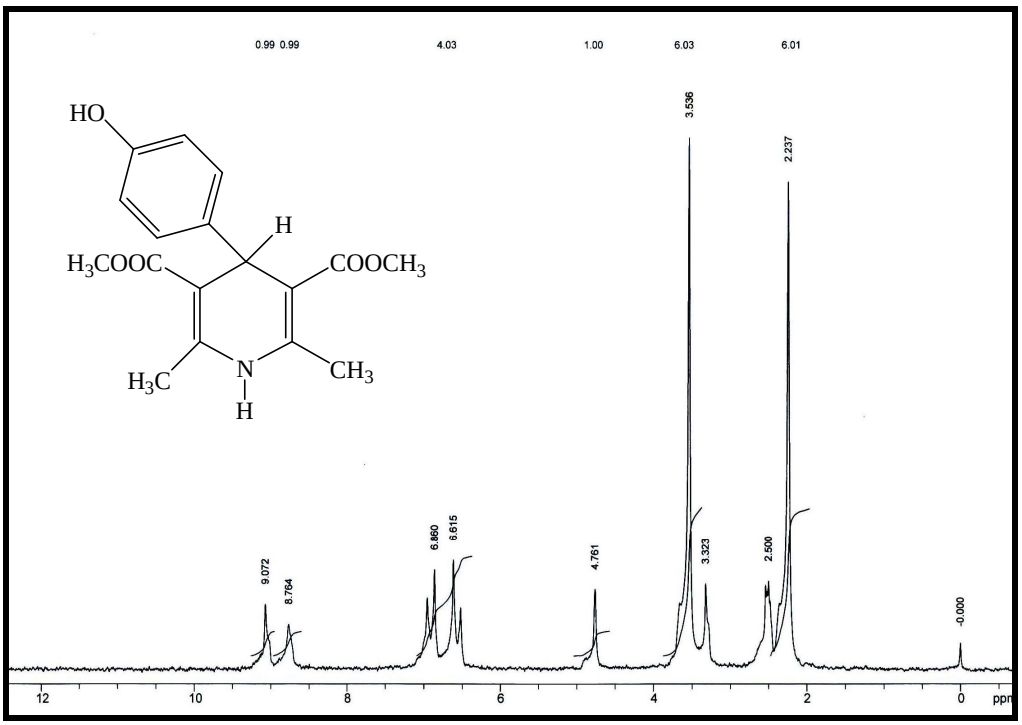

Figure 15. [1]H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl-4-(4-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate

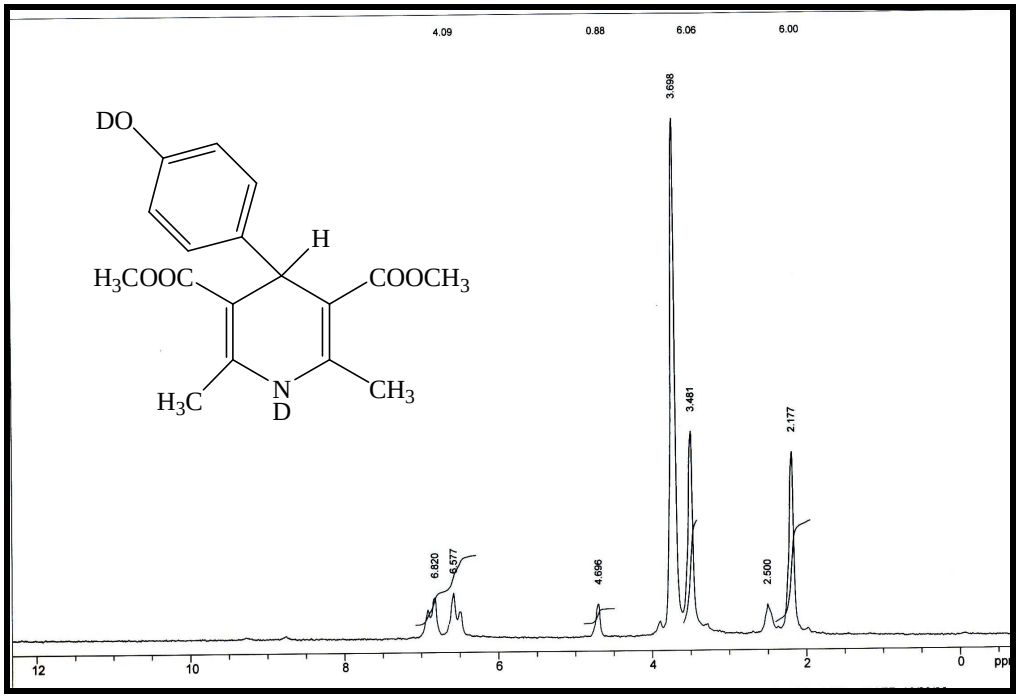

Figure 16. [1]H NMR spectrum (90 MHz, DMSO-d_6) of dimethyl 2,6-dimethyl-4-(4-hydroxy-phenyl)-1,4-dihydropyridine-3,5-dicarboxylate in D_2O

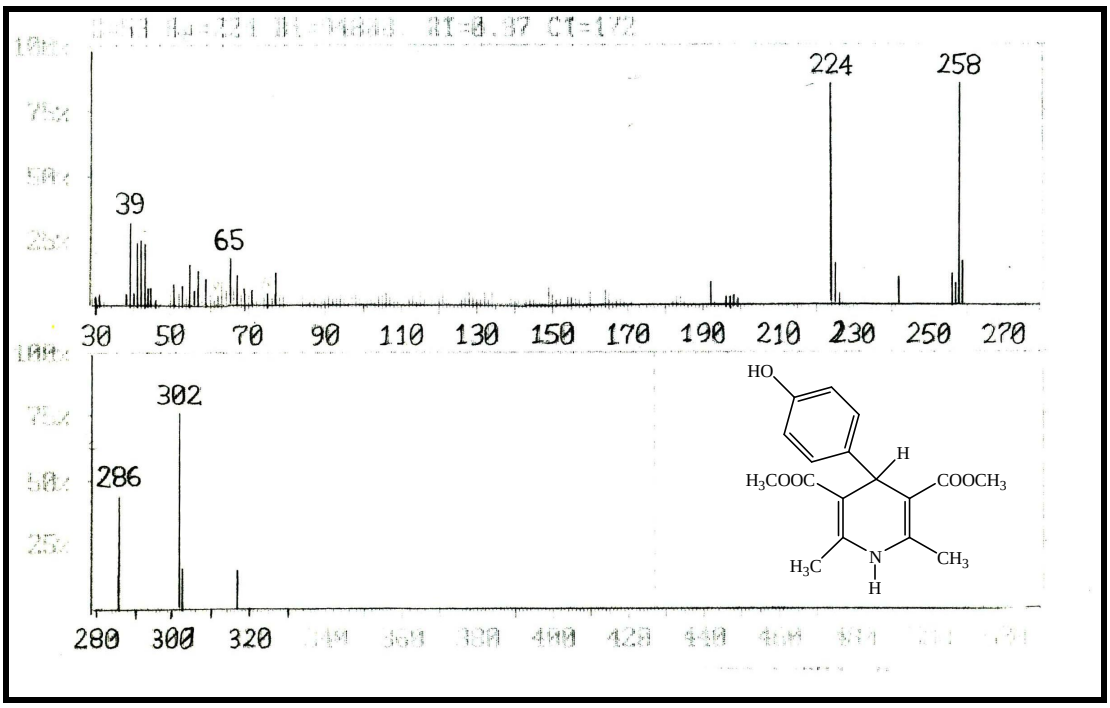

Figure 17. Mass spectrum of dimethyl 2,6-dimethyl-4-(4-hydroxy-phenyl)-1,4-dihydropyridine-3,5-dicarboxylate

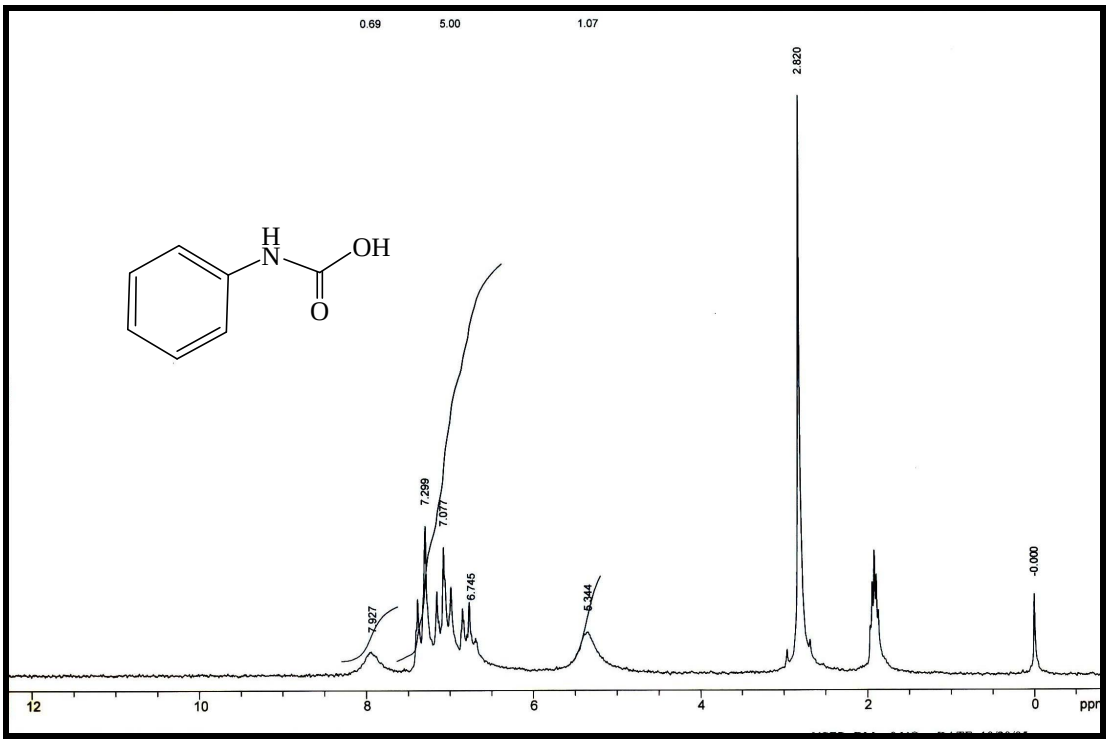

Figure 18. [1]HNMR spectrum of phenylcarbamic acid (90 MHz, acetone-d_6)

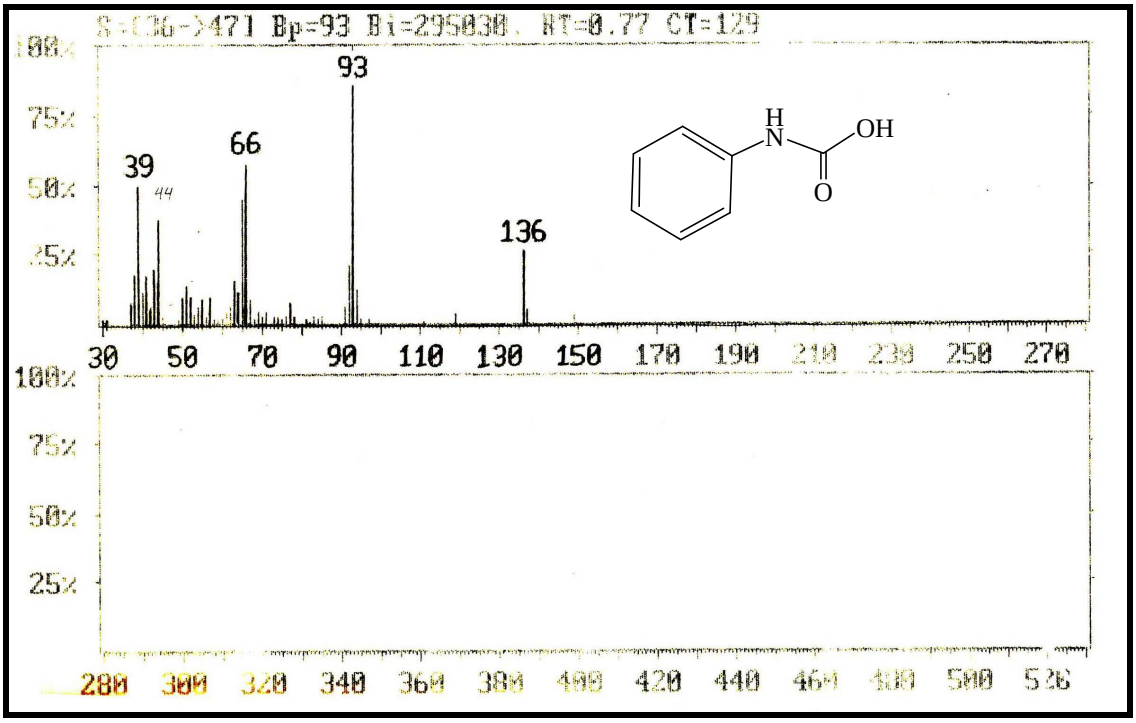

Figure 19. Mass spectrum phenylcarbamic acid