Rapid in situ generation of 2-(halomethyl)-5-phenylfuran and nucleophilic addition in a microflow reactor

Yuma Matsuura, Shinichiro Fuse*

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Nagoya 464-8601, Japan.

E-mail: fuse.shinichiro.z3@f.mail.nagoya-u.ac.jp

Table of Contents

1. General techniques

NMR spectra were recorded on a JEOL-ECS400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) or JEOL-ECZ400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts were reported in units of parts per million (ppm) relative to tetramethylsilane (0.00 ppm) in $CDCl_3$ for ^{1}H NMR and $CDCl_3$ (77.16 ppm) for ^{13}C NMR. Multiplicities were reported by using the following abbreviations: s; singlet, d; doublet, dd; double doublet, t; triplet, td; triple doublet m; multiplet, br; broad, *J*; coupling constants in Hertz (Hz). IR spectra were recorded on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrophotometer. Only the strongest and/or structurally important peaks were reported as the IR data are given in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics Compact in the electrospray ionization (ESI-TOF) method. Gel permeation chromatography (GPC) for purification was performed on Japan Analytical Industry Model LaboACE LC-5060 (recycling preparative HPLC) on a Japan Analytical Industry Model UV-2564 LA ultra violet detector and RI-700 LA refractive index detector with a polystyrene gel column (JAIGEL-2HR, 20 mm × 600 mm), using chloroform as a solvent (10 mL/min). Column chromatography was performed on Silica Gel PSQ 60B purchased from Fuji Silysia Chemical LTD. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde, ceric sulfate solution, 10% ethanolic phosphomolybdic acid. THF was dried by a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.). MeCN was dried by molecular sieves 3Å. Other solvents and reagents were purchased from commercial suppliers (FUJIFILM Wako Pure Chemical, Kanto Chemical, Sigma-Aldrich, and Tokyo Chemical Industry) and used without further purification.

2. Microflow reactor setup

Stainless steel V-shape mixers (inner diameter: 0.250 mm) were purchased from Sanko Seiki Co. Ltd. The front and side view of the V-shape mixer is shown in Fig S-1. Teflon® tubes (inner diameter: 0.800 or 0.500 mm were purchased from Senshu Scientific Co., Ltd. PEEK fittings, PEEK unions, stainless steel tubes, stainless steel fittings, and stainless steel unions (inner diameter: 0.800 mm) were purchased from GL Science Inc. Solutions were introduced to a microflow system with syringe pumps (Harvard PHD ULTRA) equipped gastight syringes (SGE 10 mL). The gastight syringes and the Teflon tubes were connected with joints purchased from Flon Industry Co., Ltd.

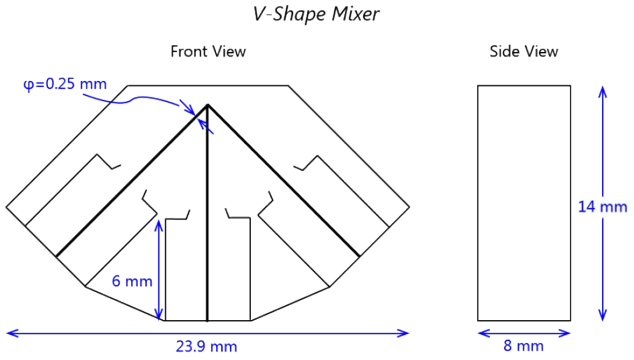


Fig. S-1. V-shape mixers used in this study

The employed microflow system is shown in Fig S-2. The gastight syringes and the 1st and 2nd V-shape mixers were connected with the Teflon tubes and stainless-steel tubes (for controlling the temperature of solutions). The 1st and 2nd V-shape mixers were connected with reaction tube 1 (Teflon tube). The 2nd V-shape mixer was connected with the reaction tube 2 (Teflon tube). These mixers and reaction tubes were immersed in a water bath.

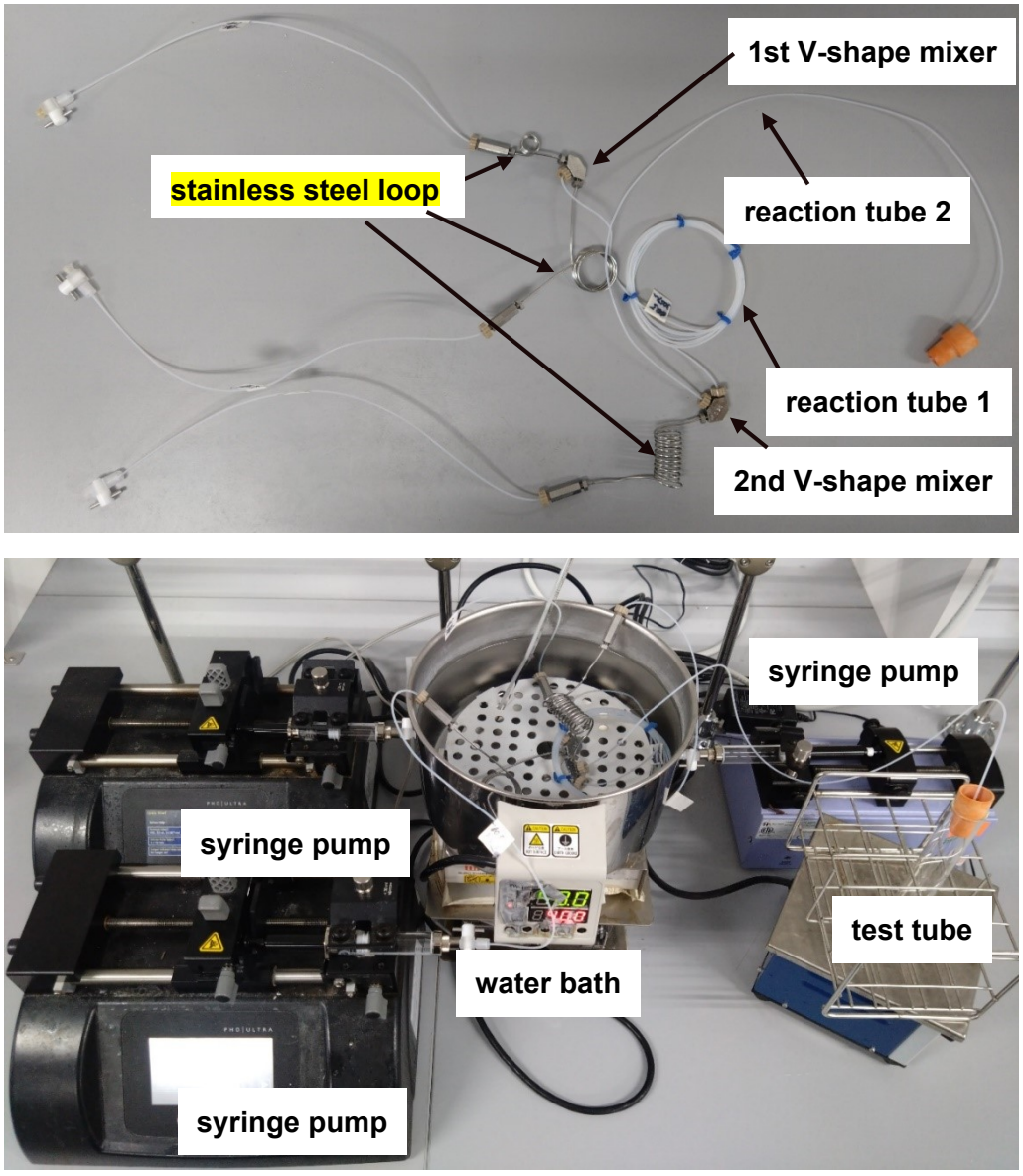
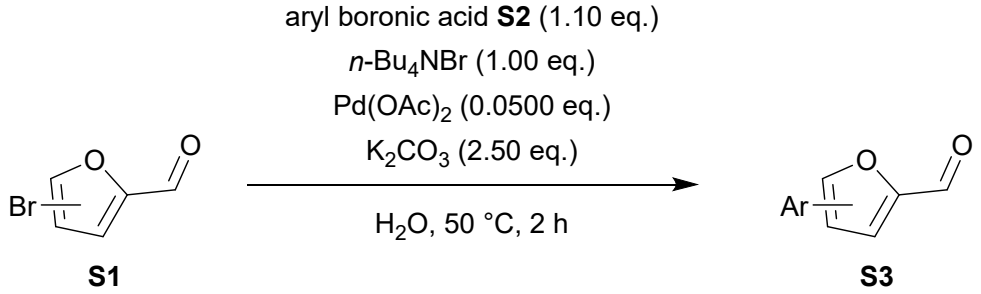


Fig. S-2. Microflow reactor setup

The stock solutions for microflow reactions were prepared as shown below. Either alcohol, activating agent, or nucleophile with NEt_3 was added to a measuring cylinder. Then, diluting in measuring cylinder to 2.5 ml (for syringe pump A), 5.0 mL (for syringe pump B), and 10.0 mL (for syringe pump C) total with indicated solvent. The prepared solutions were transferred to vials and taken by syringes.

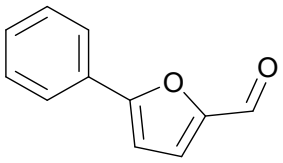
3. General procedure for arylation of 2-furaldahyde[S1]



Furaldehyde **S1** (1.00 eq.), aryl boronic acid **S2** (1.10 eq.), *n*-Bu_4NBr (1.00 eq.), $Pd(OAc)_2$ (0.0500 eq.), and K_2CO_3 (2.50 eq.) were added to a 100 mL round bottom flask. water (20 mL) was added to the flask and the resultant solution was stirred at 50 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water, filtered through Celite, and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

5-Phenyl-2-furaldehyde (S3a)

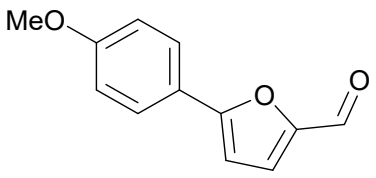
According to the general procedure for arylation of 2-furaldahyde using 5-bromo-2-furaldehyde (**S1a**) (1.75 g, 10.0 mmol, 1.00 eq.), and phenylboronic acid (**S2a**) (1.34 g, 11.0 mmol, 1.10 eq.) the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 15:1 to 5:1) to give 5-phenyl-2-furaldehyde (**S3a**) (1.48 g, 8.58 mmol, 86%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.84-7.82 (m, 2H), 7.47-7.38 (m, 3H), 7.32 (d, *J* = 3.6 Hz, 1H), 6.85 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 159.4, 152.0, 129.7, 129.0, 125.3, 123.7, 107.7. Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S2]

5-(4-Methoxyphenyl)-2-furaldehyde (S3b)

According to the general procedure for arylation of 2-furaldahyde using 5-bromo-2-furaldehyde (**S1a**) (524 mg, 3.00 mmol, 1.00 eq.), 4-methoxyphenyl boronic acid (**S2b**) (501 mg, 3.30 mmol, 1.10 eq.), the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 15:1) to give 5-(4-methoxyphenyl)-2-furaldehyde (**S3b**) (564 mg, 2.76mmol, 94%)

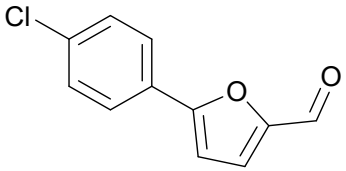


yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 4.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 4.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 160.9, 159.9, 151.7, 127.0, 124.4, 121.8, 114.5, 106.4, 55.5.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S2]

5-(4-Chlorophenyl)-2-furaldehyde (S3c)

According to the general procedure for arylation of 2-furaldahyde using 5-bromo-2-furaldehyde (**S1a**) (525 mg, 3.00 mmol, 1.00 eq.), 4-chlorophenyl boronic acid (**S2c**) (517 mg, 3.30 mmol, 1.10 eq.), the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 15:1) to give 5-(4-chlorophenyl)-2-furaldehyde (**S3c**) (389 mg, 1.88 mmol, 63%).

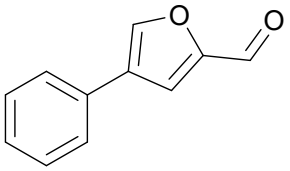


yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.78-7.74 (m, 2H), 7.44-7.41 (m, 2H), 7.32 (d, *J* = 3.6 Hz, 1H), 6.83 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 158.4, 152.3, 135.8, 129.4, 127.6, 126.7, 123.5, 108.1.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S2]

4-Phenyl-2-furaldehyde (S3e)

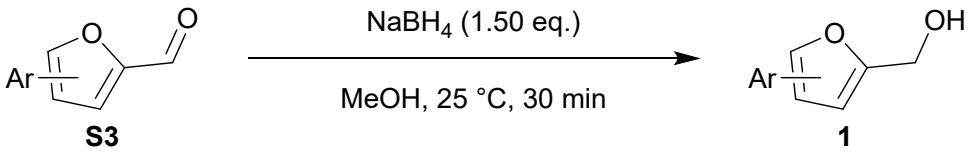
According to the general procedure for arylation of 2-furaldahyde using 4-bromo-2-furaldehyde (**S1b**) (175 mg, 1.00 mmol, 1.00 eq.), phenylboronic acid (**S2a**) (134 mg, 1.10 mmol, 1.10 eq.), the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 15:1 to 5:1) to give 4-phenyl-2-furaldehyde (**S3e**) (125 mg, 0.726 mmol, 73%).



yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.95 (s, 1H), 7.52-7.49 (m, 3H), 7.45-7.40 (m, 2H), 7.37-7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 153.7, 143.8, 130.6, 129.5, 129.3, 128.3, 126.1, 119.0.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S3]

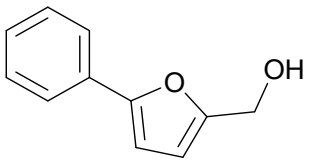
4. General procedure for arylated 2-furanmethanol[S4]



To a solution of arylated-2-furaldehyde **S3** (1.00 eq.) in MeOH was added to $NaBH_4$ (1.50 eq.) at 0 °C in an ice bath. The solution was allowed to warm to 25 °C and stirred for 30 min. The reaction was quenched by the addition of water and the aqueous layer was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

5-Phenyl-2-furanmethanol (1a)

According to the general procedure for arylated 2-furanmethanol using 5-phenyl-2-furaldehyde (S**3a**) (1.22 g, 7.51 mmol, 1.00 eq.), the residue was purified by recrystallization (hexene and EtOAc) to give 5-phenyl-2-furanmethanol (**1a**) (0.760 g, 4.36 mmol, 58%).

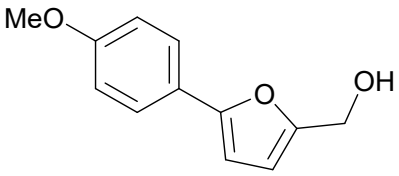


white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.26-7.22 (m, 1H), 6.57 (d, J = 3.2 Hz, 1H), 6.34 (d, J = 3.2 Hz, 1H), 4.63 (s, 2H), 2.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 153.7, 130.8, 128.8, 127.6, 123.9, 110.1, 105.8, 57.8.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S5]

5-(4-Methoxyphenyl)-2-furanmethanol (1b)

According to the general procedure for arylated 2-furanmethanol using 5-(4-methoxyphenyl)-2-furaldehyde (**S3b**) (625 mg, 3.06 mmol, 1.00 eq.), the crude product was purified by recrystallization (hexene and EtOAc) to give 5-(4-methoxyphenyl)-2-furanmethanol (**1b**) (508 mg, 2.49 mmol, 81%).

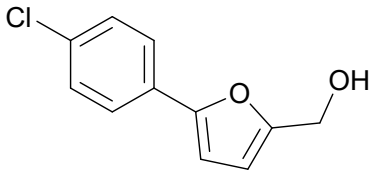


white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.58 (m, 2H), 6.94-6.90 (m, 2H), 6.46 (d, J = 3.2 Hz, 1H), 6.35 (d, J = 3.2 Hz, 1H), 4.66 (d, J = 6.4 Hz, 2H), 3.84 (s, 3H), 1.70 (t, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 154.3, 153.0, 125.4, 123.9, 114.3, 110.1, 104.2, 57.8, 55.5.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S5]

5-(4-Chlorophenyl)-2-furanmethanol (1c)

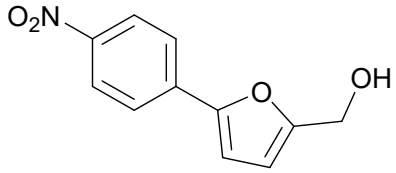
According to the general procedure for arylated 2-furanmethanol using 5-(4-chlorophenyl)-2-furaldehyde (**S3c**) (207 mg, 1.00 mmol, 1.00 eq.), the crude product was purified by recrystallization (hexene and EtOAc) to give 5-(4-chlorophenyl)-2-furanmethanol (**1c**) (181 mg, 0.867 mmol, 87%).



white solid; mp 91-94 °C, IR (neat): 3218, 1480, 1020, 961, 830, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.36-7.33 (m, 2H), 6.58 (d, *J* = 3.2 Hz, 1H), 6.38 (d, *J* = 3.2 Hz, 1H), 4.66 (d, *J* = 5.6 Hz, 2H), 1.80 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 153.1, 133.3, 129.3, 129.0, 125.2, 110.3, 106.3, 57.8; HRMS (ESI-TOF): calcd. for ($[C_{11}H_9ClO_2+Na]^+$): 231.0183, found: 231.0183.

Synthesis of 5-(4-nitrophenyl)-2-furanmethanol (1d)

To a suspension of 5-(4-nitrophenyl)-2-furaldehyde (**S3d**) (380 mg, 1.75 mmol, 1.00 eq.) in diethyl ether (7.36 mL) and water (7.36 mL) was added $NaBH_4$ (66.2 mg, 1.75 mmol, 1.00 eq.) at 25 °C. After being stirred at 25 °C for 30 min, the reaction was quenched by addition of sat. NH_4Cl aq., and the aqueous layer was extracted with diethyl ether twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by recrystallization (hexane and EtOAc) to give 5-(4-nitrophenyl)-2-furanmethanol (**1d**) (270 mg, 1.23 mmol, 70 %).

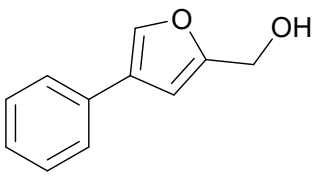


orange solid ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 9.2 Hz, 2H), 7.80 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 3.2 Hz, 1H), 6.47 (d, *J* = 3.2 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 1.81 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 151.8, 146.6, 136.4, 124.5, 124.1, 110.7, 109.9, 57.7.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S5]

4-Phenyl-2-furanmethanol (1e)

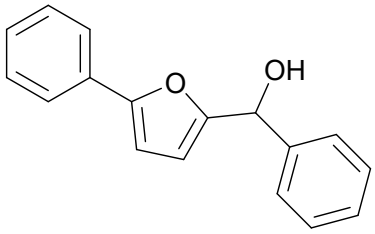
According to the general procedure for arylated 2-furanmethanol using 4-phenyl-2-furaldehyde (**S3e**) (125 mg, 0.726 mmol, 1.00 eq.), the crude product was purified by recrystallization (hexene and EtOAc) to give 4-phenyl-2-furanmethanol (**1e**) (166 mg, 0.955 mmol, 53%).



white solid; mp 97-99 °C, IR (neat): 3293, 1541, 1452, 1011, 910, 822, 751, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 0.8 Hz, 1H), 7.46 (dd, *J* = 0.8, 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28-7.25 (m, 1H), 6.62 (s, 1H), 4.65 (d, *J* = 4.4 Hz, 2H), 1.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 138.5, 132.4, 129.0, 127.4, 127.2, 125.9, 107.2, 57.8; HRMS (ESI-TOF): calcd. for ($[C_{11}H_{10}O_2+Na]^+$): 197.0573, found 197.0578.

Synthesis of *α*,5-diphenyl-2-furanmethanol (1f)[S6]

To a 50 mL dry flask equipped with a magnetic stirrer bar was added 5-phenyl-2-furaldehyde (**S3a**) (804 mg, 4.43 mmol, 1.00 eq.) under argon atmosphere and 20 mL of dry THF was added via syringe. Then, phenyl magnesium bromide (1.0 M solution in THF, 9.29 mL, 9.29 mmol, 2.31 eq.) was added dropwise at 0 °C. The solution was allowed to warm to 25 °C and stirred for 8 h. The reaction was quenched by the addition of sat. NH_4Cl aq. and the aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by recrystallization (hexene and EtOAc) to give *α*,5-diphenyl-2-furanmethanol (**1f**) (886 mg, 3.54 mmol, 80%).



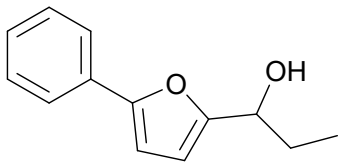
white solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.41-7.33 (m, 5H), 7.27-7.23 (m, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 5.90 (d, *J* = 4.0 Hz, 1H), 2.42 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 154.1, 140.9, 130.8, 128.8, 128.6, 128.2, 127.6, 126.8, 123.9, 109.7, 105.7, 70.4.

Spectral data of ^1H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S7]

Synthesis of *α*-ethyl-5-phenyl-2-furanmethanol (1g)[S6]

To a 50 mL dry flask equipped with a magnetic stirrer bar was added 5-phenyl-2-furaldehyde (**E3a**) (194 mg, 1.07 mmol, 1.00 eq.) under argon atmosphere and 5.0 mL of dry THF was added via syringe. Then ethyl magnesium bromide (1.0 M solution in THF, 1.61 mL, 1.61 mmol, 1.50 eq.) was added dropwise at 0 °C. The solution was allowed to warm to 25 °C and stirred for 8 h. The reaction mixture was quenched by addition of sat. NH_4Cl aq. and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column

chromatography on silica gel (hexane/EtOAc = 10:1 to 5:1) to give *α*-ethyl-5-phenyl-2-furanmethanol (**1g**) (170 mg, 0.842 mmol, 84%).



white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.26-7.22 (m, 1H), 6.58 (d, *J* = 3.6 Hz, 1H), 6.31 (d, *J* = 3.6 Hz, 1H), 4.64 (t, *J* = 6.8 Hz, 1H), 2.07 (brs, 1H), 1.98-1.88 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 153.4, 130.9, 128.8, 127.4, 123.8, 108.2, 105.6, 69.5, 28.8, 10.1.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S8]

5. Optimization of reaction conditions

5.1 Examination of activating agents and their amounts, reaction time, temperatures, concentrations, and solvents in microflow nucleophilic substitution

A solution of 5-phenyl-2-furanmethanol (**1a**) (**D** M, 1.00 eq.) in **solvent 1** (flow rate: 1.20 mL/min) and a solution of **activating agent** (**A** eq.) in **solvent 1** (flow rate: 2.40 mL/min) were introduced to the 1st V-shape mixer at **C** °C with syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.500 mm, length: 1,529 mm, volume: 300 µL (entries 1-10), inner diameter: 0.500 mm, length: 153 mm, volume: 30 µL (entries 11), inner diameter: 0.500 mm, length: 306 mm, volume: 60 µL (entries 12), inner diameter: 0.500 mm, length: 3,057 mm, volume: 600 µL (entries 13, 15-23), inner diameter: 0.800 mm, length: 7,166 mm, volume: 3,600 µL (entry 14), reaction time: **B** s) at **C** °C. The resultant mixture and a solution of NaN_3 (2**A** eq.) and NEt_3 (6.00 eq.) in **solvent 2** (flow rate: 4.80 mL/min) were introduced to the 2nd V-shape mixer at **C** °C with syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.500 mm, length: 713 mm, volume: 140 µL, reaction time: 1.0 s) at **C** °C. After being eluted for *ca.* 30 s to reach a steady state, the resultant mixture was poured into a test tube containing sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) for 90 s at 25 °C. The aqueous layer was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

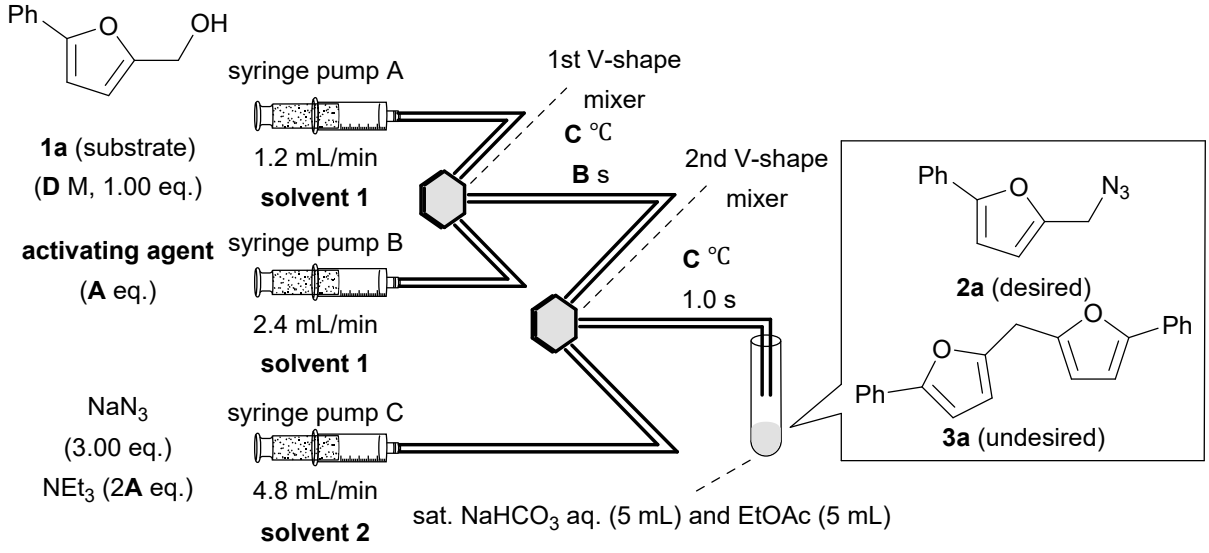


Table S-1

entry	**A** [eq.]	**B** [s]	**C** [°C]	**D** [M]	**activating agent** (pK_a[a])	**solvent 1**	**solvent 2**	yield [%] [e] **2a**	**1a**	**3a**
1	0.500	5.0	25	0.0500	PBr_3	MeCN	H_2O	87	<1	9
2	1.50	5.0	25	0.0500	$SOCl_2$	MeCN	H_2O	2	97	<1
3	1.50	5.0	25	0.0500	AcOH (10.3) [S9]	MeCN	H_2O	<1	97	<1
4	1.50	5.0	25	0.0500	HCl[b] (10.3) [S9]	MeCN	H_2O	8	66	26

5	1.50	5.0	25	0.0500	H_2SO_4 (8.7) [S10]	MeCN	H_2O	<1	5	72
6	1.50	5.0	25	0.0500	HBr[c] (5.5) [S9]	MeCN	H_2O	92	5	3
7	1.50	5.0	25	0.0500	HI[d] (2.8) [S9]	MeCN	H_2O	95	1	1
8	1.50	5.0	25	0.0500	TfOH (0.7) [S9]	MeCN	H_2O	<1	<1	<10
9	2.00	5.0	25	0.0500	HBr (5.5)	MeCN	H_2O	91	3	2
10	3.00	5.0	25	0.0500	HBr (5.5)	MeCN	H_2O	96	2	2
11	3.00	0.50	25	0.0500	HBr (5.5)	MeCN	H_2O	46	52	2
12	3.00	1.0	25	0.0500	HBr (5.5)	MeCN	H_2O	64	34	2
13	3.00	10	25	0.0500	HBr (5.5)	MeCN	H_2O	97	<1	2
14	3.00	60	25	0.0500	HBr (5.5)	MeCN	H_2O	97	<1	2
15	3.00	10	25	0.0500	HBr (5.5)	DCM	H_2O	37	62	<1
16	3.00	10	25	0.0500	HBr (5.5)	acetone	H_2O	64	<1	4
17	3.00	10	25	0.0500	HBr (5.5)	MeCN	DMSO	93	5	2
18	3.00	10	25	0.0500	HBr (5.5)	MeCN	MeOH	75	<1	2
19	3.00	10	10	0.0500	HBr (5.5)	MeCN	H_2O	75	18	2
20	3.00	10	40	0.0500	HBr (5.5)	MeCN	H_2O	97±1%[f] (95%)[g]	<1	<1
21	3.00	10	60	0.0500	HBr (5.5)	MeCN	H_2O	98	1	1
22	3.00	10	40	0.100	HBr (5.5)	MeCN	H_2O	93	1	2
23	3.00	10	40	0.200	HBr (5.5)	MeCN	H_2O	92	<1	5

24[h]	3.00	10	40	0.0500	HBr (5.5)	MeCN	H_2O	95	3	2
25[i]	3.00	10	40	0.0500	HBr (5.5)	MeCN	H_2O	95	1	2

[a]The pK_a in MeCN. [b] Aqueous solution of HCl (36 w/w%) was used. [c] Aqueous solution of HBr (47 w/w%) was used. [d] Aqueous solution of HI (57 w/w%) was used. [e] Yields were determined by ^{1}H NMR using 1,1,2-trichloroethane. [f] Three independent experiments were performed. [g] Isolated yield. [h] DBU was used instead of NEt_3. [i] Pyridine was used instead of NEt_3. TfOH = trifluoromethanesulfonic acid. DCM = dichloromethane. DMSO = dimethyl sulfoxide.

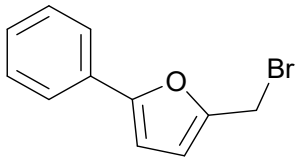
5.2 Procedure for synthesis of 2a using a batch reactor.

(Quantities of compounds, solvents, and temperature were identical to those of flow condition.) To a vigorously stirred (magnetic stirrer, 1,000 rpm) solution of 5-phenyl-2-furanmethanol (**1a**) (0.0500 M, 1.00 eq.) in MeCN (1.20 mL), a solution of HBr aq. (0.0750 M, 3.00 eq.) in MeCN (2.40 mL) was added in one portion at 40 °C under an argon atmosphere. After being stirred for 10 s at 40 °C, the resultant mixture was added in one portion at 40 °C to a vigorously stirred (magnetic stirrer, 1,000 rpm) solution of NaN_3 (0.0375 M, 3.00 eq.) and NEt_3 (0.0750 M, 6.00 eq.) in H_2O (4.80 mL). After being stirred for 10 s at 40 °C, sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) was added in one portion at 40 °C (Under the flow condition, activation and nucleophilic substitution were carried out at 10 s and 1.0 s respectively. However, under batch conditions, it was impossible to operate the reaction within 10 s. Thus, the reaction time was extended to 10 s.). The aqueous layer was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Yields were determined by ^{1}H NMR analysis using 1,1,2-trichloroethane as an internal standard. Three independent experiments were carried out.

5.3. Examination of synthesis of 5a

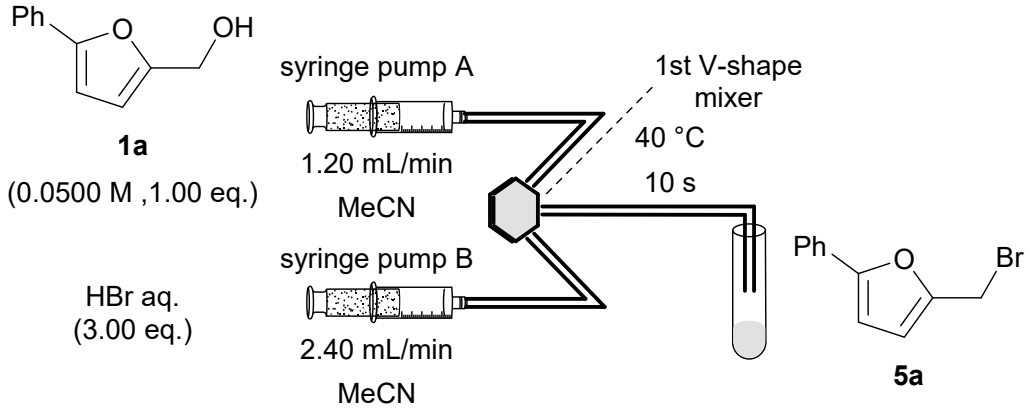
Procedure for synthesis of bromide 5a using a batch reactor

A solution of 5-phenyl-2-furanmethanol (**1a**) (17.4 mg, 0.100 mmol, 1.00 eq.) in DCM at 0 °C was added PBr_3 (4.76 µL, 0.0500 mmol, 0.500 eq.) in an ice bath. The resultant solution was allowed to warm to 25 °C and then stirred for 12 h. The reaction was quenched by addition of ice and the aqueous layer was extracted with EtOAc. The combined layers were washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* at 5 °C to give 2-(bromomethyl)-5-phenylfuran (**5a**).

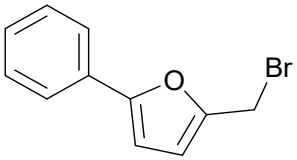


black oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 149.8, 130.4, 128.9, 128.0, 124.1, 112.3, 106.5, 24.4.

Procedure for synthesis of bromide 5a using a flow reactor



A solution of 5-phenyl-2-furanmethanol (**1a**) (0.0500 M, 1.00 eq.) in MeCN (flow rate: 1.20 mL/min) and a solution of HBr aq. (0.0750 M, 3.00 eq.) in MeCN (flow rate: 2.40 mL/min) were introduced to the 1st V-shape mixer at 40 °C with syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.500 mm, length: 3,056 mm, volume: 600 μL, reaction time: 10 s) at 40 °C. After being eluted for *ca.* 30 s to reach a steady state, the resultant mixture was poured into a test tube containing EtOAc (5 mL) for 90 s at room temperature. The solution was filtered and concentrated *in vacuo* at 5 °C to give 2-(bromomethyl)-5-phenylfuran (**5a**).



black oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 149.7, 130.3, 128.8, 127.9, 124.1, 112.3, 106.4, 24.3.

We attempted to confirm the generation of **5a** in the developed microflow synthesis. Almost identical procedures for bromination of furan derivatives were reported by Frimm et al.[S11] and Bertoni et al.[S12] However, the spectral data was not provided. To obtain NMR spectral data for alkyl bromide **5a**, we synthesized **5a** via the reported procedure. The chemical shift for the proton at the 2'-position of **5a** is 4.59 ppm and it is slightly (0.04 ppm) upfield-shifted from that of alcohol **1a** (Fig. S-3). In the case of the previously reported chemical shift for the proton at the 2'-position of **S5**[S13] is also slightly (0.06 ppm) upfield-shifted from that of alcohol **S4**[S14]. Therefore, we considered the desired **5a** was synthesized via the reported batch procedures. The observed ^{1}H and ^{13}C NMR spectra of **5a** prepared under batch conditions were well consistent with those prepared under the developed microflow conditions. Although we cannot completely rule out the possibility of generating **5a** during the concentration process (the crude mixture obtained from the outlet of the microflow reactor was concentrated *in vacuo* at 5 °C), we believe these results support the generation of **5a** in the microflow reactor (Scheme 2b).

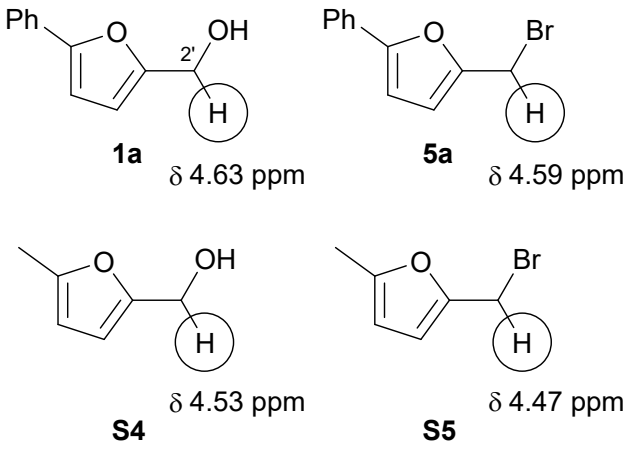
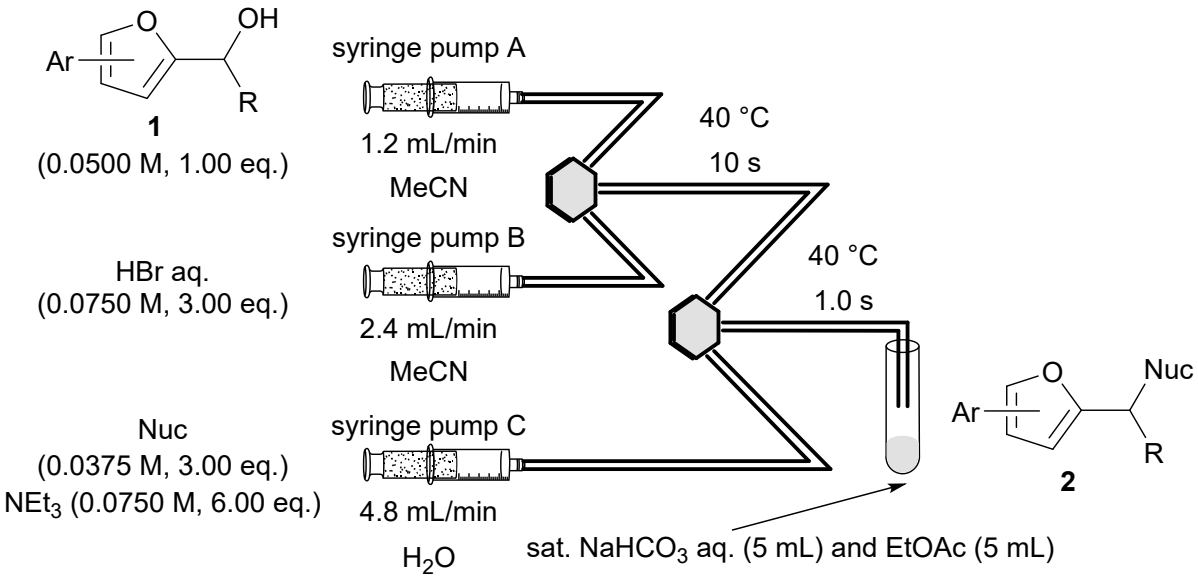


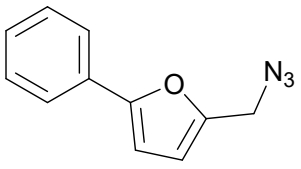
Fig. S-3. ^{1}H NMR ($CDCl_3$) chemical shifts of protons at the 2'-position of furfuryl alcohols **1a** and **S4**, and furfuryl bromide derivatives **5a** and **S5**.

6. A typical procedure for a microflow nucleophilic substitution



A solution of **arylated 2-furanmethanol 1** (0.0500 M, 1.00 eq.) in MeCN (flow rate: 1.20 mL/min) and a solution of HBr aq. (0.0750 M, 3.00 eq.) in MeCN (flow rate: 2.40 mL/min) were introduced to the 1st V-shape mixer at 40 °C with syringe pumps. The resultant mixture was passed through reaction tube 1 (inner diameter: 0.500 mm, length: 3,056 mm, volume: 600 μL, reaction time: 10 s) at 40 °C. The resultant mixture and a solution of **nucleophile** (0.0375 M, 3.00 eq.) and NEt_3 (0.0750 M, 6.00 eq.) in H_2O (flow rate: 4.80 mL/min) were introduced to the 2nd V-shape mixer at 40 °C with syringe pumps. The resultant mixture was passed through reaction tube 2 (inner diameter: 0.500 mm, length: 713 mm, volume: 140 μL, reaction time: 1.0 s) at 40 °C. After being eluted for *ca.* 30 s to reach a steady state, the resultant mixture was poured into a test tube containing sat. $NaHCO_3$ aq. (5 mL) and EtOAc (5 mL) for 90 s at room temperature. The aqueous layer was extracted with EtOAc (5 mL) twice. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

5-Phenyl-2-furanmethanazide (2a)



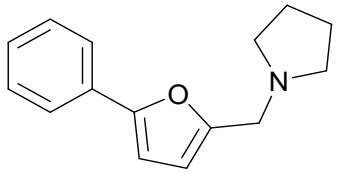
Purification method: PTLC (DCM: hexane = 1: 2, 3 times)

17.1 mg, 0.0858 mmol, 95%

yellow oil; IR (neat): 2095, 1486, 1021, 793, 760, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (m, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.29-7.25 (m, 1H), 6.61 (d, J = 3.2 Hz, 1H), 6.42 (d, J = 3.2 Hz, 1H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 148.6, 130.5, 128.9, 127.8, 124.0, 111.6, 105.8, 47.4; HRMS (ESI-TOF):

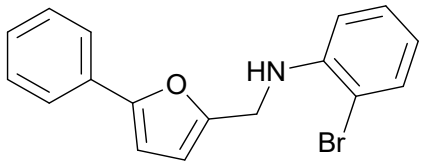
calcd. for ($[C_{11}H_9N_3O+Na]^+$): 222.0638, found 222.0638.

5-Phenyl-2-furanmethanpyrrolidine (2b)



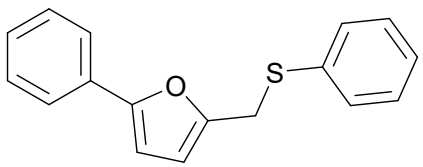
Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1:1)
14.6 mg, 0.0642 mmol, 71% (Nucleophile was dissolved in MeCN instead of H_2O and reaction time of **5a** with the nucleophile was extended to 10 s. 6.0 eq. pyrrolidine was used instead of 6.0 eq. NEt_3.)
colorless oil; IR (neat): 2964, 2789, 1542, 1522, 1508, 1021, 759, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.26-7.21 (m, 1H), 6.58 (d, *J* = 3.2 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 3.71 (s, 2H), 2.64-2.59 (m, 4H), 1.84-1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 152.9, 131.1, 128.7, 127.2, 123.8, 110.1, 105.8, 54.0, 52.2, 23.7; HRMS (ESI-TOF): calcd. for ($[C_{15}H_{17}NO+Na]^+$): 228.1383, found 228.1383.

5-Phenyl-2-furanmethan-2-bromoaniline (2c)



Purification method: PTLC (5%NEt_3 in EtOAc: hexane = 1:2)
9.8 mg, 0.0299 mmol, 33% (The Nucleophile was dissolved in MeCN instead of H_2O and the reaction time of **5a** with the nucleophile was extended to 10 s.)
colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66-7.64 (m, 2H), 7.44 (dd, J = 1.6, 8.0 Hz, 1H), 7.37 (t, J = 7.2 Hz, 2H), 7.27-7.23 (m, 1H), 7.21-7.17 (m, 1H), 6.77 (dd, J = 1.6, 8.0 Hz, 1H), 6.63-6.58 (m, 2H), 6.32 (d, J = 3.2 Hz, 1H), 4.77 (brs, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 151.8, 144.6, 132.6, 130.9, 128.8, 128.6, 127.5, 123.8, 118.6, 111.9, 110.1, 109.4, 105.9, 41.6
Spectral data of ^1H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S15]

5-Phenyl-2-furanmethanthiophenol (2d)

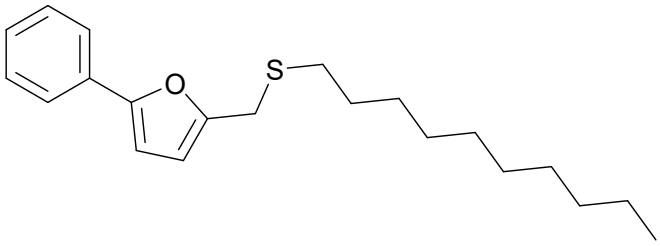


Purification method: PTLC (EtOAc: hexane = 1:2)

18.2 mg, 0.0683 mmol, 76% (Nucleophile was dissolved in MeCN instead of H_2O, and 6.0 eq. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of 6.0 eq. of NEt_3.)

colorless oil; IR (neat): 1542, 1508, 1020, 759, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.40-7.33 (m, 4H), 7.28 (td, J = 1.2, 7.6 Hz, 2H), 7.25-7.20 (m, 2H), 6.51 (d, J = 3.2 Hz, 1H), 6.16 (d, J = 3.2 Hz, 1H), 4.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 151.0, 135.7, 131.0, 130.8, 129.0, 128.8, 127.4, 127.0, 123.8, 110.0, 106.0, 32.1; HRMS (ESI-TOF): calcd. for ($[C_{17}H_{14}OS + Na]^+$): 289.0658, found 289.0658.

5-Phenyl-2-furanmethandecanthiol (2e)

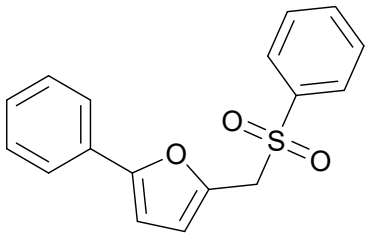


Purification method: PTLC (EtOAc: hexane = 1:2)

19.1 mg, 0.578 mmol, 64% (Nucleophile was dissolved in MeCN instead of H_2O, and 6.0 eq. of DBU was used instead of 6.0 eq. of NEt_3.)

red solid; mp 34-37 °C, IR (neat): 2924, 2852, 1542, 1457, 1019, 758, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.25-7.21 (m, 1H), 6.57 (d, J = 3.2 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 3.76 (s, 2H), 2.56 (t, J = 7.6 Hz, 2H), 1.63-1.54 (m, 2H), 1.38-1.35 (m, 2H) 1.29-1.25 (m, 12H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 152.0, 131.0, 128.8, 127.3, 123.7, 109.5, 105.9, 32.1, 32.0, 29.70, 29.68, 29.45, 29.40, 29.0, 28.6, 22.8, 14.3; HRMS (ESI-TOF): calcd. for ($[C_{21}H_{30}OS + Na]^+$): 353.1910, found 353.1911.

5-Phenyl-2-furanmethanphenylsulfone (2f)



Purification method: PTLC (EtOAc: hexane = 1:2)

24.3 mg, 0.0814 mmol, 90%

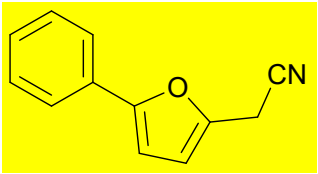
Purification method: recrystallization

0.722 g, 2.42 mmol, 63% (scaled-up synthesis: the resultant mixture was collected for 960 s)

Although the observed yield in scaled-up synthesis was decreased (90% to 63%), this is mainly due to the high crystallinity of **2f**, which decreased mixing efficiency. Although we could readily purify the desired **2f** by recrystallization, the further extension of pumping time for scaling up resulted in an undesired clog of the reaction channel.

white solid; mp 136-138 °C, IR (neat): 1716, 1542, 1508, 1316, 1155, 685, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79-7.77 (m, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.50-7.46 (m, 2H), 7.41-7.39 (m, 2H), 7.34-7.30 (m, 2H), 7.26-7.22 (m, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 6.39 (d, *J* = 3.2 Hz, 1H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 141.9, 138.6, 134.0, 130.1, 129.2, 128.8, 128.7, 127.9, 123.9, 114.4, 106.4, 56.4; HRMS (ESI-TOF): calcd. for ($[C_{17}H_{14}O_3S$ +Na$]^+$): 321.0556, found 321.0556.

2-(5-Phenylfuran-2-yl)acetonitrile (2h)



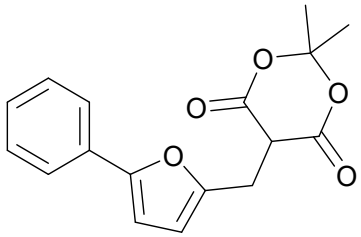
Purification method: PTLC (1%NEt_3 in EtOAc: hexane = 1:4)

9.7 mg, 0.0529 mmol, 59%

colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 3.6 Hz, 1H), 6.41 (d, *J* = 3.6 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 142.4, 130.2, 128.9, 127.9, 123.9, 115.6, 110.7, 106.0, 17.9

Spectral data of ^1H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S16]

5-Phenyl-2-furanmethan1-2,2-dimethyl-1,3-dioxane-4,6-dione (2i)

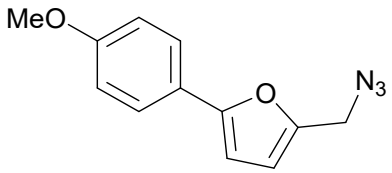


Purification method: GPC

14.9 mg, 0.0496 mmol, 55% (*t*-BuOK was used for deprotonating Meldrum's acid.)

yellow solid; mp 130-133 °C, IR (neat): 1786, 1742, 1358, 1205, 1069, 951, 758, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.37-7.33 (m, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 3.2 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 3.86 (t, *J* = 5.2 Hz, 1H), 3.59 (d, *J* = 5.2 Hz, 2H), 1.80 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 153.1, 150.1, 130.8, 128.8, 127.4, 123.7, 110.2, 106.1, 105.4, 45.5, 28.5, 27.4, 25.6; HRMS (ESI-TOF): calcd. for ($[C_{17}H_{16}O_5$+Na$]^+$): 323.0890, found 323.0890.

5-(4-Methoxyphenyl)-2-furanmethanazide (2j)

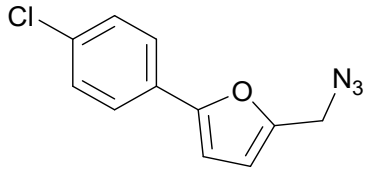


Purification method: PTLC (1%NEt_3 in DCM: hexane = 1:2, twice)

17.8 mg, 0.0776 mmol, 86%

yellow oil, IR (neat): 2093, 1542, 1497, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62-7.58 (m, 2H), 6.94-6.91 (m, 2H), 6.47 (d, *J* = 3.2 Hz, 1H), 6.39 (d, *J* = 3.2 Hz, 1H), 4.33 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 155.0, 147.9, 125.5, 123.6, 114.3, 111.6, 104.2, 55.5, 47.4; HRMS (ESI-TOF): calcd. for ($[C_{12}H_{11}N_3O_2+Na]^+$): 252.0743, found 252.0743.

5-(4-Chlorophenyl)-2-furanmethanazide (2k)

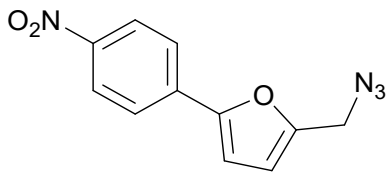


Purification method: PTLC (1%NEt_3 in DCM: hexane = 1:2, twice)

19.8 mg, 0.0847 mmol, 94%

yellow oil; IR (neat): 2095, 1542, 1481, 1092, 830, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.37-7.34 (m, 2H), 6.60 (d, *J* = 3.2 Hz, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 149.0, 133.5, 129.1, 129.0, 125.2, 111.7, 106.3, 47.3; HRMS (ESI-TOF): calcd. for ($[C_{11}H_8ClN_3O+Na]^+$): 256.0250, found 256.0248.

5-(4-Nitrophenyl)-2-furanmethanazide (2l)

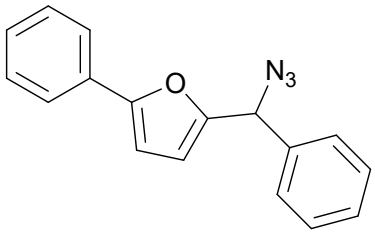


Purification method: PTLC (1%NEt_3 in DCM: hexane = 1:2, twice)

7.4 mg, 0.303 mmol, 34%

yellow solid; mp 71-75 °C, IR (neat): 2093, 1541, 1508, 1332, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 4.0 Hz, 1H), 6.51 (d, *J* = 4.0 Hz, 1H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 151.0, 146.8, 136.0, 124.5, 124.3, 112.1, 109.8, 47.2; HRMS (ESI-TOF): calcd. for ($[C_{11}H_8N_4O_3+Na]^+$): 267.0489 found 267.0489.

α,5-Diphenyl-2-furanmethanazide (2n)



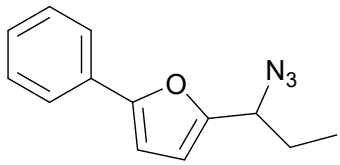
Purification method: PTLC (1%NEt_3 in DCM: hexane = 1:2, 2 times)

18.8 mg, 0.683 mmol, 76%

yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (dd, *J* = 0.8, 8.0 Hz, 2H), 7.45-7.34 (m, 7H), 7.28-7.24 (m, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 6.23 (d, *J* = 3.6 Hz, 1H), 5.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 151.8, 136.9, 130.5, 128.9, 128.8, 128.7, 127.8, 127.6, 124.0, 111.2, 105.7, 62.4; HRMS (ESI-TOF): calcd. for ($[C_{17}H_{13}N_3O$ +Na$]^+$): 298.0951, found 298.0964.

Spectral data of ^{1}H NMR and ^{13}C NMR were well consistent with those reported in the previous literature.[S17]

α-Ethyl-5-phenyl-2-furanmethanazide (2o)



Purification method: PTLC (1%NEt_3 in DCM: hexane = 1:2, 2 times)

8.8 mg, 0.0390 mmol, 43%

yellow oil; IR (neat): 2970, 2096, 1241, 1021, 791, 760, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 2H), 7.41-7.36 (m, 2H), 7.29-7.25 (m, 2H), 6.61 (d, *J* = 3.2 Hz, 1H), 6.38 (d, *J* = 3.2 Hz, 1H), 4.36 (t, *J* = 7.2 Hz, 1H), 2.03-1.91 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 152.0, 130.6, 128.8, 127.7, 124.0, 109.8, 105.6, 60.8, 26.1, 10.9. We measured HRMS of **2o** using ESI and DART, however, the desired MS was not observed probably due to difficulty in ionization. In addition, this compound is unstable.

7. References

S1) Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965–967.

S2) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680.

S3) Zhang, Y.; Zhang, Z.; Wang, B.; Liu, L.; Che, Y. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1885–1888.

S4) Ghahramani, F.; Meyer, M.; Unone, S.; Janssen-Müller, D. *Chem. Eur. J.* **2023**, *29*, e202302038.

S5) Chacón-Huete, F.; Lasso, J. D.; Szavay, P.; Covone, J.; Forgione, P. *J. Org. Chem.* **2021**, *86*, 515–524.

S6) Yang, S.; Tang, W.; Yang, Z; Xu, J. *ACS Catal.* **2018**, *8*, 9320−9326.

S7) Ji, K.-G.; Shen, Y.-W.; Shu, X.-Z.; Xiao, H.-Q.; Bian, Y.-J.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 1275–1280.

S8) Huang, G.; Lu, L.; Jiang, H.; Yin, B. *Chem. Commun.* **2017**, *53*, 12217–12220.

S9) Raamata, E.; Kaupmeesa, K.; Ovsjannikova, G.; Trummalb, G.; Kütta, A.; Saamea, J.; Koppela, I.; Kaljuranda, I.; Lippinga, L.; Rodimaa, T.; Pihla, V.; Koppela, I. A.; Leitoa, I. *J. Phys. Org. Chem.* **2013**, *26*, 162–170.

S10) Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, L. A.; Garlyauskayte, R. Y.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391–395.

S11) Krutosikoca, A.; Kovac, J.; Frimm, R. *Chem. Zvesti.* **1973**, *27*, 107–111.

S12) Gatti, R, A.; Du, L.; Damoiseaux, R.; Lai, C.-H.; Jung, M.; Ku, J.-M.; Bertoni, C. WO2012021707, **2012**.

S13) Pevzner, L. M. *Russ. J. Gen. Chem.* **2009**, *79*, 362–372.

S14) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.

S15) Yin, B.; Cai, C.; Zeng, G.; Zhang, R.; Li, X.; Jiang, H. *Org. Lett.* **2012**, *14*, 1098–1101.

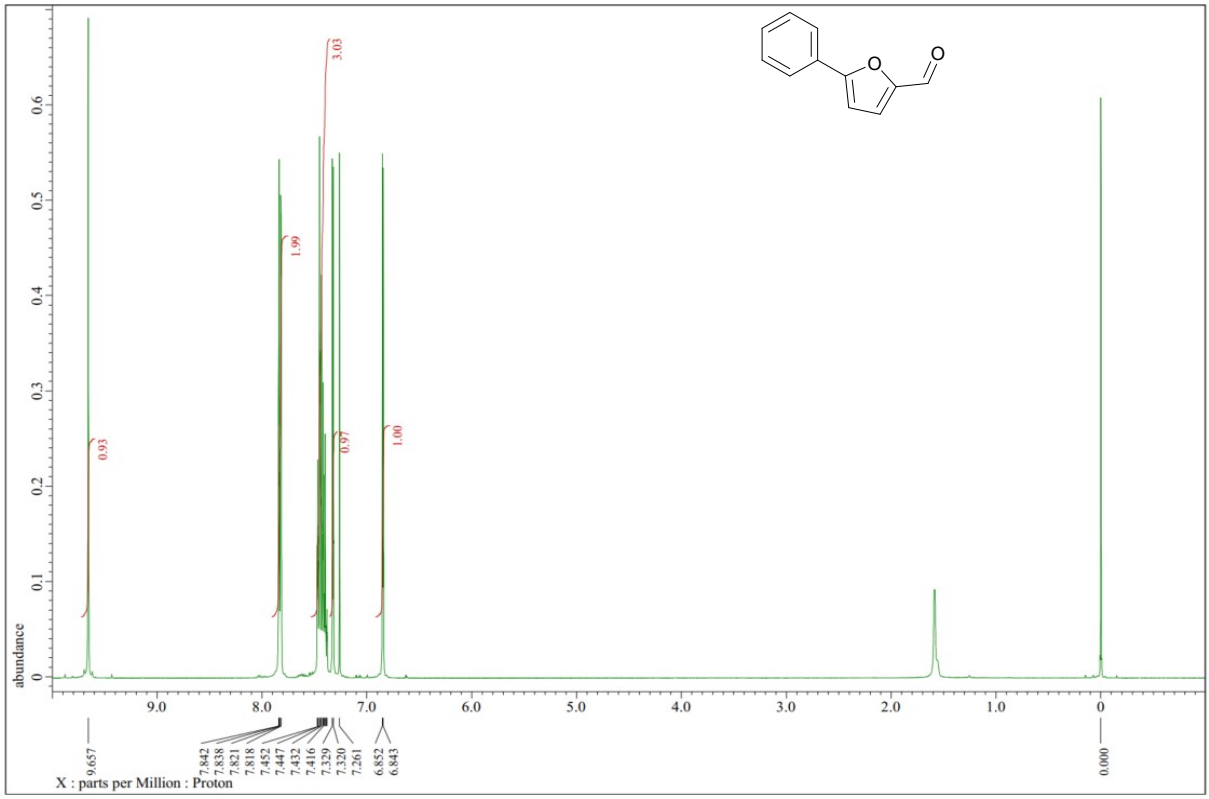
S16) Liu, Z.-Q.; Li, Z. *Chem. Commun.* **2016**, *52*, 14278–14281.

S17) Ji, K.-G.; Shu, X.-Z.; Chen, J.; Zhao, S.-C.; Zheng, Z.-J.; Liua, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2009**, *7*, 2501–2505.

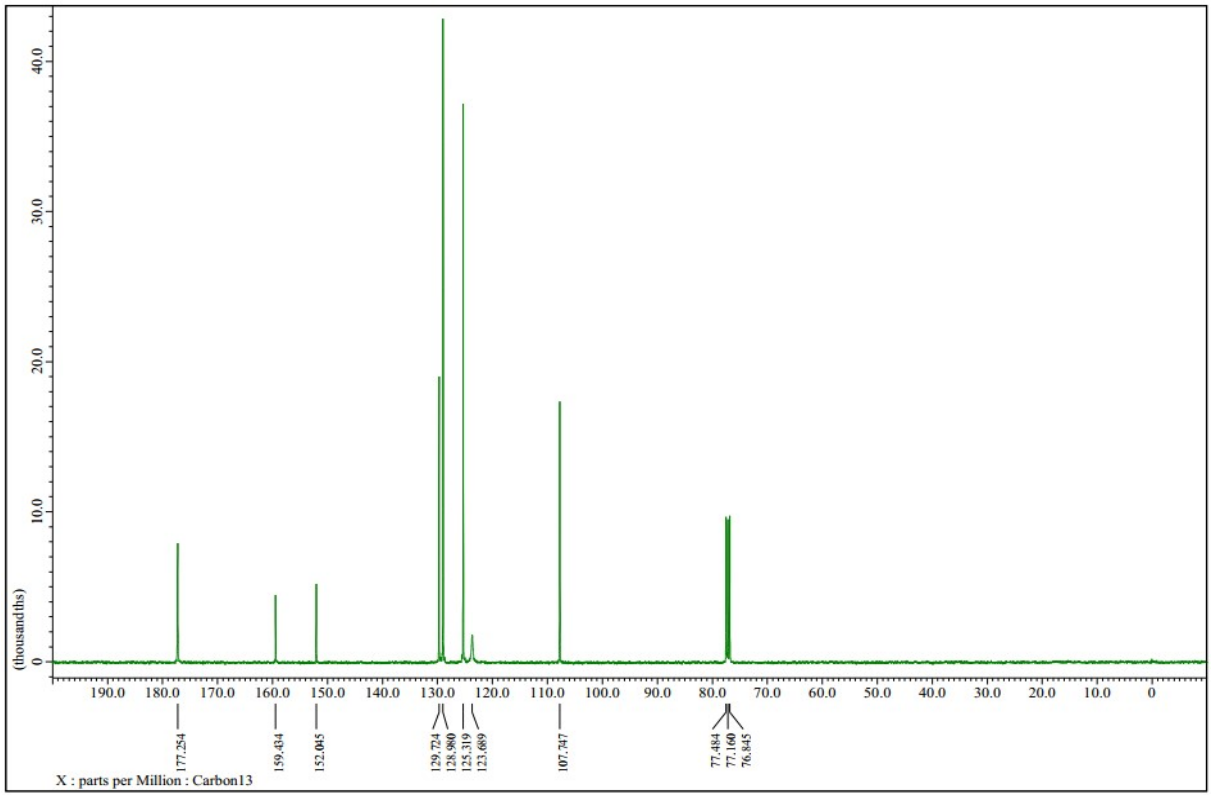
8. NMR chart

5-Phenyl-2-furaldehyde (S3a)

(^{1}H NMR, 400 MHz, $CDCl_3$)

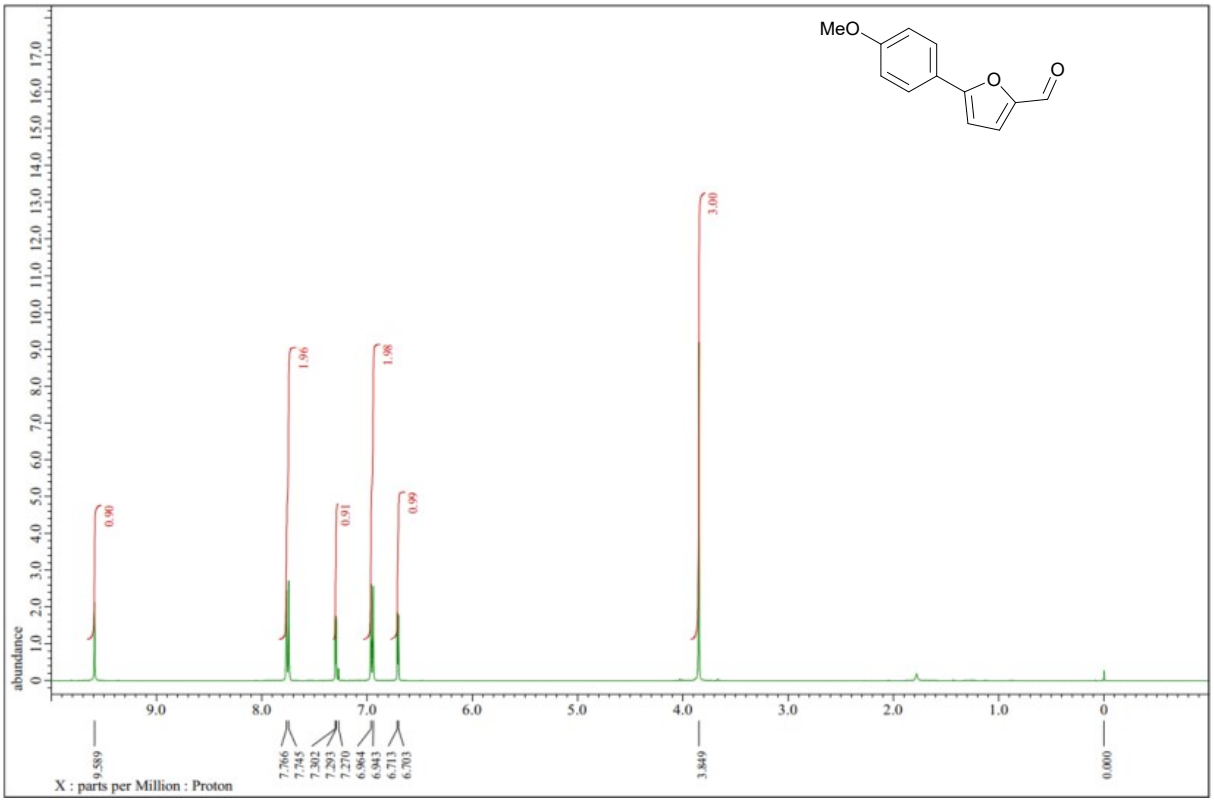


(^{13}C NMR, 100 MHz, $CDCl_3$)

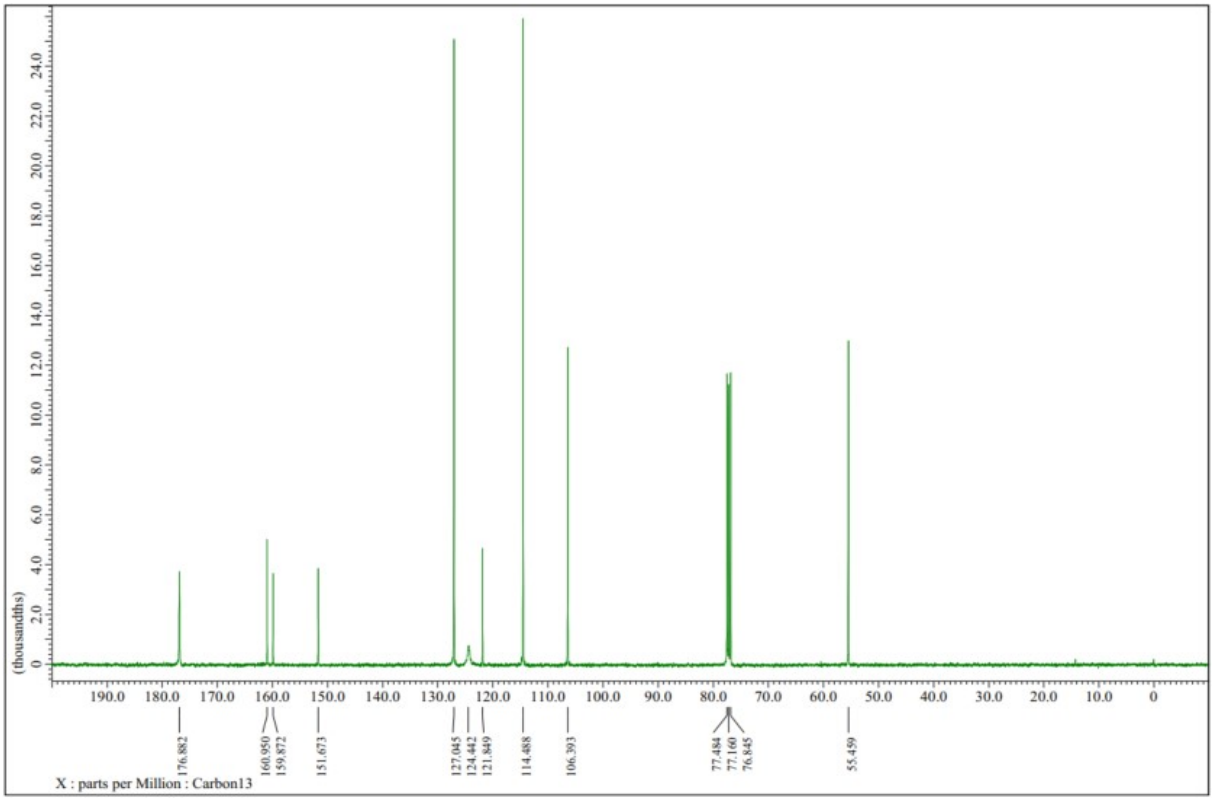


5-(4-Methoxyphenyl)-2-furaldehyde (S3b)

(^{1}H NMR, 400 MHz, $CDCl_3$)

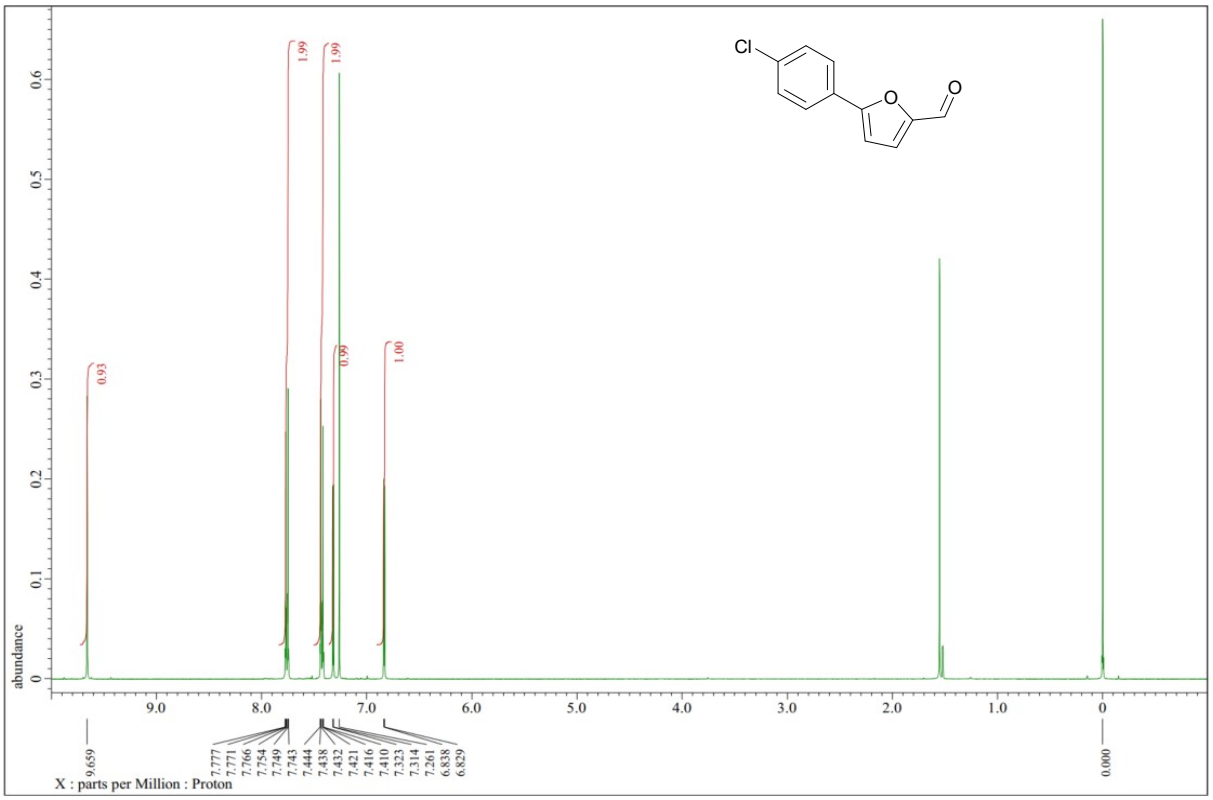


(^{13}C NMR, 100 MHz, $CDCl_3$)

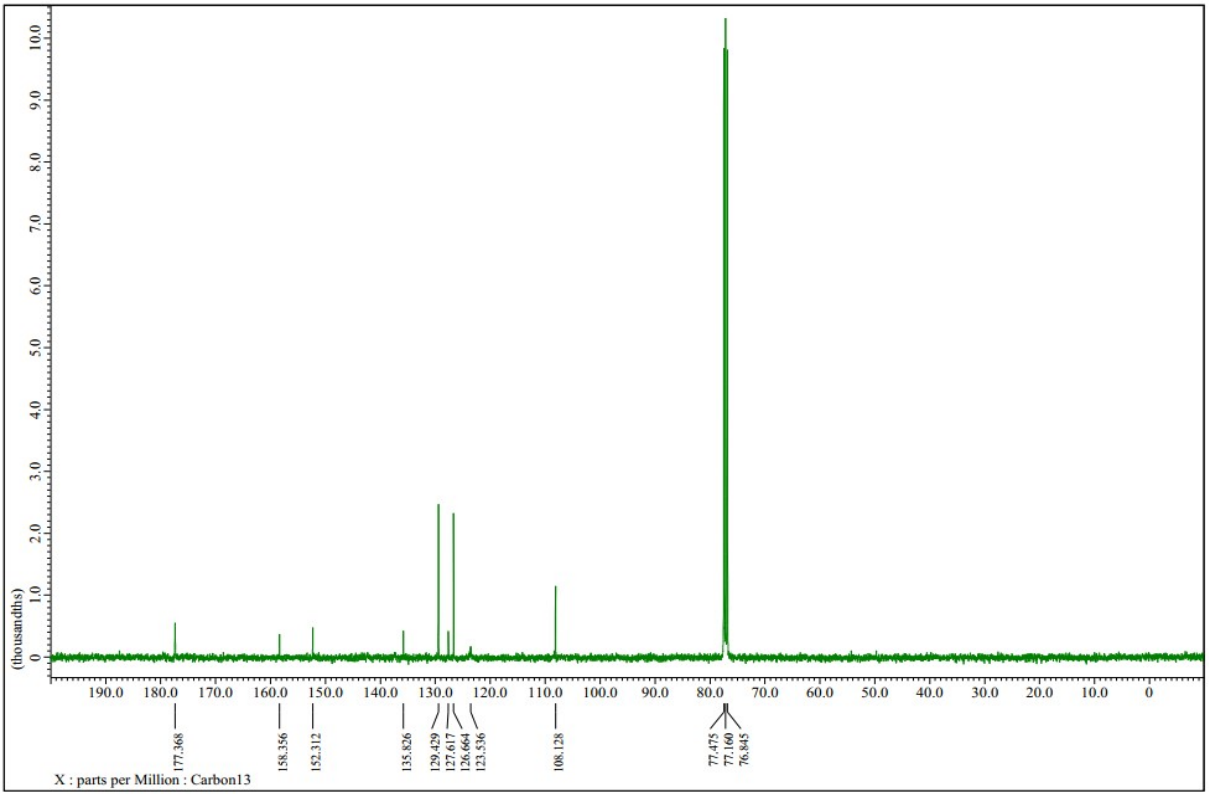


5-(4-Chlorophenyl)-2-furaldehyde (S3c)

(^{1}H NMR, 400 MHz, $CDCl_3$)

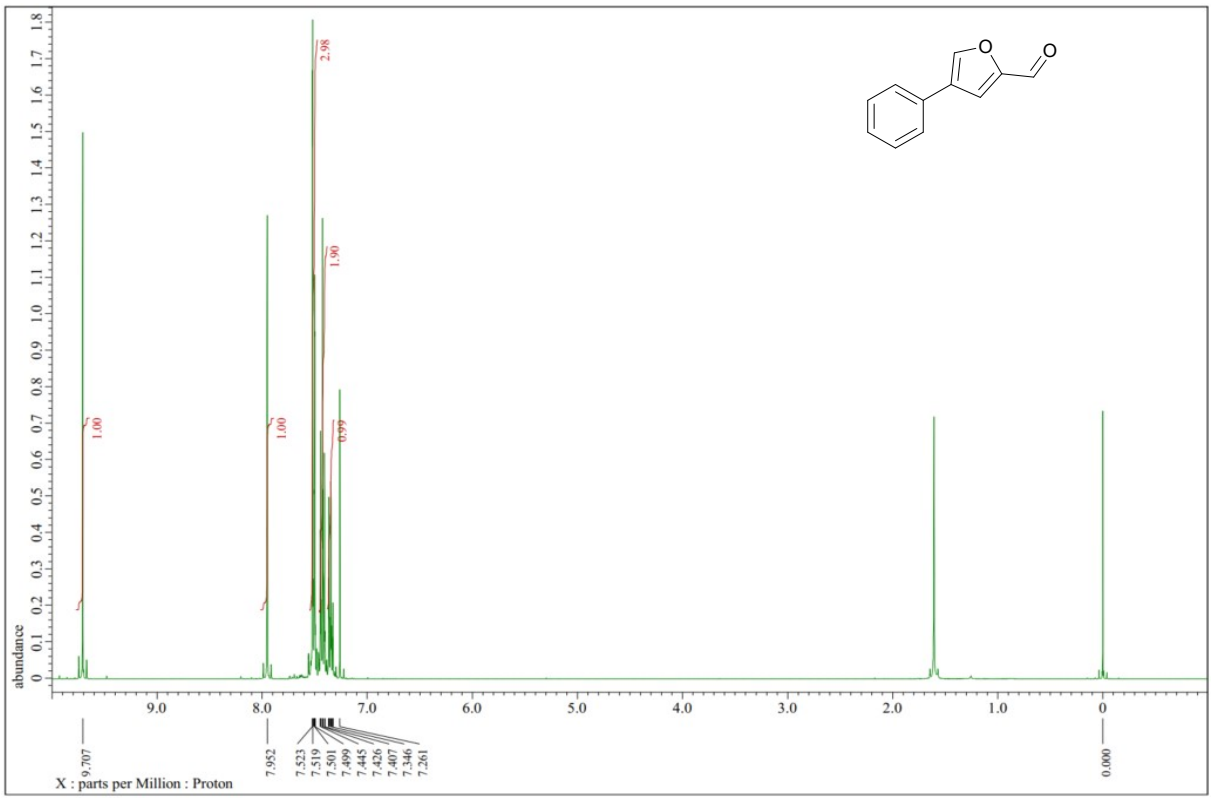


(^{13}C NMR, 100 MHz, $CDCl_3$)

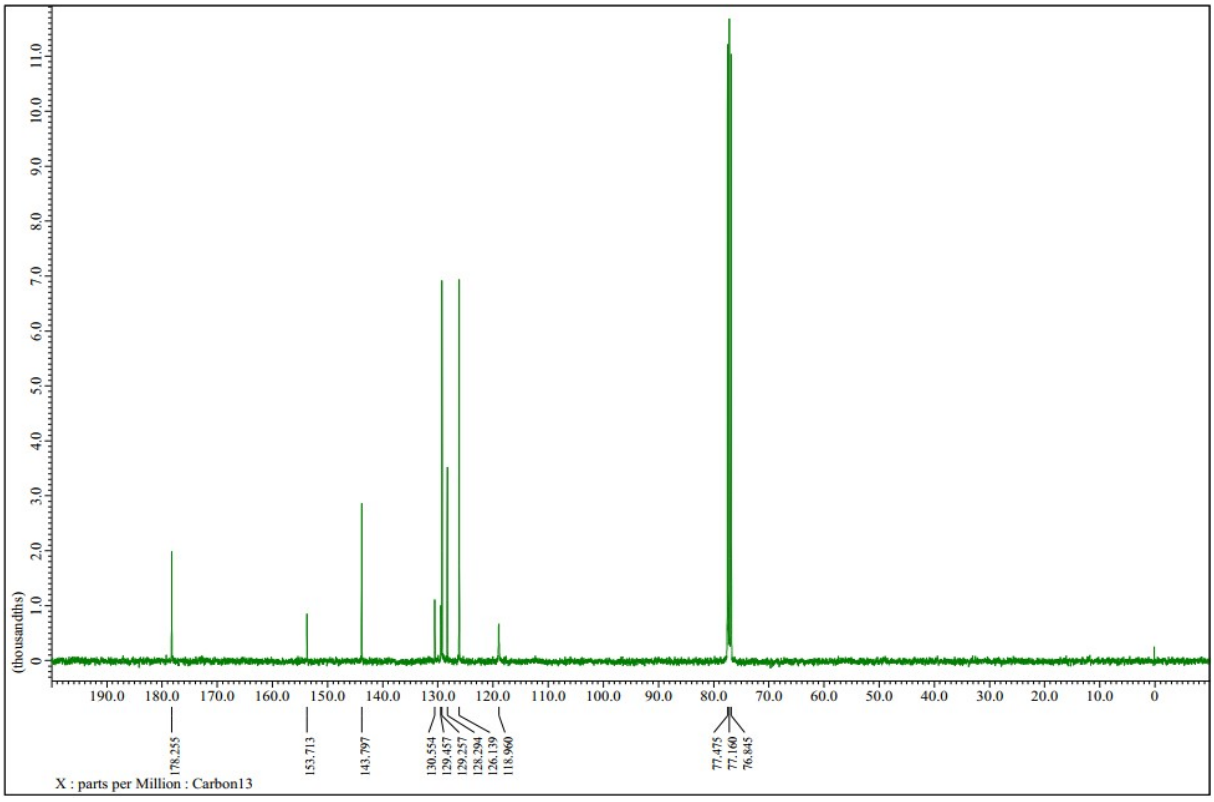


4-Phenyl-2-furaldehyde (S3e)

(^{1}H NMR, 400 MHz, $CDCl_3$)

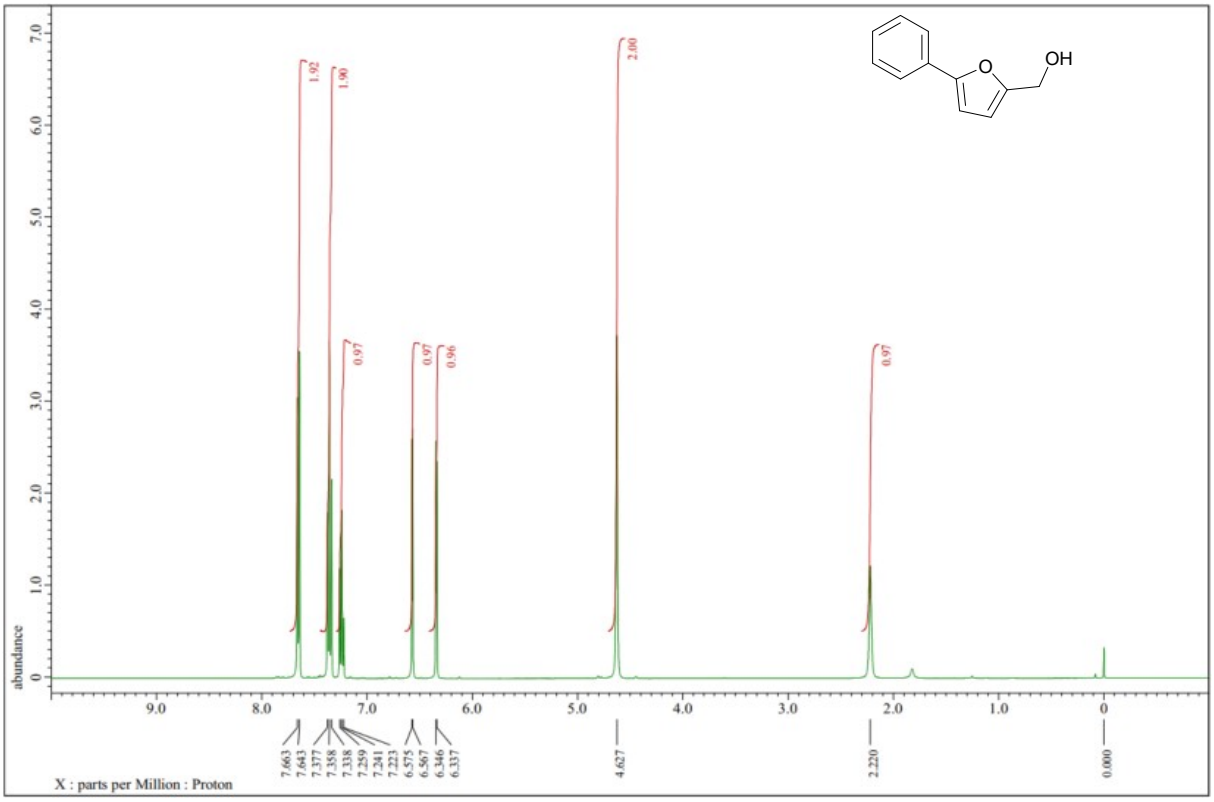


(^{13}C NMR, 100 MHz, $CDCl_3$)

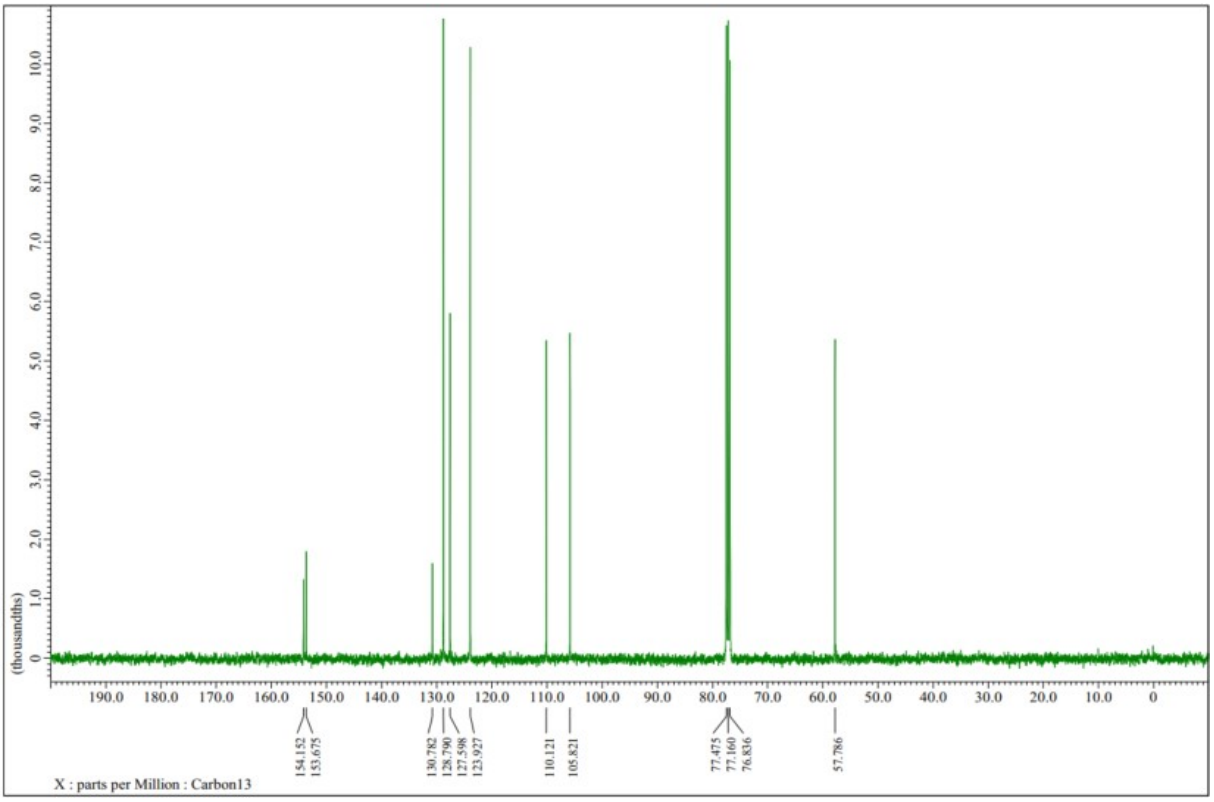


5-Phenyl-2-furanmethanol (1a)

(^{1}H NMR, 400 MHz, $CDCl_3$)

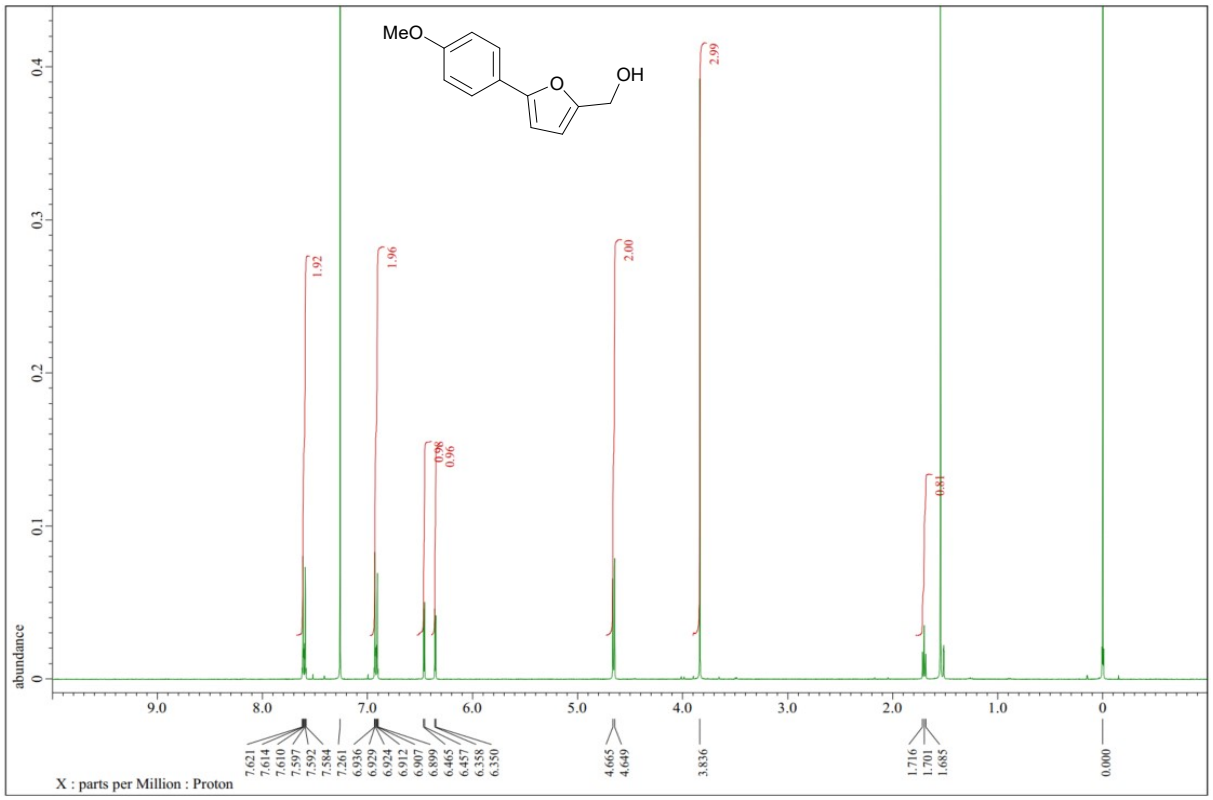


(^{13}C NMR, 100 MHz, $CDCl_3$)

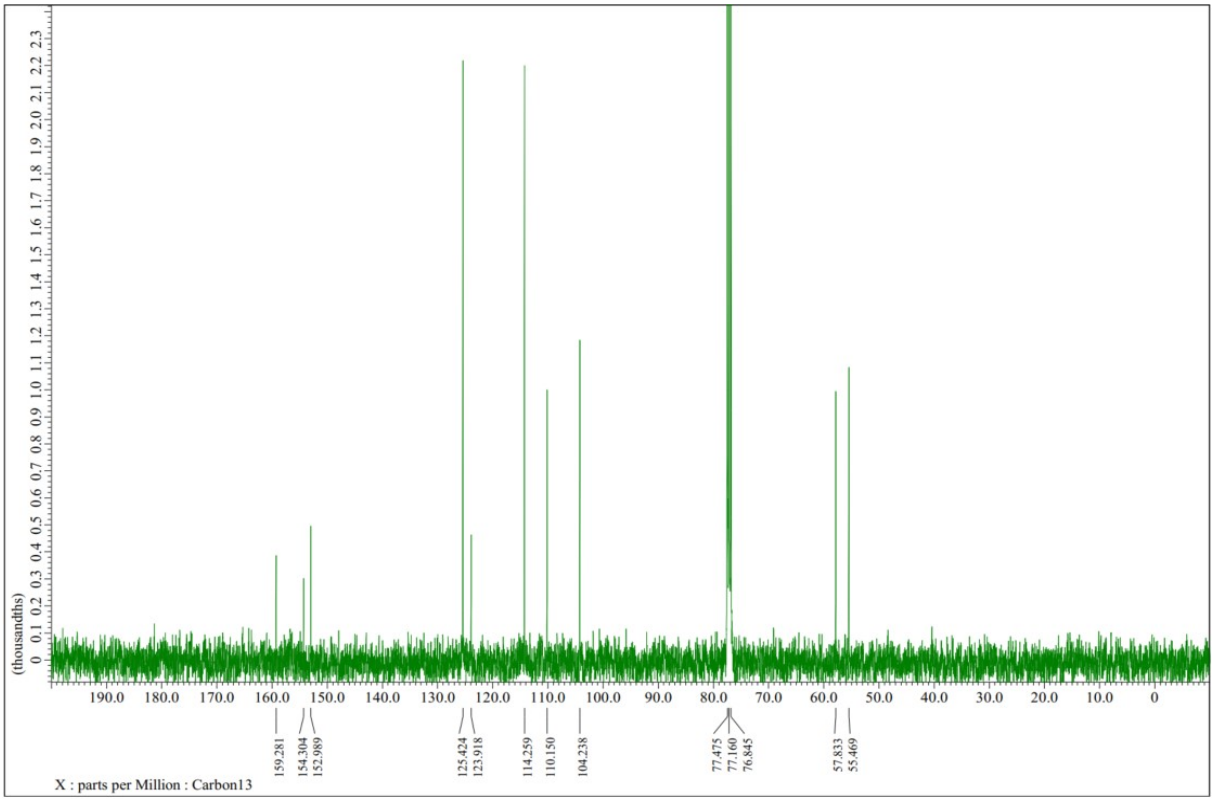


5-(4-Methoxyphenyl)-2-furanmethanol (1b)

(^{1}H NMR, 400 MHz, $CDCl_3$)

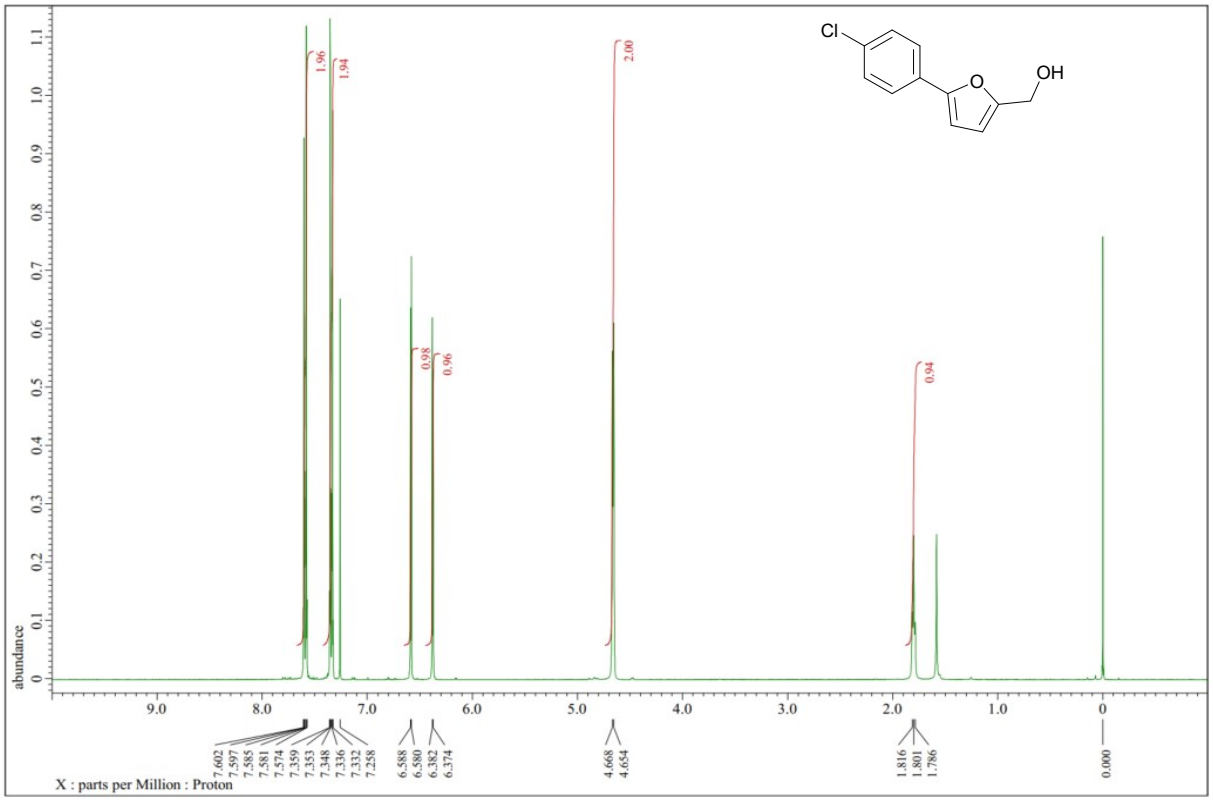


(^{13}C NMR, 100 MHz, $CDCl_3$)

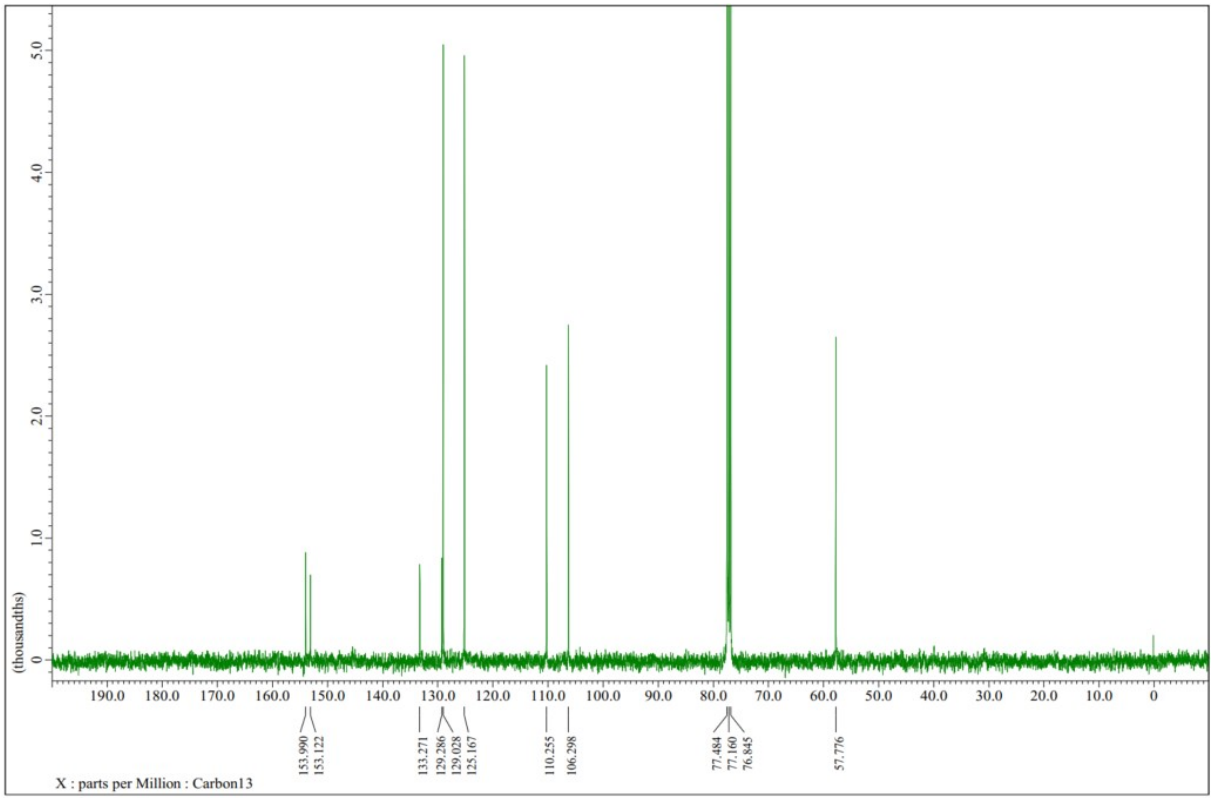


5-(4-Chlorophenyl)-2-furanmethanol (1c)

(^{1}H NMR, 400 MHz, $CDCl_3$)

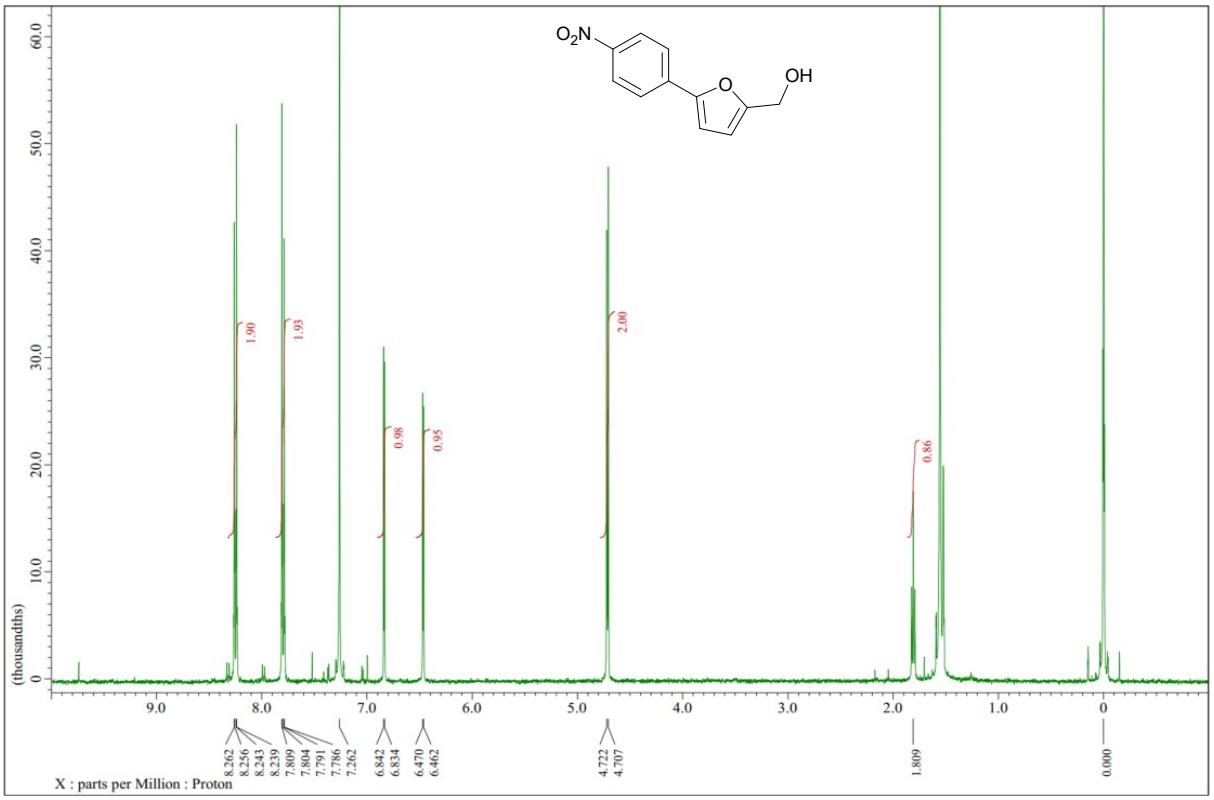


(^{13}C NMR, 100 MHz, $CDCl_3$)

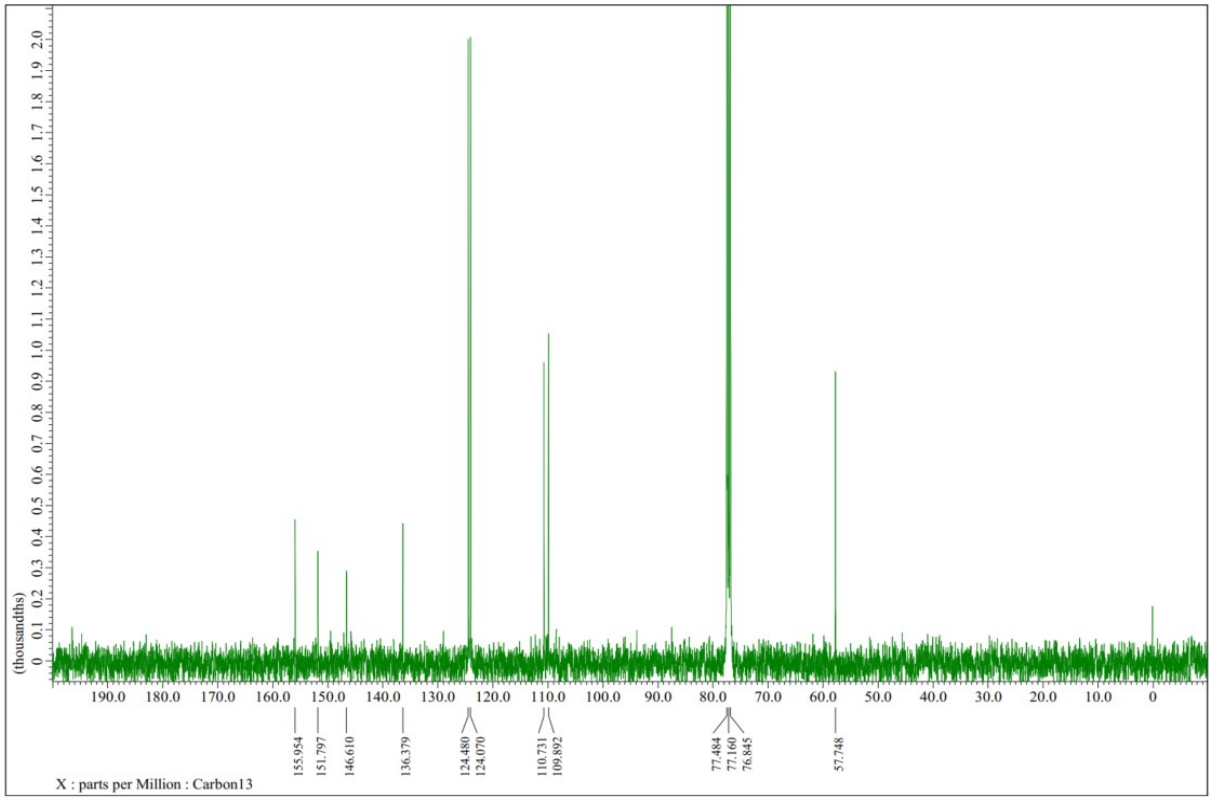


5-(4-Nitorophenyl)-2-furanmethanol (1d)

(^{1}H NMR, 400 MHz, $CDCl_3$)

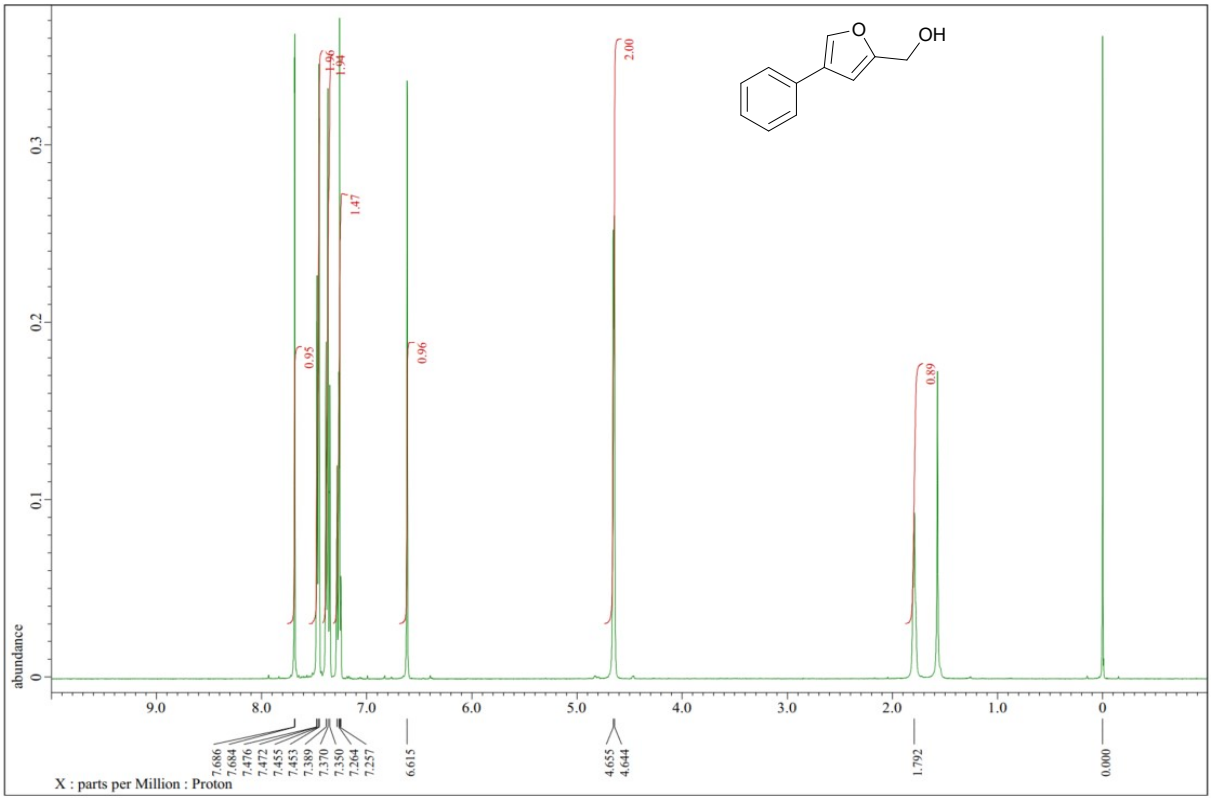


(^{13}C NMR, 100 MHz, $CDCl_3$)

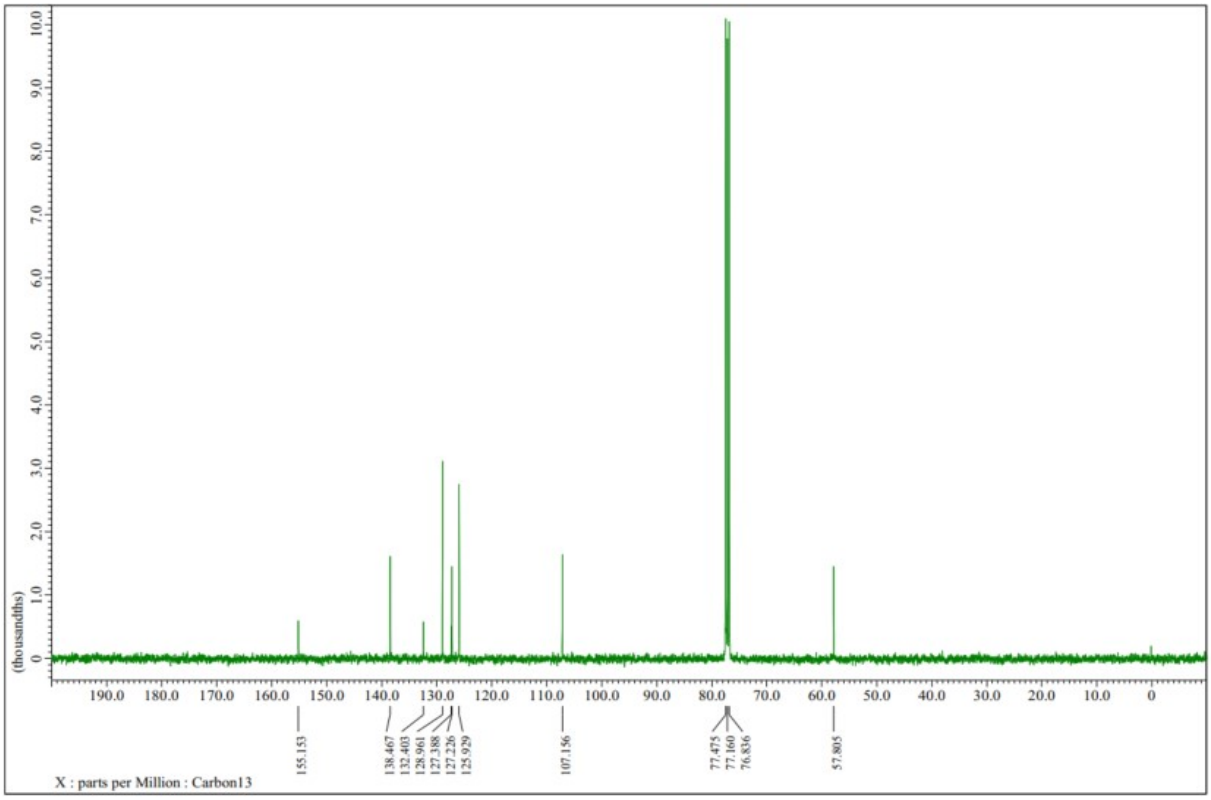


4-Phenyl-2-furanmethanol (1e)

(^{1}H NMR, 400 MHz, $CDCl_3$)

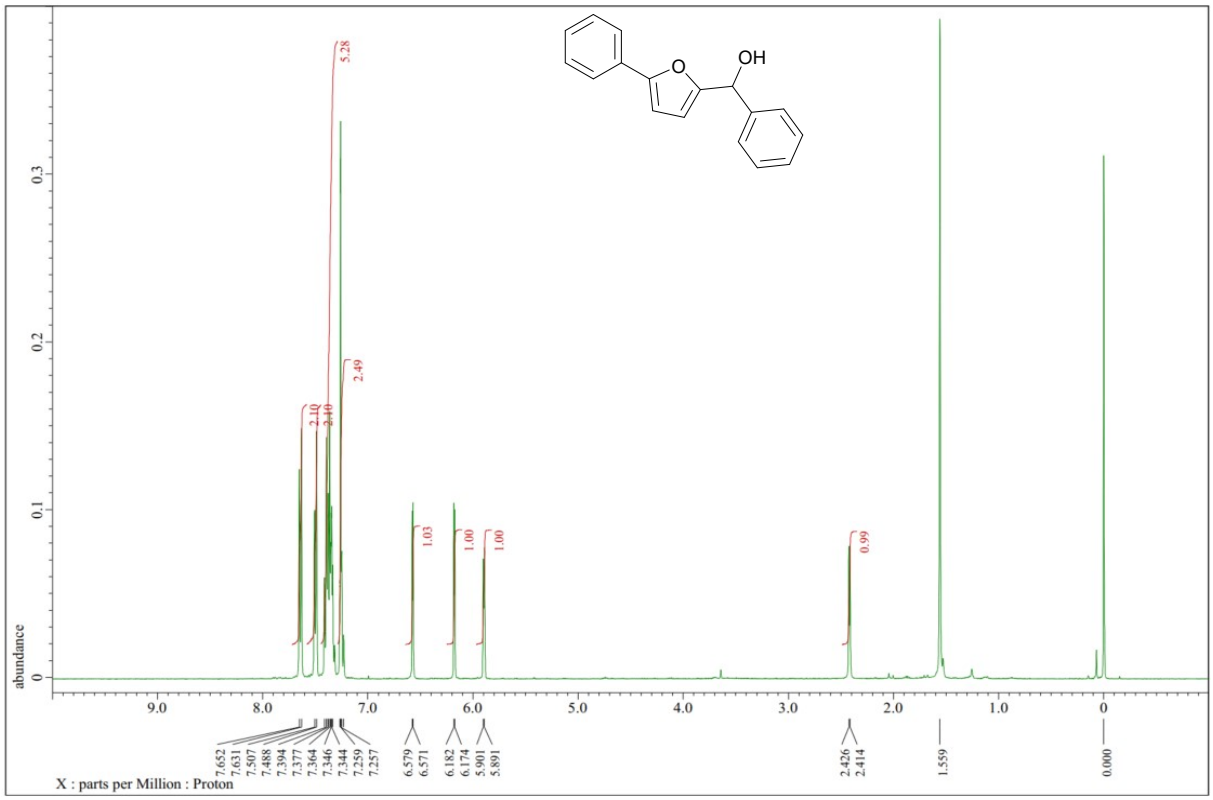


(^{13}C NMR, 100 MHz, $CDCl_3$)

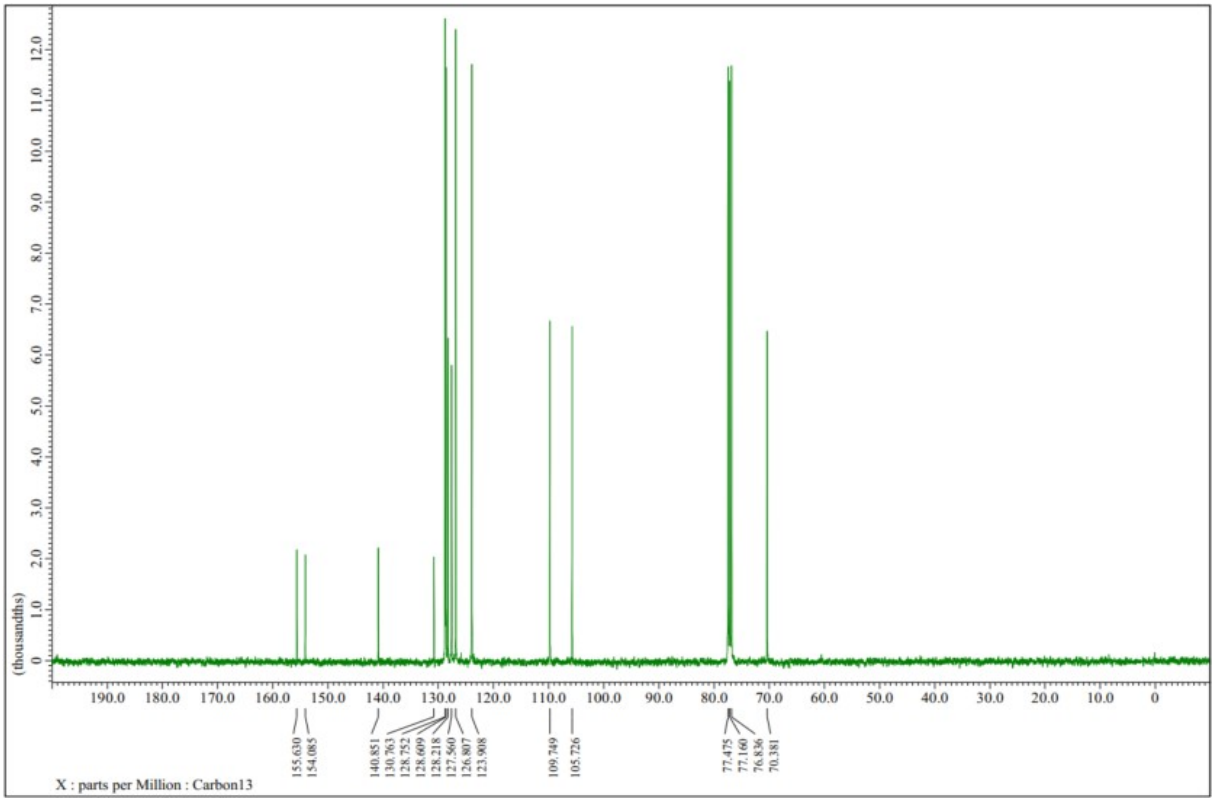


***α*,5-Diphenyl-2-furanmethanol (1f)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

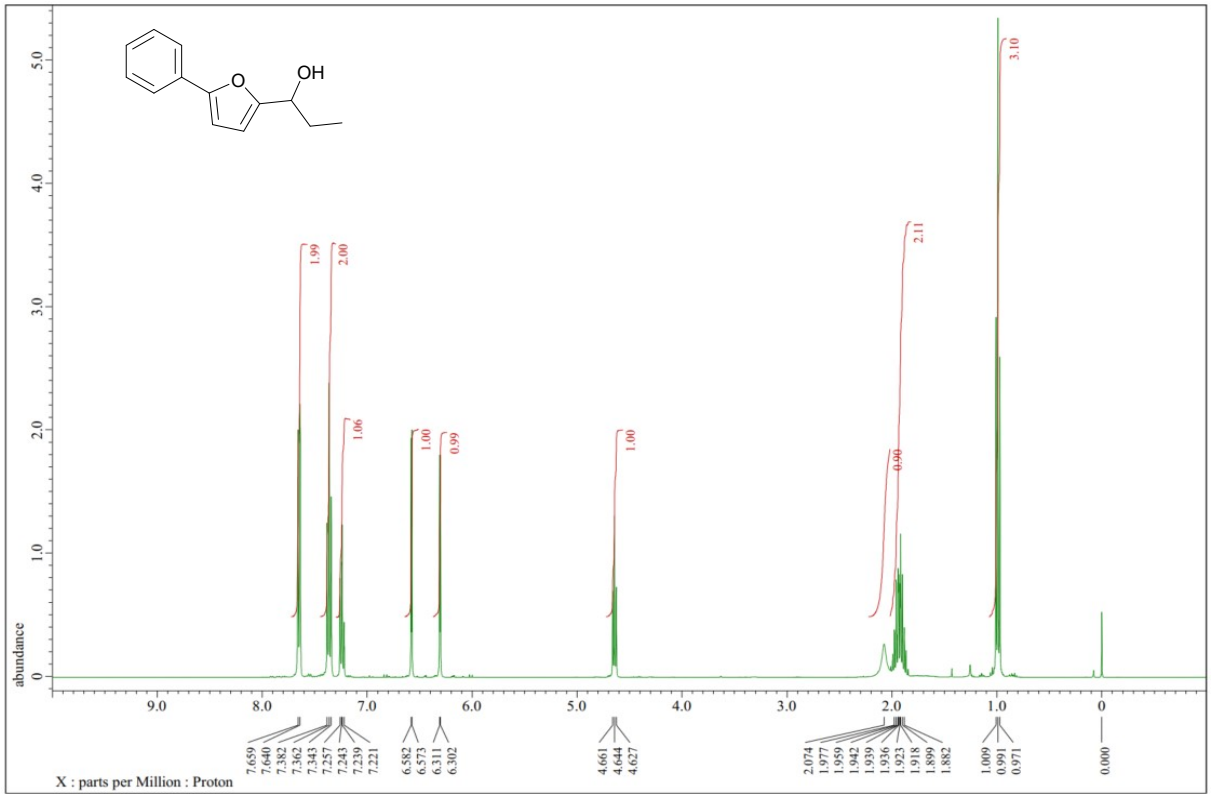


(^{13}C NMR, 100 MHz, $CDCl_3$)

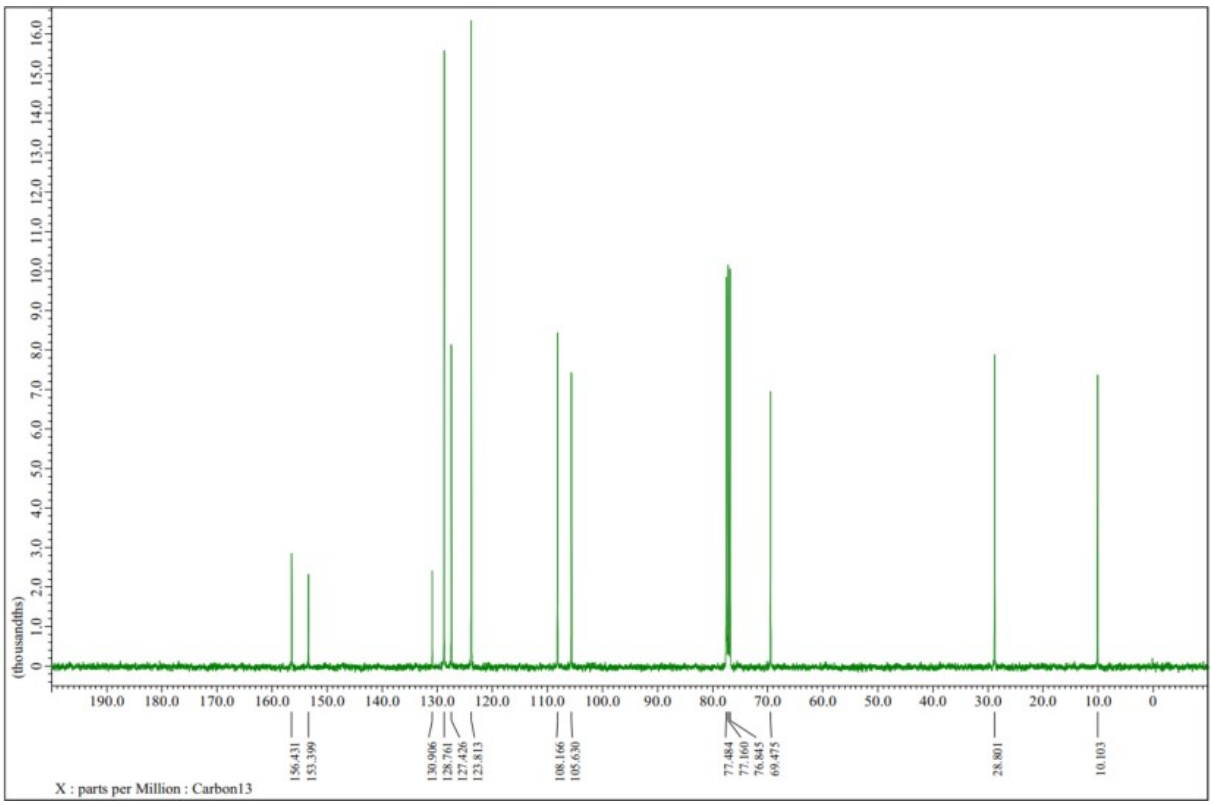


Synthesis of *α*-ethyl-5-phenyl-2-furanmethanol (1g)

(^{1}H NMR, 400 MHz, $CDCl_3$)

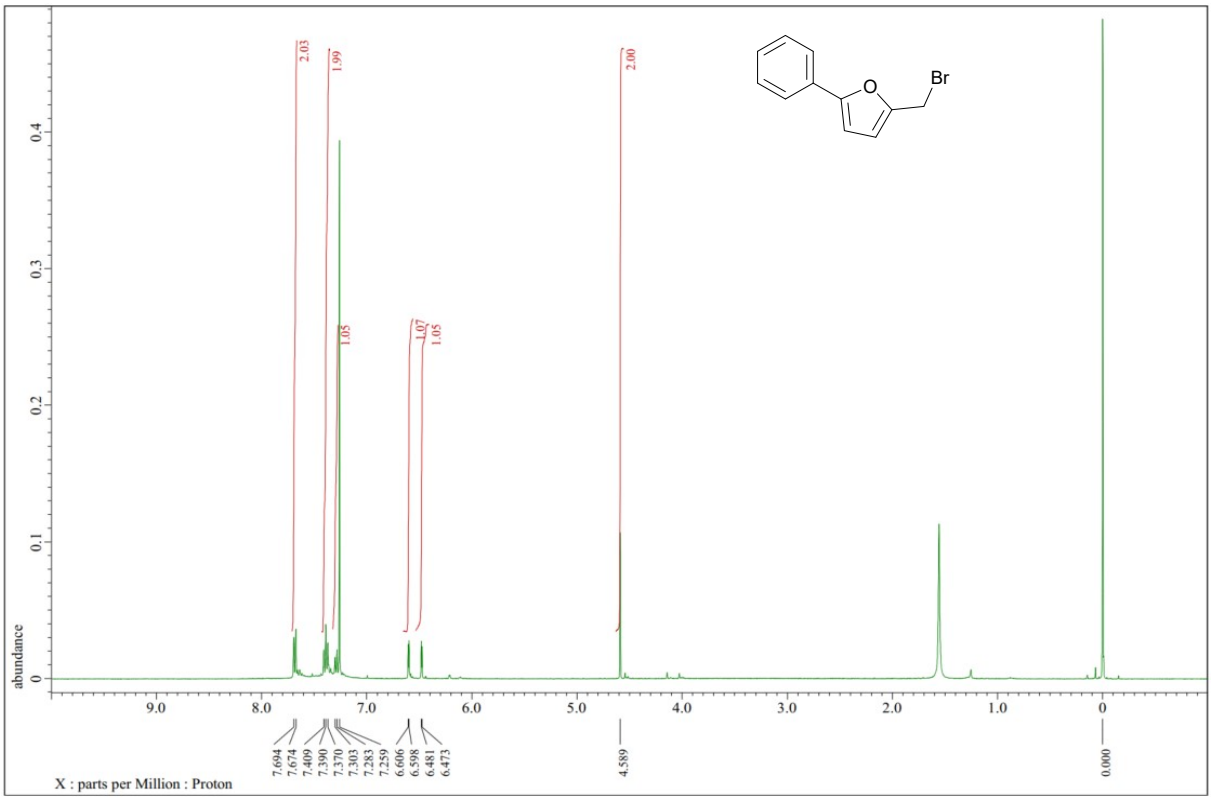


(^{13}C NMR, 100 MHz, $CDCl_3$)

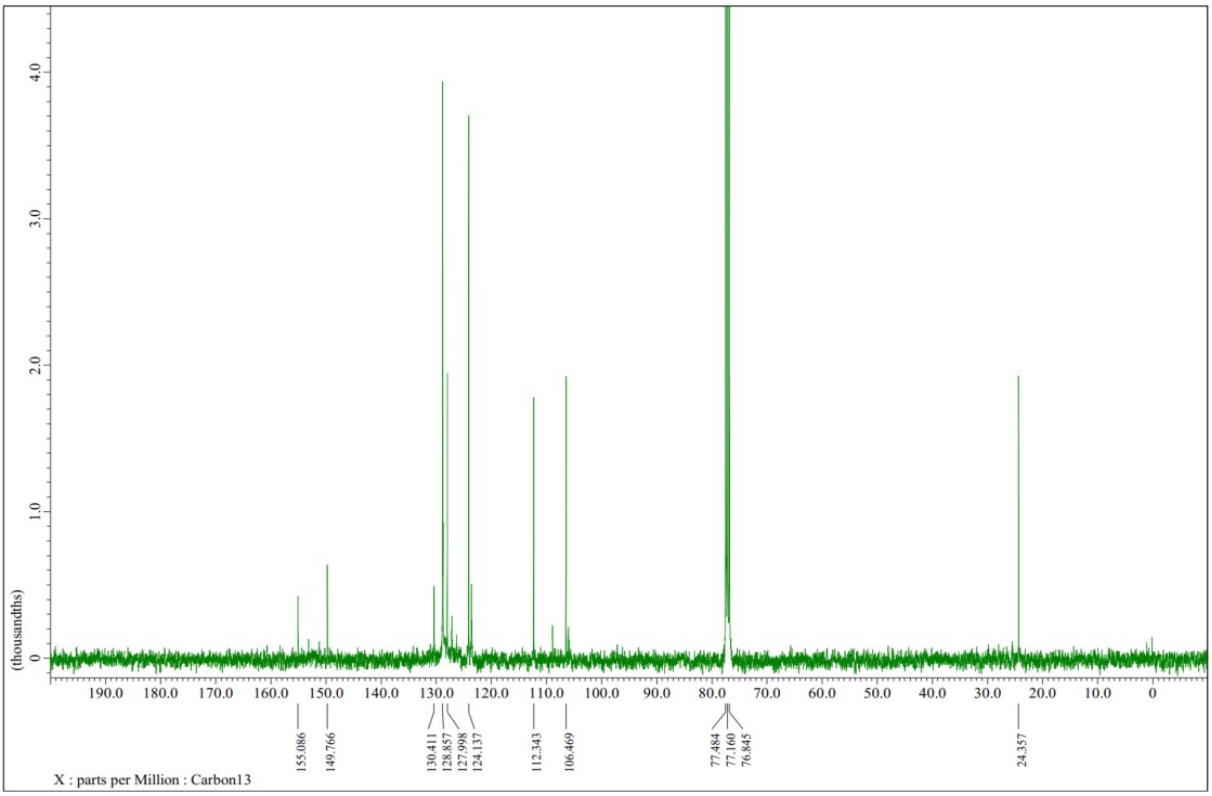


5-Phenyl-2-furanbromide (batch reactor) **(5a)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

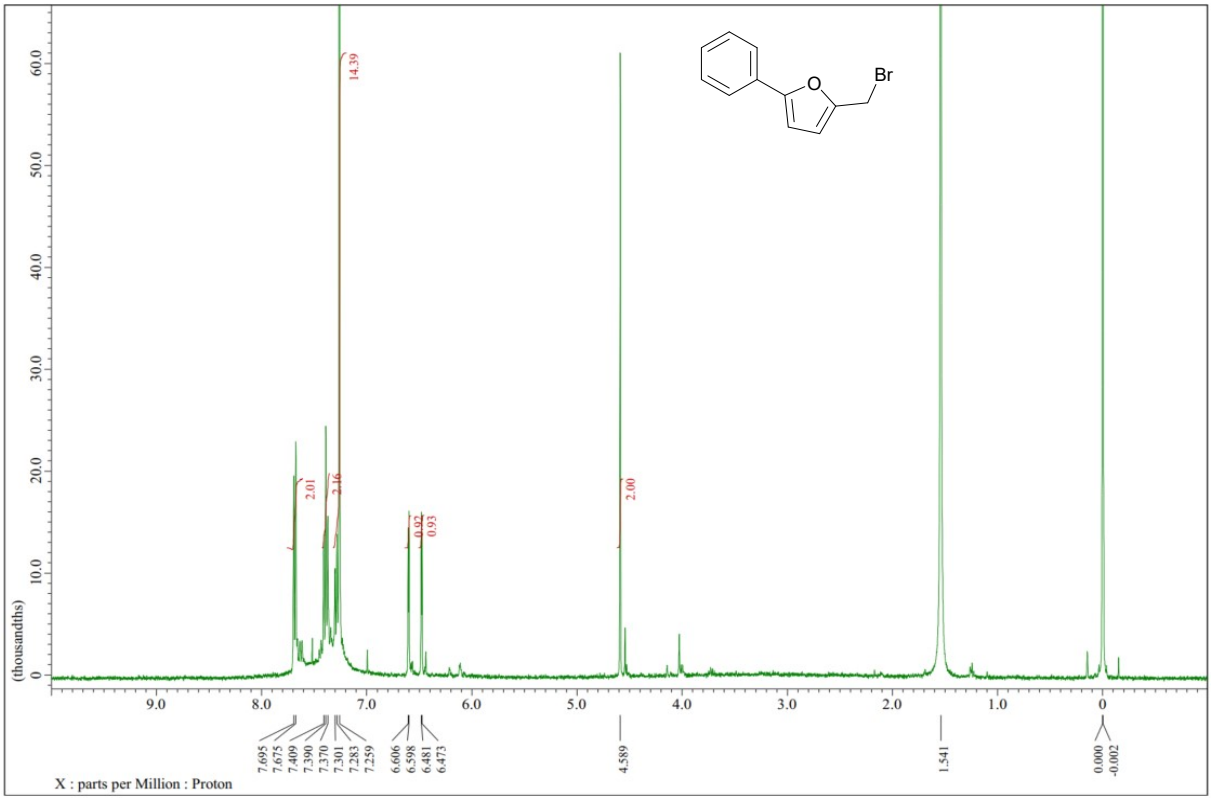


(^{13}C NMR, 100 MHz, $CDCl_3$)

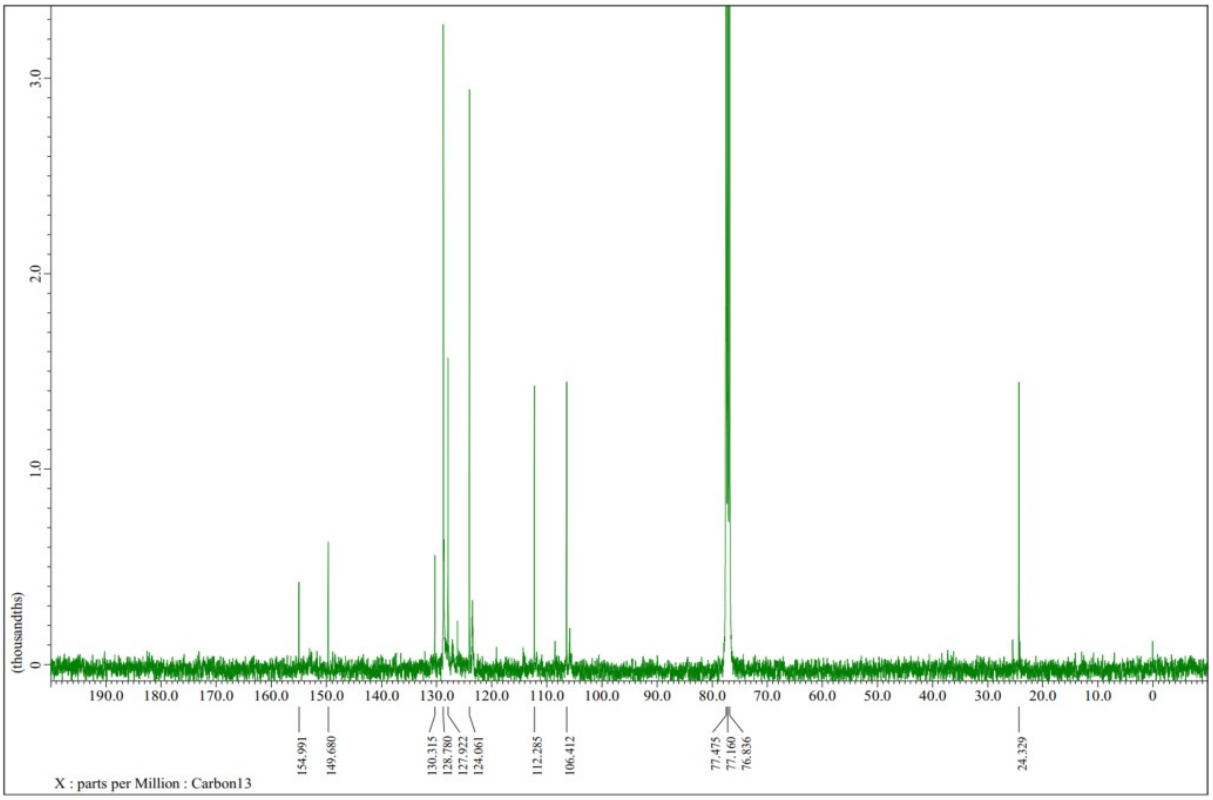


5-Phenyl-2-furanbromide (microflow reactor) **(5a)**

(^{1}H NMR, 400 MHz, $CDCl_3$)

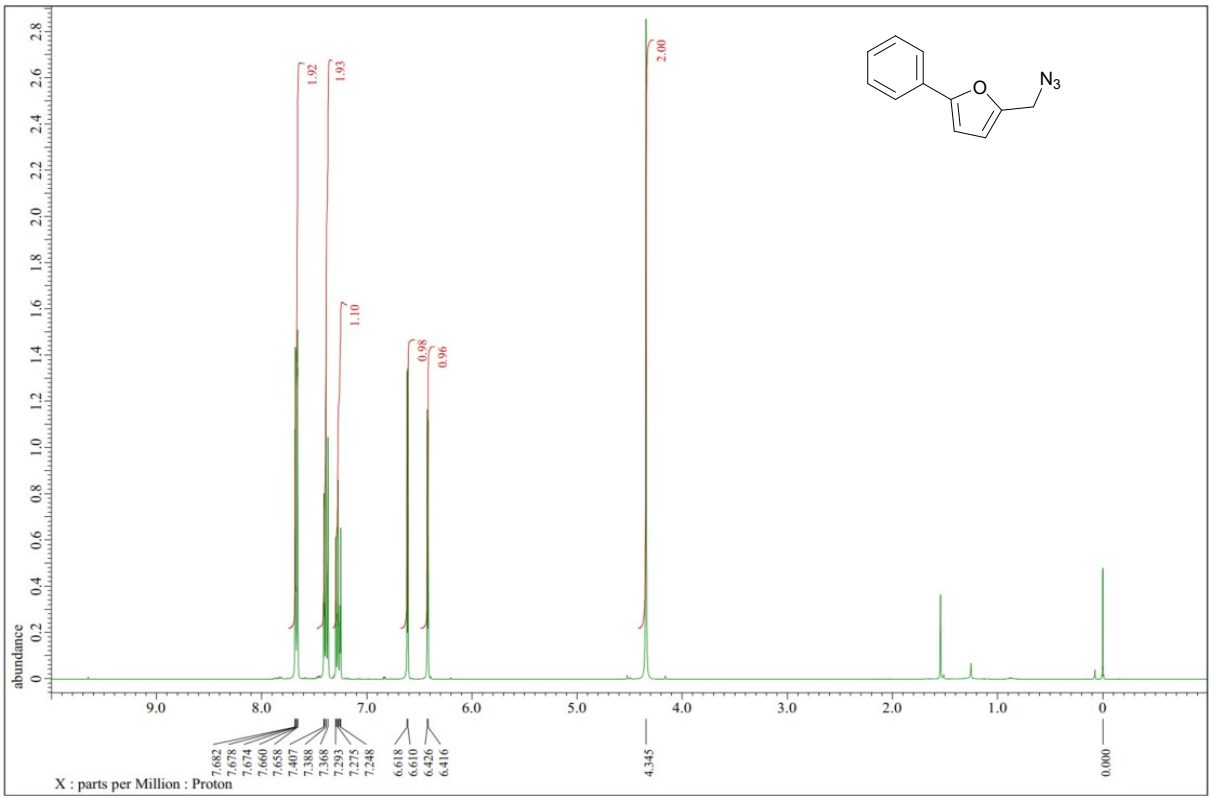


(^{13}C NMR, 100 MHz, $CDCl_3$)

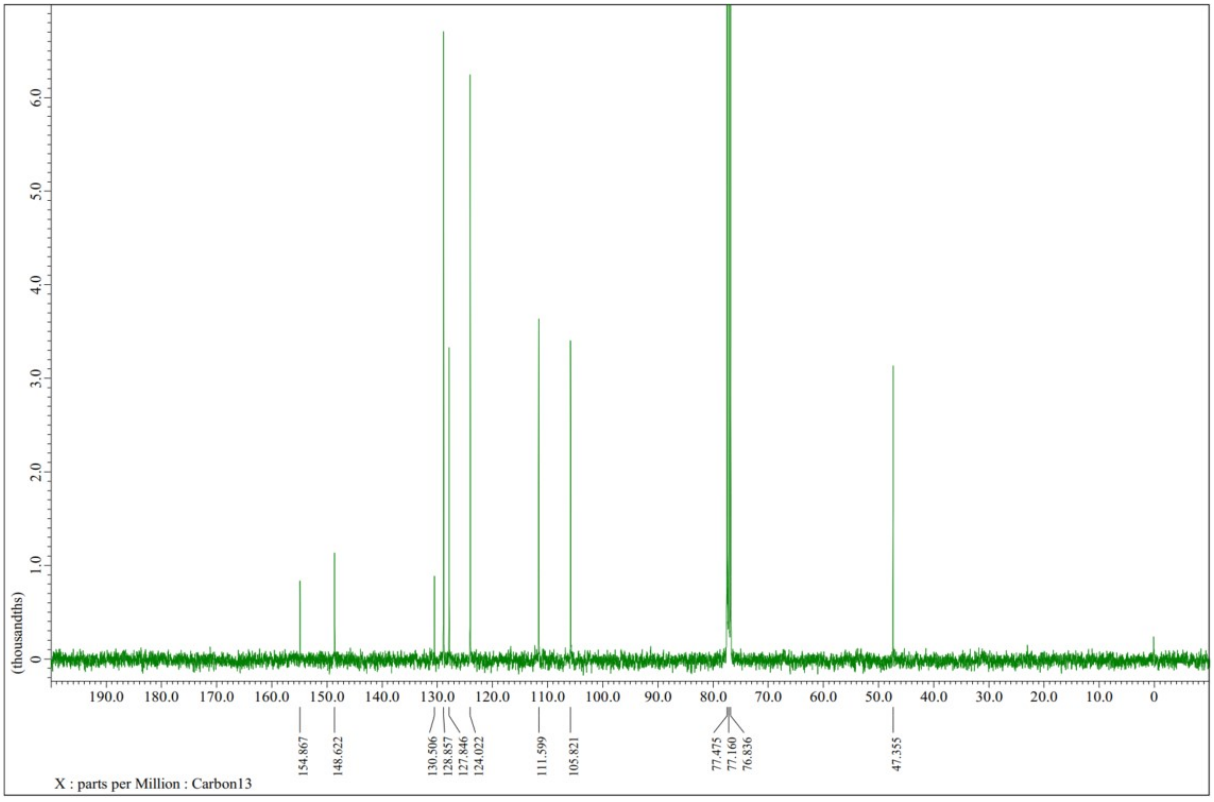


5-Phenyl-2-furanmethanazide (2a)

(^{1}H NMR, 400 MHz, $CDCl_3$)

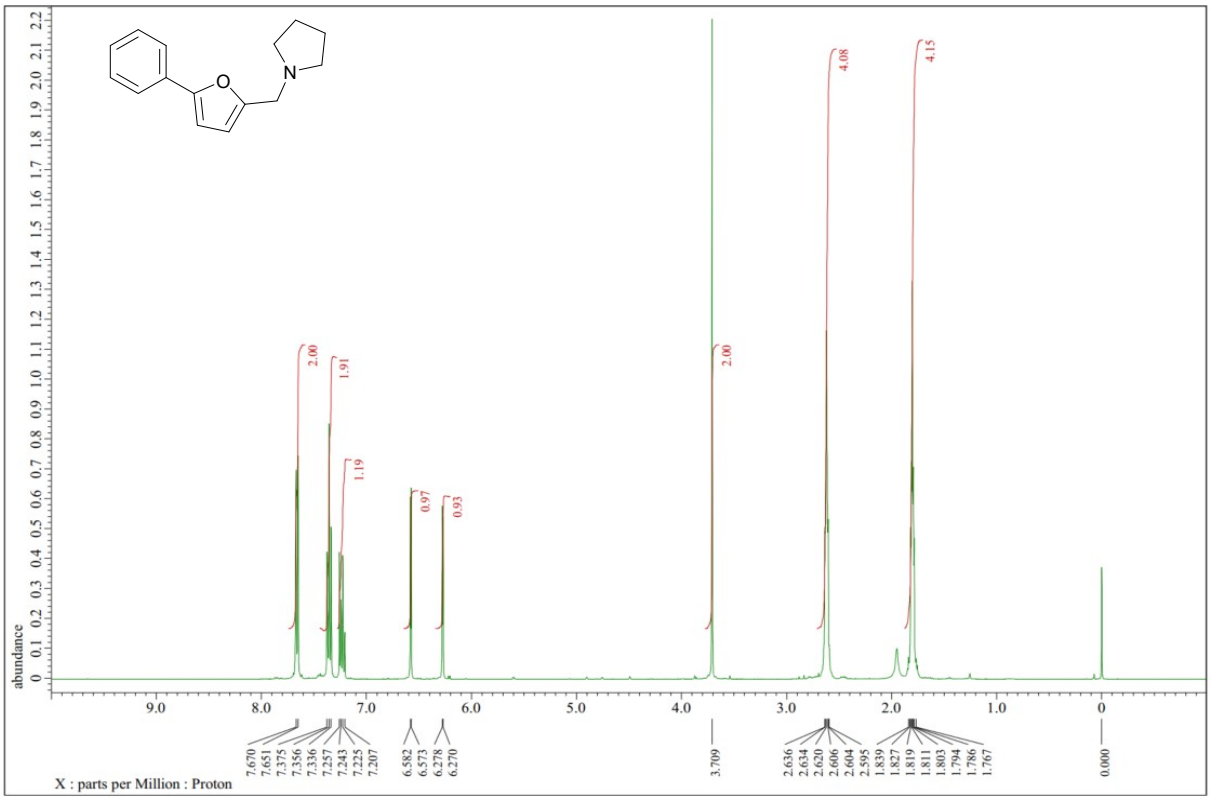


(^{13}C NMR, 100 MHz, $CDCl_3$)

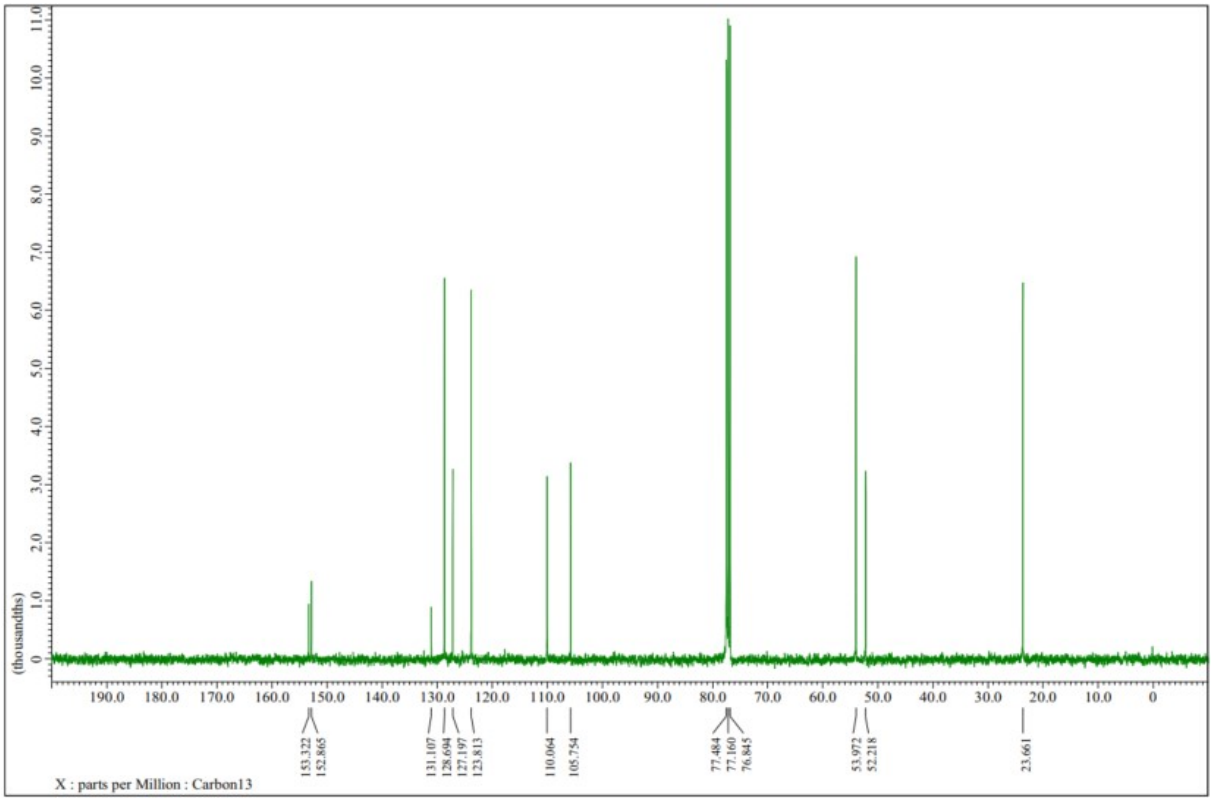


5-Phenyl-2-furanmethanpyrrolidine (2b)

(^{1}H NMR, 400 MHz, $CDCl_3$)

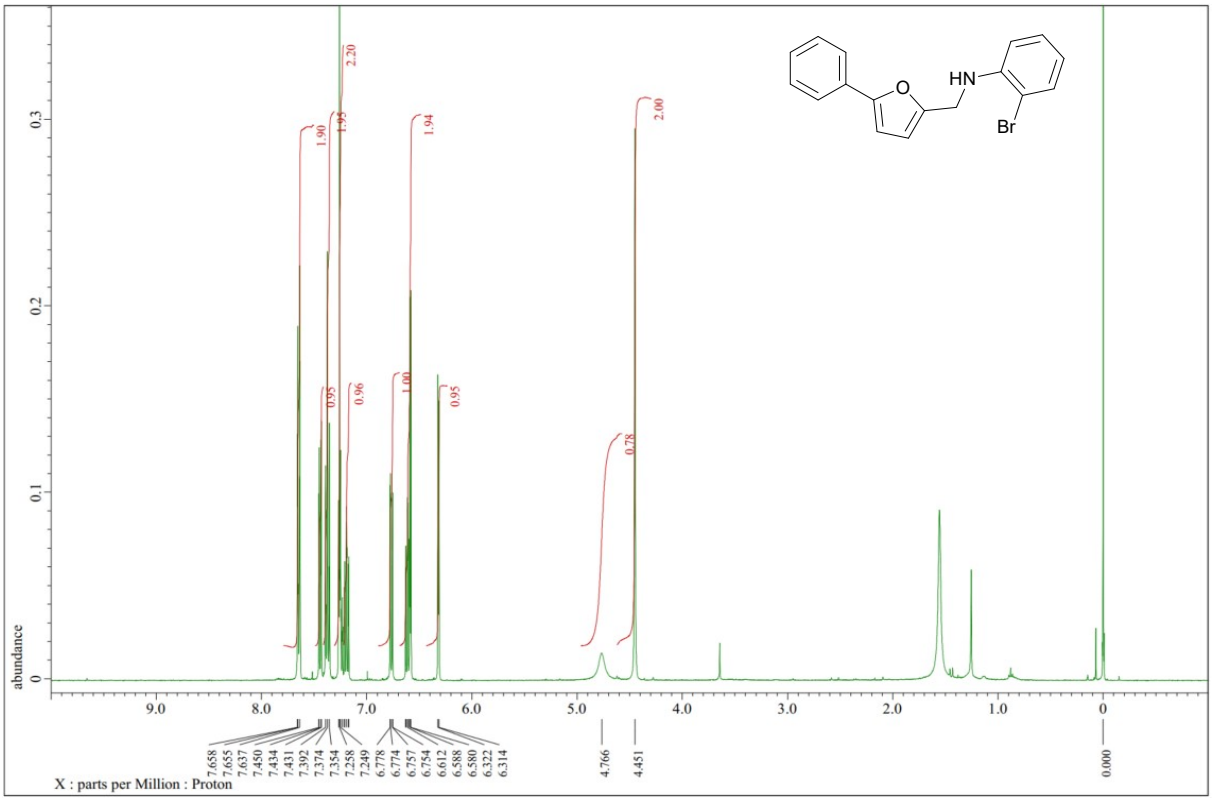


(^{13}C NMR, 100 MHz, $CDCl_3$)

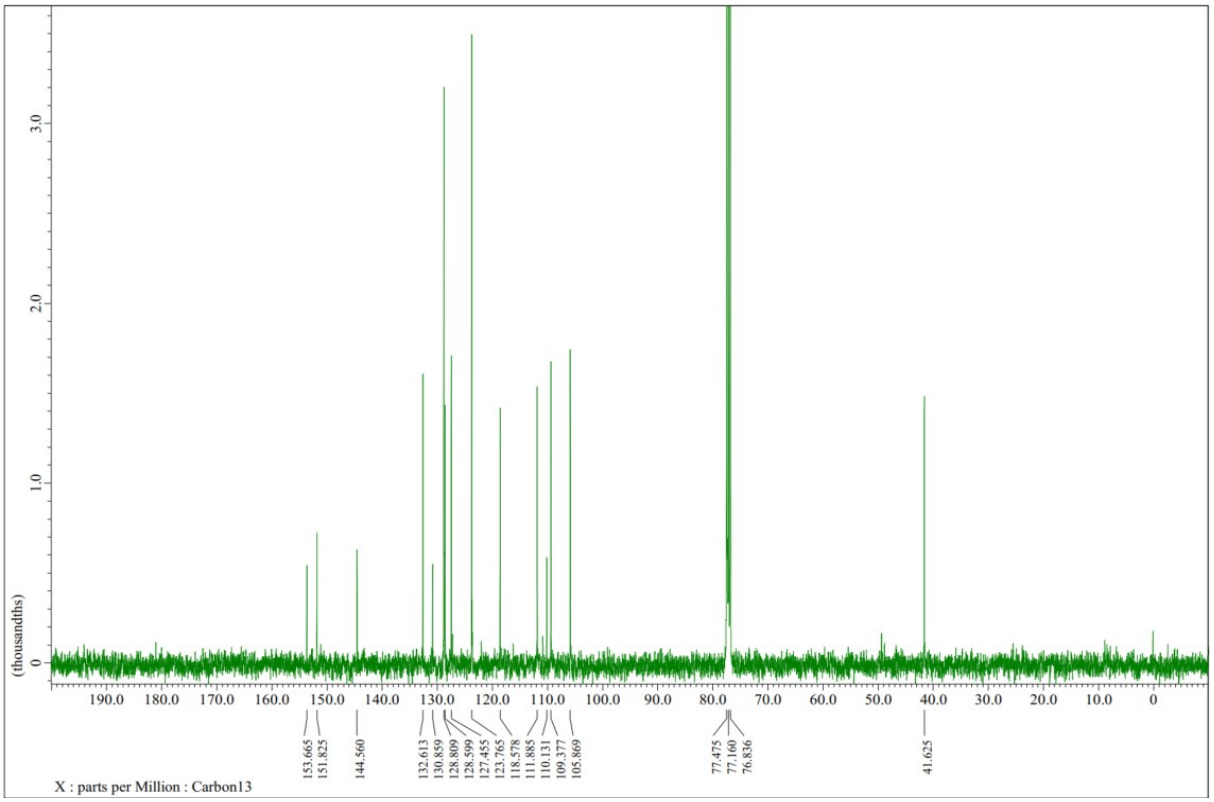


5-Phenyl-2-furanmethan-2-bromoaniline (2c)

(^{1}H NMR, 400 MHz, $CDCl_3$)

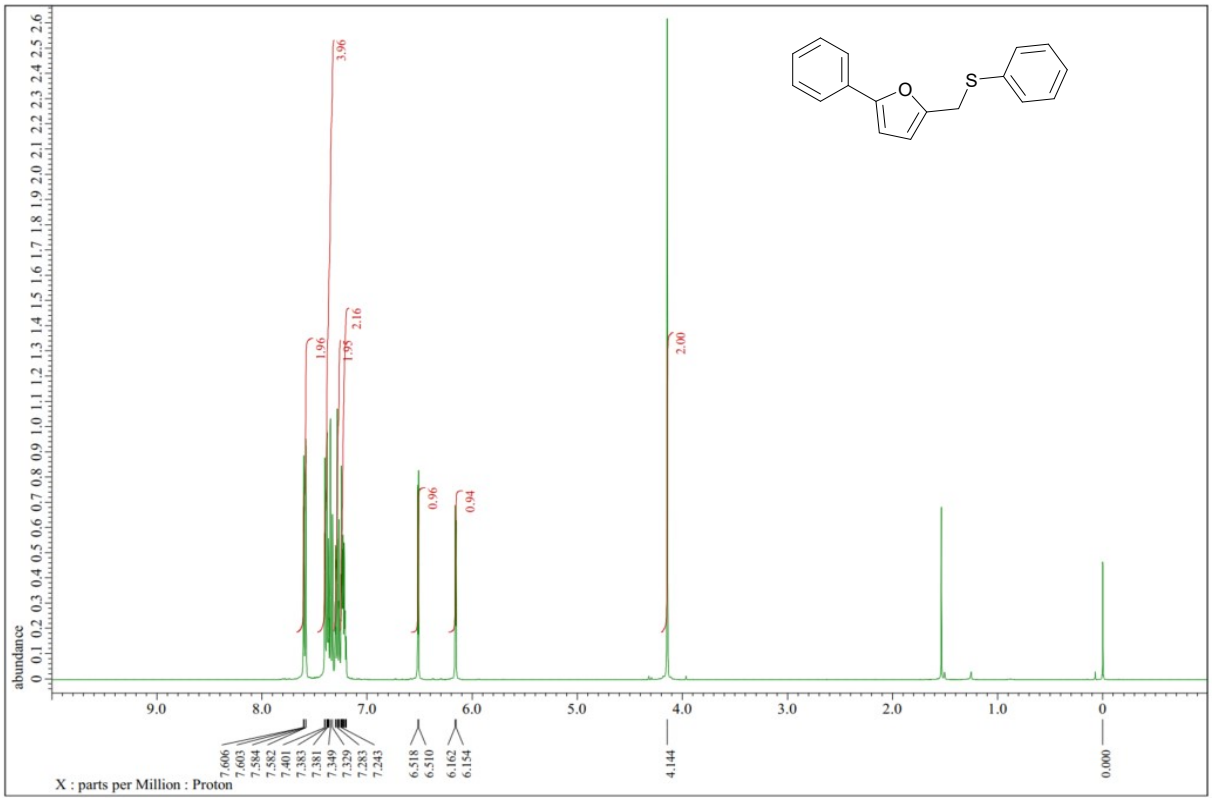


(^{13}C NMR, 100 MHz, $CDCl_3$)

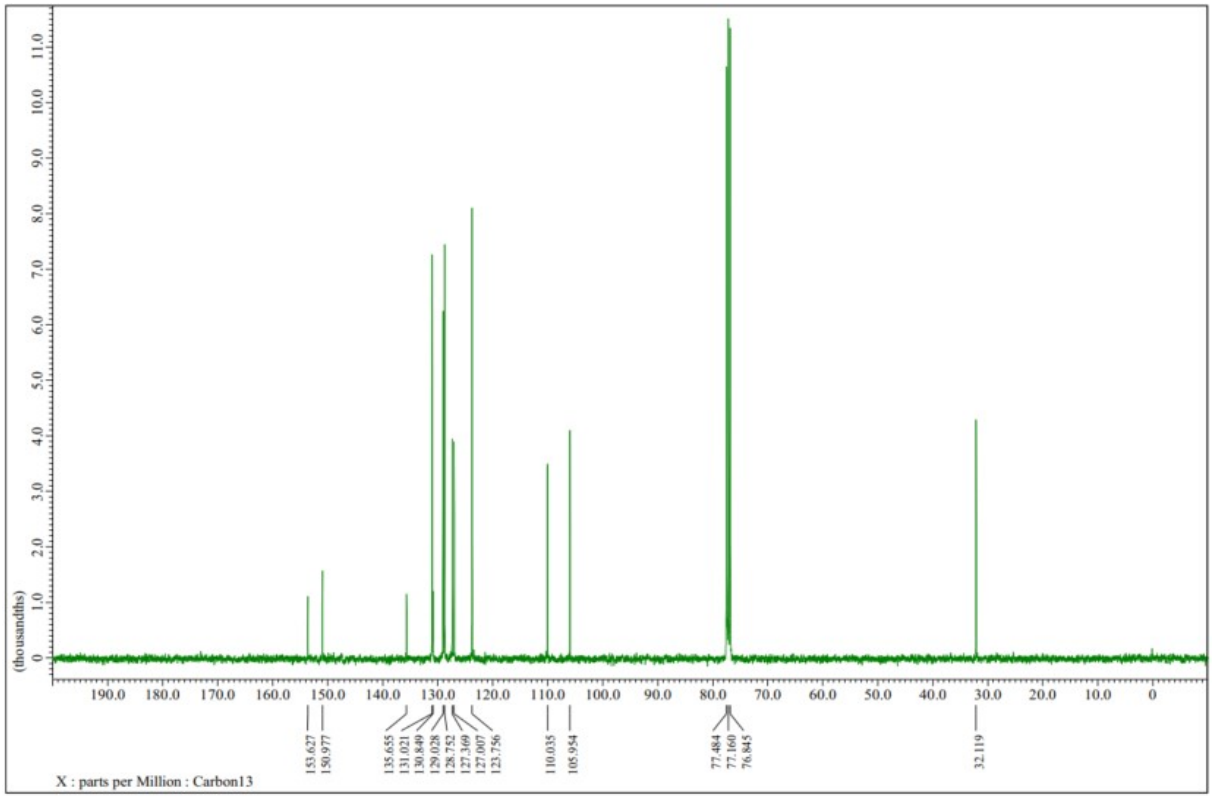


5-Phenyl-2-furanmethanthiophenol (2d)

(^{1}H NMR, 400 MHz, $CDCl_3$)

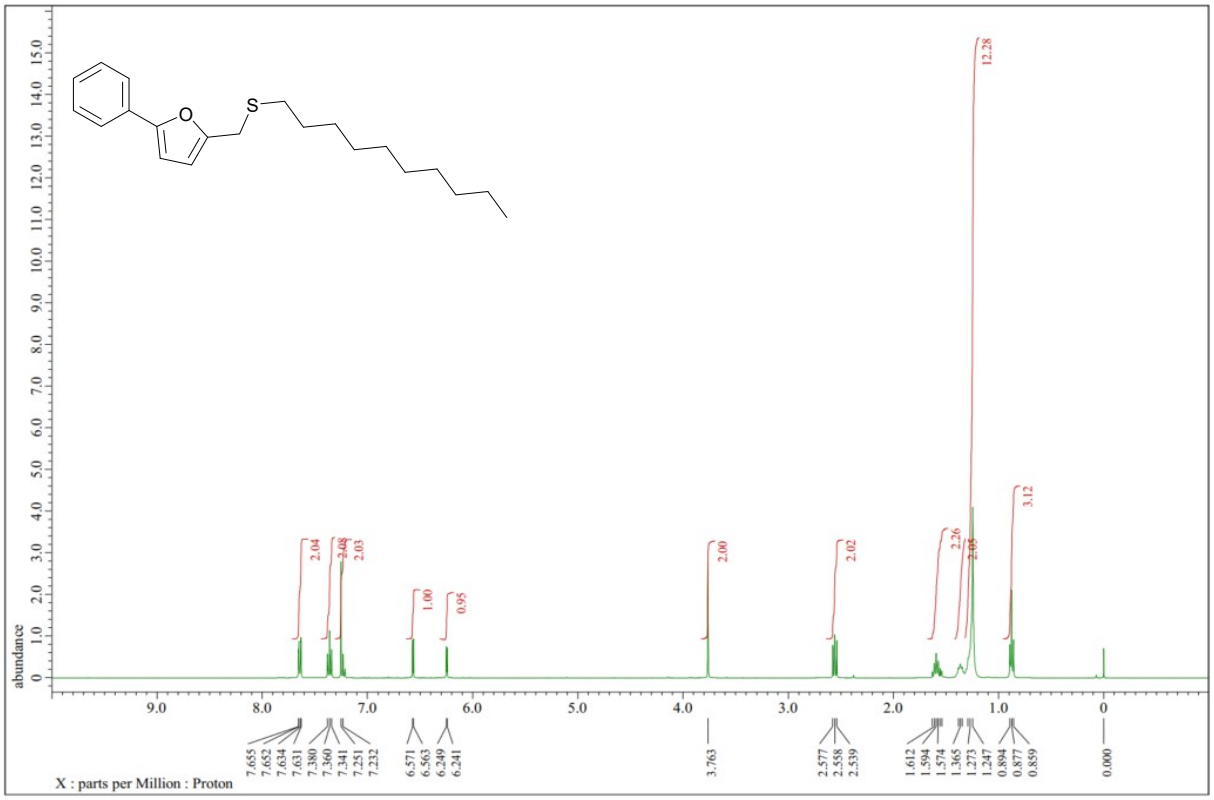


(^{13}C NMR, 100 MHz, $CDCl_3$)

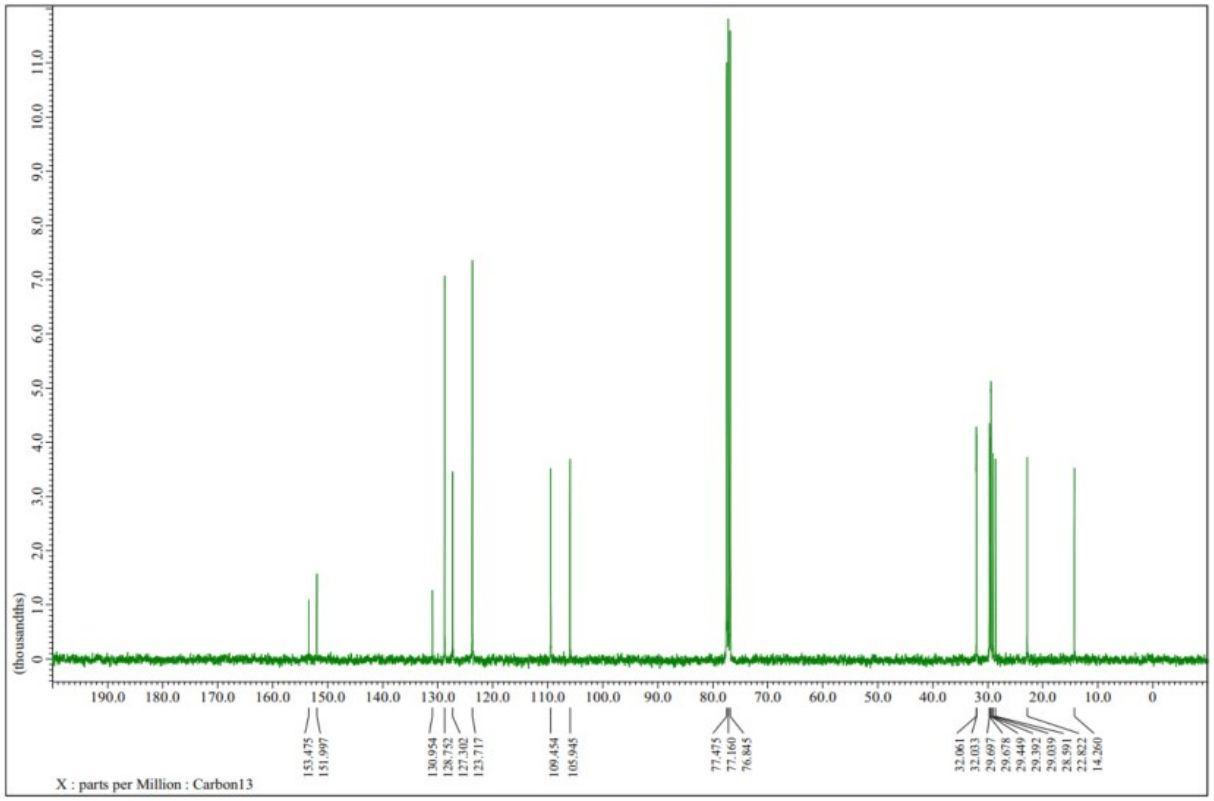


5-Phenyl-2-furanmethandecanthiol (2e)

(^{1}H NMR, 400 MHz, $CDCl_3$)

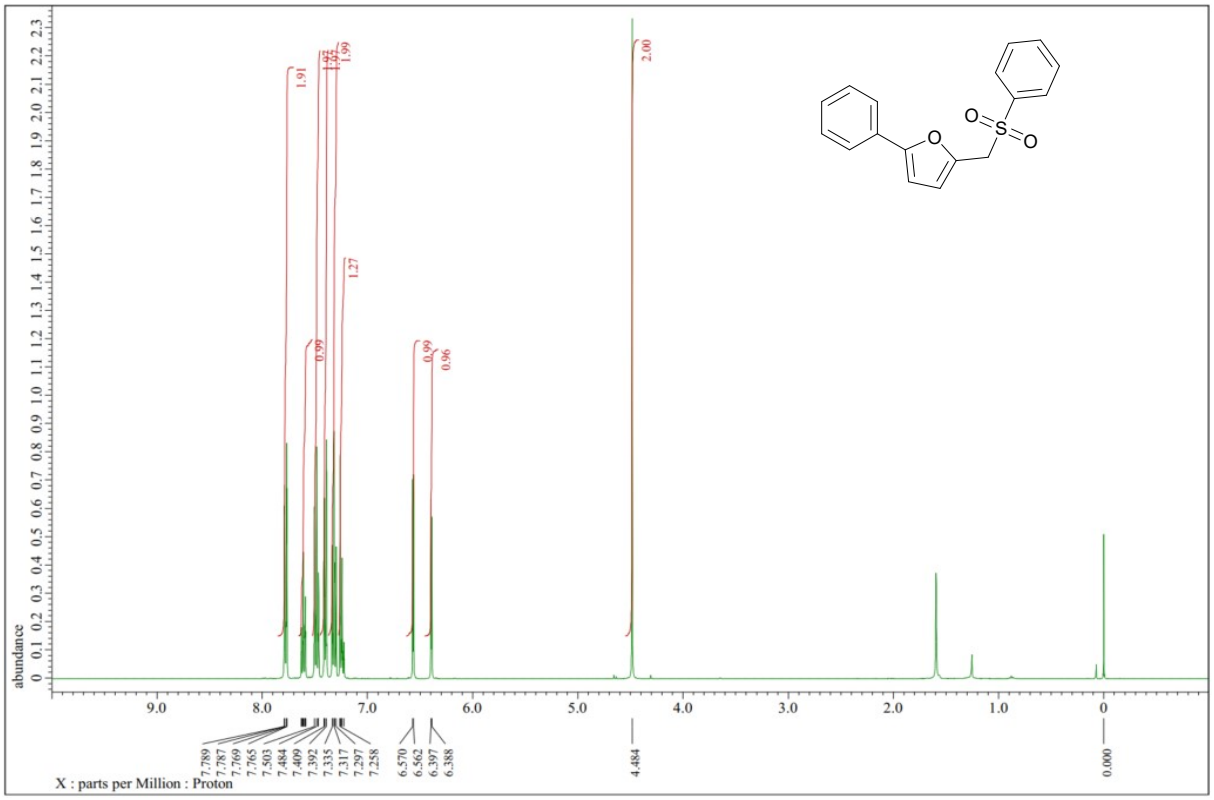


(^{13}C NMR, 100 MHz, $CDCl_3$)

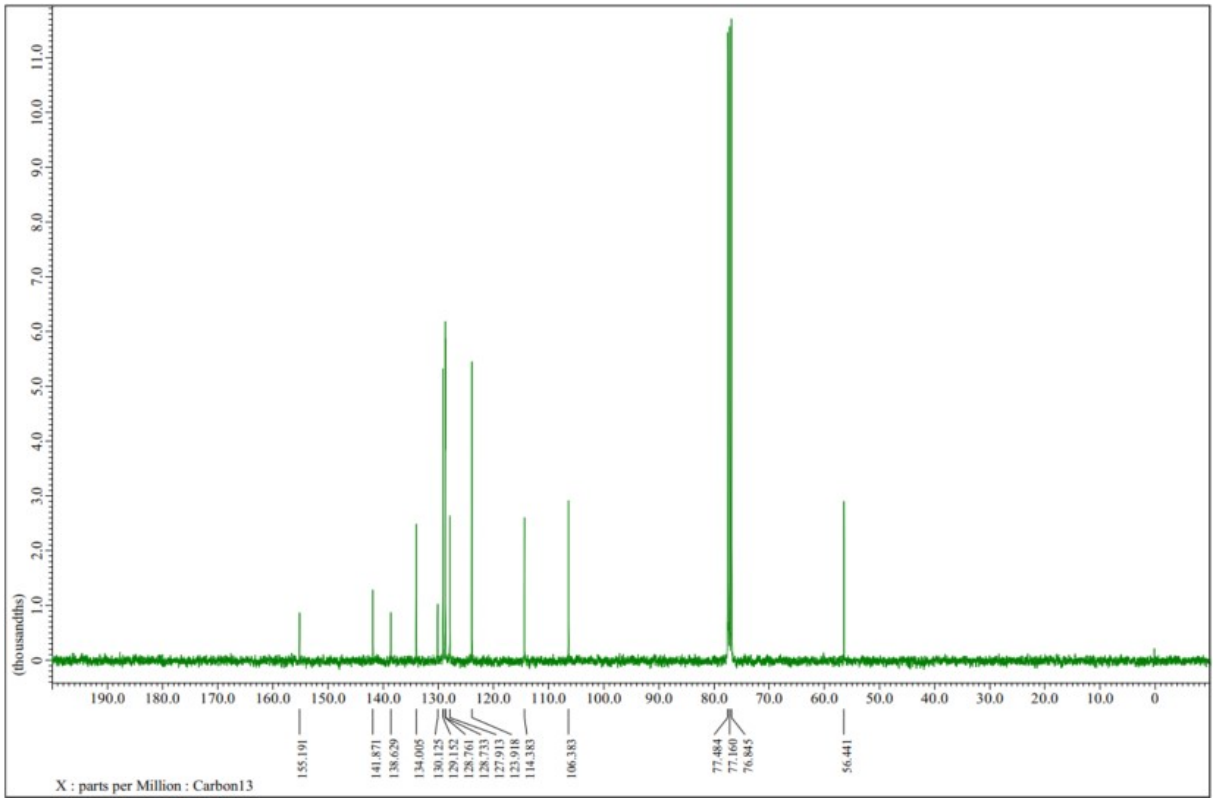


5-Phenyl-2-furanmethanphenylsulfone (2f)

(^{1}H NMR, 400 MHz, $CDCl_3$)

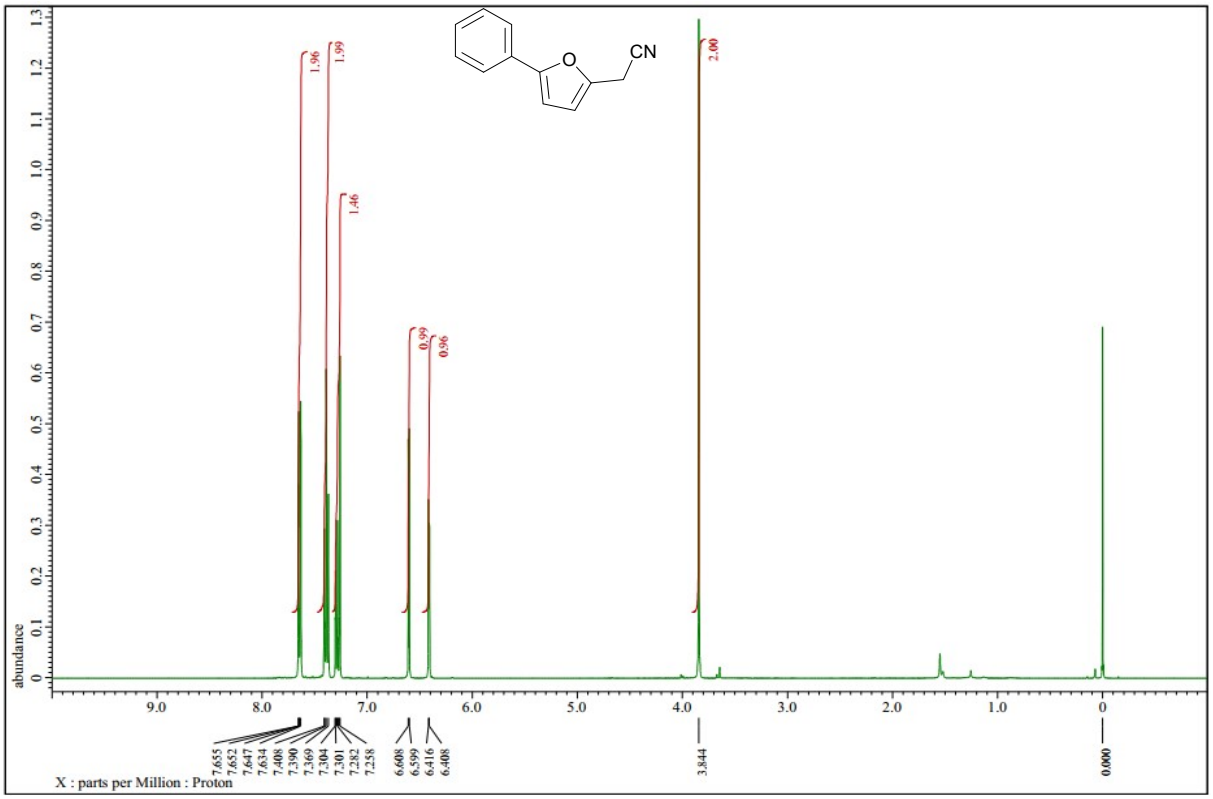


(^{13}C NMR, 100 MHz, $CDCl_3$)

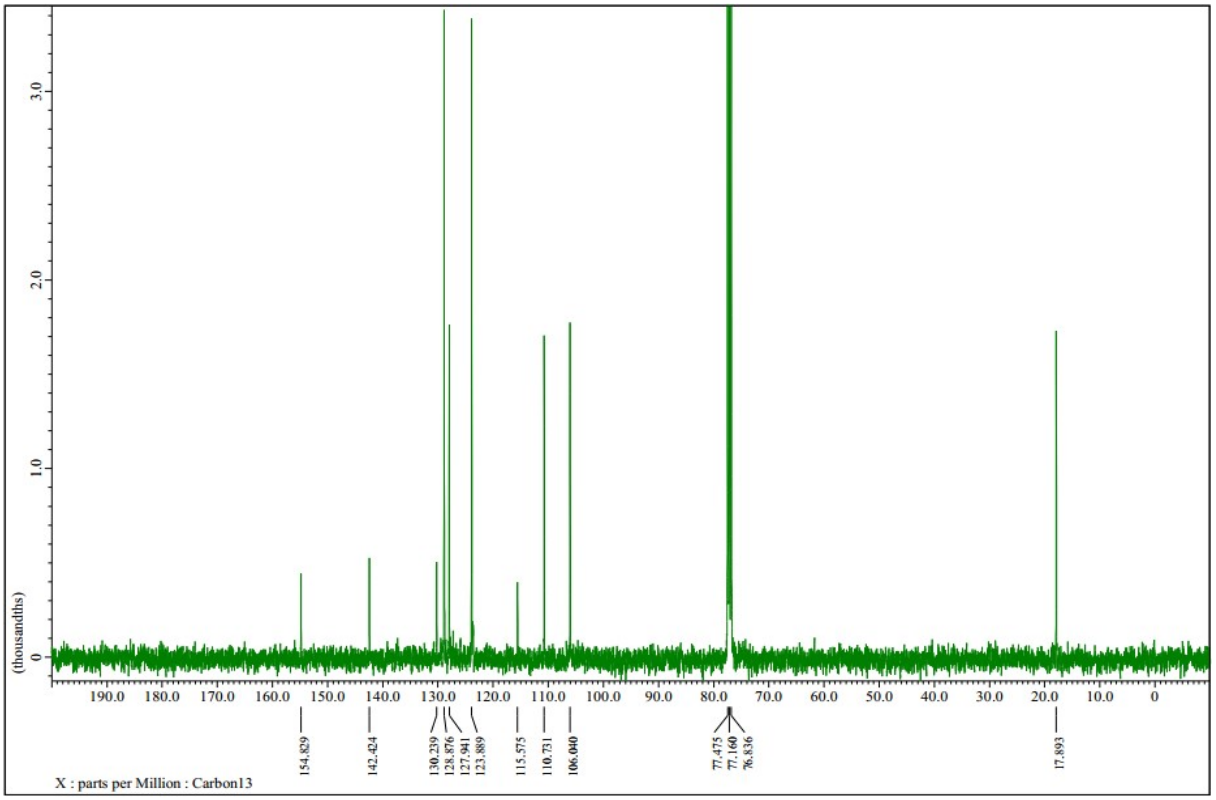


2-(5-Phenylfuran-2-yl)acetonitrile (2h)

(^{1}H NMR, 400 MHz, $CDCl_3$)

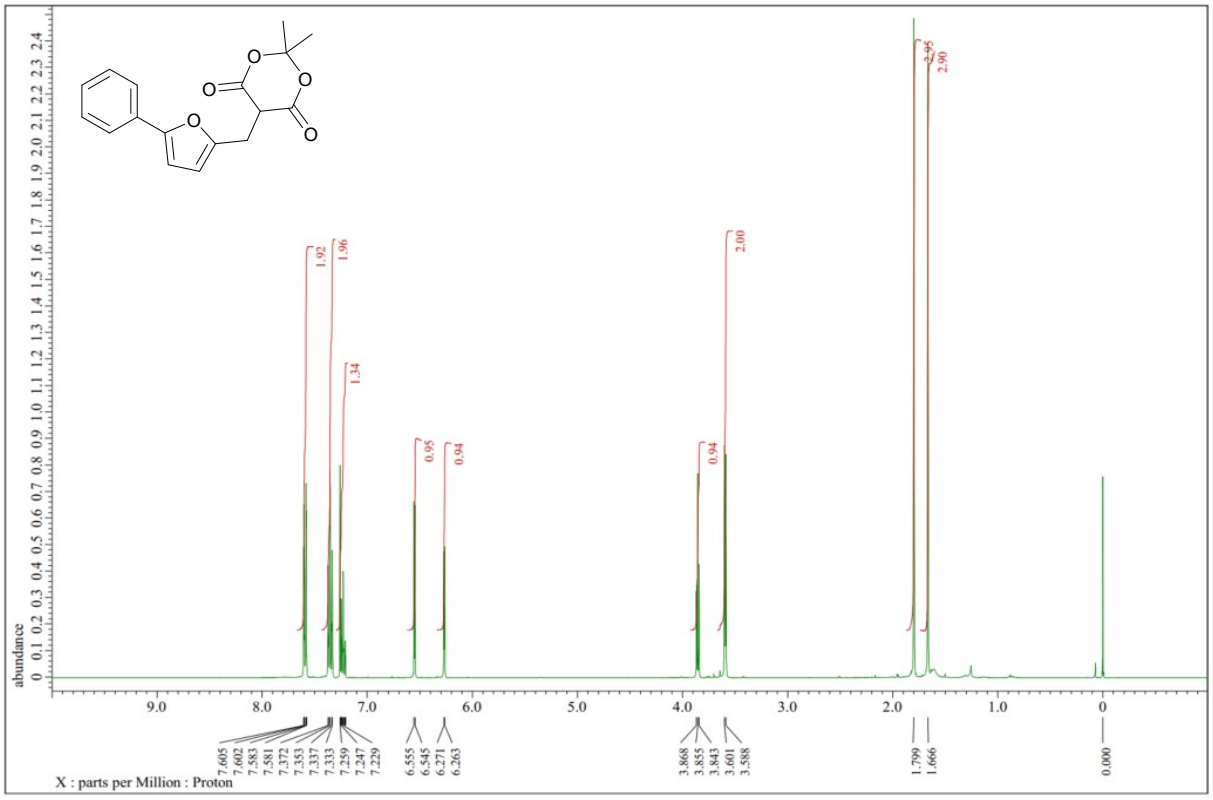


(^{13}C NMR, 100 MHz, $CDCl_3$)

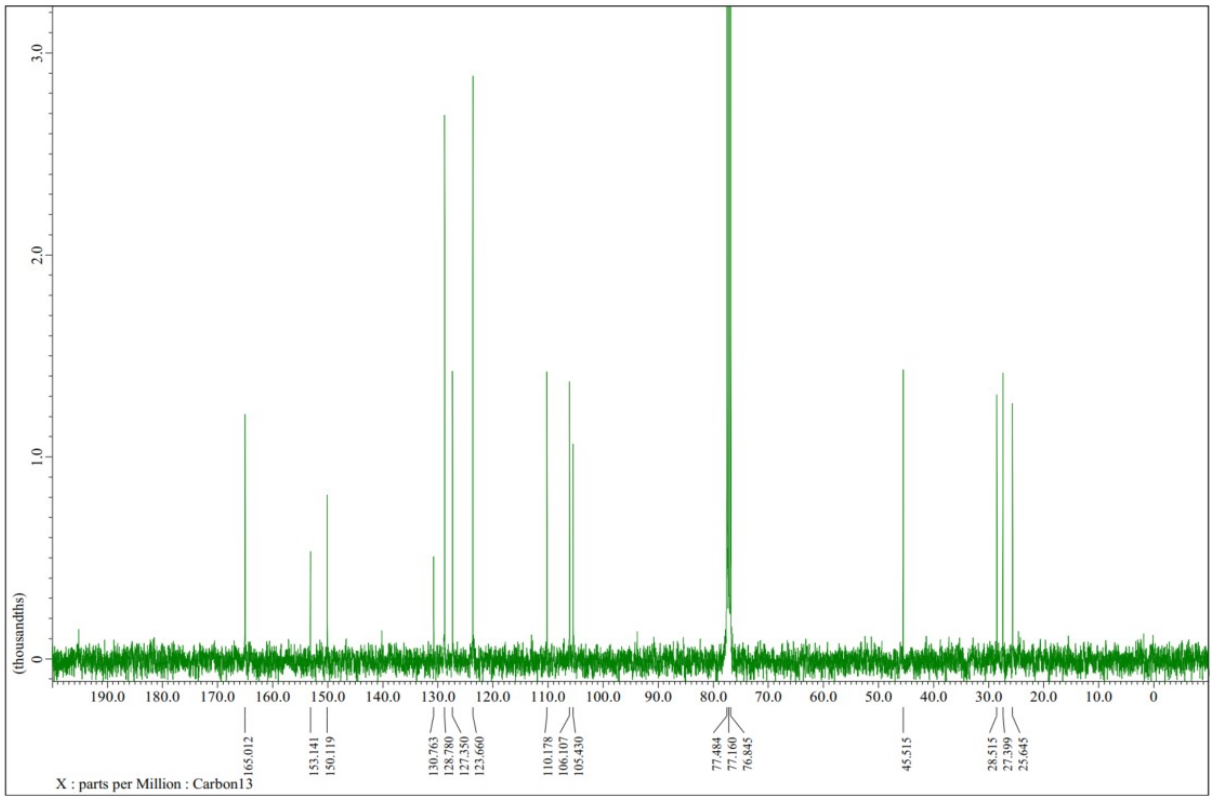


5-Phenyl-2-furanmethan1-2,2-dimethyl-1,3-dioxane-4,6-dione (2i)

(^{1}H NMR, 400 MHz, $CDCl_3$)

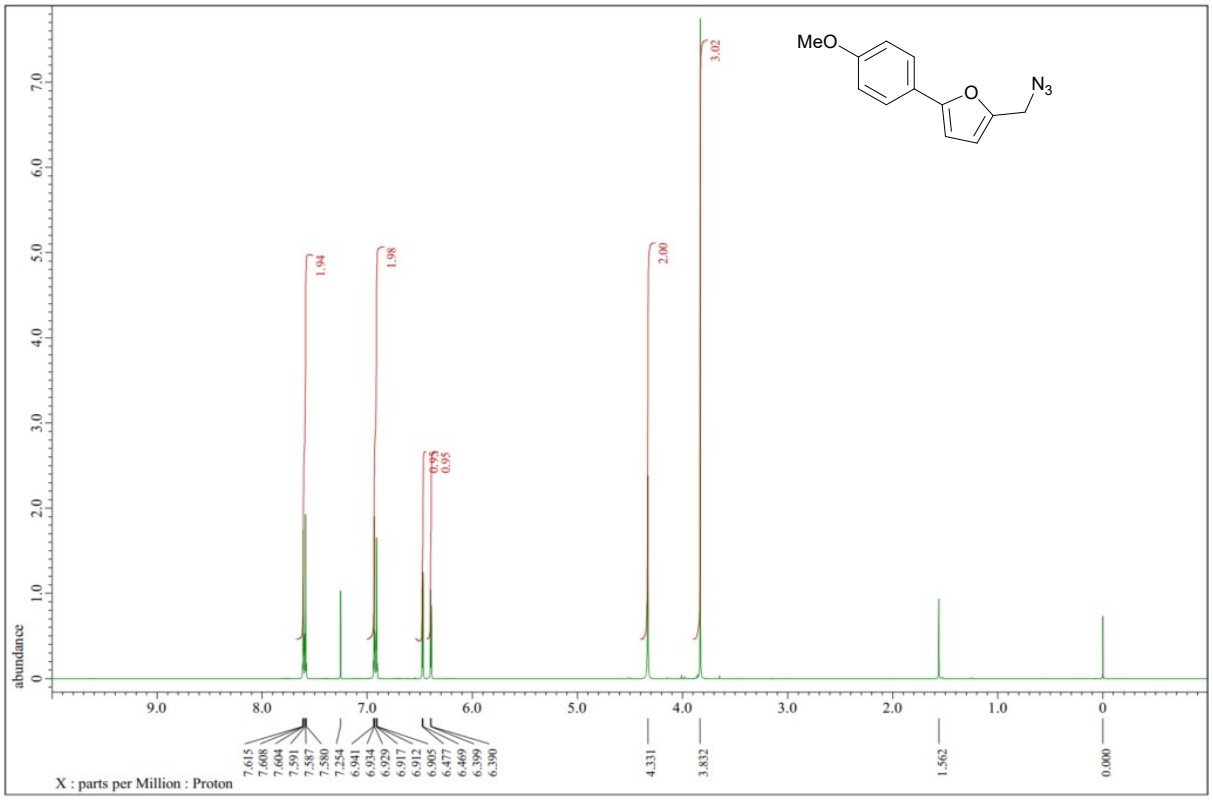


(^{13}C NMR, 100 MHz, $CDCl_3$)

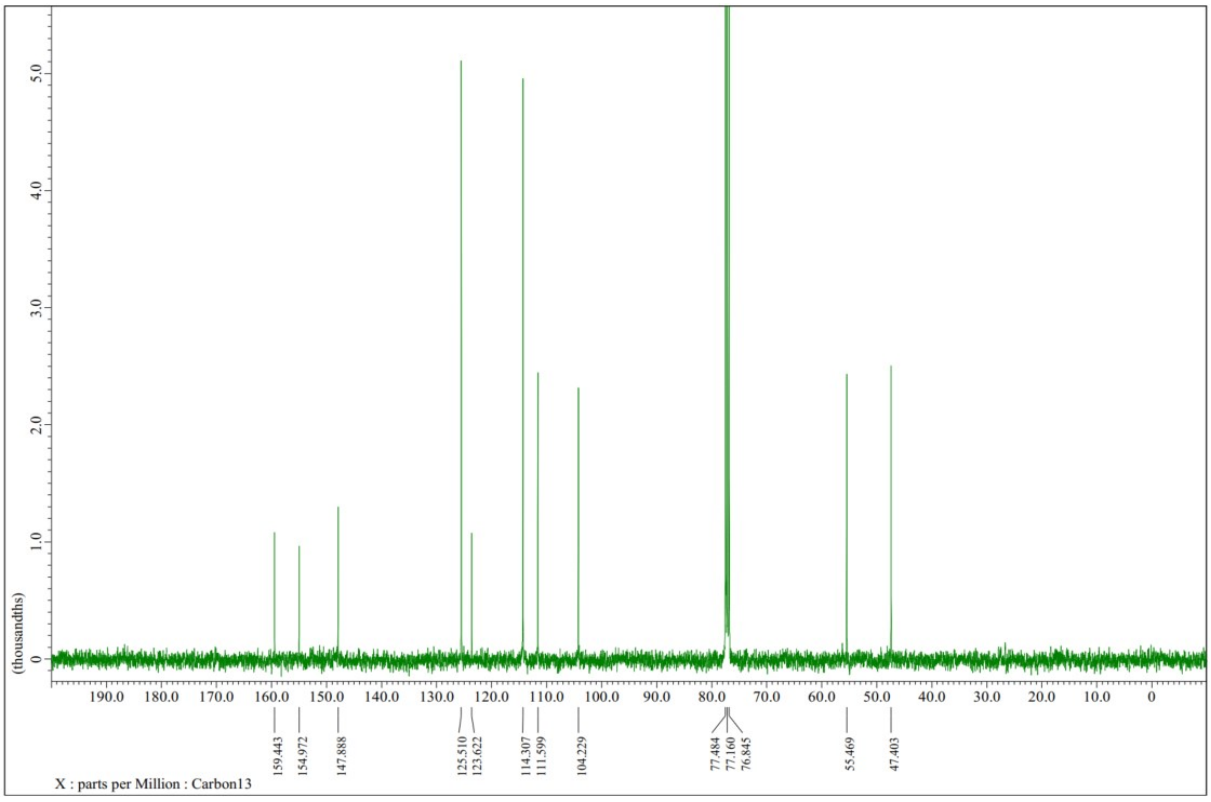


5-(4-Methoxyphenyl)-2-furanmethanazide (2j)

(^{1}H NMR, 400 MHz, $CDCl_3$)

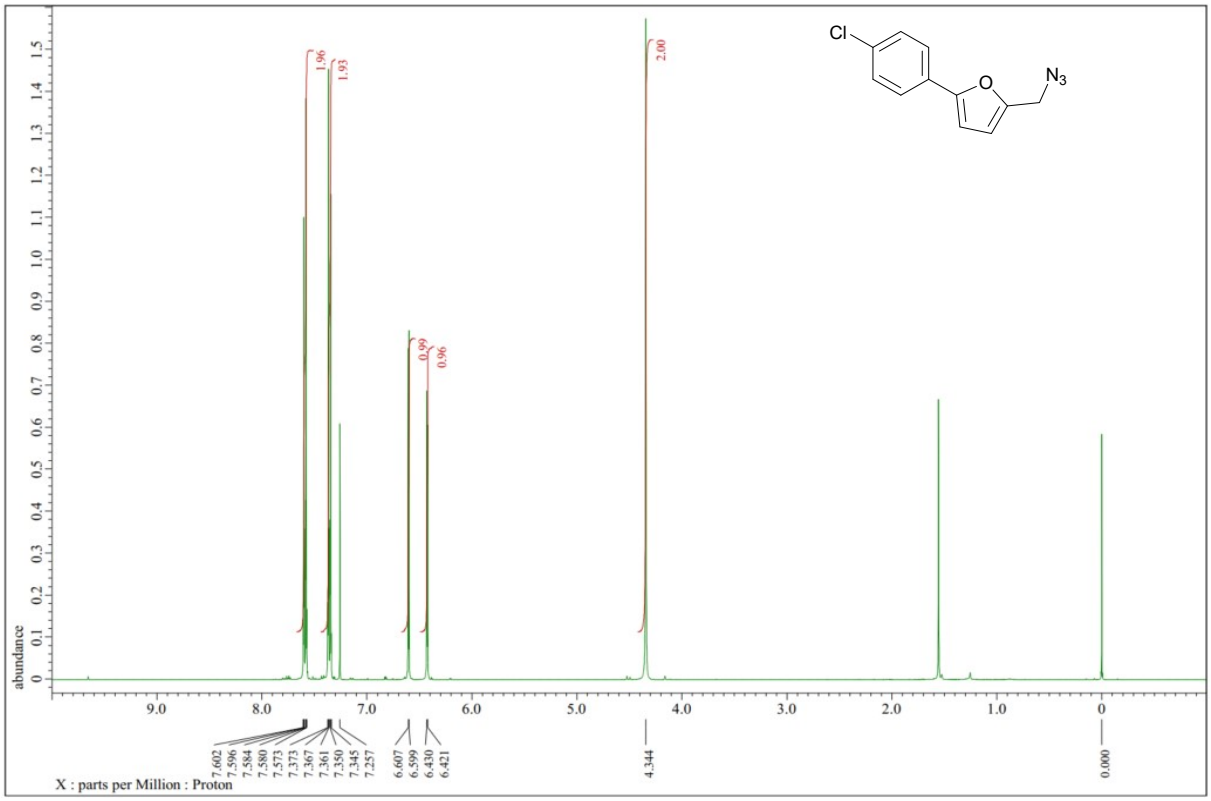


(^{13}C NMR, 100 MHz, $CDCl_3$)

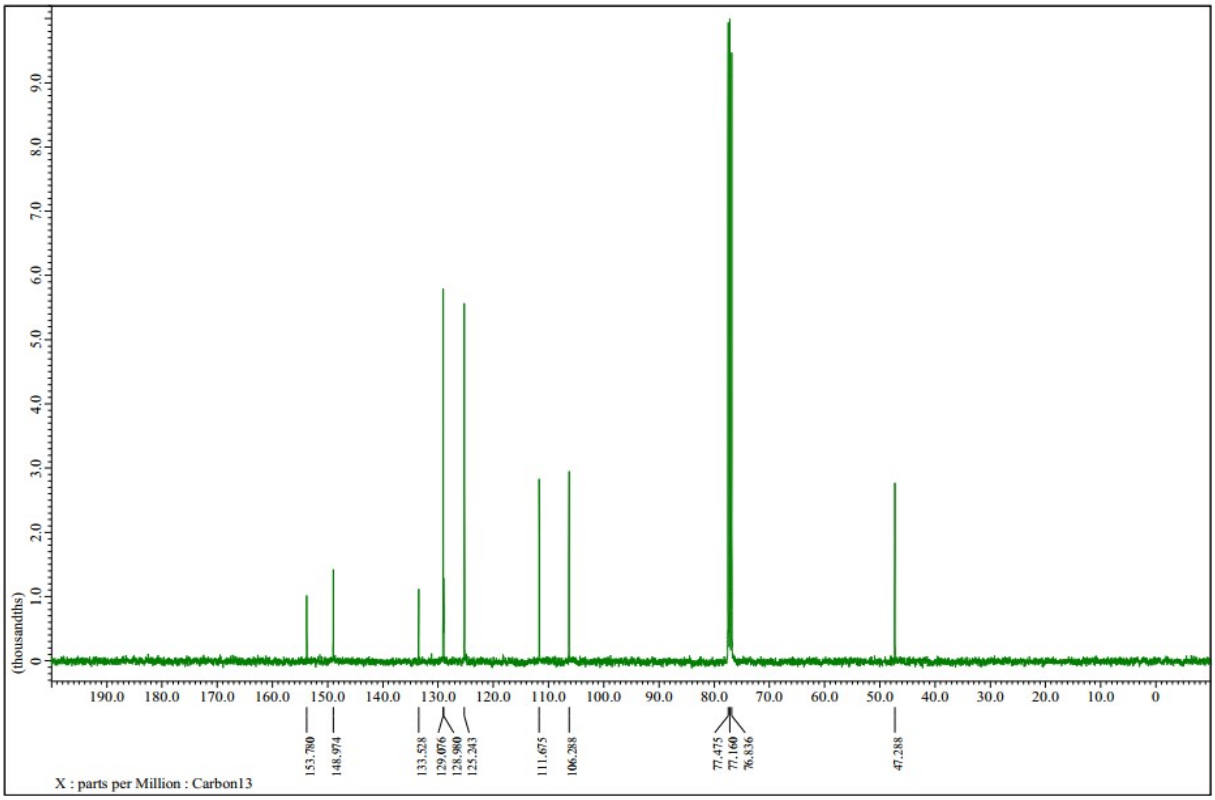


5-(4-Chlorophenyl)-2-furanmethanazide (2k)

(^{1}H NMR, 400 MHz, $CDCl_3$)

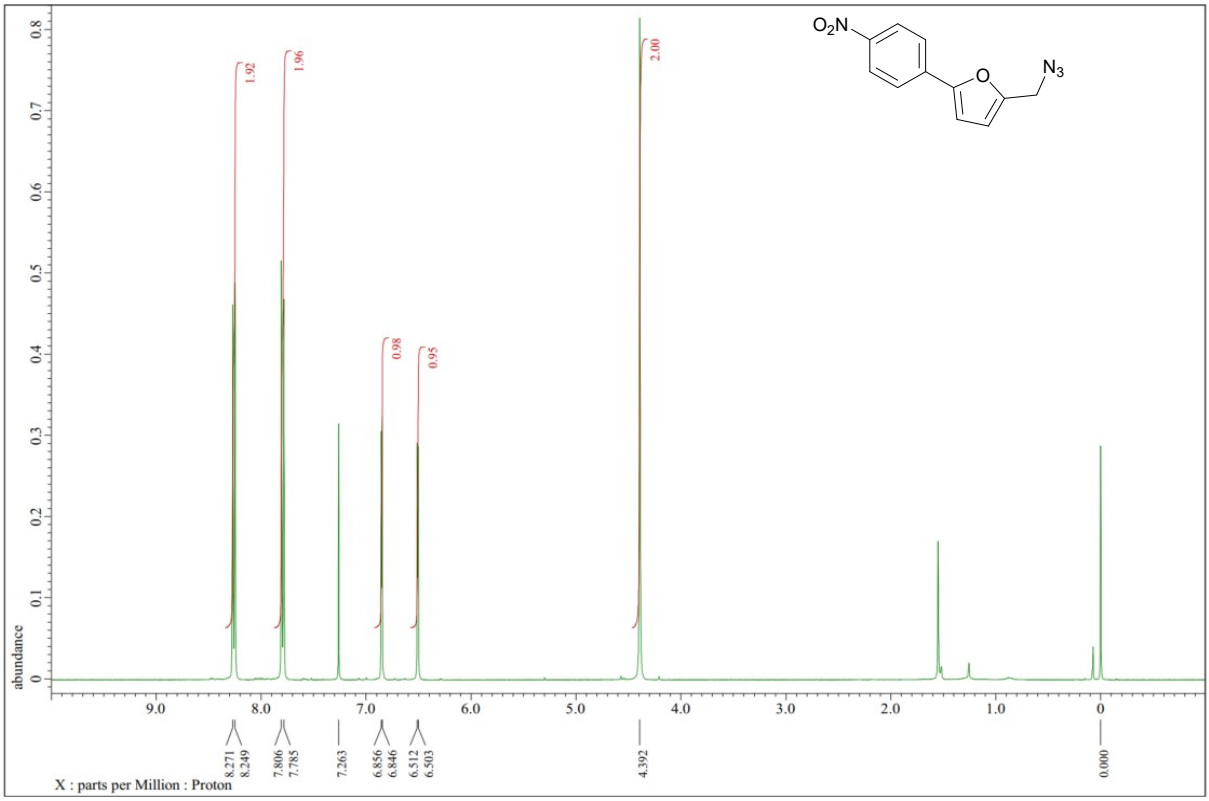


(^{13}C NMR, 100 MHz, $CDCl_3$)

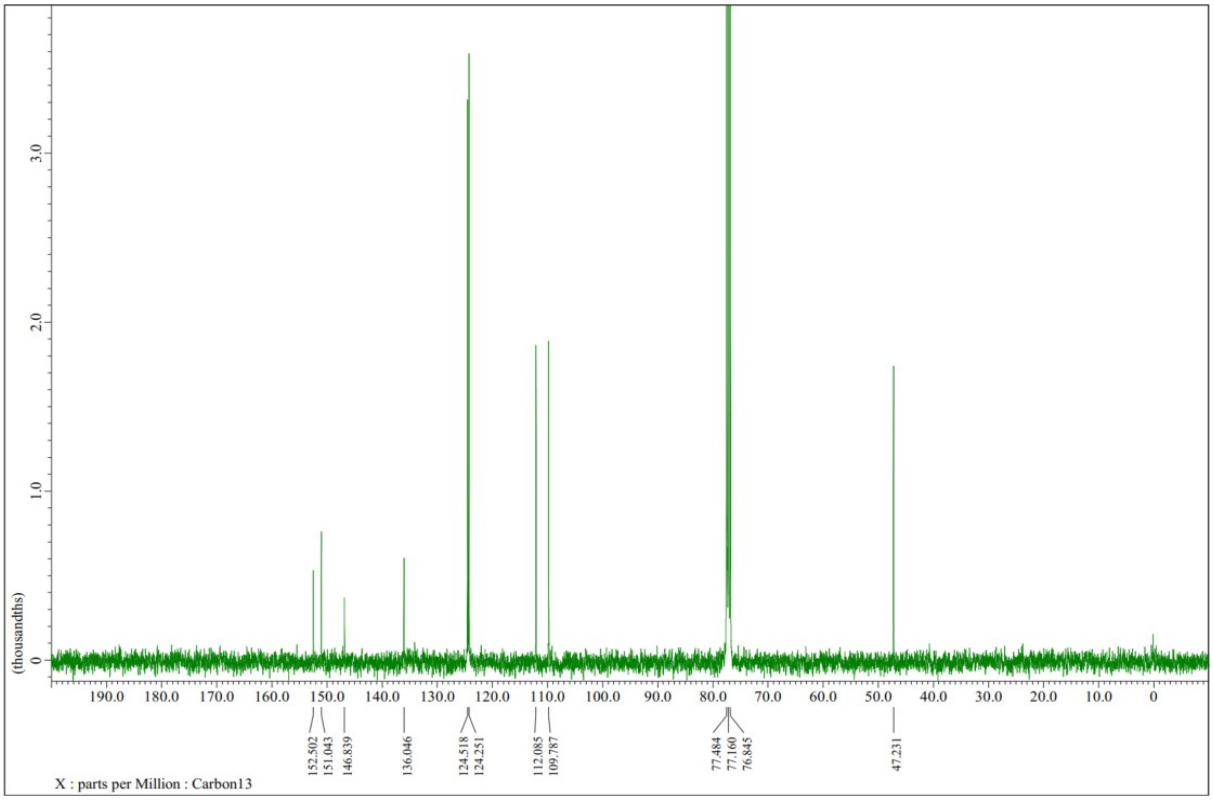


5-(4-Nitrophenyl)-2-furanmethanazide (2l)

(^{1}H NMR, 400 MHz, $CDCl_3$)

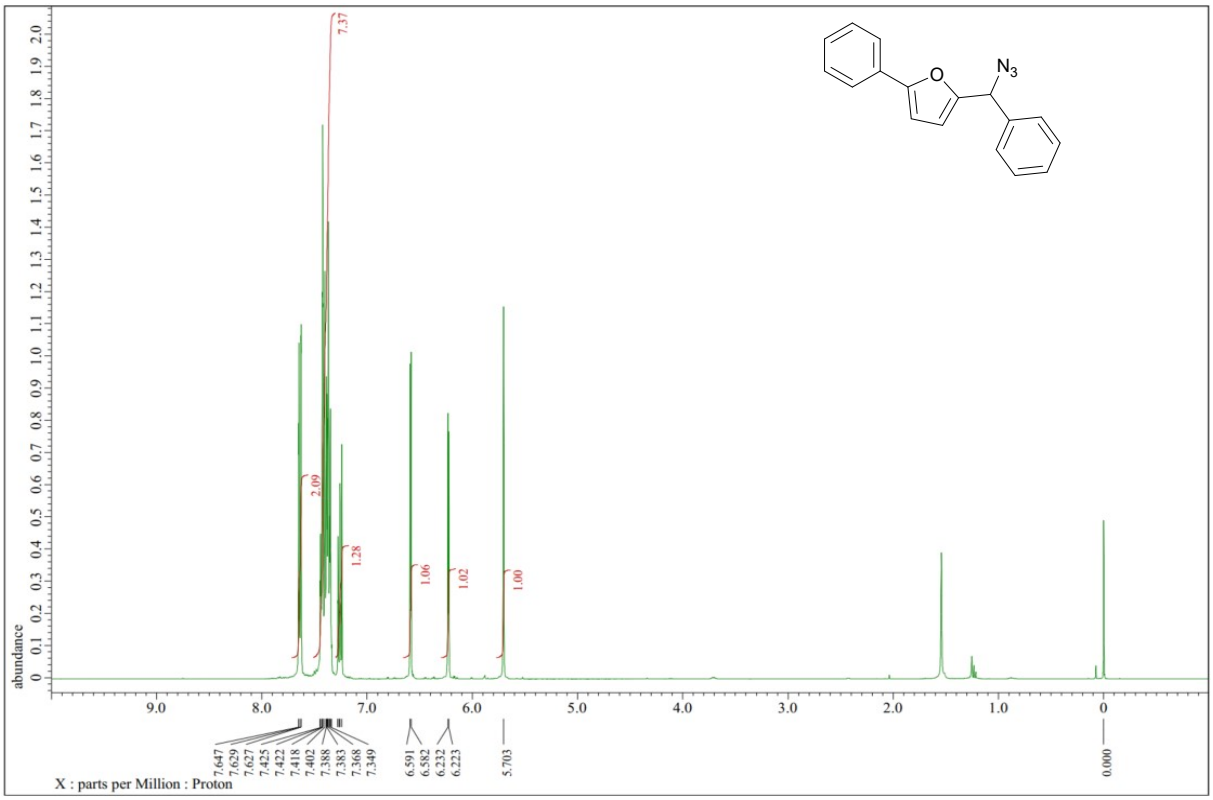


(^{13}C NMR, 100 MHz, $CDCl_3$)

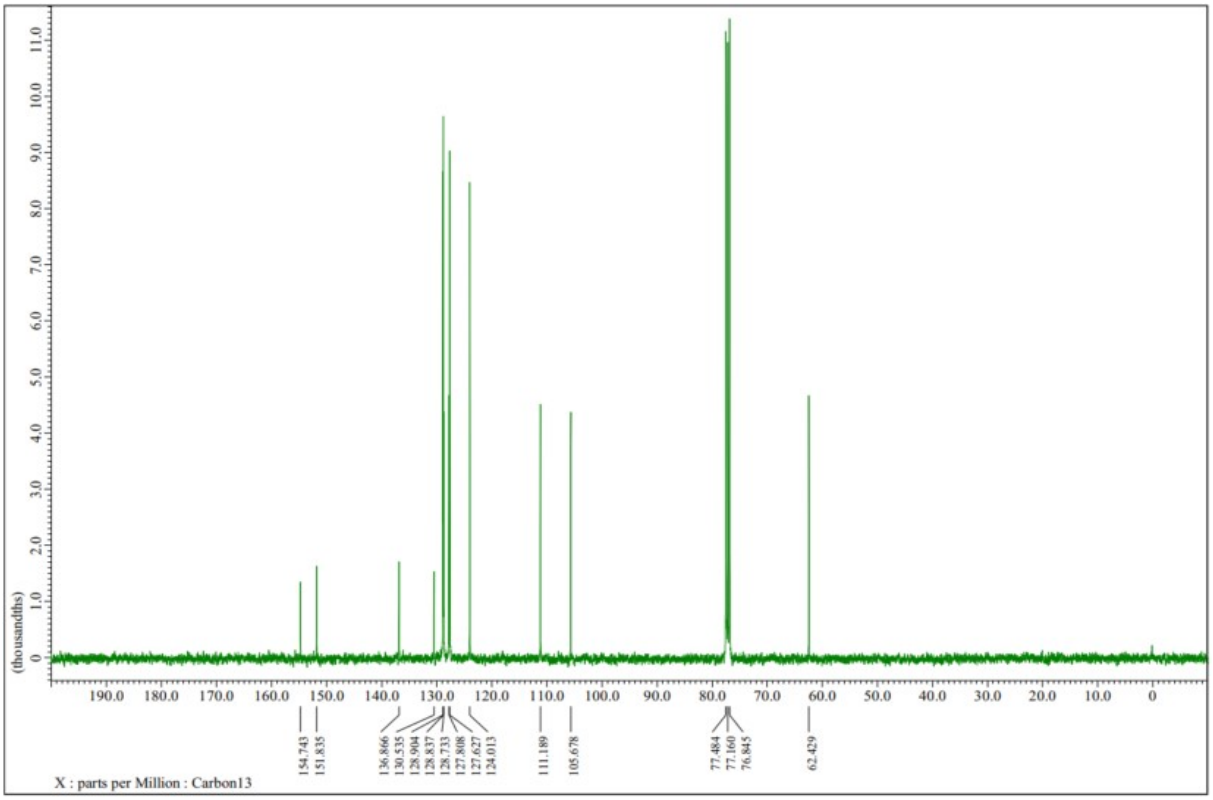


α,5-Diphenyl-2-furanmethanazide (2n)

(^{1}H NMR, 400 MHz, $CDCl_3$)

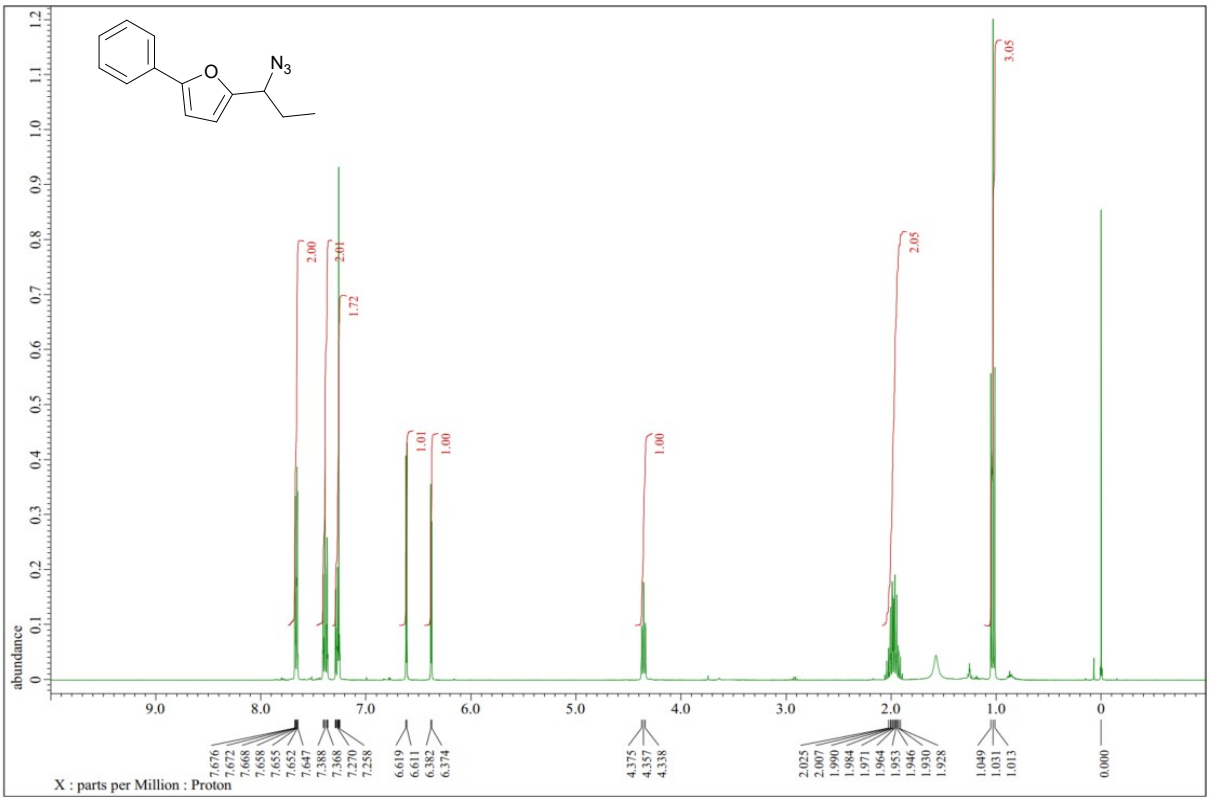


(^{13}C NMR, 100 MHz, $CDCl_3$)



α-Ethyl-5-phenyl-2-furanmethanazide (2o)

(^{1}H NMR, 400 MHz, $CDCl_3$)



(^{13}C NMR, 100 MHz, $CDCl_3$)