Supporting Information

Synthesis and analysis of small molecules to restrain the function of tissue factor within tumour cells

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Supporting Information

Synthesis of PIN1 Inhibitors

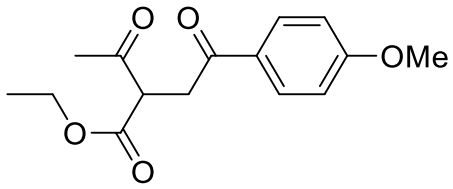
General

All solvents used were of analytical grade, and commercially sourced chemicals were used without further purification. Merck 200-300 mesh silica gel was used for column chromatography, and Merck 60 mesh size precoated aluminium plates were used for thin layer chromatography. UV visualization of TLC bands was at 254 nm using a MINERALIGHT® UV lamp Model UVG-54. NMR spectra were obtained using a Jeol JNM ECP400 spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C), and the internal standards used were TMS δH = 0, $CDCl_3$ δH = 7.26, or $(CD_3)_2SO$ δH = 2.50, being residual protic solvents. Chemical shifts and coupling constants are given in ppm (δ) and Hertz (Hz) respectively. The following notations are used to denote peak multiplicity: s, d, t, q and m for singlet, doublet, triplet, quartet and multiplet respectively. Internal references for ^{13}C spectra were the central peak of residual solvent peaks for ^{13}C at 25 °C (298 K) was $(CD_3)_2SO$ (δC = 39.5 ppm) or $CDCl_3$ (δC =77.0 ppm). DEPT 135 sequence was on occasions used in assigning ^{13}C signals. ES-MS data were collected on HCT ultra ETD II and melting points were taken using a Fisher-Johns apparatus. CHN combustion elemental microanalyses were performed using a Fisons CHN Analyzer Carlo-Erba EA1108.

The furan-containing moiety of this set of compounds was synthesized a modified form of a procedure described described by Poretta *et al.* with slight modifications detailed below.

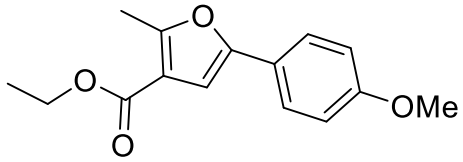
[G. Porretta, M. Scalzo, F. Chimenti, A. Bolasco, M. Biava, M. Fischetti and F. Riccardi, Research on antibacterial and antifungal agents. III. Synthesis and antimicrobial activity of 2-methyl-5-aryl-3-furoic acids and 2-methyl-3-imidazolylmethyl-5-aryl furans*, Il Farmaco*, 1987, **42**, 629 - 639.]

Preparation of ethyl 2-(*p*-methoxyphenacyl)acetoacetate



To a suspension of sodium pellets (0.09 mol) in toluene (120 mL) was added ethyl acetoacetate (0.132 mol) dropwise with stirring. The mixture was stirred at room temperature for 3 days. After cooling at 0 °C a solution of 2-bromo-4'-methoxyacetophenone (0.09 mol) in toluene (210 mL) was added dropwise. The resulting suspension was stirred at 0 °C for 1 h then it was kept stirring at room temperature for 3 days. After filtration, the solution was evaporated under reduced pressure at bath temperature of 30 °C. The crude product obtained (a reddish-brown oil, 88%) was used in subsequent reactions without further purification. (21.9 g, 88%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 2H, Ar-H_o), 6.90 (d, J = 9.0 Hz, 2H, Ar-H_m), 4.20 (m, 3H, H_2 & CH_2 $_{Et}$), 3.85 (s, 3H, *p*-OMe), 3.55 (ABX-q, J = 18.3, 8.3, 6.0 Hz, 2H, -CH_2COAr), 2.42 (s, 3H, CH_3C=O), 1.26 (t, 3H, CH_3 $_{Et}$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 203.60, 195.80, 169.60, 164.00, 130.86, 129.41, 111.82, 61.00, 56.00, 54.50, 37.49, 27.78, 14.19.

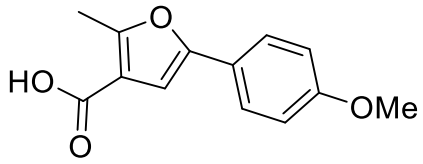
Preparation of ethyl 2-methyl-5-(*p*-methoxyphenyl)-3-furoate



Concentrated hydrochloric acid (20 mL) was added to a solution of ethyl 2-(*p*-methoxyphenacyl)phenacylacetoacetate (0.020 mol) in ethanol (200 mL) and the resulting solution was heated at reflux with stirring for 24 h. The solution was evaporated under reduced pressure to a small volume and transferred into water (200 mL) then extracted with diethyl ether. The organic layer was separated, washed with water, dried over anhydrous sodium sulphate and the solvent removed using a rotary evaporator. The residue was dissolved in toluene and passed through an aluminium oxide column. The central eluates were collected and evaporated to give a residue which was crystallized from ethanol. (4.06 g, 78%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.7 Hz, 2H, Ar-H_o), 6.89 (d, J = 8.7 Hz, 2H, Ar-H_m), 6.93 (s, 1H, H_4 $_{furan}$), 4.27 (q, 2H, CH_2 $_{Et}$), 3.82 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3 $_{furan}$), 1.36 (s, 3H, CH_3 $_{Et}$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 164.37,

159.32, 158.05, 151.86, 125.35, 123.23, 115.27, 114.50, 103.93, 60.53, 55.59, 14.55, 13.58. m/z (ES-MS): $[M_2+Na]^+$, 543.12, $[MH]^+$, 261.07, $[M-C_3H_5O_2]$,188.03

Preparation of 2-methyl-5-(*p*-methoxyphenyl)-3-furoic acid



To ethanol (300 mL) stirred at room temperature was added slowly small pieces of sodium (0.15 mol). After the reaction was stopped a solution of the ethyl ester (0.03 mol) in ethanol (50 mL) was added and the solution was refluxed overnight. The solution was reduced to a small volume, poured into water (200 mL) and extracted with diethyl ether (200 mL x 2). The aqueous layer was separated and acidified with hydrochloric acid (2M). The precipitate formed on cooling was filtered and recrystallized from ethanol to give a white solid. (5.1 g, 73%) ^{1}H-NMR (400 MHz, d_6-DMSO) δ 7.59 (d, J = 9.0 Hz, 2H Ar-H_o), 6.94 (d, J = 9.0 Hz, 2H Ar-H_m), 6.89 (s, 1H, H-$_{4\ furan}$), 3.74 (s, 3H, *p*-OCH_3), 2.54 (s, 3H, CH_3). ^{13}C-NMR (101 MHz, d_6-DMSO) δ 165.28, 159.43, 157.78, 151.58, 125.47, 122.87, 116.14, 114.87 (Ar-C_m), 104.97 (C_4), 55.70 (OCH_3), 14.01 (CH_3). Anal. Calcd. For $C_{13}H_{12}O_4$ (232.23): C, 67.23; H, 5.21; O, 27.56; found C, 67.09; H, 5.33; O, 27.58 m/z (ES-MS): $[M_2+Na]^+$, 487.30; $[MH]^+$, 233.06

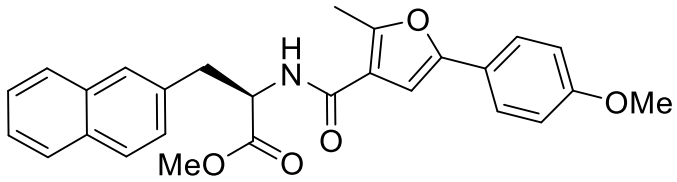
Coupling of 2-methyl-5-(*p*-methoxyphenyl)-3-furoic acid with amino acid esters

The coupling of D-tryptophan methyl ester, D-tyrosine methyl ester, D-phenylalanine methyl ester, or 3-(2'-naphthyl)-D-alanine methyl ester with 5-(*p*-methoxyphenyl)-2-methylfuran-3-carboxylic acid followed the procedure as follows.

Diisopropylethylamine (3.9 mL, 22.6 mmol) was added dropwise to a solution of the appropriate methyl ester hydrochloride (8.6 mmol) in dichloromethane (40 mL) at 0 °C, and the clear colourless solution was stirred for 20 min. Then, 5-(*p*-methoxyphenyl)-2-methylfuran-3-carboxylic acid (8.6 mmol) in dichloromethane (20 mL) was added in portions to the reaction mixture. After the addition of 1-hydroxybenzotriazole (1.6 g, 10.4 mmol), the solution was stirred for 20 min at 0 °C and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (2.3 g, 11.8 mmol) was added in portions. The resulting mixture was stirred at 0 °C for 30 min and stirred at room temperature for 24 h. Then, 10% monosodium citrate solution (30 mL) was added. The organic layer was separated,

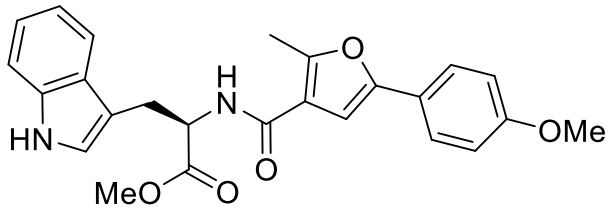
washed with saturated $NaHCO_3$ solution (20 mL x 2), H_2O (20 mL x 2), and saturated brine (20 mL x 2), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to obtain the corresponding crude furoate ester as yellow 'oily solid'. Recrystallization from ethyl acetate provided the corresponding amide.

Methyl (*R*)-(2-methyl-5-(p-methoxyphenyl)-3-furoyl)-3-(2-naphthyl)alaninate



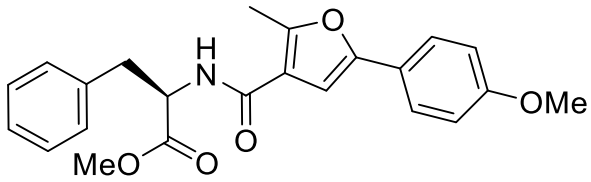
(2.6 g, 72%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.7 Hz, 3H), 7.63 (d, J = 9.1 Hz, 2H), 7.48 (q, J = 9.3 Hz, 4H), 7.26 (d, J = 6.4 Hz, 2H), 6.96 (d, J = 5.9 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H, $H_{m\ \text{Ar-furan}}$), 6.42 (s, 1H, $H_{4\ \text{furan}}$), 6.20 (d, J = 9.1 Hz, 1H, NH), 5.13 (s, 1H, $H_{\alpha\ \text{Naph}}$), 3.81 (s, 3H, $OCH_{3\ \text{Ar-furan}}$), 3.76 (s, 3H, $OCH_{3\ \text{Naph}}$), 3.39 (m, 2H, $H_{\beta\ \text{Naph}}$), 2.58 (s, 3H, $CH_{3\ \text{furan}}$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.32, 163.29, 159.35, 155.94, 151.87, 133.52, 132.59, 128.41, 128.26, 127.80, 127.65, 127.49, 126.34, 125.91, 125.23, 123.02, 117.01, 114.24, 101.66, 55.26, 53.13, 52.59, 38.10, 13.70. Anal. calcd. for $C_{27}H_{25}NO_5$ (443.50): C, 73.12; H, 5.68; N, 3.16; Found: C; 71.34; H, 5.68; N, 3.62. *m/z* (ES-MS): $[MH]^+$,444.13.

Methyl (*R*)-(2-methyl-5-(p-methoxyphenyl)-3-furoyl)tryptophanate



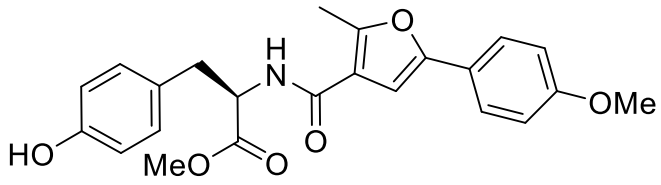
(2.8 g, 76%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (s,1H, NH $_{indole}$), 7.57 (d, J = 7.8 Hz, 1H, $H_{4\ indole}$), 7.47 (d, J = 9.1 Hz, 2H, $H_{o\ Ar\text{-}furan}$), 7.37 (d, J = 7.8 Hz, 1H, $H_{7\ indole}$), 7.20 (t, 1H, $H_{6\ indole}$), 7.11 (t, 1H, $H_{5\ indole}$), 7.00 (s, 1H, $H_{2\ indole}$), 6.89 (d, J = 8.7 Hz, 2H, $H_{m\ Ar\text{-}furan}$), 6.28 (s, 1H, $H_{4\ furan}$), 6.25 (d, J = 7.8 Hz, 1H, NH $_{Trp}$), 5.08 (q, 1H, $H_{\alpha\ Trp}$), 3.82 (s, 3H, p-OCH_3), 3.71 (s, 3H, $OCH_{3\ Trp}$), 3.41 (d, J = 5.0 Hz, 2H, $H_{\beta\ Trp}$), 2.57 (s, 3H, $CH_{3\ furan}$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.59, 163.46, 159.41, 155.80, 152.00, 136.23, 127.80, 125.16, 123.07, 122.97, 122.41, 119.87, 118.80, 116.98, 114.23, 111.48, 110.00, 101.79, 55.42, 53.16, 52.63, 27.72, 13.73. Anal. calcd. for $C_{25}H_{24}N_2O_5$ (432.48): C, 69.43; H, 5.59; N, 6.48; Found: C, 69.29; H, 5.53; N, 6.52. m/z (ES-MS): $[M_2H]^+$, 865.00; $[MH]^+$, 433.19.

Methyl (*R*)-(2-methyl-5-(p-methoxyphenyl)-3-furoyl)phenylalaninate



(2.4 g, 75%) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 11.9 Hz, 2H, $H_{o\ Ar\text{-}furan}$), 7.24-7.29 (m, 3H, H_{m} & $H_{p\ Phe}$), 7.12 (d, J = 6.4 Hz, 2H, $H_{o\ Phe}$), 6.90 (d, J = 2.3 Hz, 2H, $H_{m\ Ar\text{-}furan}$), 6.45 (s, 1H, $H_{4\ furan}$), 6.16 (d, J = 7.8 Hz, 1H, NH), 5.04 (q, 1H, $H_{\alpha\ Phe}$), 3.82 (s, 3H, *p*-OCH_3), 3.75 (s, 3H, $OCH_{3\ Phe}$), 3.22 (ABX q, J = 23.0, 13.8, 5.6 Hz, 2H, $H_{\beta\ Phe}$), 2.58 (s, 3H, $CH_{3\ furan}$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 172.29, 163.35, 159.37, 155.90, 151.97, 135.94, 129.45, 128.72, 127.30, 125.25, 123.04, 117.01, 114.26, 101.55, 55.43, 53.08, 52.54, 38.06, 13.77. Anal. calcd. for $C_{23}H_{23}NO_5$ (393.44): C, 70.21; H, 5.89; N, 3.56; Found: C; 69.90; H, 5.97; N, 3.72. *m/z* (ES-MS): $[M_2]^+$, 786.78; $[MH]^+$,394.19; [M-$C_{10}H_{11}NO_2$], 214;

Methyl (*R*)-(2-methyl-5-(p-methoxyphenyl)-3-furoyl)tyrosinate



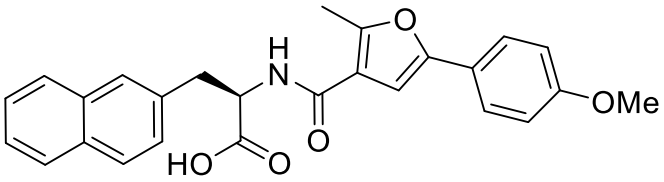
(2.7 g, 81%) ^{1}H-NMR (400 MHz, $CDCl_3$/TFA) δ 7.52 (d, J = 8.7 Hz, 2H, $H_{o\ Ar\text{-}furan}$), 6.98 (d, J = 8.7 Hz, 2H, $H_{m\ Ar\text{-}furan}$), 6.92 (d, J = 8.7 Hz, 2H, $H_{o\ Tyr}$), 6.76 (d, J = 8.7 Hz, 2H,$H_{m\ Tyr}$), 6.62 (d, J = 8.2 Hz, 1H, NH), 6.49 (s, 1H,$H_{4\ furan}$), 5.02 (q, 1H, $H_{\alpha\ Tyr}$), 3.84 (s, 3H, *p*-OCH_3), 3.81 (s, 3H, $OCH_{3\ Tyr}$), 3.14 (ABX q, J = 13.8, 5.8 Hz, 2H, $H_{\beta\ Tyr}$), 2.52 (s, 3H, $CH_{3\ furan}$). ^{13}C-NMR (101 MHz, $CDCl_3$/TFA) δ 173.00, 165.50, 159.54,156.61, 154.78, 152.66,

130.58, 127.31, 125.40, 122.56, 115.66, 114.35, 113.25, 101.44, 55.51, 53.66, 52.85, 37.03, 13.84. Anal. calcd. for $C_{23}H_{23}NO_6$ (409.44): C, 67.47; H, 5.66; N, 3.42; Found: C, 66.79; H, 5.69; N, 3.50. *m/z* (ES-MS): $[M_2]^+$, 818.82; $[MH]^+$, 410.18; $[M\text{-}C_{10}H_{12}NO_3]^+$, 215.03.

Hydrolysis of methyl ester of the coupled amides

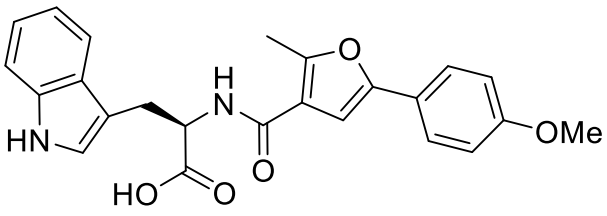
Methanol (30 mL) was added to the white powder of the coupled amide (3.4 mmol) in a 100 mL three-necked flask equipped with a magnetic stirrer and a condenser. The mixture was then stirred for 20 min. Aqueous 5% KOH solution (10 mL) was added to the mixture and the resulting mixture was allowed to stir at room temperature overnight. The resulting solution was concentrated on a rotary evaporator to a smaller volume (10 mL). A solution of 1M hydrochloric acid was added to the concentrated solution in drops until a precipitate was formed. The precipitate was filtered and washed with more 1M HCl. The solid was dried *in vacuo* to obtain a cream colour solid.

(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)-3-(2-naphthyl)alanine (4a)



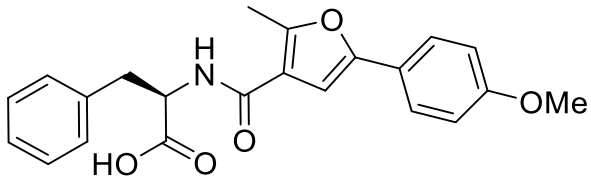
(0.80 g, 55%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.44-7.79 (m, 9H, Ar-H), 6.88-6.97 (m, 3H, Ar-H), 6.42 (s, 1H, $H_{4\ furan}$), 6.20 (d, J = 7.8 Hz, 1H, NH), 5.12 (dd, J = 13.0, 5.7 Hz, 1H, $H_{\alpha\ Naph}$), 3.39 (t, J = 5.7 Hz, 2H, $H_{\beta\ Naph}$), 2.58 (s, 3H, $CH_{3\ furan}$). ^{13}C-NMR (101 MHz, d_6-DMSO) δ 172.10, 171.24, 163.64, 159.37, 133.59, 133.53, 132.60, 128.39, 128.21, 127.77, 127.64, 127.47, 126.31, 125.88, 125.21, 123.03, 117.04, 114.23, 101.70, 60.47, 38.22, 13.70. Anal. calcd. for $C_{26}H_{23}NO_5$ (429.47): C, 72.71; H, 5.40; N, 3.26; Found: C, 71.89; H, 5.35; N, 3.15. *m/z* (ES-MS): $[MH]^+$, 430.14.

(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)tryptophan (4b)



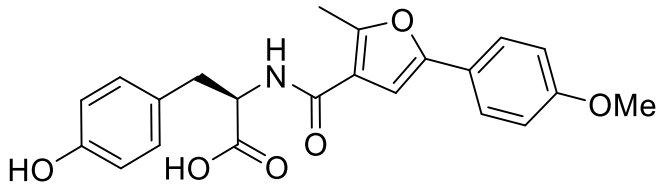
(1.05 g, 74%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H, OH), 8.11 (d, J = 7.8 Hz, 1H, NH $_{indole}$), 7.55 (d, J = 7.8 Hz, 1H, NH $_{Trp}$), 7.50 (d, J = 9.2 Hz, 2H, $H_{o\ Ar\text{-}furan}$), 7.29 (d, J = 7.8 Hz, 1H, $H_{7\ indole}$), 7.16 (s, 1H, $H_{2\ indole}$), 7.13 (s, 1H, $H_{4\ furan}$), 6.93-7.04 (m, 4H, $H_{m\ Ar\text{-}furan}$, $H_{5\&6\ indole}$), 4.58 (t, J = 12.8, 4.9 Hz, 1H, $H_{\alpha\ Trp}$), 3.74 (s, 3H, *p*-OCH_3), 3.09-3.27 (m, 2H, $H_{\beta\ Trp}$), 2.44 (s, 3H, $CH_{3\ furan}$). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 174.14, 163.35, 159.38, 155.59, 150.99, 136.63, 127.65, 125.18, 124.14, 123.10, 121.46, 118.89, 118.64, 117.78, 115.02, 111.97, 110.80, 103.55, 55.73, 53.56, 27.25, 13.79. Anal. calcd. for $C_{24}H_{22}N_2O_5$ (418.45): C, 68.89; H, 5.30; N, 6.69; Found: C, 66.63; H, 5.62; N, 7.74. *m/z* (ES-MS) : $[M_2]^+$, 836.32; $[MH]^+$, 419.16

(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)phenylalanine (4c)



(0.86 g, 67%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 8.2 Hz, 1H, NH), 7.50 (d, J = 9.1 Hz, 2H, $H_{o\ Ar\text{-}furan}$), 7.21-7.28 (m, 4H, H_{o} & $H_{m\ Phe}$), 7.14 (t, J = 7.1 Hz, 2H, $H_{p\ Phe}$ & $H_{4\ furan}$), 6.97 (d, J = 8.7 Hz, 2H, $H_{m\ Ar\text{-}furan}$), 4.50-4.56 (m, 1H,$H_{\alpha\ Phe}$), 3.74 (s, 3H,*p*-OCH_3), 2.96-3.15 (m, 2H,$H_{\beta\ Phe}$), 2.43 (s, 3H,$CH_{3\ furan}$). ^{13}C-NMR (101 MHz, d_6-DMSO) δ 173.79, 163.36, 159.36, 155.56, 150.99, 138.66, 129.59, 128.74, 126.89, 125.19, 123.07, 117.77, 115.02, 103.56, 55.73, 54.20, 36.78, 13.79. Anal. calcd. for $C_{22}H_{21}NO_5$ (379.14): C, 69.65; H, 5.58; N, 3.69; Found: C, 67.59; H, 5.53; N, 3.87. *m/z* (ES-MS): $[MH]^+$, 380.13.

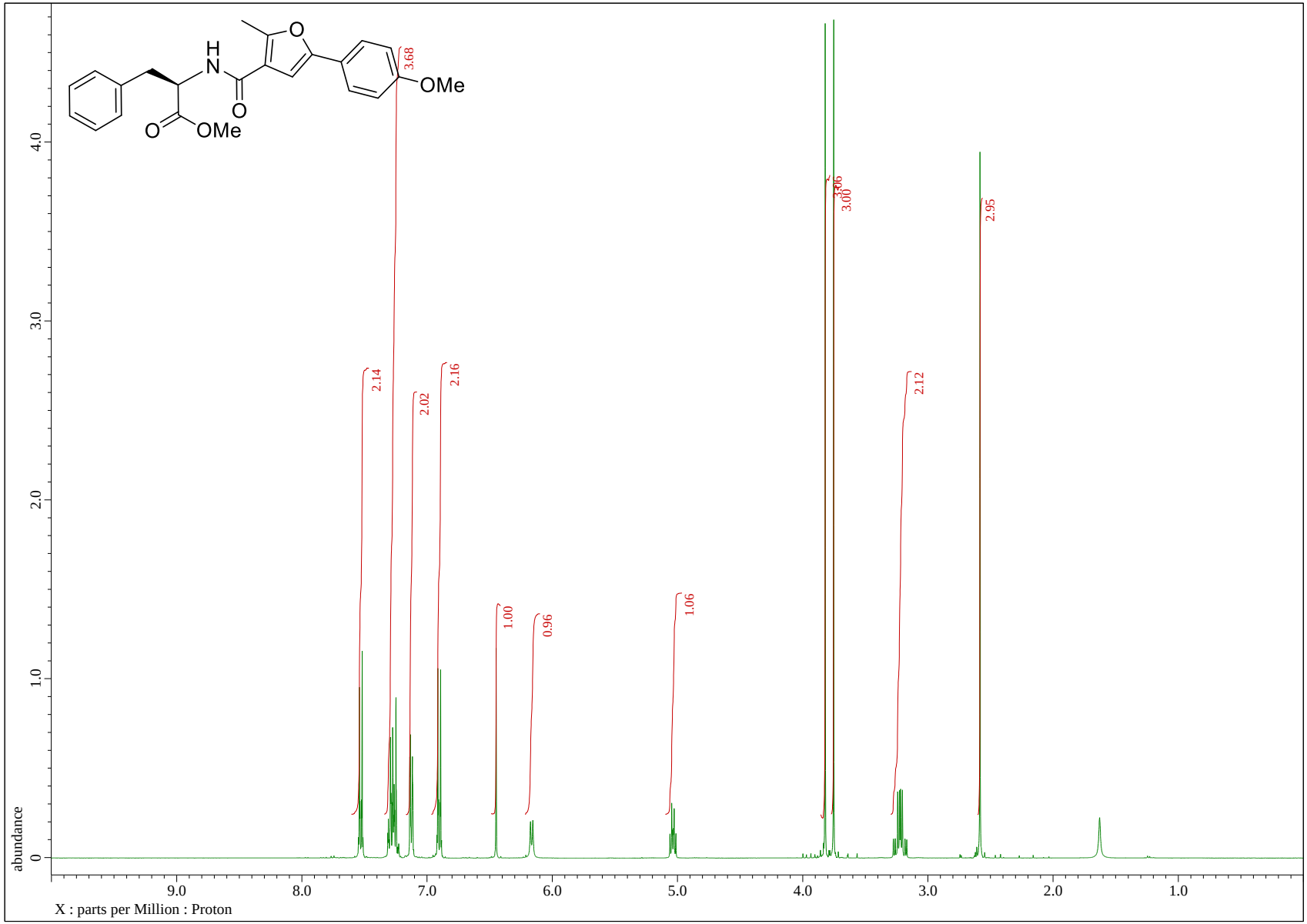
(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)tyrosine (4d)



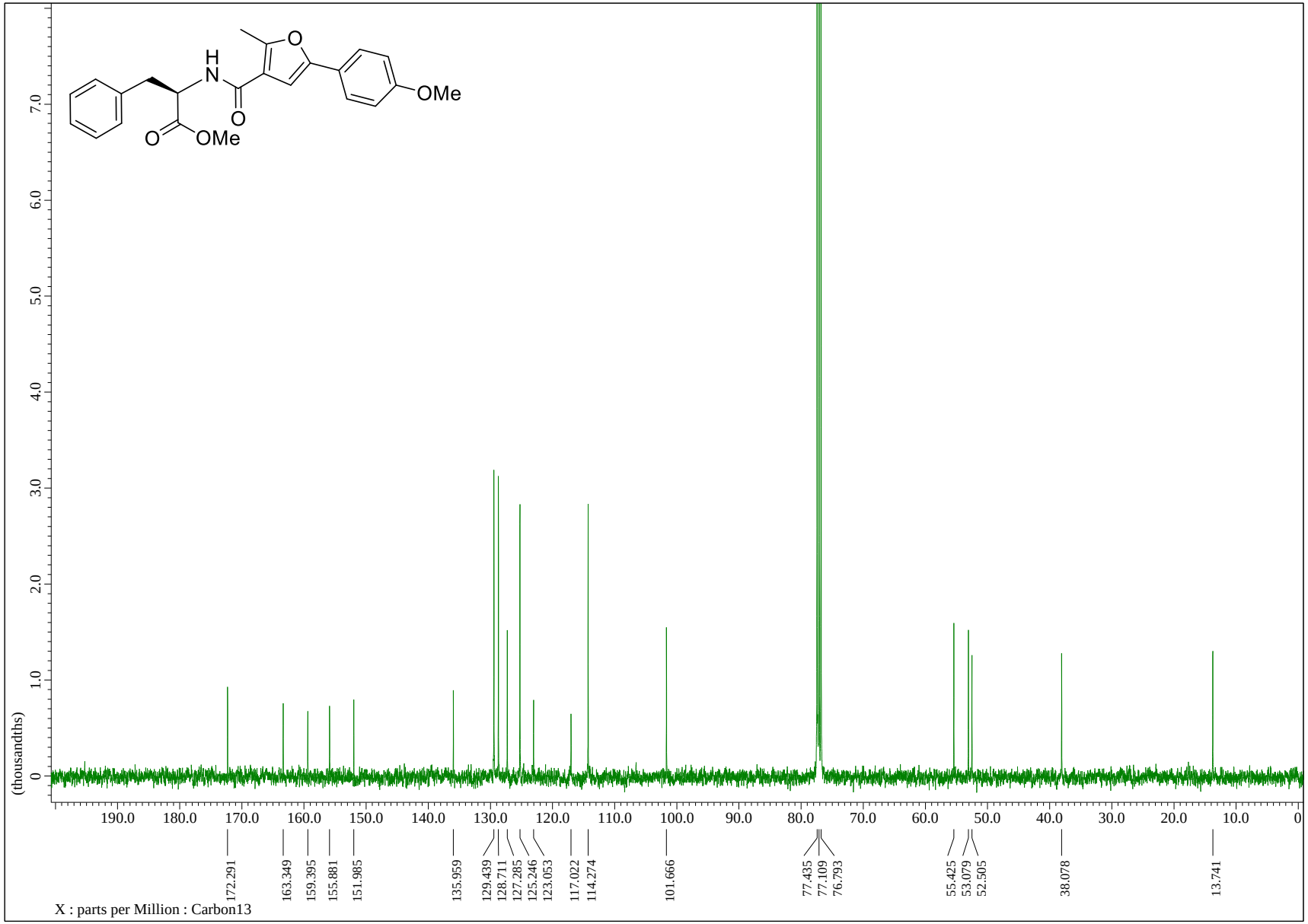
(0.82 g, 61%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 7.8 Hz, 1H, NH), 7.51 (d, J = 8.7 Hz, 2H, $H_{o\ Ar\text{-}furan}$), 7.10 (s, 1H, $C_{4\ furan}$), 7.04 (d, J = 8.7 Hz, 2H, $H_{m\ Ar\text{-}furan}$), 6.97 (d, J = 9.1 Hz, 2H, $H_{o\ Tyr}$), 6.60 (d, J = 8.7 Hz, 2H, $H_{m Tyr}$), 4.42 (t, J = 5.0 Hz, 1H, $H_{\alpha\ Tyr}$), 3.74 (s, 3H, *p*-OCH_3), 2.82-3.03 (m, 2H, $H_{\beta\ Tyr}$), 2.52 (s, 3H, $CH_{3\ furan}$). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 174.00, 163.22, 159.35, 156.32, 155.41, 150.99, 130.53, 128.74, 125.21, 123.10, 117.91, 115.48, 115.01, 103.54, 55.72, 54.73, 36.20, 13.79. Anal. calcd. for $C_{22}H_{21}NO_6$

(395.41): C, 66.83; H, 5.35; N, 3.54; Found: C, 66.51; H, 5.44; N, 3.37. *m/z* (ES-MS): $[M_2H]^+$, 791.03; $[MH]^+$,396.13.

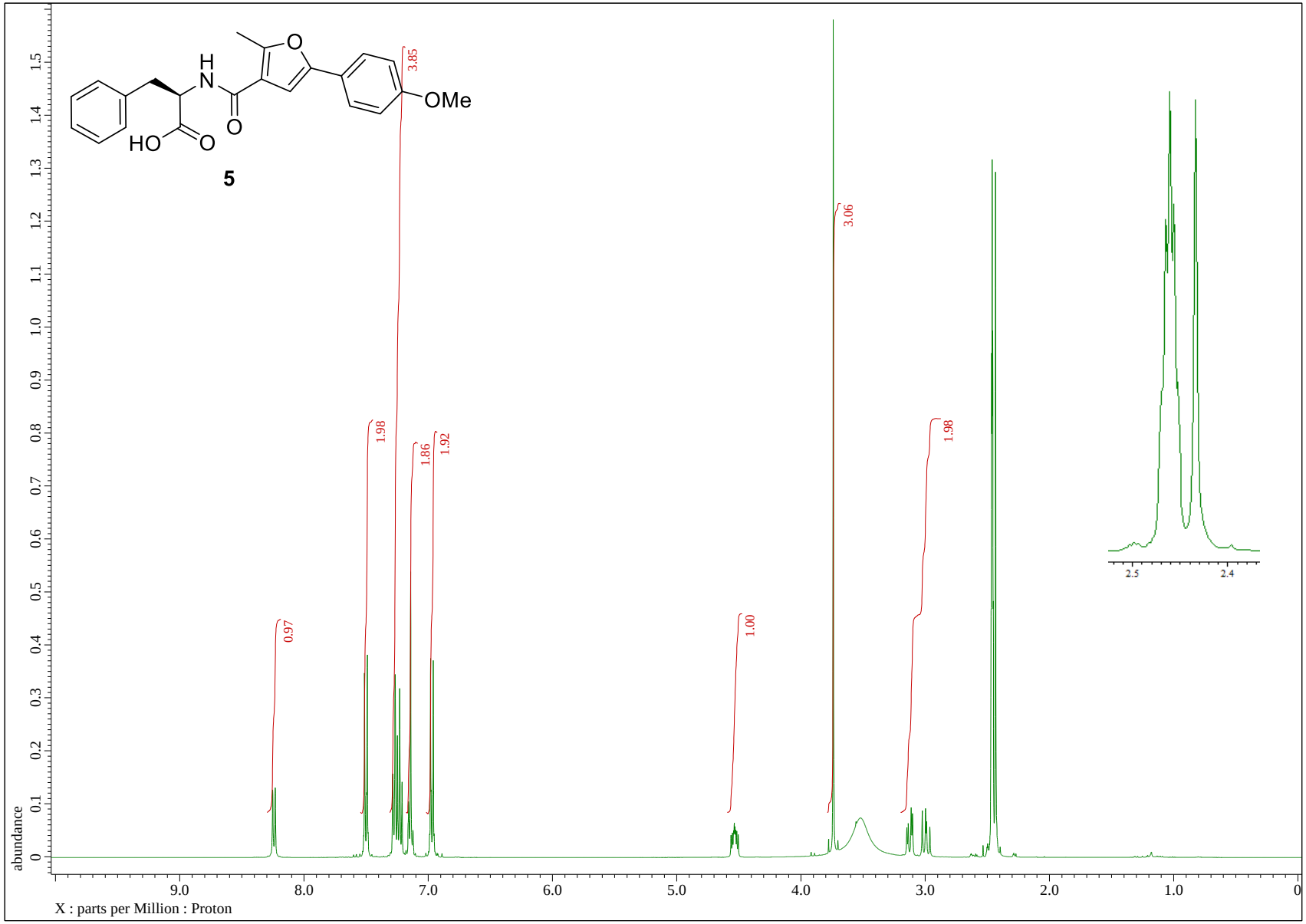
Methyl (*R*)-(2-methyl-5-(*p*-methoxyphenyl)-3-furoyl)phenylalaninate: ^{1}H NMR spectrum



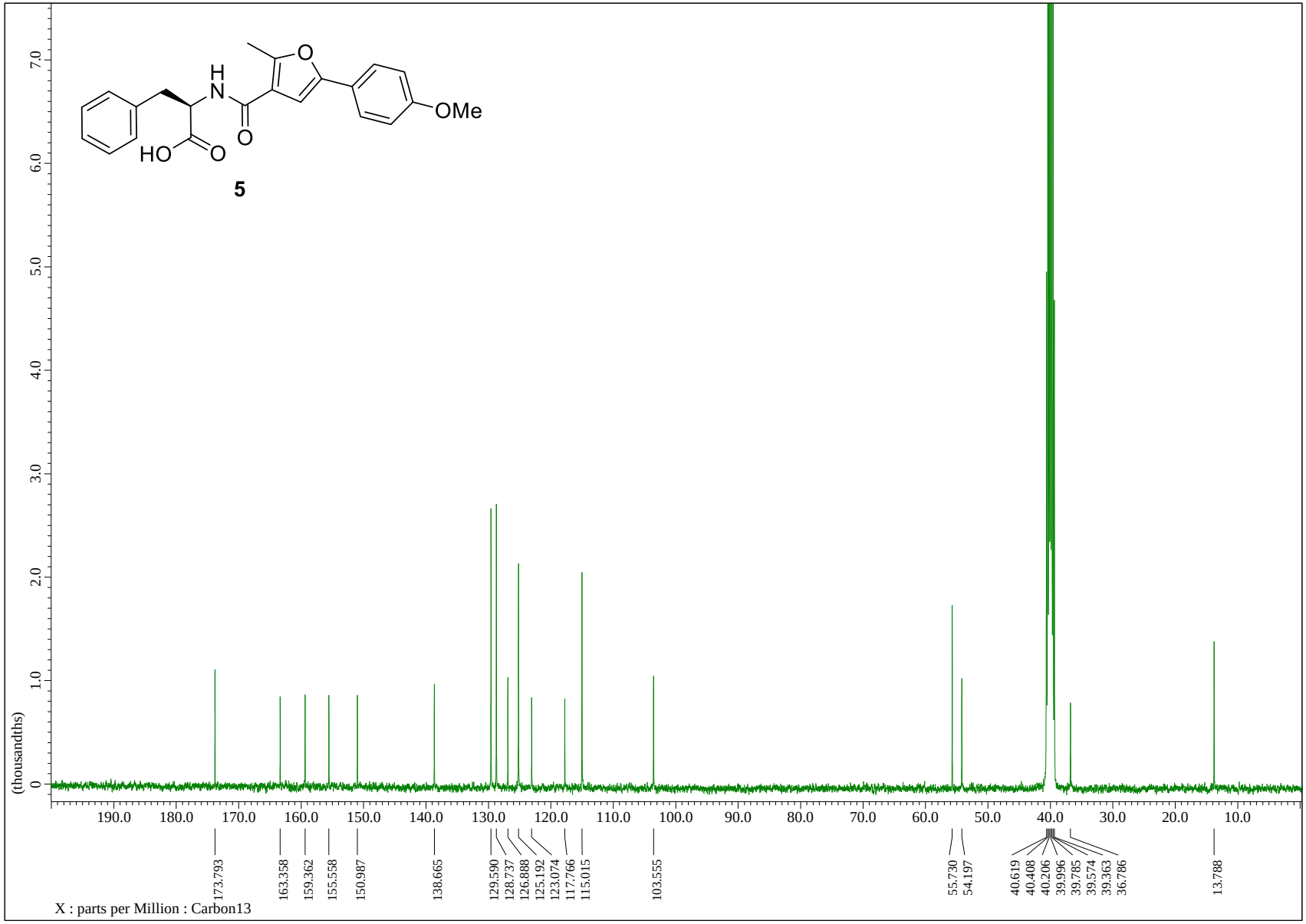
Methyl (*R*)-(2-methyl-5-(*p*-methoxyphenyl)-3-furoyl)phenylalaninate: ^{13}C NMR spectrum



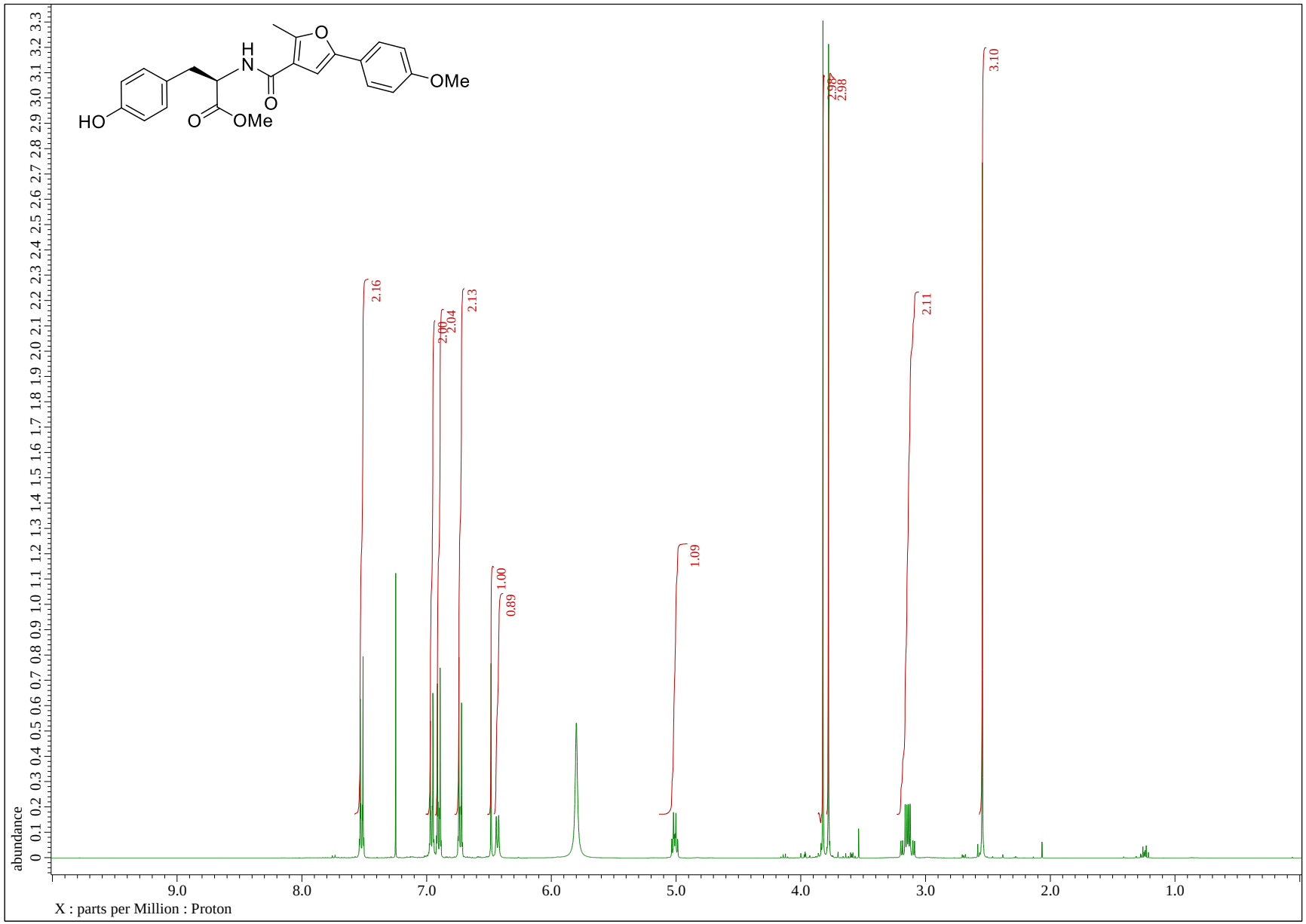
(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)phenylalanine (**5**): ^{1}H NMR spectrum



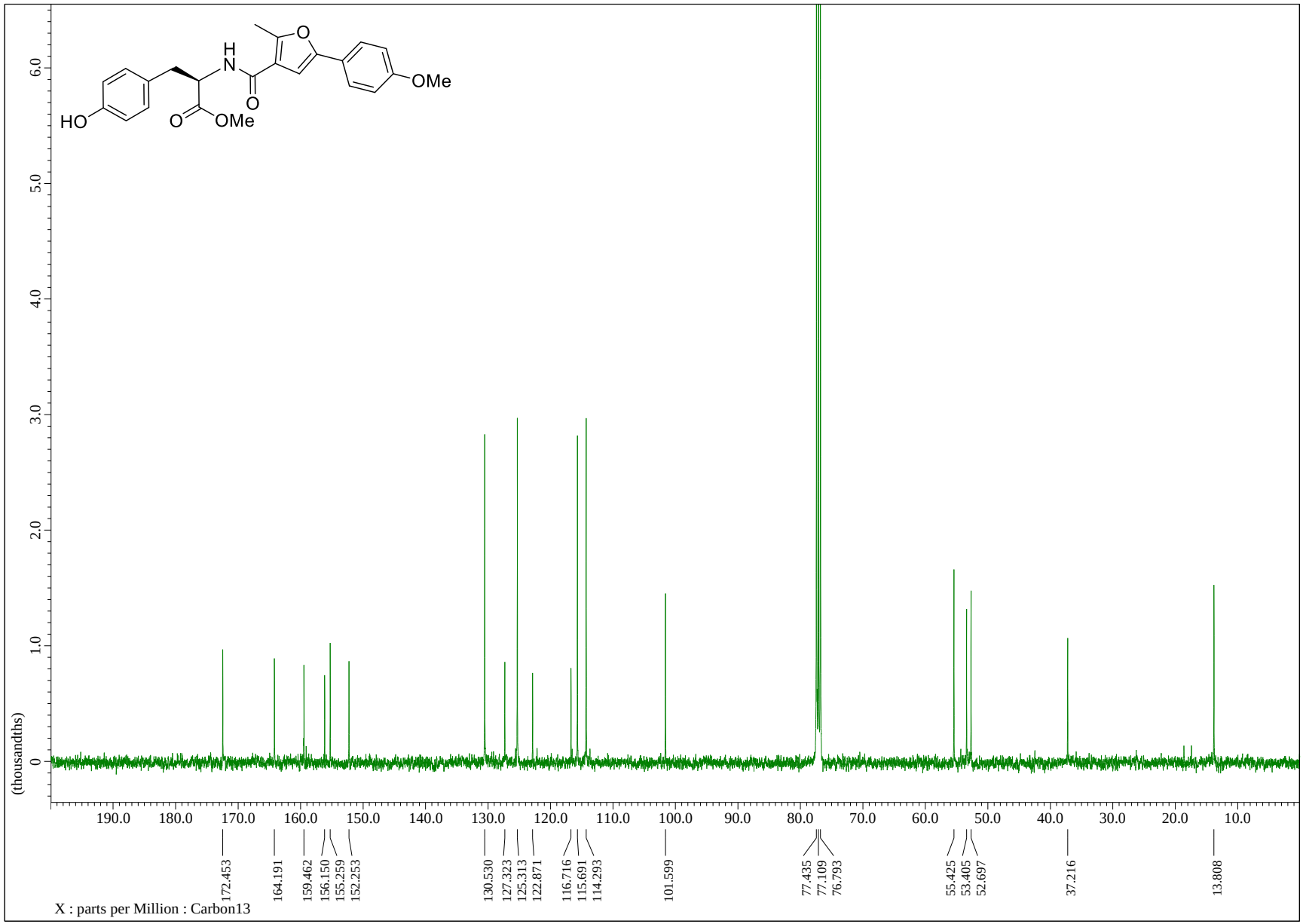
(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)phenylalanine (**5**): ^{13}C NMR spectrum



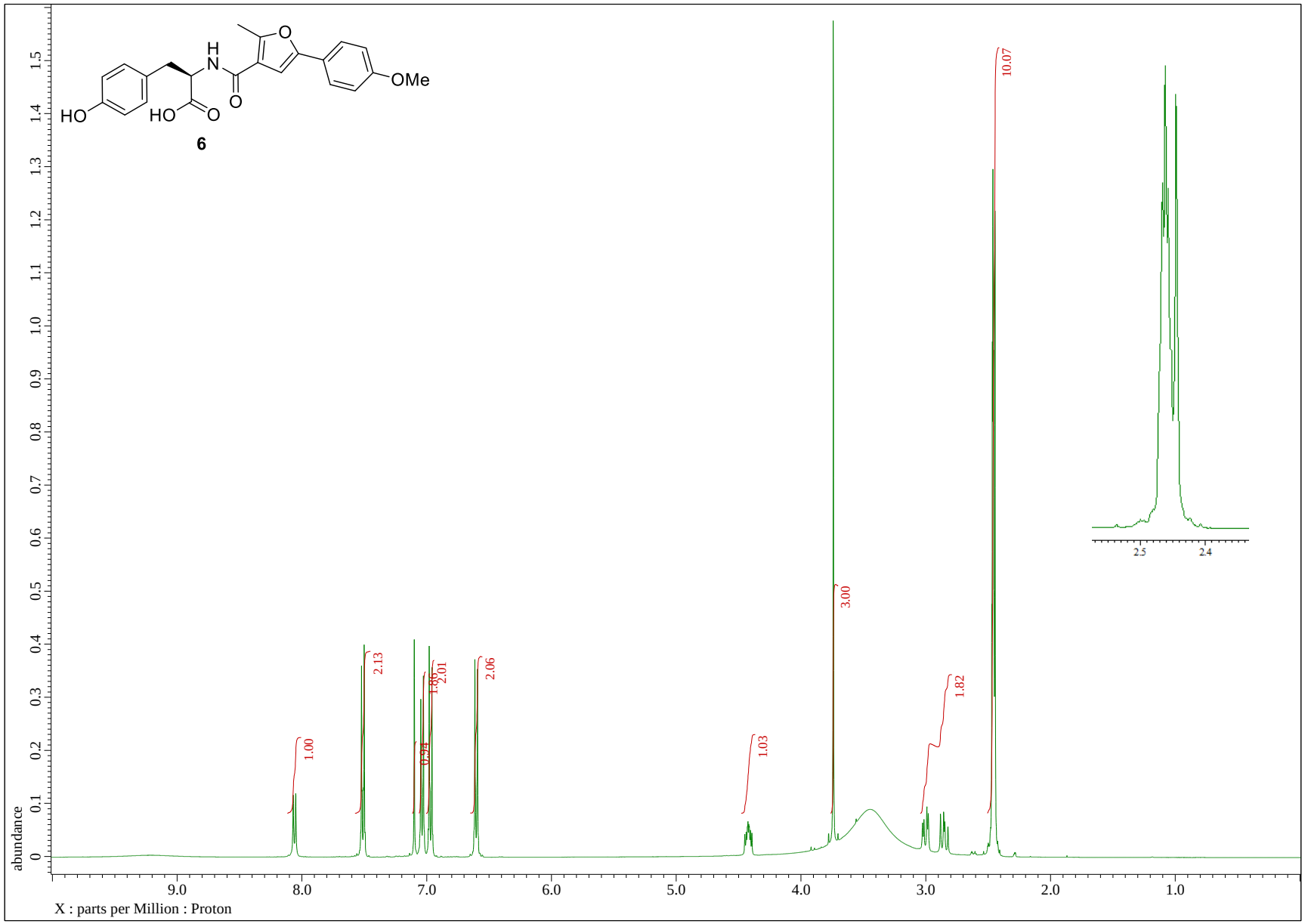
Methyl (*R*)-(2-methyl-5-(*p*-methoxyphenyl)-3-furoyl)tyrosinate: ^{1}H NMR spectrum



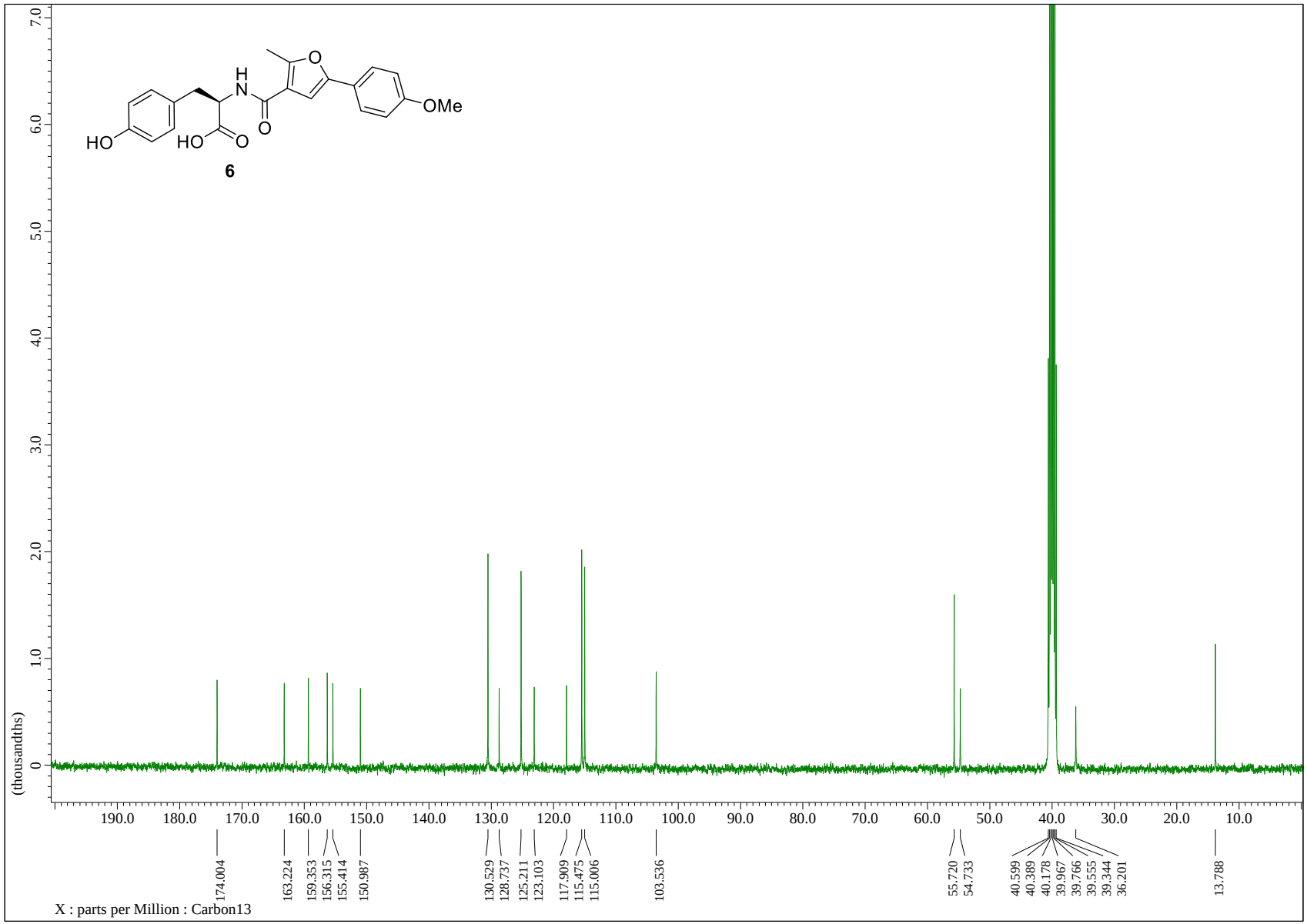
Methyl (*R*)-(2-methyl-5-(*p*-methoxyphenyl)-3-furoyl)tyrosinate: ^{13}C NMR spectrum



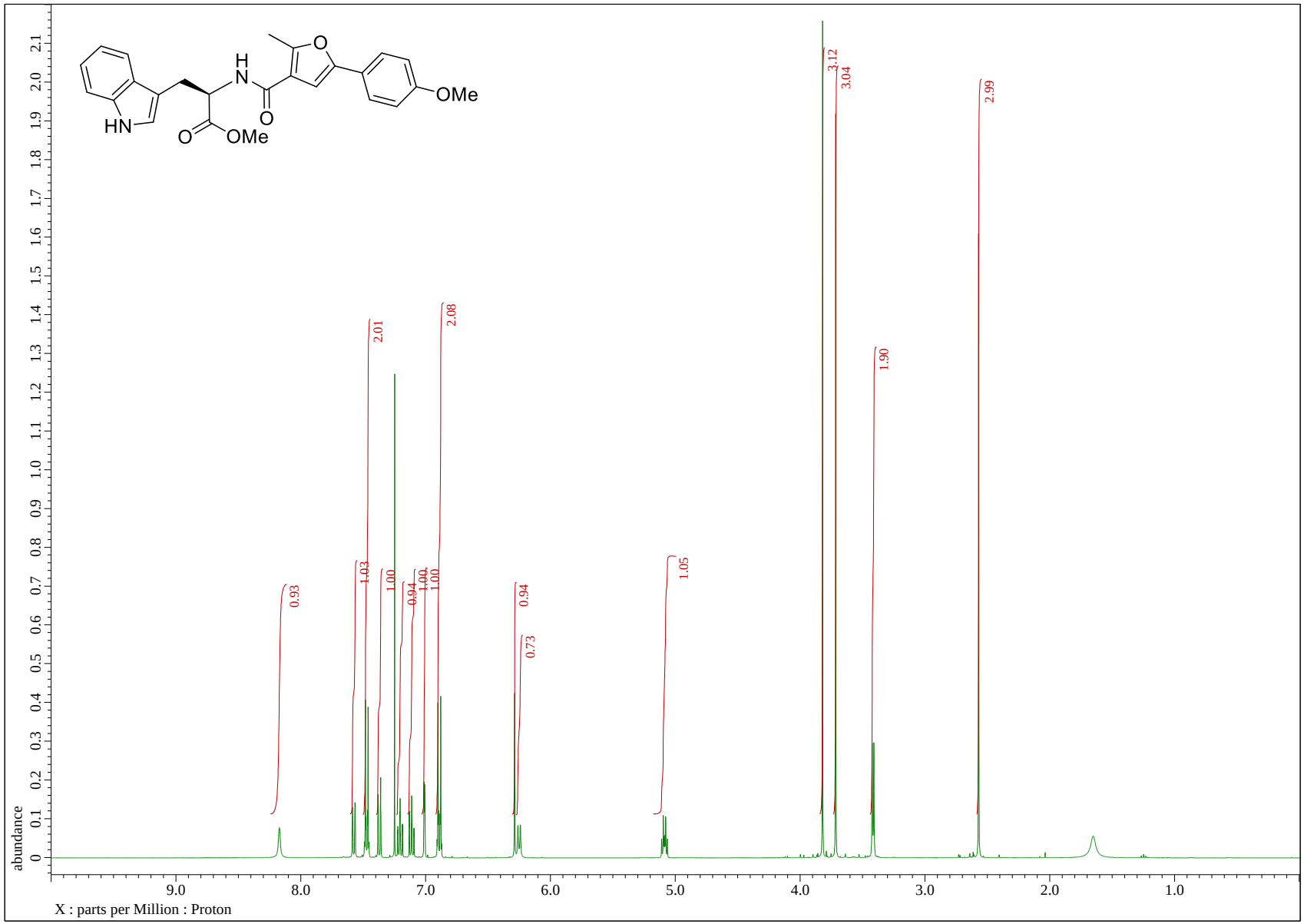
(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)tyrosine (**6**): ^{1}H NMR spectrum



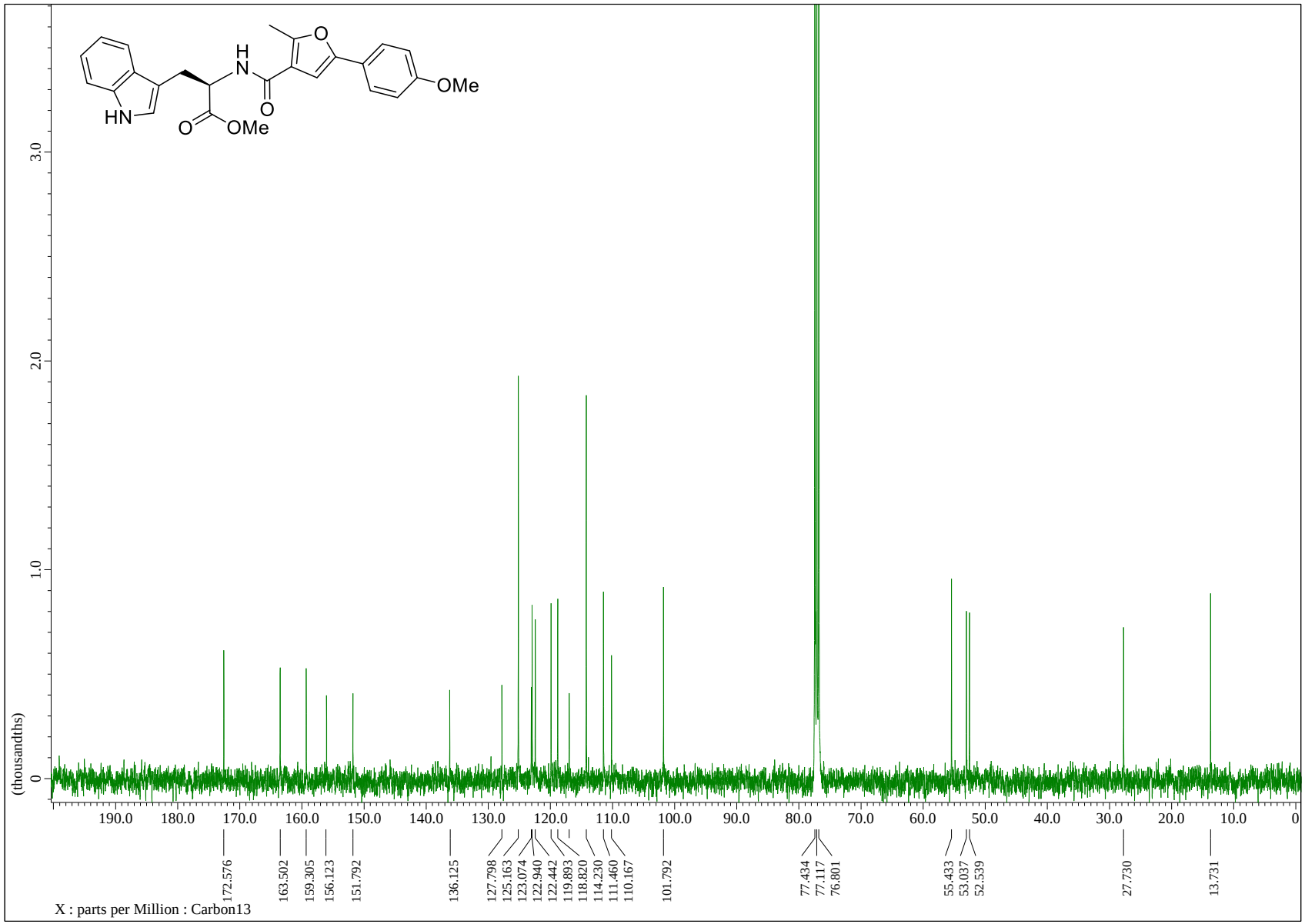
(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)tyrosine (**6**): ^{13}C NMR spectrum



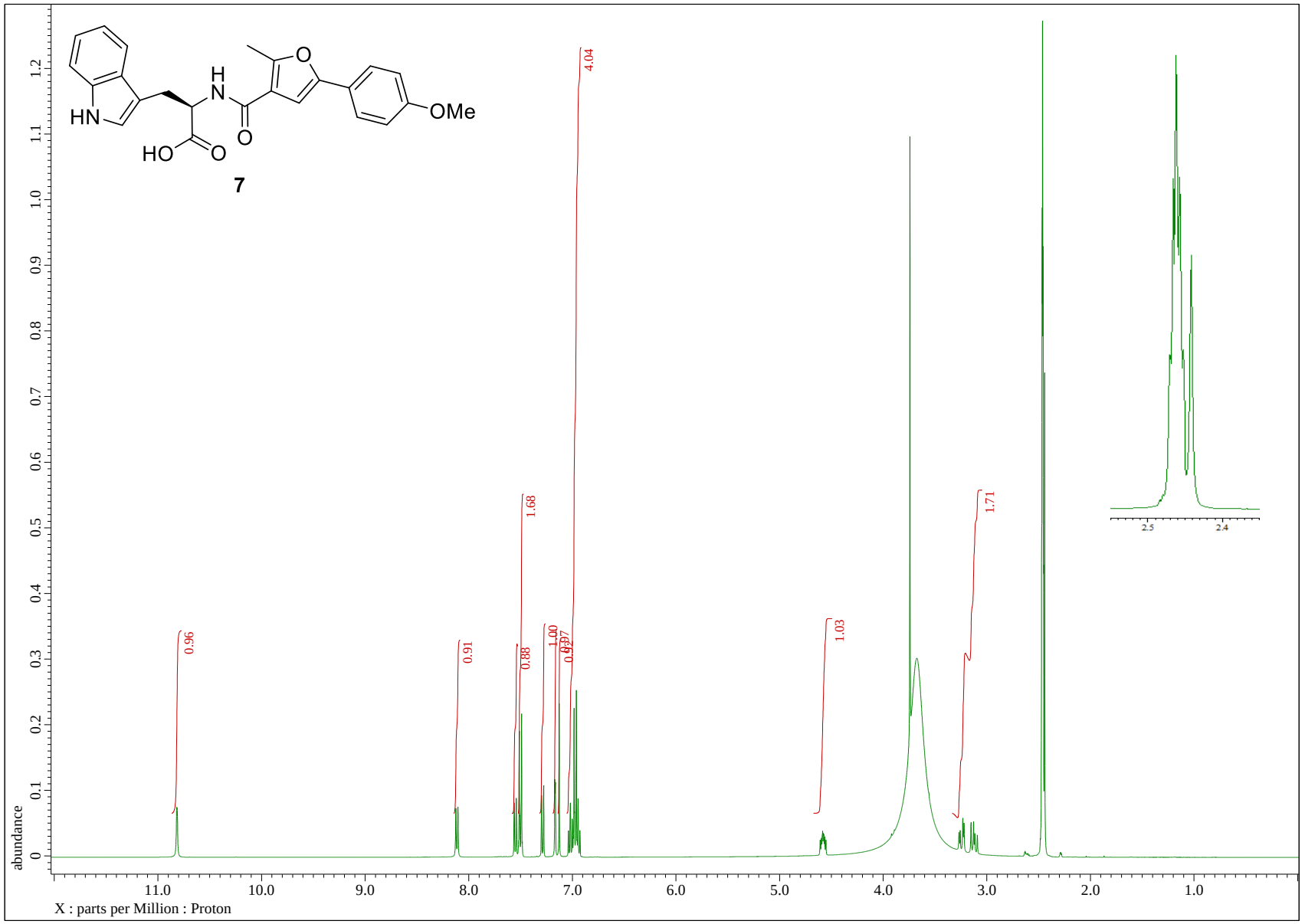
Methyl (*R*)-(2-methyl-5-(*p*-methoxyphenyl)-3-furoyl)tryptophanate: ^{1}H NMR spectrum



Methyl (*R*)-(2-methyl-5-(*p*-methoxyphenyl)-3-furoyl)tryptophanate: ^{13}C NMR spectrum



(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)tryptophan (**7**): ^{1}H NMR spectrum



(*R*)-(2-Methyl-5-(*p*-methoxyphenyl)-3-furoyl)tryptophan (**7**): ^{13}C NMR spectrum