Supplementary Information

Microwave-assisted solution phase synthesis of novel pyridine carboxamides in neat water and ADMET and protein-compounds interaction analysis and antibacterial activity

Visagamoorthy Babu[a,*], Prabu Dharman[a] & K Anver Basha[b,*]

[a]Research & Development Centre, Bharathiar University, Coimbatore-641 046, Tamil Nadu, India

[b]P G and Research Department of Chemistry, C. Abdul Hakeem College, Melvisharam 632 509, Tamil Nadu, India

*E-mail: vishag0717@gmail.com (VB), kanverbasha@rediffmail.com (KAB)

1. General description

All the reagents and solvents used were of reagent grade and used without purification. MW irradiation were performed employing CEM Discover® microwave reactor. Rection completion was monitored by TLC on silica gel coated aluminum sheets (using Type 60 GF254). ^{1}H NMR spectra of all compounds were recorded on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H NMR and ^{13}C NMR in DMSO (Dimethyl sulfoxide) with tetramethylsilane as an internal standard. Chemical shift values (d) were provided in ppm. The mass spectra recorded on the Agilent 6140 quadrupole LC/MS using 1200 series spectrometer. All the reagents employed were analytical grade reagent and chemically pure. All the analytical data of the synthesized amide compounds are provided in the supplementary material of this paper.

2. General experimental procedure:

General procedure for the preparation of amide using TBTU (2a-2h). To a solution of 5-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (4.0 mmol), aromatic amine ($R\text{-}NH_2$) (4.4 mmol) and DMF (10.0 mL) were added TBTU (6.0 mmol) and DIPEA (12.0 mmol). The reaction mixture was stirred at 25-30 °C for 12 - 16 hr under the nitrogen atmosphere. The resulting reaction mss were diluted with water (50.0 mL) and then extracted with dichloromethane (2 × 30.0 mL). The resulting organic layer was washed with brine solution (5.0 mL) and further dried with anhydrous sodium sulfate. The solvent were removed under reduced pressure to get the target compounds 2a-2h.

General procedure for the preparation of amide using HATU (2a-2h). To a solution of 5-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (4.0 mmol), aromatic amine ($R\text{-}NH_2$) (4.4 mmol) and DMF (10.0 mL) were added HATU (6.0 mmol) and DIPEA (12.0 mmol). The reaction mixture was stirred at 25-30 °C for 12 - 16 hr under the nitrogen atmosphere. The resulting reaction mss were diluted with water (50.0 mL) and then extracted with dichloromethane (2 × 30.0 mL). The resulting organic layer was washed with brine solution (5.0 mL) and further dried with anhydrous sodium sulfate. The solvent were removed under reduced pressure to get the target compounds 2a-2h.

General procedure for the preparation of amide using TBTU under MW irradiation (2a-2h). In a 10 mL microwave vial set with a magnetic stir bar, 5-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (1.0 mmol), aromatic amine ($R\text{-}NH_2$) (1.1 mmol), DIPEA (3.0 mmol), water (2.5 mL) and TBTU (1.5 mmol) were added. The resulting reaction mixture were subjected to MW irradiation (employing CEM Discover® microwave reactor) with gas cooling (pressure of 40 psi were maintained during the irradiation) for 30 min at 40W along with magnetic stirring with temperature limit of 60 ˚C (reaction time refers to hold time at the preferred set temperature). Water was evaporated, the reaction mass were purified with 1:2 ethyl acetate : hexanes and isolated by filtration to obtain wet solids. The wet solids were dried under vacuum at below 40 °C for 3 hr to get the target compounds 2a-2h.

3. Spectral data of all compounds:

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(1-(4-nitrophenyl)ethyl)picolinamide (2a): Pale brown solid, yield 81 %, ^{1}H NMR (400 MHz, DMSO-d6): d 1.59 (d, J = 6.80 Hz, 3H, CH3), 3.96 (s, 3H, CH3), 5.31 (m, J = 6.80 Hz, 1H, CH), 7.43 (t, J = 8.00 Hz, 1H, Ar-H), 7.54 (q, J = 8.40 Hz, 1H, Ar-H), 7.72 (d, J = 8.40 Hz, 2H, Ar-H), 8.11 (d,J = 8.00 Hz, 1H, Py-H), 8.21 (d, J = 8.80 Hz, 3H, Py-H & Ar-H), 8.87 (s, 1H, Py-H), 9.44 (d, J = 8.00 Hz, 1H, NH). ^{13}C NMR (400 MHz, DMSO-*d_6)*: 25.83, 43.65, 62.14, 123.26, 123.30, 126.28, 126.42, 128.82, 128.97, 129.14, 129.17, 129.20, 135.67, 135.74, 142.18, 142.24, 148.45, 152.38**,** 152.43, 154.90, 164.77.Exact mass calcd. (M+H) for $C_{21}H_{17}ClFN_3O_4$: 430.09; found: 430.1.

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(5-chloro-2-methylphenyl)picolinamide(2b): Pale brown solid, yield 87 %.^{1}H NMR (400 MHz, DMSO-d6): d 2.33 (s, 3H, CH3), 3.97 (s, 3H, CH3), 7.22 (d, J = 7.60 Hz, 1H, Ar-H), 7.34 (d, J = 8.00 Hz, 1H, Ar-H), 7.50 (m, J = 8.00 Hz, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 8.29 (s, 2H, Py-H), 8.95 (s, 1H, Py-H).^{13}C NMR (400 MHz, DMSO-*d_6)*: 18.18, 62.14, 119.90, 123.44, 126.04, 126.33, 128.82, 128.96, 129.04, 129.07, 134.42, 135.64, 135.76, 136.84, 136.98, 148.11, 152.26, 152.33, 154.84, 164.74. Exact mass calcd. (M+H) for $C_{20}H_{15}Cl_2FN_2O_2$: 406.05;found: 407.1.

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(1-phenylethyl)picolinamide (2c): Brown solid, yield 89 %.^{1}H NMR (400 MHz, DMSO-d6): d 1.55 (d, J = 6.80 Hz, 3H, CH3), 3.96 (s, 3H, CH3), 5.20 (t, J = 7.60 Hz, 1H, CH), 7.24 (t, J = 7.60 Hz, 1H, Ar-H), 7.34 (t, J = 8.00 Hz, 2H, Ar-H), 7.45 (t, J = 5.20 Hz, 3H, Ar-H), 7.51 (d, J = 8.80 Hz, 1H, Ar-H), 8.12 (d, J = 8.00 Hz, 1H, Py-H), 8.20 (d, J = 8.00 Hz, 1H, Py-H), 8.85 (s, 1H, Py-H), 9.15 (d, J = 8.80 Hz, 1H, NH).^{13}C NMR (400 MHz, DMSO-*d_6)*: 44.15, 25.73, 62.12, 122.82, 122.86, 124.33, 125.49, 125.56, 125.63, 128.49, 128.54, 128.63, 128.67, 135.34, 136.44, 138.53, 146.32, 151.96, 151.96, 154.42, 164.43. Exact mass calcd. (M+H) for $C_{21}H_{18}ClFN_2O_2$:385.11;found: 385.1.

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(isoxazol-3-yl)picolinamide (2d): Pale brown solid, yield 82 %.^{1}H NMR (400 MHz, DMSO-d6):d 3.97 (s, 3H, CH3), 6.19 (s, J = 7.60 Hz, 1H, CH), 7.07 (s, J = 7.60 Hz, 1H, CH), 7.57 (d, J = 60.4 Hz, 2H, Ar-H), 8.28 (s, J = 8.00 Hz, 1H, Py-H), 8.54 (s, J = 8.00 Hz, 1H, Py-H), 8.94 (d, J = 0 Hz, 1H, Py-H), 11.30 (s, J = 8.80 Hz, 1H, NH).^{13}C NMR (400 MHz, DMSO-*d_6)*: 62.14, 123.40, 123.44, 126.04, 126.33, 128.82, 128.96, 129.04, 129.07, 134.42, 135.64, 135.76, 136.84, 136.98, 148.11, 152.26, 152.33, 154.84, 158.4, 164.74. 166.2. Exact mass calcd. (M+H) for $C_{16}H_{11}ClFN_3O_3$: 348.05; found: 348.1.

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(2-isopropylphenyl)picolinamide (2e): Brown solid, yield 86 %.^{1}H NMR (400 MHz, DMSO-d6): d 1.22 (d, J = 8.80 Hz, 6H, CH3), 3.19 (t, J = 9.20 Hz, 1H, CH),3.97 (s, 3H, CH3), 7.26 (d, J = 5.20 Hz, 2H, Ar-H), 7. 46 (m, J = 4.40 Hz, 3H, Ar-H), 7.66 (d, J = 5.60 Hz, 1H, Ar-H), 8.27 (s, 2H, Py-H), 8.93 (s, 1H, Py-H),10.39 (s, 1H, NH).^{13}C NMR (400 MHz, DMSO-*d_6)*: 25.6, 25.6, 43.6, 62.14, 123.26, 123.30, 126.28, 126.42, 128.82, 128.97, 129.14, 129.17, 129.20, 135.67, 135.74, 136.81, 136.94, 148.44, 152.28, 152.33, 154.80, 164.78. Exact mass calcd. (M+H) for $C_{22}H_{20}ClFN_2O_2$: 399.12; found: 399.1.

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(2-isopropyl-6-methylphenyl)picolinamide(2f): Pale brown solid, yield 89 %.^{1}H NMR (400 MHz, DMSO-d6): d 1.13 (d, J = 8.80 Hz, 6H, CH3), 2.17 (s, J = 9.20 Hz, 3H, CH3),3.12(s,1H, CH),3.97 (s, 3H, CH3), 7.21(m, J = 111.6 Hz, 5H, Ar-H), 8.23 (s, J = 4.40 Hz, 2H, Py-H), 8.91 (s, 1H, Py-H), 10.27 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-*d_6)*: 19.2,25.6, 25.6, 43.6, 62.14, 123.26, 123.30, 126.28, 126.42, 128.82, 128.97, 129.14, 129.17, 129.20,

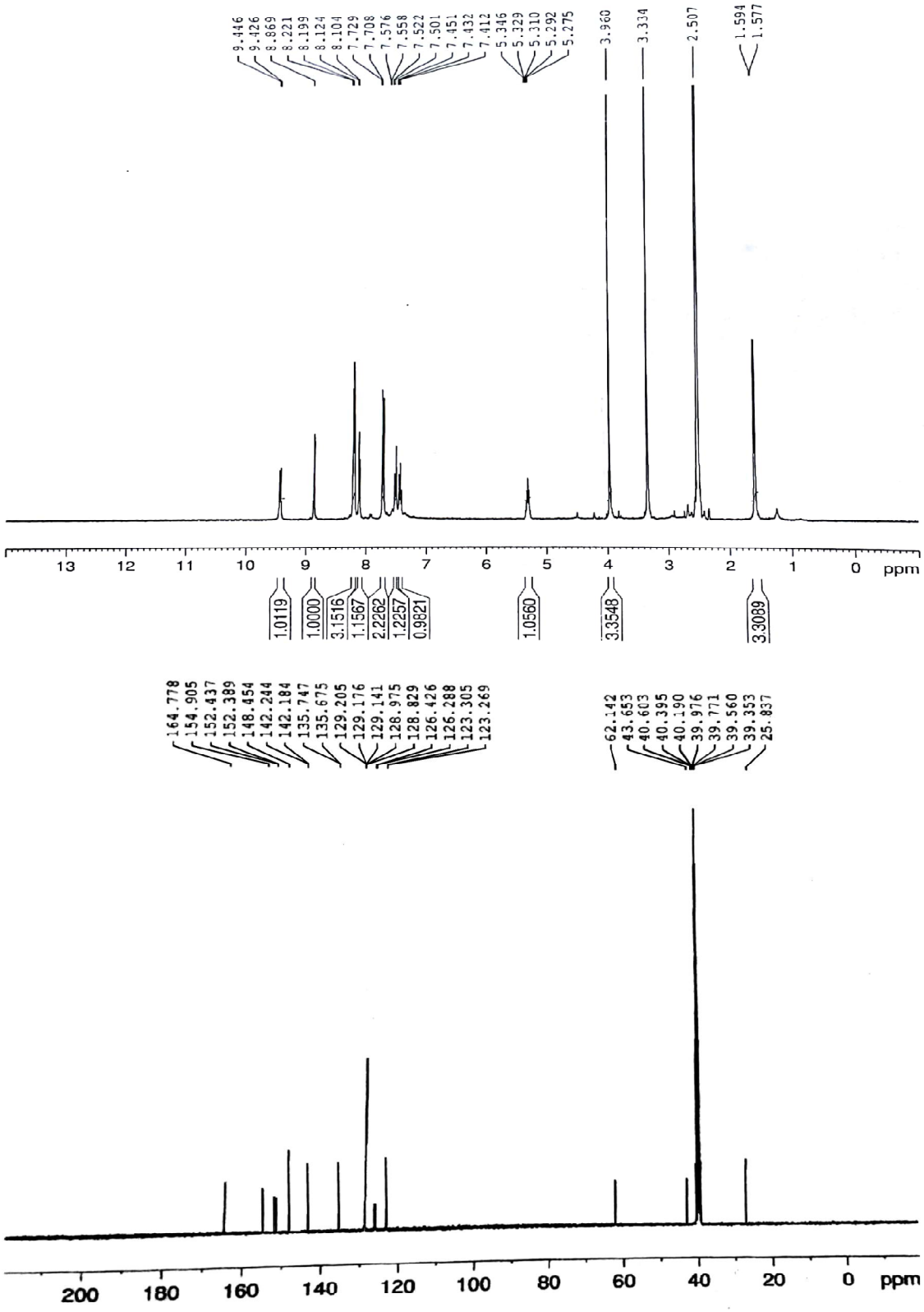
135.67, 135.74, 136.81, 136.94, 148.44, 152.28, 152.33, 154.80, 164.78. Exact mass calcd. (M+H) for $C_{23}H_{22}ClFN_2O_2$: 413.14; found: 413.1.

5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(2-chloropyridin-4-yl)picolinamide (2g): Brown solid, yield 82 %.^{1}H NMR (400 MHz, DMSO-d6): d 3.95 (s, 3H, CH3), 7.47 (m, J = 12.40 Hz, 3H, Ar-H), 7. 60 (t, J = 10.0 Hz, 1H, Ar-H), 8.20 (d, J = 9.60 Hz, 1H, Ar-H), 8.27 (s, 1H, Py-H), 8.45 (s, 1H, Py-H), 8.92 (s, 1H, Py-H), 11.09 (s, 1H, NH).^{13}C NMR (400 MHz, DMSO-*d_6)*: 62.15, 109.9, 118.86, 122.37, 122.37, 123.01, 128.49, 128.54, 135.33, 136.41, 137.54, 146.33, 151.91, 151.91, 154.42, 161.8, 161.8, 164.33.Exact mass calcd. (M+H) for $C_{18}H_{12}Cl_2FN_3O_2$: 392.03; found: 392.0.

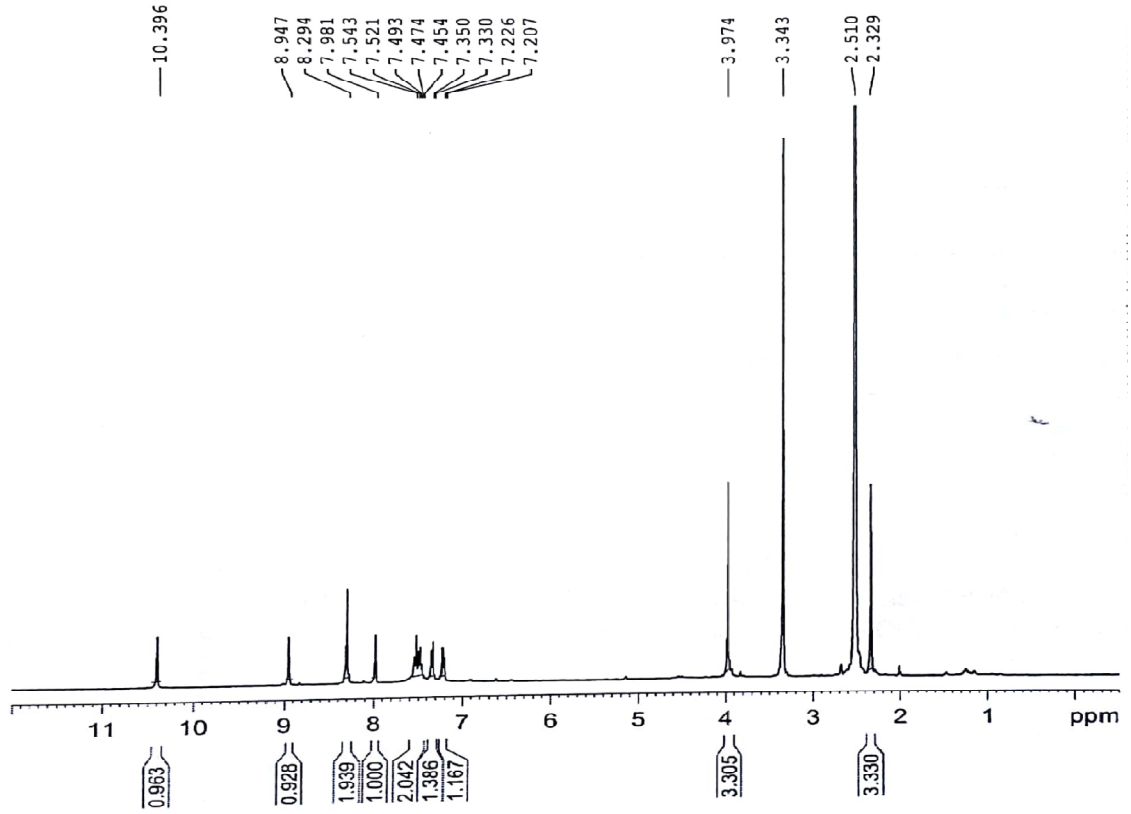
5-(4-chloro-2-fluoro-3-methoxyphenyl)-N-(4-(trifluoromethyl)phenyl)picolinamide(2h): Brown solid, yield 85 %.^{1}H NMR (400 MHz, DMSO-d6): d 3.95 (s, 3H, CH3), 7.55 (t, J = 44.4 Hz, 6H, Ar-H),8.27 (s, J = 9.60 Hz, 1H, Py-H), 8.45 (s, 1H, Py-H), 8.91 (s, 1H, Py-H), 11.08 (s, 1H, NH).^{13}C NMR (400 MHz, DMSO-*d_6)*: 62.14, 117.24, 117.24, 122.1, 122.2, 123.26, 123.30, 126.28, 126.42, 128.82, 128.97, 129.14,135.67, 135.74,139.82,148.44, 152.28,152.33, 154.80,164.78. Exact mass calcd. (M+H) for $C_{20}H_{13}ClF_4N_2O_2$: 425.06; found: 425.1.

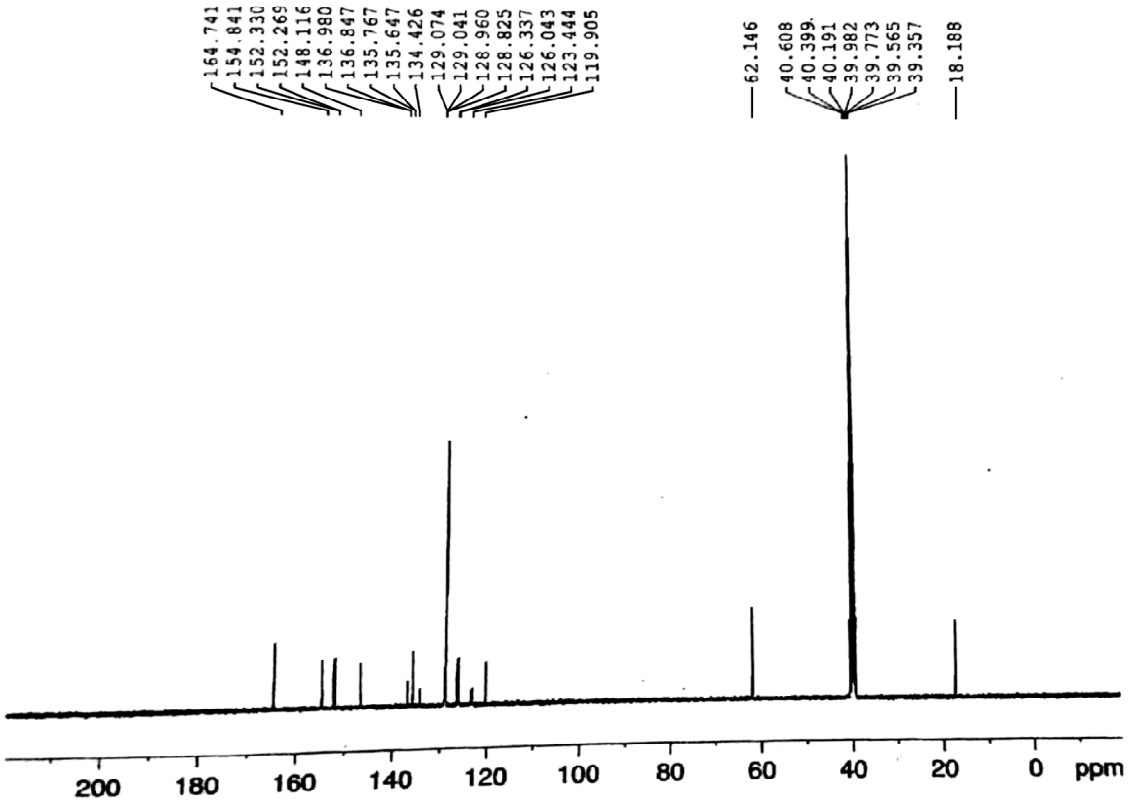
4. ^{1}H NMR and ^{13}C NMR charts of new compounds

1. Compound (2a)

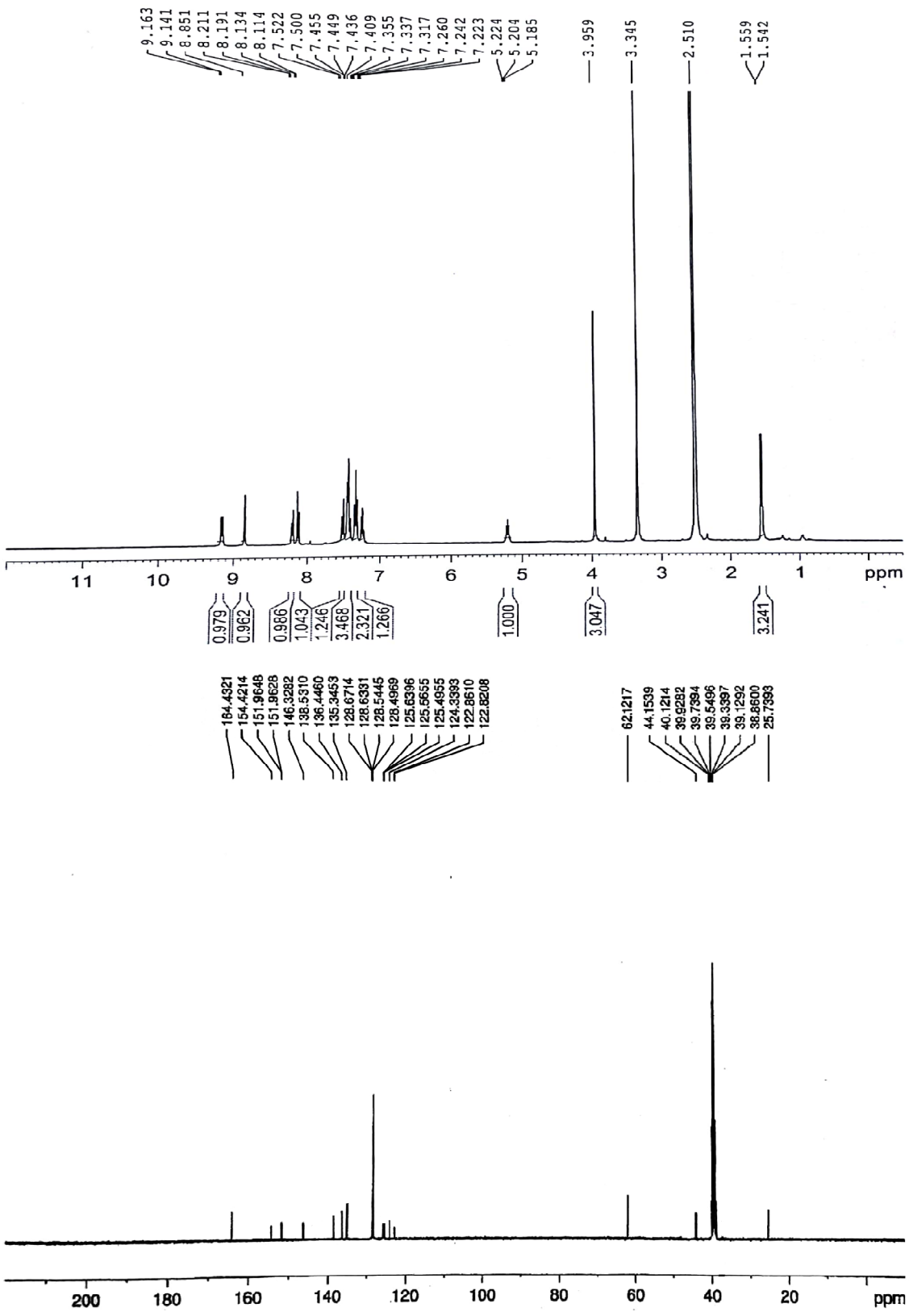


3. Compound (2b)

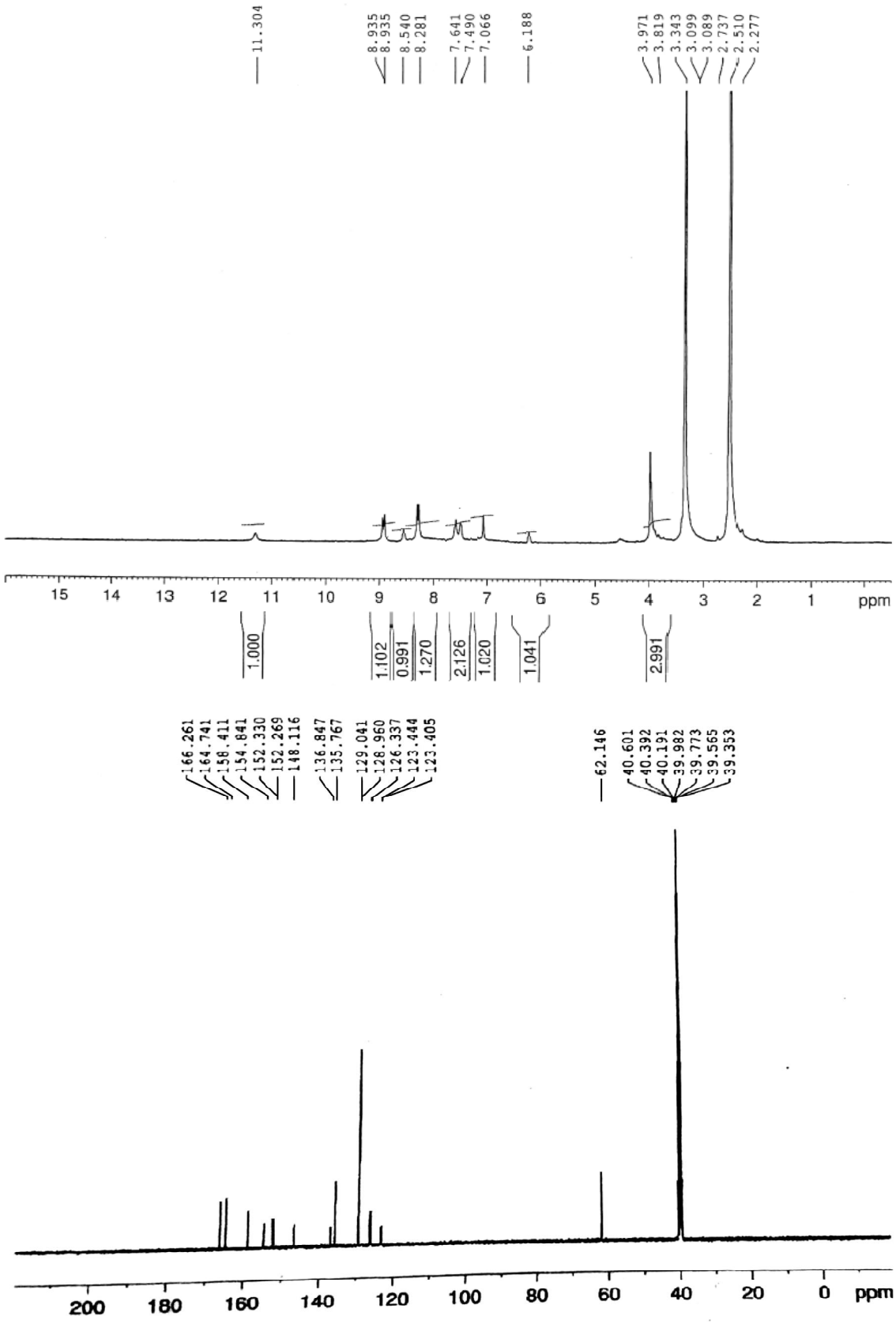




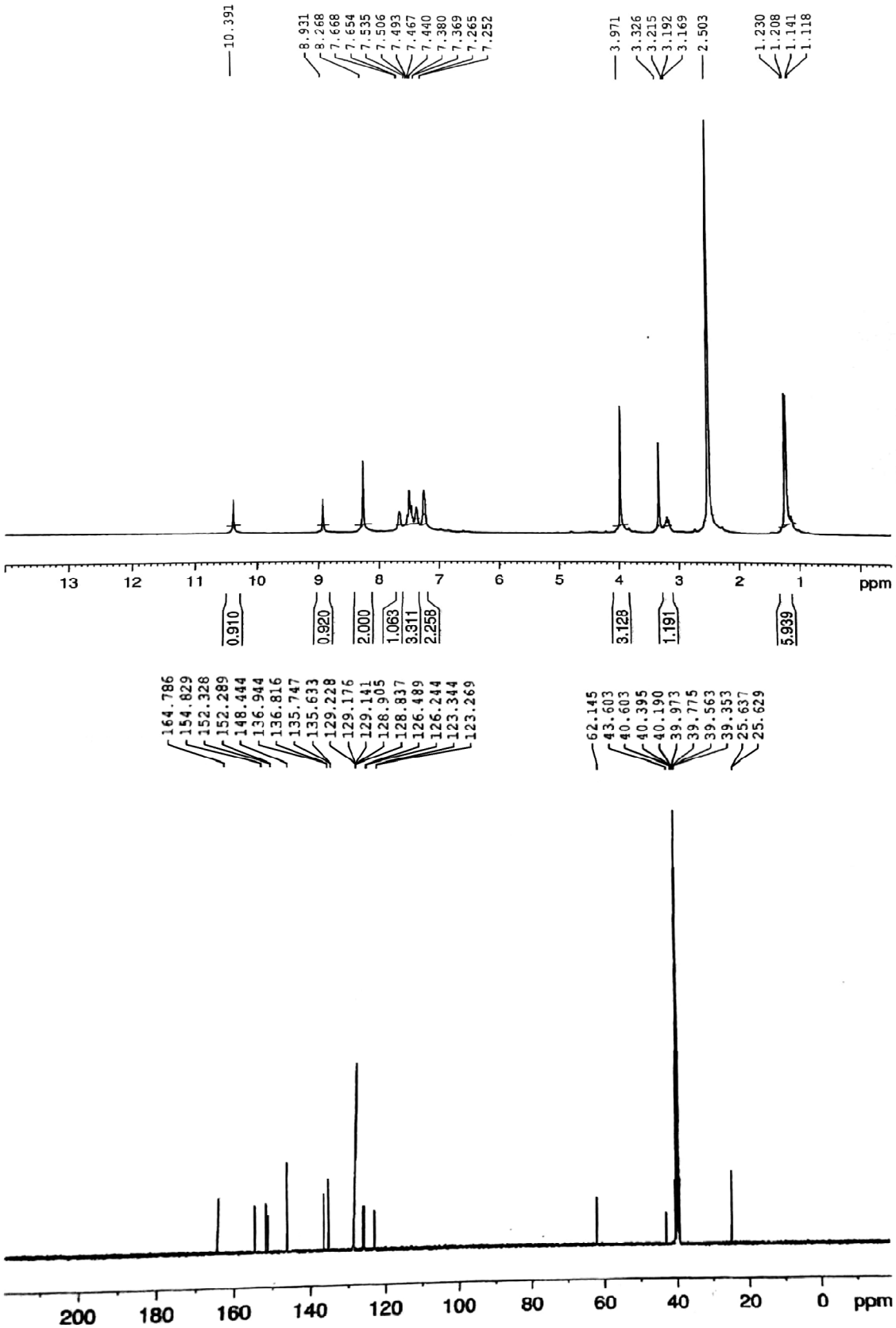
4. Compound (2c)



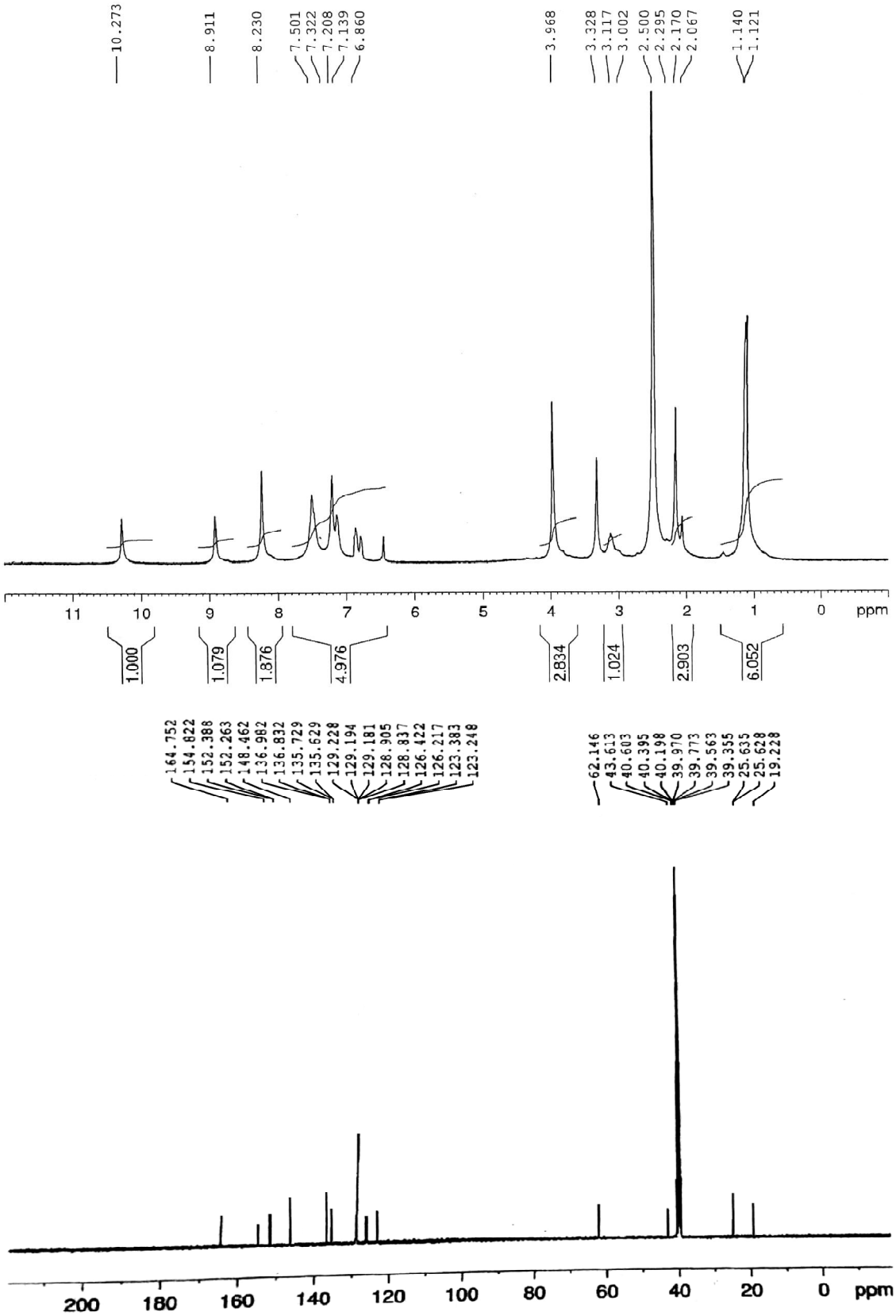
5. Compound (2d)



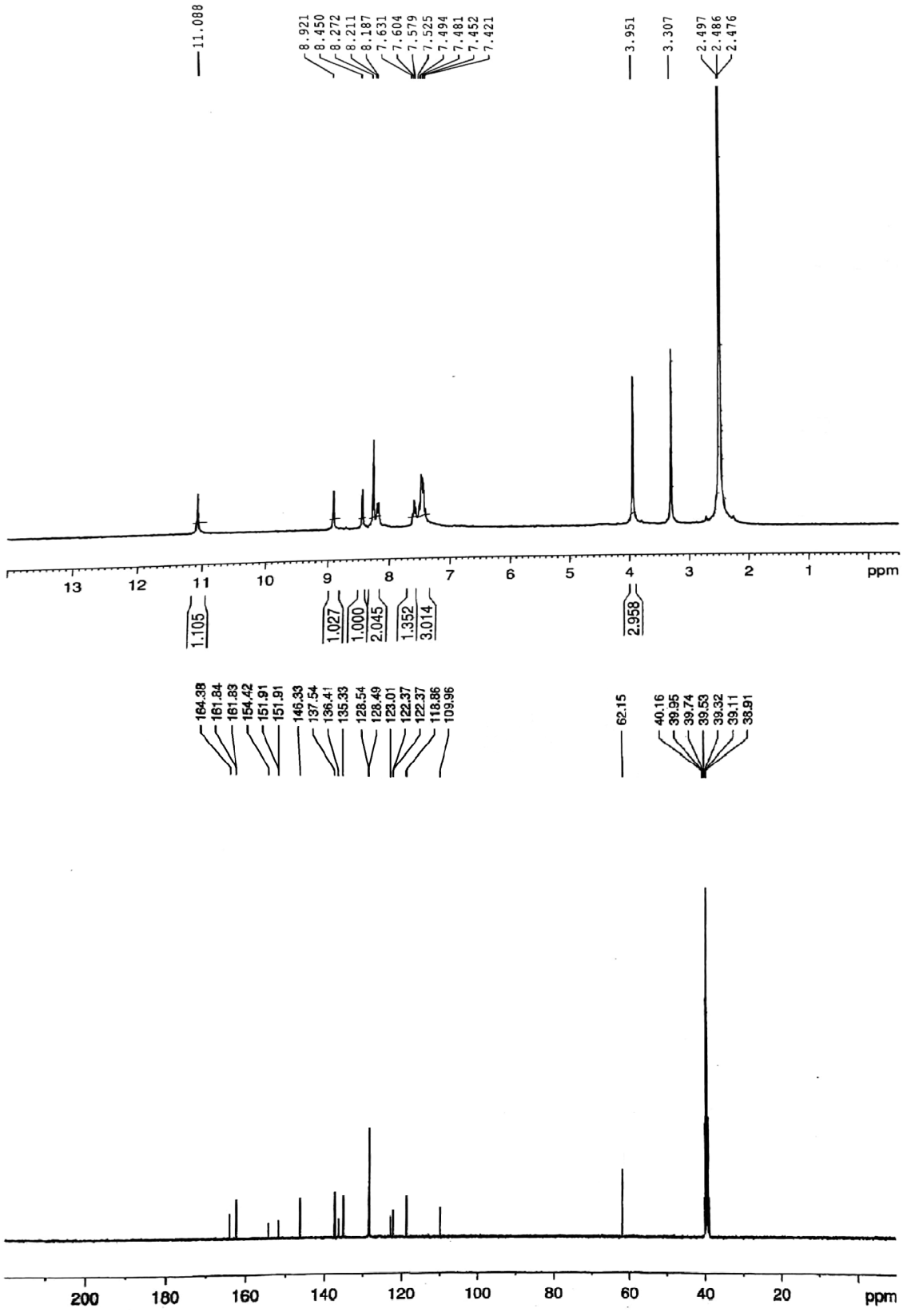
6. Compound (2e)



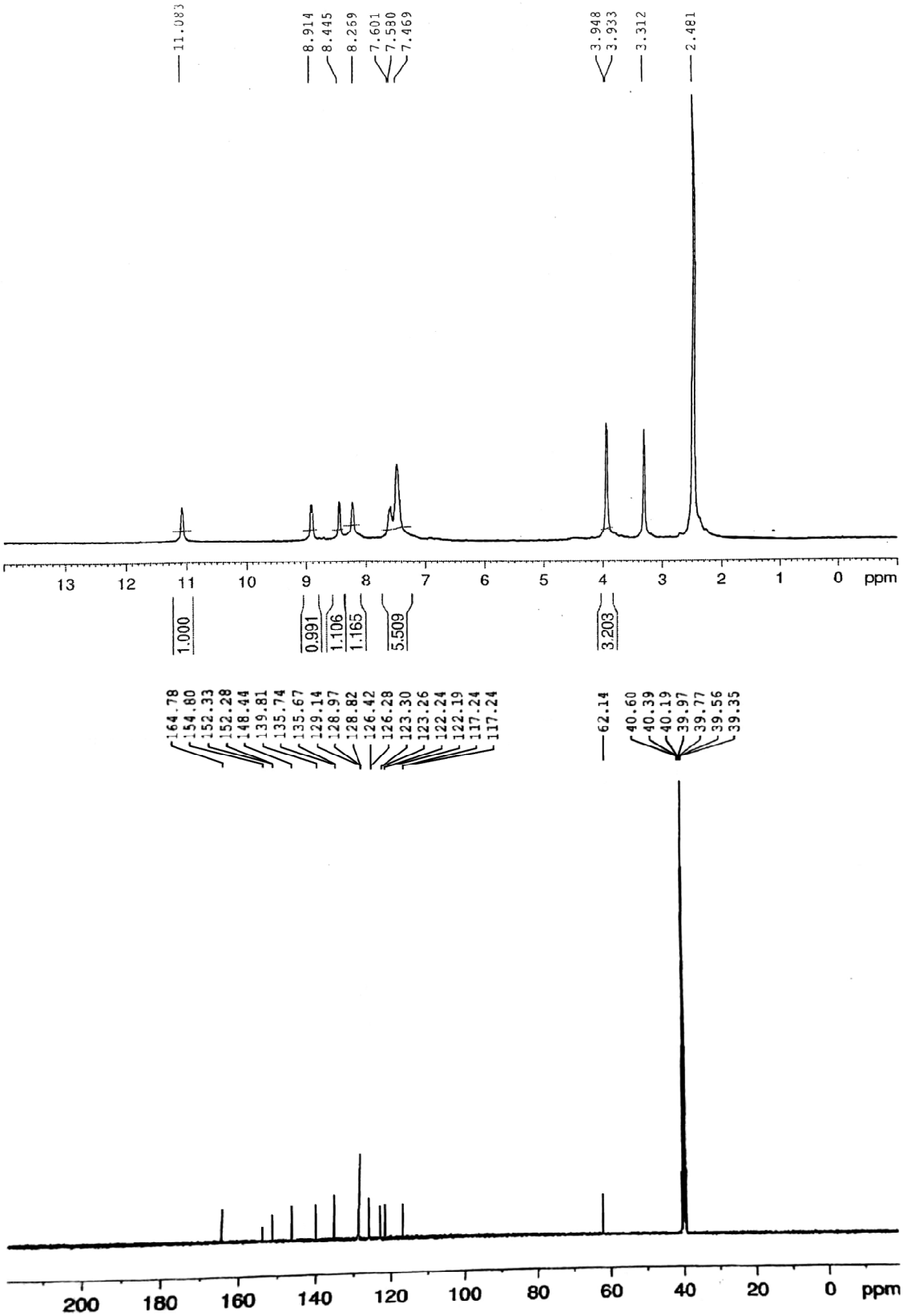
7. Compound (2f)



8. Compound (2g)



9. Compound (2h)


11.083
8.914
8.445
8.269
7.601
7.580
7.469
3.948
3.933
3.312
2.481
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.000
0.991
1.106
1.165
5.509
3.203
164.78
154.80
152.33
152.28
148.44
139.81
135.74
135.67
129.14
128.97
128.82
126.42
126.28
123.30
123.26
122.24
122.19
117.24
117.24
62.14
40.60
40.39
40.19
39.97
39.77
39.56
39.35
200 180 160 140 120 100 80 60 40 20 0 ppm

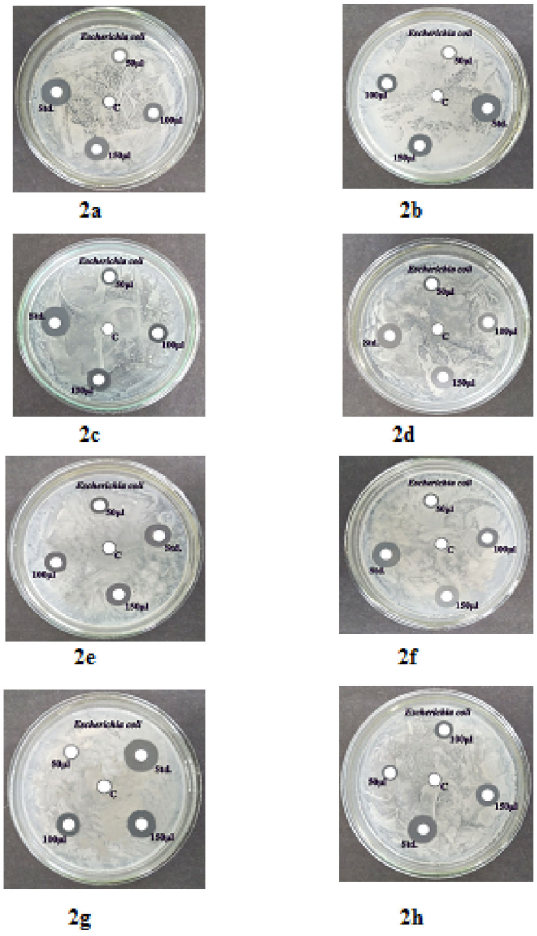


Fig. S9 Antibacterial activity of samples 2a-2h