Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Catalytic cycloaddition of 2-hydroxy ketones with 1,1-dicyanoalkenes

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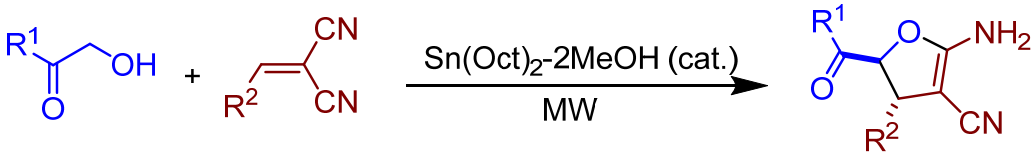


General

Analysis. IR spectra were recorded as thin film on a Nicolet iS5 spectrometer. All ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JMTC-400/54/SS (400 and 100 MHz, respectively) in deuteriochloroform ($CDCl_3$) containing 0.03% (w/v) of tetramethylsilane as internal standard. Mass spectra were recorded on a JEOL JMS-DS-303 spectrometer. Flash column chromatography was performed by YAMAZEN YFLC-AI-580 using Hi-Flash Silica gel 2L Hi-Flash Column 20-3-mL/min eluted by Hexane/EtOAc with gradation mode changing from 9/1 to 3/7. Purification of products by recycle GPC system was performed by JAPAN ANALYTICAL INDUSTRY CO., LTD. LC-908 eluted by $CHCl_3$.

Materials. Di-*n*-butyltin dimethoxide [$^{n}Bu_2Sn(OMe)_2$] was prepared according to the reported method using $^{n}Bu_2SnO$ and dimethyl carbonate (A. G. Davies, D. C. Kleinschmidt, P. R. Palan, S. C. Vasishtha, *J. Chem. Soc. (C)* **1971**, 3972-3975.). $Sn(OCOC_7H_{17})_2$ was purchased from Nakarai Tesque Co., Ltd. Substrates **1a**-**1e** were commercially available. All reactions were carried out under dry nitrogen.

Representative procedure

Representative procedure for the preparation of product 3a under microwave irradiation. (Table 1, entry 8)

Microwave assisted reactions were carried out using a focused microwave unit (CEM Discover microwave). The instrument consists of a continuous focused microwave power delivery system with operator selectable power output from 0-300 W. In all experiments, a constant power was applied to ensure reproducibility. Reactions were performed in glass vessels (10 mL) sealed with a septum. Pressure experiment is accomplished by a non-invasive sensor integrated into the cavity lid, which measures the deformation of the Teflon seal of the vessels (maximal 20 bar). Temperature controlled is achieved by means of an IR sensor and the indicated temperature corresponds to the maximal temperature reached during each experiment. The specified reaction time corresponds to the total irradiation time. Efficient cooling is accomplished by means of a pressurized air during the entire experiment.

A 5 mL of vial was dried by flame under reduced pressure. After nitrogen was filled, Tin catalyst $Sn(OCOC_7H_{17})_2$ (0.0405 g, 0.1 mmol), MeOH (0.0064 g, 0.2 mmol), MeCN (1.0 mL), α-hydroxy acetone (**1a**) (0.148g, 2 mmol) and benzalmalononitrile (**2a**) (0.154g, 1 mmol) were added. The vial was sealed with a septum and was set in microwave reactor. The mixture was stirred under microwave irradiation at 30W for 10 min. The reaction temperature was measured by an IR sensor. After the reaction, the mixture was quenched by H_2O (0.5 mL), diluted with ether (10 mL) and the layers were quickly separated. The aqueous phase was further extracted with ether (5 mL x3), and the combined extracts were dried over sodium sulfate and concentrated. The yield of **3a** and the *trans*:*cis* selectivity was determined by ^{1}H NMR (0.110 g, 96%, *trans*:*cis*= 67:33). The crude product was then purified by flash column chromatography eluted by Hexane/EtOAc with gradation mode changing from 9/1 to 5/5. The desired product was obtained at Hexane/EtOAc=7:3.

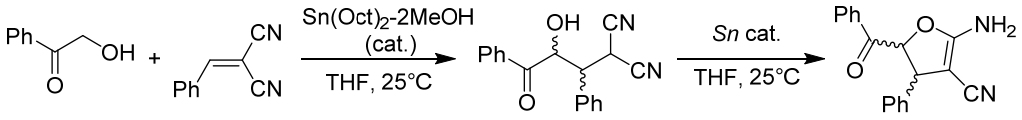
Reaction Profile

Mechanistic consideration about the formation of products

The reaction profile was shown in the case of α-hydroxy acetophenone (**1b**) with **2a** (Table S1 and Fig. S1). Each reaction was carried out independently under 1 atom at 25 °C.

The reaction took 360 minutes to attain a quantitative yield of cyclic product **3i**. Starting substrate **1b** was decreased gradually with the reaction time and was disappeared completely within 180 minutes. At the initial stage, a linear type of adduct **4b** was formed, and the yield was increased to 50% in 50 minutes. Whereas after 50 minutes, the yield of **4b** started to decrease. Hence, it is supposed that cyclic **3i** was formed through the linear adduct **4b**.

Table S1



1b **2a** **4b** **3i**

Time (min)	0 min	5	10	21	30	45	60	97	120	180	240	360
1b	100%	38	48	22	38	18	7	1	0	0	0	0
3i	0	19	14	28	17	32	48	81	84	95	97	100
4b	0	43	38	50	45	50	45	18	16	5	3	0

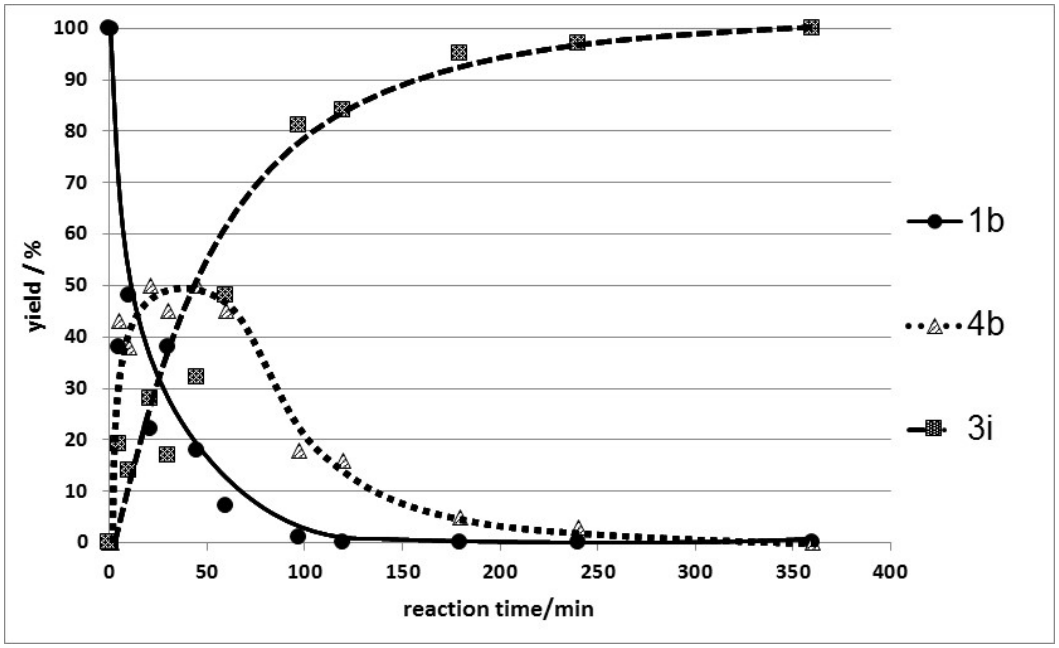


Fig. S1

Mechanistic consideration about the formation of diastereo isomers

The products obtained here include diastereo isomers. In the reaction of **1b** with **2a**, the yield of each diastereomer was determined (Table S2 and Fig. S2). It was cleared that the formation of *anti*-**4b** followed by *trans*-**3i** is faster than that of *syn*-**4b** to *cis*-**3i**.

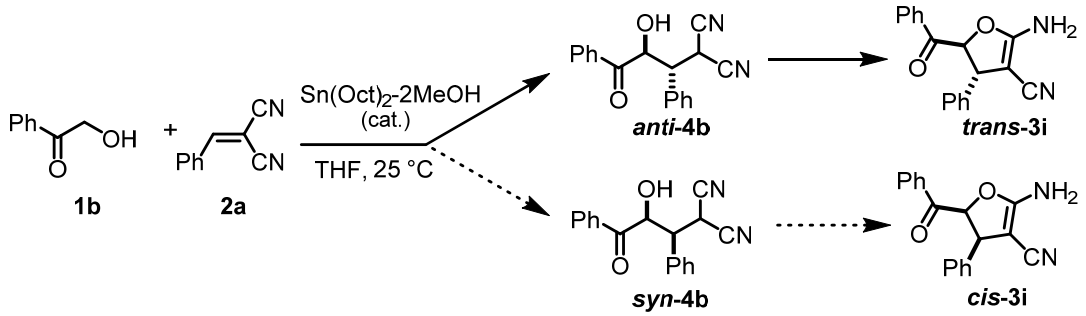


Table S2

Time (min)	0 min	5	10	21	30	45	60	97	120	180	240	360
anti-**4b**	0%	17%	12%	26%	15%	29%	42%	67%	67%	69%	71%	72%
syn-**4b**	0	2	2	2	2	3	6	14	17	26	26	28
trans-**3i**	0	21	21	23	25	25	19	2	2	0	0	0
cis-**3i**	0	22	17	27	20	25	26	16	14	5	3	0

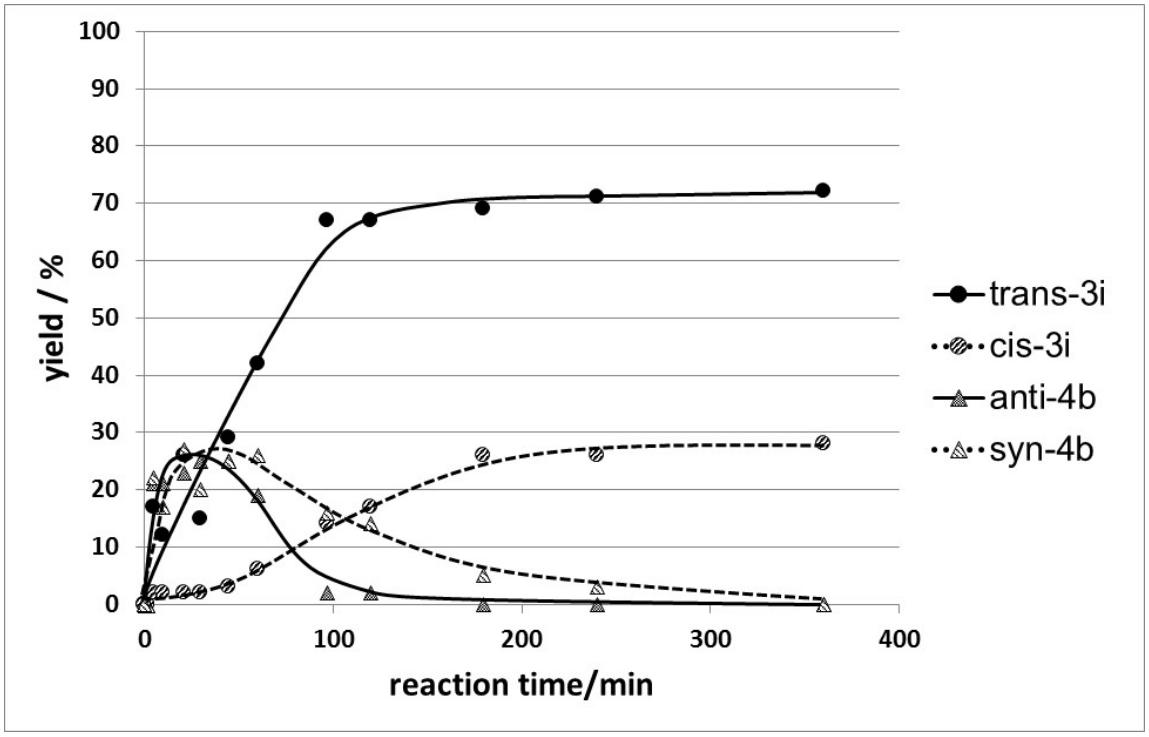


Fig. S2

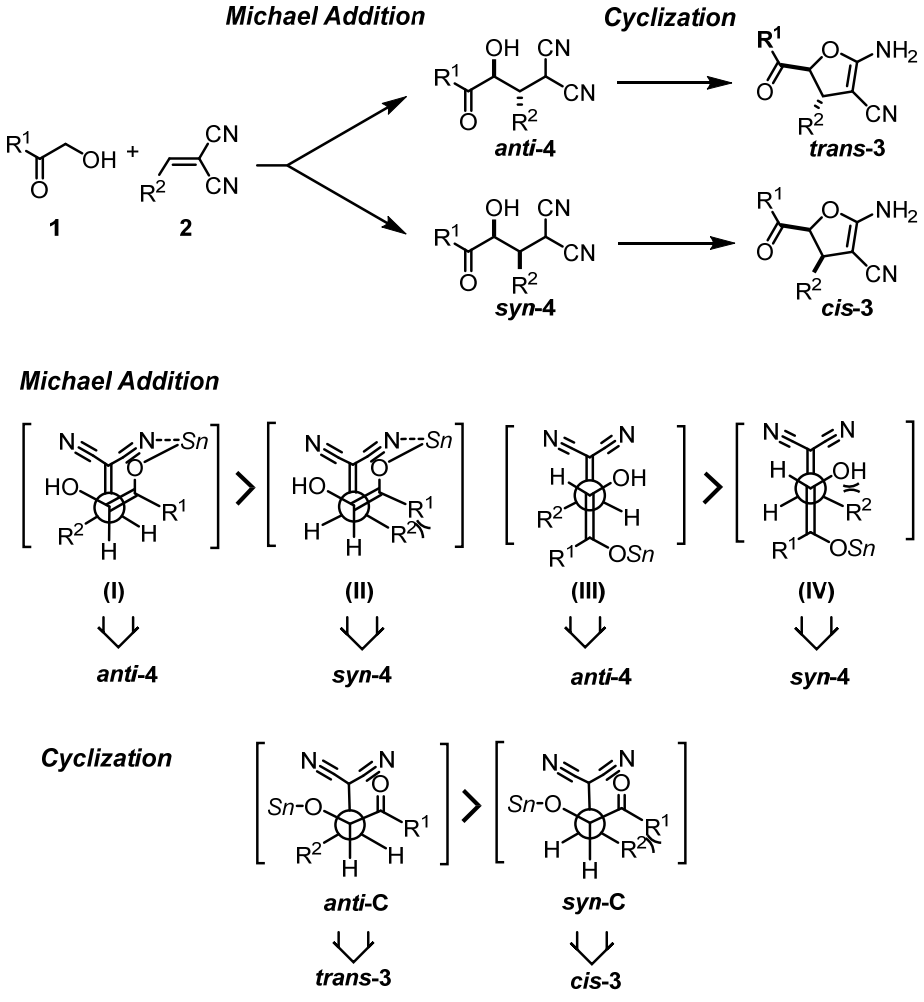
The *trans*-selectivity of **3** is dependent upon the substituent R^1 of α-hydroxy ketones **2**. Namely, a bulky R^1 substituent such as *t*-Bu group underwent highly *trans*-selective reactions (Table 2 in text, entries 12-19). *trans*-**3** was formed *via anti*-**4** in a stereospecific manner. The *anti*-selectivity of **4** was determined at the step of C-C bond formation (Michael addition) between tin *Z*-enolate **A'** and dicyanoalkene **2**.

A plausible transition state of Michael addition is the eight-membered cyclic transition state (text ref 15,16)

(Scheme S1). Transition structure (**I**) leading to *anti*-adducts **4** is favored than TS-(**II**) in consideration of steric repulsion between R^1 and R^2. The effect was significant especially for the case of large R^1 such as *t*-Bu group. Another possible transition state leading to *anti*-**4a** is acyclic TS-(**III**) which is favored than (**IV**) because the steric repulsion between OH and R^2 groups is an important factor.[1] However, this model could not be considered because the large R^1 effect is not explainable.

After the Michael addition, in the cyclization step, the course from *anti*-**C** to *trans*-**3** is also favored than the *syn*-**C** to *cis*-**3** in consideration of steric repulsion between R^1 and R^2.

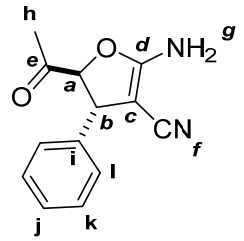
(1) (a) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.*, *102*, **1980**, 7107-7109. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles*, *18*, **1982**, 357-386. (c) Ysmamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *40*, 2239-2246.



Scheme S1

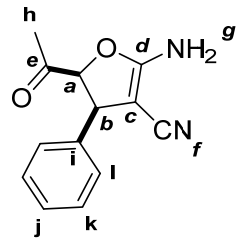
Analytical data for Products including major and minor ones.
Assignment of ^{1}H and ^{13}C was included.

(4S*, 5S*)-5-acetyl-2-amino-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3a**)



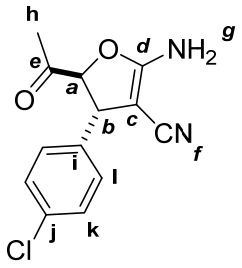
Light brown solid
Mp.81-85 °C
IR (KBr) 3441 cm^{-1} (NH_2), 2188 cm^{-1} (CN), 1662 cm^{-1} (C=O)
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.23 (3H, s, h), 4.31 (1H, d, J = 5.3 Hz, b), 4.72 (1H, d, J = 5.3 Hz, a), 5.43 (2H, s, g), 7.26-7.36 (5H, m).
^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.0 (h), 50.4 (b), 55.9 (c), 92.0 (a), 118.1 (f), 127.0 (l), 127.9 (j), 129.0 (k), 140.8 (i), 166.9 (d), 204.4 (e).
MS (CI) m/z 229(M^{+}＋1, 100)
HRMS (CI) m/z calcd. for $C_{13}H_{13}N_2O_2$: 229.0977, found: 229.0978.

(4R*,5S*)-5-acetyl-2-amino-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3a**)



Pale yellow solid
Mp.70 °C
IR (KBr) 3418 cm^{-1} (NH_2), 2190 cm^{-1} (CN), 1660 cm^{-1} (C=O)
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.70 (3H, s, h), 4.60 (1H, d, J = 9.7 Hz, b), 5.07 (2H, s, g), 5.25 (1H, d, J = 9.7 Hz, a), 7.16 (2H, d, J = 6.8 Hz, l), 7.28-7.31 (3H, m).
As this minor product was isolated as a small amount, no clear ^{13}C NMR spectra could be obtained.
MS (CI) m/z 229(M^{+}＋1, 100).
HRMS (CI) m/z calcd. for $C_{13}H_{13}N_2O_2$: 229.0977, found: 229.0979.

(4S*, 5S*)-5-acetyl-2-amino-4-(4-chlorophenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3b**)



Pale yellow wax

Rf= 0.33 (in hexane:ethyl acetate = 4:6)

IR (neat) 3343 cm^{-1} (NH_2), 2190 cm^{-1} (CN), 1663cm^{-1} (C=O)

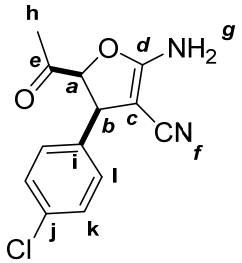
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.26 (3H, s, h), 4.33 (1H, d, J = 5.3 Hz, b), 4.66 (1H, d, J = 5.3 Hz, a), 5.46 (2H, s, g), 7.24 (2H, d, J = 8.2 Hz, k), 7.34 (2H, d, J = 8.2 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.1 (h), 49.9 (b), 55.9 (c), 91.9 (a), 117.7 (f), 128.5 (k), 129.2 (l), 133.7 (j), 139.4 (i), 166.9 (d), 204.3 (e).

MS (CI) m/z 263(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{13}H_{12}ClN_2O_2$: 263.0587, found: 263.0580.

(4R*,5S*)-5-acetyl-2-amino-4-(4-chlorophenyl)-4,5-dihydrofuran-3-carbonitrile (*cis*-**3b**)



Pale yellow solid

Mp.194°C

IR (KBr) 3420 cm^{-1} (NH_2), 2188 cm^{-1} (CN), 1687cm^{-1} (C=O)

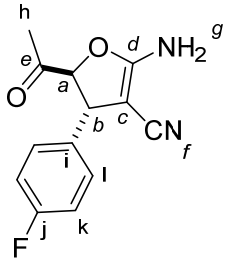
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.76 (3H, s, h), 4.57 (1H, d, J = 9.7 Hz, b), 4.95 (2H, s, g), 5.23 (1H, d, J = 9.7 Hz, a), 7.10 (2H, d, J = 8.2 Hz, k), 7.30 (2H, d, J = 8.2 Hz, l).

As this minor product was isolated as a small amount, clear ^{13}C NMR spectra could not be obtained.

MS (CI) m/z 263(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{13}H_{12}ClN_2O_2$: 263.0587, found: 263.0586.

(4S*, 5S*)-5-acetyl-2-amino-4-(4-fluorophenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3c**)



Pale yellow wax

Rf= 0.66 (in hexane/ethyl acetate = 2:8)

IR (neat) 3347 cm^{-1} (NH_2), 2190 cm^{-1} (CN), 1665 cm^{-1} (C=O)

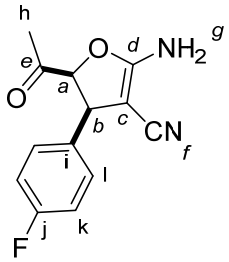
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.25 (3H, s, h), 4.34 (1H, d, J = 5.3 Hz, b), 4.67 (1H, d, J = 5.3 Hz, a), 5.40 (2H, s, g), 7.05 (2H, t, J = 8.7 Hz, k), 7.27 (2H, dd, J = 8.7, 5.3 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.0 (m), 49.8 (b), 56.2 (c), 92.1 (a), 116.0 (d, J = 22.1 Hz, k), 117.8 (f), 128.8 (d, J = 8.2 Hz, l), 136.6 (d, J = 3.3 Hz, i), 162.4 (d, J = 246.6 Hz, j), 166.8 (d), 204.4 (e).

MS (CI) m/z 247 ($M^+ + 1$, 100).

HRMS (CI) m/z calcd. for $C_{13}H_{12}FN_2O_2$: 247.0883, found: 247.0881.

(4R*,5S*)-5-acetyl-2-amino-4-(4-fluorophenyl)-4,5-dihydrofuran-3-carbonitrile (*cis*-**3c**)



white solid

Mp. 226-229°C

IR (KBr) 3414 cm^{-1} (NH_2), 2197 cm^{-1} (CN), 1660 cm^{-1} (C=O)

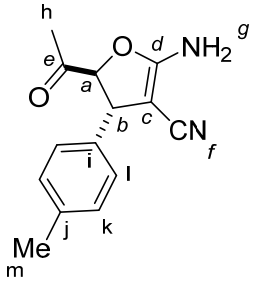
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.74 (3H, s, h), 4.59 (1H, d, J = 9.7 Hz, b), 4.98 (2H, s, g), 5.22 (1H, d, J = 9.7 Hz, a), 7.02 (2H, t, J = 8.7 Hz, k), 7.14 (2H, dd, J = 8.7, 5.3 Hz, l).

As this minor product was isolated as a small amount, clear ^{13}C NMR spectra could not be obtained.

MS (CI) m/z 247($M^+ + 1$, 100).

HRMS (CI) m/z calcd. for $C_{13}H_{12}FN_2O_2$: 247.0883, found: 247.0882.

(4S*, 5S*)-5-acetyl-2-amino-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3d**)



Pale yellow wax

Rf= 0.75 (in hexane/ethyl acetate = 2:8).

IR (neat) 3346 cm^{-1} (NH_2), 2189 cm^{-1} (CN), 1663 cm^{-1} (C=O).

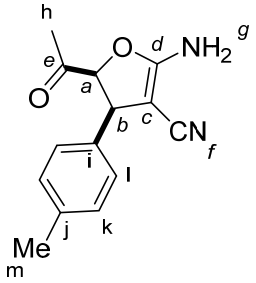
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.23 (3H, s, h), 2.33 (3H, s, m), 4.28 (1H, d, J = 5.6 Hz, b), 4.70 (1H, d, J = 5.6 Hz, a), 5.33 (2H, s, g), 7.10-7.25 (4H, m, Ar).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.0 (m), 26.0 (h), 50.3 (b), 56.5 (c), 92.3 (a), 117.9 (f), 127.0 (l), 129.7 (k), 137.6 (j), 137.8 (i), 166.8 (d), 204.3 (e).

MS (CI) m/z 243(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{14}H_{15}N_2O_2$: 243.1134, found: 243.1137.

(4R*,5S*)-5-acetyl-2-amino-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (*cis*-**3d**)



Pale yellow solid

Mp. 226-228°C

IR (KBr) 3422 cm^{-1} (NH_2), 2188 cm^{-1} (CN), 1683 cm^{-1} (C=O).

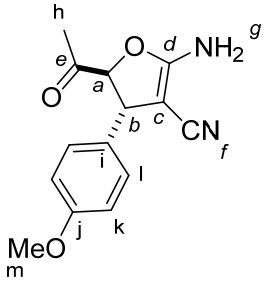
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.72 (3H, s, h), 2.31 (3H, s, m), 4.57 (1H, d, J = 9.7 Hz, b), 4.87 (2H, s, g), 5.23 (1H, d, J = 9.7 Hz, a), 7.03 (2H, d, J = 8.2 Hz, k), 7.11 (2H, d, J = 8.2 Hz, l).

^{13}C-NMR (ACETONE-D_6, 100MHz) δ 21.0 (m), 27.7 (h), 50.7 (b), 57.0 (c), 89.9 (a), 118.3 (f), 129.3 (l), 129.9 (k), 136.5 (j), 138.2 (i), 168.5 (d), 202.8 (e).

MS (CI) m/z 243(M^+＋1, 100)

HRMS (CI) m/z calcd. for $C_{14}H_{15}N_2O_2$: 243.1134, found: 243.1134.

(4S*, 5S*)-5-acetyl-2-amino-4-(4-methoxyphenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3e**)



Pale yellow wax

Rf=0.24 (in hexane:ethyl acetate = 4:6)

IR (neat) 3347 cm^{-1} (NH_2), 2188 cm^{-1} (CN), 1667 cm^{-1} (C=O).

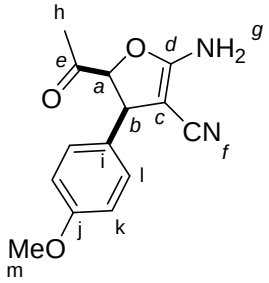
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.25 (3H, s, h), 3.81 (3H, s, m), 4.29 (1H, d, J = 5.6 Hz, b), 4.70 (1H, d, J = 5.6 Hz, a), 5.12 (2H, s, g), 6.90 (2H, d, J = 8.7 Hz, k), 7.21 (2H, d, J = 8.7 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.0 (h), 50.0 (b), 55.3 (m), 57.2 (c), 92.5 (a), 114.5 (k), 117.7 (f), 128.2 (l), 132.8 (i), 159.3 (j), 166.4 (d), 204.2 (e).

MS (CI,) m/z 259 (M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{13}H_{15}N_2O_3$: 259.1083, found: 259.1079.

(4R*,5S*)-5-acetyl-2-amino-4-(4-methoxyphenyl)-4,5-dihydrofuran-3-carbonitrile (*cis*-**3e**)



Pale orange solid

Mp.145°C

IR (KBr) 3327 cm^{-1} (NH_2), 2186 cm^{-1} (CN), 1676 cm^{-1} (C=O).

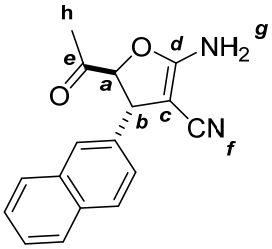
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.72 (3H, s, h), 3.78 (3H, s, m), 4.57 (1H, d, J = 9.7 Hz, b), 5.02 (2H, s, g), 5.21 (1H, d, J = 9.7 Hz, a), 6.84 (2H, d, J = 8.7 Hz, k), 7.08 (2H, d, J = 8.7 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.6 (h), 49.7 (b), 55.2 (m), 58.0 (c), 89.6 (a), 114.2 (k), 117.6 (f), 128.4 (i), 129.4 (l), 159.5 (j), 166.7 (d), 203.1 (e).

MS (CI) m/z 259 (M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{13}H_{15}N_2O_3$: 259.1083, found: 259.1082.

(4S*, 5S*)-5-acetyl-2-amino-4-(naphthalen-2-yl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3f**)



Pale orange solid

Mp.55°C

IR (KBr) 3341 cm^{-1} (NH_2), 2188 cm^{-1} (CN), 1661 cm^{-1} (C=O).

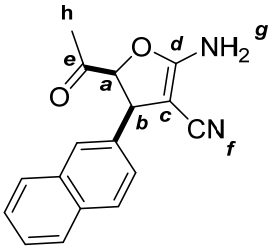
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.20 (3H, s, h), 4.46 (1H, d, J = 5.3 Hz, b), 4.74 (1H, d, J = 5.3 Hz, a), 5.48 (2H, s, g), 7.37-7.79 (7H, m).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.0 (h), 50.7 (b), 56.1 (c), 91.9 (a), 118.0 (f), 124.7, 126.1, 126.1, 126.4, 127.6, 127.9, 129.2, 132.9, 133.3, 138.1, 167.0 (d), 204.4 (e).

MS (CI) m/z 279(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{17}H_{15}N_2O_2$: 279.1134, found: 279.1134.

(4R*,5S*)-5-acetyl-2-amino-4-(naphthalen-2-yl)-4,5-dihydrofuran-3-carbonitrile (*cis*-**3f**)



Yellow solid

Mp.165-170°C

IR (KBr) 3424 cm^{-1} (NH_2), 2187 cm^{-1} (CN), 1676 cm^{-1} (C=O)

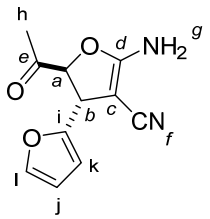
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.69 (3H, s, h), 4.75 (1H, d, J = 9.7 Hz, b), 5.10 (2H, s, g), 5.31 (1H, d, J = 9.7 Hz, a), 7.23-7.80 (7H, m).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.6 (h), 50.6 (b), 58.2 (c), 89.7 (a), 117.6 (f), 125.8, 126.4, 126.4, 127.5, 127.7, 128.0, 128.8, 133.2, 134.2, 142.6, 166.9 (d), 202.7 (e).

MS (CI) m/z 279 (M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{17}H_{15}N_2O_2$: 279.1134, found: 279.1136.

(4S*, 5S*)-2'-acetyl-5'-amino-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile (*trans*-**3g**)



Pale yellow solid

Mp.123 °C

IR (KBr) 3446 cm^{-1} (NH_2), 2189 cm^{-1} (CN), 1657 cm^{-1} (C=O).

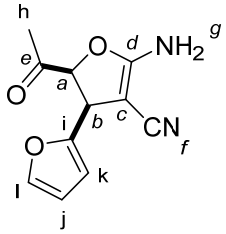
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.28 (3H, s, h), 4.43 (1H, d, J = 4.8 Hz, b), 4.93 (1H, d, J = 4.8 Hz, a), 5.34 (2H, s, g), 6.30 (1H, dd, J = 3.4, 0.7 Hz, k), 6.34 (1H, dd, J = 3.4, 1.9 Hz, j), 7.40 (1H, dd, J = 1.9, 0.7 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.9 (h), 43.9 (b), 54.1 (c), 88.8 (a), 107.2 (k), 110.6 (j), 117.5 (f), 142.8 (l), 152.8 (i), 166.9 (d), 203.5 (e).

MS (CI) m/z 219 (M^+ + 1, 100).

HRMS (CI) m/z calcd. for $C_{11}H_{11}N_2O_3$: 219.0770, found: 229.0771.

(4R*,5S*)-2'-acetyl-5'-amino-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile (*cis*-**3g**)



White solid

Mp.201-203°C

IR (KBr) 3393 cm^{-1} (NH_2), 2202 cm^{-1} (CN), 1673 cm^{-1} (C=O).

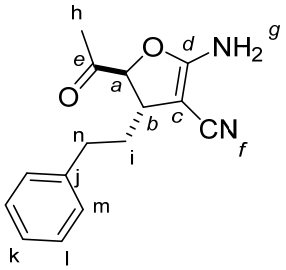
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.95 (3H, s, h), 4.72 (1H, d, J = 9.7 Hz, b), 4.89 (2H, s, g), 5.12 (1H, d, J = 9.7 Hz, a), 6.26 (1H, dd, J = 3.4, 0.7 Hz, k), 6.32 (1H, dd, J = 3.4, 1.9 Hz, j), 7.33 (1H, dd, J = 1.9, 0.7 Hz, l).

As this minor product was isolated as a small amount, clear ^{13}C NMR spectra could not be obtained.

MS (CI) m/z 219(M^+ + 1, 100).

HRMS (CI) m/z calcd. for $C_{11}H_{11}N_2O_3$: 219.0770, found: 229.0771.

(4S*, 5S*)-5-acetyl-2-amino-4-phenethyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3h**)



Pale yellow liquid

Rf= 0.49 (in hexane:ethyl acetate = 4:6)

IR (neat) 3342 cm^{-1} (NH_2), 2185 cm^{-1} (CN), 1663 cm^{-1} (C=O)

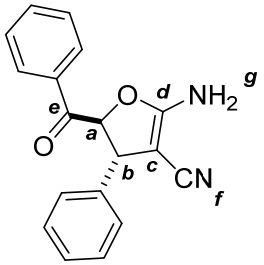
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.86-2.06 (2H, m, i), 2.20 (3H, s, h), 2.75 (2H, t, J = 8.0 Hz, n), 3.16-3.21 (1H, m, b), 4.55 (1H, d, J = 4.8 Hz, a), 4.98 (2H, s, g), 7.15-7.35 (5H, m, Ph).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7 (h), 32.2 (i), 37.4 (n), 45.0 (b), 56.3 (c), 89.9 (a), 118.2 (f), 126.1 (k), 128.4 (m or l), 128.5 (m or l), 140.8 (j), 166.3 (d), 205.4 (e).

MS (EI) m/z 256 (M^+, 18), 109(100), 91(55), 43(41).

HRMS (EI) m/z calcd. for $C_{13}H_{16}N_2O_2$: 256.1212, found: 256.1213.

(4S*, 5S*)-2-amino-5-benzoyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3i**)



Light brown solid

Mp.145-150 °C

IR (KBr) 3432 cm^{-1} (NH_2), 2191 cm^{-1} (CN), 1670 cm^{-1} (C=O)

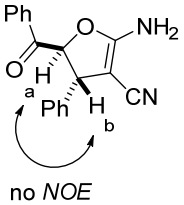
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.33 (1H, d, J = 4.8 Hz, b), 5.46 (2H, s, g), 5.68 (1H, d, J = 4.8 Hz, a), 7.25 (2H, d, J = 7.0 Hz), 7.32-7.36 (3H, m), 7.42 (2H, t, J = 7.7 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.77 (2H, d, J = 7.7 Hz).

^{13}C-NMR ($CDCl_3$, 100MHz) δ 50.9 (b), 56.9 (c), 89.0 (a), 118.1 (f), 127.4, 128.1 , 128.8 , 128.9, 129.1, 133.1, 134.2, 140.9, 167.2 (d), 193.0 (e).

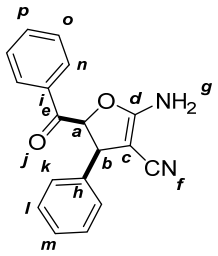
MS (CI) m/z 291(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{18}H_{15}N_2O_2$: 291.1134, found: 291.1130.

NOESY



(4R*,5S*)-2-amino-5-benzoyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3i**)



Pale yellow solid

Mp.165-170°C

IR (KBr) 3420 cm^{-1} (CN), 2187 cm^{-1} (CN), 1661 cm^{-1} (C=O)

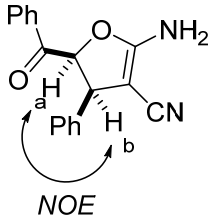
^{1}H-NMR ($CDCl_3$, 400MHz) δ 4.72 (1H, d, J = 9.7 Hz, b), 5.19 (2H, s, g), 6.27 (1H, d, J = 9.7 Hz, a), 6.85 (2H, d, J = 6.0 Hz, k), 7.00-7.05 (3H, m, l,m), 7.32 (2H, t, J = 7.6 Hz, o), 7.48-7.51 (3H, m, n,p).

^{13}C-NMR ($CDCl_3$, 150MHz) δ 51.7 (b), 58.3 (c), 86.9 (a), 117.6 (f), 127.7 (n), 127.9 (m), 128.2 (l), 128.5 (k), 128.6 (o), 133.7 (p), 135.1 (i), 136.3 (h),167.0 (d), 192.7 (e).

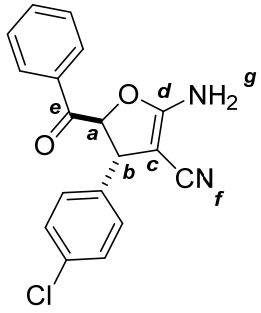
MS (EI) m/z 290 (M^+, 25), 136 (35), 105 (100), 77 (47).

HRMS (EI) m/z calcd. for $C_{18}H_{14}N_2O_2$: 290.1055, found: 290.1054.

NOESY



(4S*, 5S*)-2-amino-5-benzoyl-4-(4-chlorophenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3j**)



Pale yellow solid

Mp.130-132 °C

IR (KBr) 3396 cm^{-1} (NH_2), 2184 cm^{-1} (CN), 1660 cm^{-1} (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.39 (1H, d, J = 4.8 Hz, b), 5.03 (2H, s, g), 5.64 (1H, d, J = 4.8 Hz, a), 7.22-7.26 (2H, m), 7.32-7.36 (2H, m), 7.42 (2H, d, J = 7.7 Hz), 7.62-7.65 (1H, m), 7.79 (2H, d, J = 7.7 Hz).

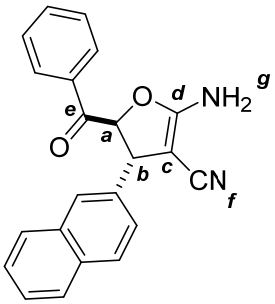
(*cis*-**3j**: δ 4.65 (1H, d, J = 10.0 Hz, b), 5.41 (2H, s, g), 6.21 (1H, d, J = 10.0 Hz, a)).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 50.2 (b), 56.7 (c), 88.8 (a), 117.7 (f), 128.7, 128.8, 128.9, 129.3, 133.1, 133.9, 134.4, 139.3,167.2 (d), 192.6 (e).

MS (CI) m/z 325(M^++1, 100)

HRMS (CI) m/z calcd. for $C_{18}H_{14}ClN_2O_2$: 325.0774, found: 325.0776.

(4S*, 5S*)-2-amino-5-benzoyl-4-(naphthalen-2-yl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3k**)



Pale yellow solid

Mp.140-142°C

IR (KBr) 3325 cm^{-1} (NH_2), 2180 cm^{-1} (CN), 1656 cm^{-1} (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.54 (1H, d, J = 4.8 Hz, b), 5.02 (2H, s, g), 5.81 (1H, d, J = 4.8 Hz, a), 7.41-7.59 (5H, m), 7.59-7.67 (2H, m), 7.80-7.92 (5H, m).

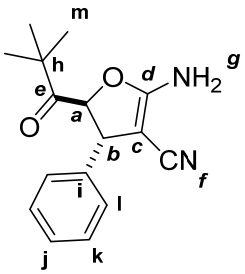
(*cis*-**3k**: δ 4.85 (1H, d, J = 9.6 Hz, b), 5.29 (2H, s, g), 6.29 (1H, d, J = 9.6 Hz, a)).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 51.1 (b), 56.8 (c), 88.7 (a), 118.1 (f), 124.7, 126.1, 126.3, 126.5, 127.6, 127.8, 128.7, 128.8 , 128.9, 129.3 133.0, 133.2, 134.1, 138.0, 167.3 (d), 193.0 (e).

MS (CI) m/z 341(M^++1, 100).

HRMS (CI) m/z calcd. for $C_{22}H_{17}N_2O_2$: 341.1290, found: 341.1291.

(4S*, 5S*)-2-amino-4-phenyl-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3l**)



White solid

Mp.199-202°C

IR (neat) 3420 cm^{-1} (NH_2), 2196 cm^{-1} (CN), 1672 cm^{-1} (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.14 (9H, s, m), 4.30 (1H, d, J = 5.3 Hz, b), 4.94 (2H, s, g), 5.18 (1H, d, J = 5.3 Hz, a), 7.26-7.39 (5H, m).

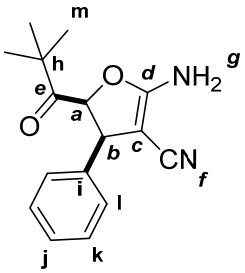
^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.0 (m), 43.5 (h), 51.0 (b), 58.11 (c), 87.9 (a), 117.8 (f), 127.3 (l),

128.0 (j), 129.1 (k), 140.8 (i), 166.5 (d), 208.6 (e).

MS (CI) m/z 271(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{16}H_{19}N_2O_2$: 271.1447, found: 271.1448.

(4R*,5S*)-2-amino-4-phenyl-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile(diastereo mixture) (*cis*-**3l**)



White solid

Mp.173-177°C

IR (neat) 3420 cm^{-1} (NH_2), 2196 cm^{-1} (CN), 1671 cm^{-1} (C=O)

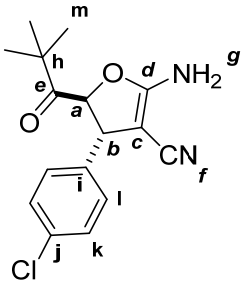
^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.85 (9H, s, m), 4.55 (1H, d, J = 9.4 Hz, b), 5.09 (2H, s, g), 5.69 (1H, d, J = 9.4 Hz, a), 7.14-7.39 (5H, m).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7 (m), 43.1 (h), 51.3 (b), 58.9 (c), 86.3 (a), 117.9 (f), 128.2 (j), 128.4 (l), 129.2 (k), 137.3 (i), 166.7 (d), 208.7 (e).

MS (CI) m/z 271(M^+＋1, 100).

HRMS (CI) m/z calcd. for $C_{16}H_{19}N_2O_2$: 271.1447, found: 271.1439.

(4S*, 5S*)-2-amino-4-(4-chlorophenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3m**)



White solid

Mp.145-148°C

IR (neat) 3337 cm^{-1} (NH_2), 2187 cm^{-1} (CN), 1659 cm^{-1} (C=O)

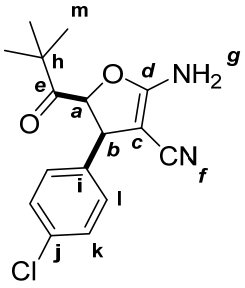
^{1}H-NMR ($CDCl_3$, 400 MHz) δ1.13 (9H, s, m), 4.31 (1H, d, J = 5.3 Hz, b), 5.09 (1H, d, J = 5.3 Hz, a), 5.48 (2H, s, g), 7.22 (2H, d, J = 8.5 Hz, k), 7.33 (2H, d, J = 8.5 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.8 (m), 43.5 (h), 50.2 (b), 56.4 (c), 87.7 (a), 118.0 (c), 128.7 (k), 129.1 (l), 133.5 (j), 139.5 (i), 167.0 (d), 208.8 (e).

MS (EI) m/z 304(M^+, 4), 247(100), 57(35).

HRMS (EI) m/z calcd. for $C_{16}H_{17}ClN_2O_2$: 304.0979, found: 304.0973.

(4R*,5S*)-2-amino-4-(4-chlorophenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3m**)



White solid

Mp.170-173°C

IR (neat) 3384 cm^{-1} (NH_2), 2196 cm^{-1} (CN), 1662 cm^{-1} (C=O)

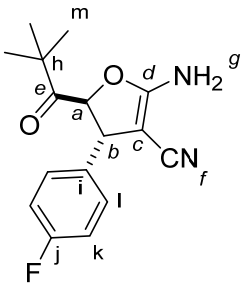
^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s, m), 4.53 (1H, d, J = 9.2 Hz, b), 5.11 (2H, s, g), 5.67 (1H, d, J = 9.2 Hz, a), 7.10 (2H, d, J = 8.5 Hz, k), 7.27 (2H, d, J = 8.5 Hz, l).

^{13}C-NMR ($CDCl_3$) δ 25.6 (m), 43.2 (h), 50.8 (b), 58.7 (c), 85.9 (a), 117.5 (f), 128.6 (k), 130.5 (l), 134.1 (j), 135.9 (i), 166.8 (d), 208.2 (e).

MS (EI) m/z 304(M^+, 31), 247(27), 57(100).

HRMS (EI) m/z calcd. for $C_{16}H_{17}ClN_2O_2$: 304.0979, found: 304.0975.

(4S*, 5S*)-2-amino-4-(4-fluorophenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3n**)



White solid

Mp.206-207°C

IR (neat) 3419 cm^{-1} (NH_2), 2195 cm^{-1} (CN), 1672 cm^{-1} (C=O).

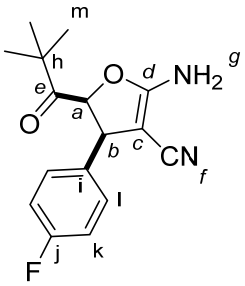
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.15 (9H, s, m), 4.33 (1H, d, J = 5.6 Hz, b), 4.92 (2H, s, g), 5.11 (1H, d, J = 5.6 Hz, a), 7.06 (2H, t, J = 8.7 Hz, k), 7.25 (2H, dd, J = 8.7, 5.3 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.9 (m), 43.6 (h), 50.3 (b), 58.1 (c), 88.0 (a), 116.0 (d, J = 22.1 Hz, k), 117.5 (f), 129.0 (d, J = 8.2 Hz, l), 136.5 (d, J = 3.3 Hz, i), 161.2 (j), 166.4 (d), 208.5 (e).

MS (EI) m/z 288(M^+, 6), 231(100).

HRMS (EI) m/z calcd. for $C_{16}H_{17}FN_2O_3$: 288.1274, found: 288.1273.

(4R*,5S*)-2-amino-4-(4-fluorophenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3n**)



White solid

Mp.217-220°C

IR (neat) 3441 cm^{-1} (NH_2), 2184 cm^{-1} (CN), 1671 cm^{-1} (C=O).

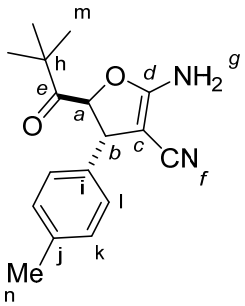
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.89 (9H, s, m), 4.56 (1H, d, J = 9.4 Hz, b), 4.95 (2H, s, g), 5.68 (1H, d, J = 9.4 Hz, a), 6.98 (2H, t, J = 8.7 Hz, k), 7.14 (2H, dd, J = 8.7, 5.3 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.6 (m), 43.2 (h), 50.7 (b), 59.2 (c), 86.0 (a), 115.4 (d, J = 21.3 Hz, k), 117.5 (f), 130.9 (d, J = 8.2 Hz, l), 132.9 (d, J = 4.9 Hz, i), 161.3 (j), 166.5 (d), 208.3 (e).

MS (EI) m/z 288(M^+, 54), 57(100).

HRMS (EI) m/z calcd. for $C_{16}H_{17}FN_2O_3$: 288.1274, found: 288.1275.

(4S*, 5S*)-2-amino-5-pivaloyl-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-**3o**)



White solid

Mp.143-145°C

IR (neat) 3428 cm^{-1} (NH_2), 2186 cm^{-1} (CN), 1666 cm^{-1} (C=O).

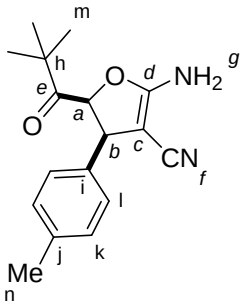
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.13 (9H, s, m), 2.34 (3H, s, n), 4.25 (1H, d, J = 5.3 Hz, b), 5.07 (2H, s, g), 5.15 (1H, d, J = 5.3 Hz, a), 7.16-7.23 (4H, m, l and k).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.0 (n), 26.0 (m), 43.5 (h), 50.7 (b), 57.9 (c), 87.9 (a), 118.0 (f), 127.2 (l), 129.7 (k), 137.6 (j), 137.9 (i), 166.7 (d), 208.8 (e).

MS (EI) m/z 284(M^+, 5), 227(100), 57(28), 43(26).

HRMS (EI) m/z calcd. for $C_{17}H_{20}N_2O_2$: 284.1525, found: 284.1521.

(4R*,5S*)-2-amino-5-pivaloyl-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (*cis*-**3o**)



White solid

Mp.213°C

IR (neat) 3407 cm^{-1} (NH_2), 2189 cm^{-1} (CN), 1663 cm^{-1} (C=O)

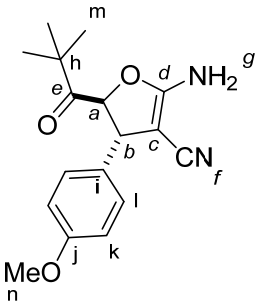
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.87 (9H, s, m), 2.29 (3H, s, n), 4.52 (1H, d, J = 9.4 Hz, b), 4.92 (2H, s, g), 5.67 (1H, d, J = 9.4 Hz, a), 7.03 (2H, d, J = 8.0 Hz, k), 7.08 (2H, d, J = 8.0 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.1 (n), 25.7 (m), 43.1 (h), 51.1 (b), 59.5 (c), 86.3 (a), 117.7 (f), 129.0 (l), 129.1 (k), 134.1 (j), 137.9 (i), 166.5 (d), 208.5 (e).

MS (CI) m/z 285(M^+＋1, 32), 231(100).

HRMS (CI) m/z calcd. for $C_{17}H_{20}N_2O_2$: 285.1603, found: 285.1595.

(4S*, 5S*)-2-amino-4-(4-methoxyphenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3p**)



White solid

Mp.162-163°C

IR (neat) 3423 cm^{-1} (NH_2), 2193 cm^{-1} (CN), 1670 cm^{-1} (C=O)

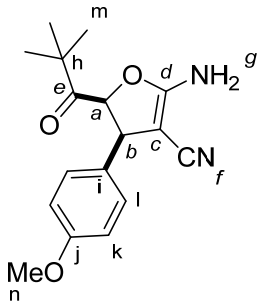
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.14 (9H, s, m), 3.81 (3H, s, n), 4.26 (1H, d, J = 5.6 Hz, b), 4.91 (2H, s, g), 5.14 (1H, d, J = 5.6 Hz, a), 6.89 (2H, d, J = 8.7 Hz, k), 7.19 (2H, d, J = 8.7 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.0 (m), 43.5 (h), 50.5 (b), 55.3 (n), 58.4 (c), 88.0 (a), 114.4 (k), 117.8 (f), 128.5 (l), 132.8 (i), 159.3 (j), 166.4 (d), 208.7 (e).

MS (EI) m/z 300(M^+, 5), 243(100), 57(29).

HRMS (EI) m/z calcd. for $C_{17}H_{20}N_2O_3$: 300.1474, found: 300.1476.

(4R*,5S*)-2-amino-4-(4-methoxyphenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3p**)



White solid

Mp.191-193°C

IR (neat) 3411 cm^{-1} (NH_2), 2187 cm^{-1} (CN), 1664 cm^{-1} (C=O).

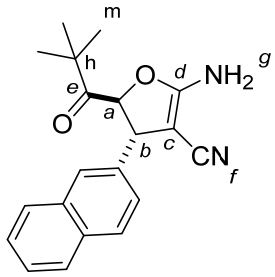
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.88 (9H, s, m), 3.77 (3H, s, n), 4.53 (1H, d, J = 9.4 Hz, b), 4.97 (2H, s, g), 5.66 (1H, d, J = 9.4 Hz, a), 6.81 (2H, d, J = 8.7 Hz, k), 7.07 (2H, d, J = 8.7 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7 (m), 43.1 (h), 50.7 (b), 55.2 (n), 59.4 (c), 86.2 (a), 113.8 (k), 117.8 (f), 129.1 (i), 130.3 (l), 159.4 (j), 166.5 (d), 208.7 (e).

MS (EI) m/z 300(M^+, 37), 243(68), 241(100), 57(80).

HRMS (EI) m/z calcd. for $C_{17}H_{20}N_2O_3$: 300.1474, found: 300.1469.

(4S*, 5S*)-2-amino-4-(naphthalen-2-yl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3q**)



Pale yellow solid

Mp.169-173°C

IR (neat) 3418 cm^{-1} (NH_2), 2197 cm^{-1} (CN), 1665 cm^{-1} (C=O).

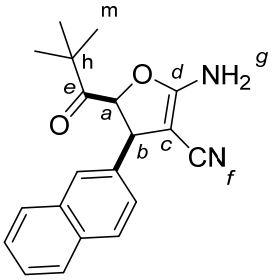
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.13 (9H, s, m), 4.47 (1H, d, J = 5.3 Hz, b), 5.21 (2H, s, g), 5.25 (1H, d, J = 5.3 Hz, a), 7.40 (1H, dd, J = 8.5, 1.7 Hz), 7.46-7.49 (2H, m), 7.70 (1H, d, J = 1.7 Hz), 7.82 (2H, m), 7.86 (1H, d, J = 8.5 Hz).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.9 (m), 43.5 (h), 51.2 (b), 57.5 (c), 87.7 (a), 118.0 (f), 124.8, 126.1, 126.4, 126.4, 127.7, 127.9, 129.2, 133.0, 133.3, 138.1, 166.8 (d), 208.8 (e).

MS (EI) m/z 320(M^+, 4), 263(48), 57(28), 43(100).

HRMS (EI) m/z calcd. for $C_{20}H_{20}N_2O_2$: 320.1525, found: 320.1523.

(4R*,5S*)-2-amino-4-(naphthalen-2-yl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3q**)



Pale yellow solid

Mp.212-215°C

IR (neat) 3427 cm^{-1} (NH_2), 2191 cm^{-1} (CN), 1672 cm^{-1} (C=O)

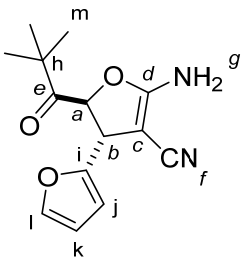
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (9H, s, m), 4.72 (1H, d, J = 9.4 Hz, b), 5.05 (2H, s, g), 5.75 (1H, d, J = 9.4 Hz, a), 7.26 (1H, dd, J = 8.5, 1.9 Hz), 7.45-7.47 (2H, m), 7.62 (1H, d, J = 1.4 Hz), 7.78 (3H, m).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7 (m), 43.2 (h), 51.6 (b), 59.3 (c), 86.4 (a), 117.7 (f), 126.2, 126.2, 126.6, 127.7, 127.9, 128.1, 128.4, 132.9, 133.1, 134.9, 166.6 (d), 208.7 (e).

MS (EI) m/z 320(M^+, 35), 263(26), 57(100).

HRMS (EI) m/z calcd. for $C_{20}H_{20}N_2O_2$: 320.1525, found: 320.1522.

(4S*, 5S*)-5'-amino-2'-pivaloyl-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile (*trans*-**3r**)



White solid

Mp.114-117°C

IR (neat) 3327 cm^{-1} (NH_2), 2181 cm^{-1} (CN), 1656 cm^{-1} (C=O).

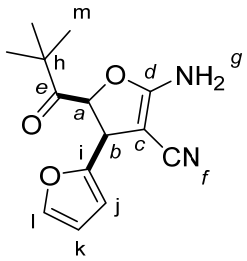
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (9H, s, m), 4.40 (1H, d, J = 5.1 Hz, b), 5.35 (1H, d, J = 5.1 Hz, a), 5.40 (2H, s, g), 6.28 (1H, dd, J = 3.1, 1.0 Hz, j), 6.34 (1H, dd, J = 3.1, 1.9 Hz, k), 7.39 (1H, dd, J = 1.9, 1.0 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.9 (m), 43.5 (h), 44.2 (b), 53.8 (c), 84.1 (a), 107.3 (j), 110.5 (k), 117.9 (f), 142.5 (l), 152.9 (i), 167.3 (d), 208.5 (e).

MS (EI) m/z 271(M^+, 4), 203(100), 57(81).

HRMS (EI) m/z calcd. for $C_{16}H_{19}N_2O_2$: 260.1161, found: 260.1160.

(4R*,5S*)-5'-amino-2'-pivaloyl-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile (*cis*-**3r**)



White solid

Mp.184-186°C

IR (neat) 3391cm^{-1} (NH_2), 2186 cm^{-1} (CN), 1662 cm^{-1} (C=O).

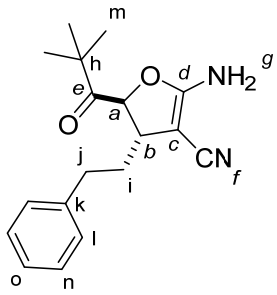
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.08 (9H, s, m), 4.68 (1H, d, J = 8.9 Hz, b), 5.01 (2H, s, g), 5.57 (1H, d, J = 8.9 Hz, a), 6.25 (1H, dd, J = 3.4, 0.7 Hz, j), 6.31 (1H, dd, J = 3.4, 1.9 Hz, k), 7.30 (1H, dd, J = 1.9, 0.7 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.6 (m), 43.7 (h), 44.6 (b), 49.1 (c), 83.8 (a), 109.7 (j), 111.0 (k), 117.4 (f), 142.3 (l), 150.4 (i), 167.2 (d), 207.7 (e).

MS (EI) m/z 271(M^+, 20), 201(35), 57(100).

HRMS (EI) m/z calcd. for $C_{16}H_{19}N_2O_2$: 260.1161, found: 260.1157.

(4S*, 5S*)-2-amino-4-phenethyl-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3s**)



White solid

Mp.120-122°C

IR (neat) 3403 cm^{-1} (NH_2), 2183 cm^{-1} (CN), 1668 cm^{-1} (C=O)

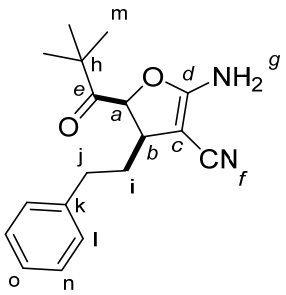
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.15 (9H, s, m), 1.89-2.05 (2H, m, i), 2.66-2.85 (2H, m, j), 3.20 (1H, dt, J = 7.0, 4.8 Hz, b), 4.90 (1H, d, J = 4.8 Hz, a), 5.16 (2H, s, g), 7.16-7.30 (5H, m, Ph).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 26.06 (m), 32.03 (i), 37.23 (j), 43.40 (h), 44.53 (b), 55.27 (c), 86.34 (a), 118.91 (f), 125.97 (o), 128.36 (l or n), 128.38 (l or n), 141.02 (k), 167.00 (d), 209.22 (e).

MS (EI) m/z 298(M^+, 25), 241(92), 130(27), 109(42), 91(97), 57(100)

HRMS (EI) m/z calcd. for $C_{18}H_{22}N_2O_2$: 298.1681, found: 298.1683.

(4R*,5S*)-2-amino-4-phenethyl-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3s**)



White solid

Mp.194-197°C

IR (neat) 3441 cm^{-1} (NH_2), 2184 cm^{-1} (CN), 1642 cm^{-1} (C=O)

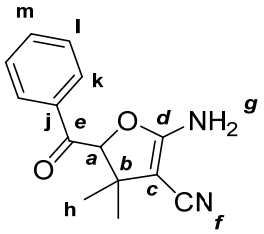
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.15 (9H, s, m), 1.43-1.80 (2H, m, i), 2.58-2.92 (2H, m, j), 3.26 (1H, ddd, J = 11.0, 8.2, 3.6 Hz, b), 4.78 (2H, s, g), 5.42 (1H, d, J = 8.2 Hz, a), 7.17-7.29 (5H, m).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7 (m), 32.3 (i), 34.8 (j), 37.2 (h), 43.7 (b), 56.9 (c), 85.5 (a), 110.9 (f), 126.0 (o), 128.5 (l or n), 128.5 (l or n), 141.0 (k), 170.3 (d), 207.2 (e).

MS (EI) m/z 298(M^+, 18), 241(19), 215(28), 130(39), 109(26), 91(51), 57(100).

HRMS (EI) m/z calcd. for $C_{18}H_{22}N_2O_2$: 298.1681, found: 298.1680.

2-amino-5-benzoyl-4,4-dimethyl-4,5-dihydrofuran-3-carbonitrile (**3t**)



White solid

Mp.191-194°C

IR (KBr) 3401 cm^{-1} (NH_2), 2173 cm^{-1} (CN), 1661 cm^{-1} (C=O)

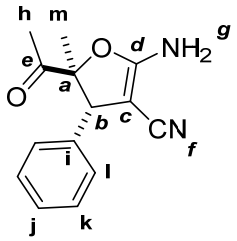
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.99 (3H, s, h), 1.46 (3H, s, h), 4.86 (2H, s, g), 5.64 (1H, s, a), 7.52 (2H, t, J = 7.7 Hz, l), 7.65 (1H, t, J = 7.7 Hz, m), 7.89 (2H, d, J = 7.7 Hz, k).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.0 (h), 28.7 (h), 46.6 (b), 54.1 (c), 90.8 (a), 117.4 (f), 128.4 (l), 129.0 (k), 134.1 (m), 135.9 (j), 164.9 (d), 194.3 (e).

MS (EI) m/z 242(M^+,9), 227(10), 137(10), 105(100), 77(22).

HRMS (EI) m/z calcd. for $C_{14}H_{14}N_2O_2$: 242.1055, found: 242.1056.

(4S*, 5S*)-5-acetyl-2-amino-5-methyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*trans*-**3u**)



Yellow wax

Rf=0.45 (in hexane/ethyl acetate = 5:5)

IR (neat) 3345 cm^{-1} (NH_2), 2190 cm^{-1} (CN), 1662 cm^{-1} (C=O).

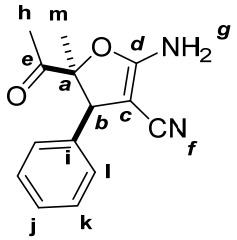
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.90 (3H, s, m), 2.26 (3H, s, h), 4.41 (1H, s, b), 5.68 (2H, s, g), 7.19-7.37 (5H, m, Ph).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.5 (m), 24.9 (h), 52.6 (b), 55.0 (c), 95.1 (a), 118.5 (f), 127.7 (j), 128.4 (l), 128.4 (k), 137.2 (i), 166.8 (d), 209.8 (e).

MS (EI) m/z 242(M^+, 100)

HRMS (EI) m/z calcd. for $C_{14}H_{14}N_2O_2$: 242.1055, found: 242.1054.

(4R*,5S*)-5-acetyl-2-amino-5-methyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*cis*-**3u**)



White solid

Mp.169-172°C

IR (KBr) 3328 cm^{-1} (NH_2), 2173 cm^{-1} (CN), 1662 cm^{-1} (C=O).

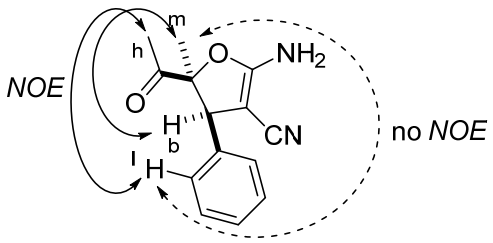
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.68 (3H, s, m), 1.73 (3H, s, h), 4.14 (1H, s, b), 5.14 (2H, s, g), 7.14-7.32 (5H, m, 5H).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.4 (m), 27.4 (h), 56.2 (c), 57.7 (b), 96.6 (a), 118.2 (f), 128.2 (j), 128.2 (l), 128.7 (k), 137.1 (i), 166.3 (d), 205.9 (e).

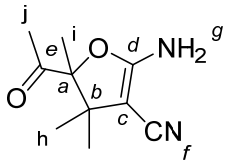
MS (EI) m/z 242(M^+, 100).

HRMS (EI) m/z calcd. for $C_{14}H_{14}N_2O_2$: 242.1055, found: 242.1054.

NOESY



5-acetyl-2-amino-4,4,5-trimethyl-4,5-dihydrofuran-3-carbonitrile (**3v**)



White solid

Mp.177-178°C

IR (KBr) 3398 cm^{-1} (NH_2), 2175 cm^{-1} (CN), 1653 cm^{-1} (C=O)

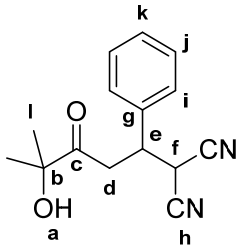
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.08 (3H, s, h), 1.26 (3H, s), 1.39 (3H, s), 2.28 (3H, s, j), 4.70 (2H, s, g).

As this minor product was isolated as a small amount, clear ^{13}C NMR spectra could not be obtained.

MS (EI) m/z 194(M^+,28), 179(27), 151(38), 137(100), 43(37)

HRMS (EI) m/z calcd. for $C_{10}H_{14}N_2O_2$: 194.1055, found: 194.1054.

2-(4-hydroxy-4-methyl-3-oxo-1-phenylpentyl)malononitrile (**4a**)



Yellow liquid

Rf= 0.66 (in hexane:ethyl acetate = 3:7).

IR (neat), 3500 cm^{-1} (OH), 2257 cm^{-1} (CN), 1713 cm^{-1} (C=O)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.32 (3H, s, l), 1.36 (3H, s, l), 3.14 (1H, a), 3.31 (2H, d, J = 7.0 Hz, d), 3.81 (1H, dt, J = 5.8, 7.0 Hz, e), 4.40 (1H, d, J = 5.8 Hz, f), 7.36-7.44 (5H, m).

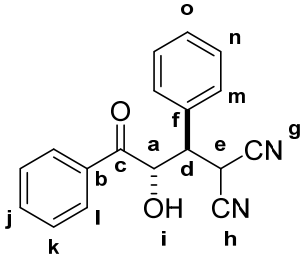
^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.4 (l), 28.6 (e), 38.1 (d), 40.9 (f), 76.8 (b), 111.5 (h), 111.6 (h), 127.8 (i), 129.2 (k), 129.3 (j), 136.1 (g), 211.8 (c).

MS (CI) m/z 257 (M^+ + 1, 100).

HRMS (CI) m/z calcd. for $C_{15}H_{17}N_2O_2$: 257.1290, found: 257.1291.

2-((1R*,2S*)-2-hydroxy-3-oxo-1,3-diphenylpropyl)malononitrile (**4b Major**)

This product was isolated from the reaction mixture by flash column chromatography eluted by Hexane/EtOAc= 7/3. Further purfication was performed by GPC eluted with $CHCl_3$.



White wax

Rf=0.45 (in hexane:ethyl acetate = 8:2)

IR (neat), 2189 cm^{-1} (CN), 1687 cm^{-1} (C=O)

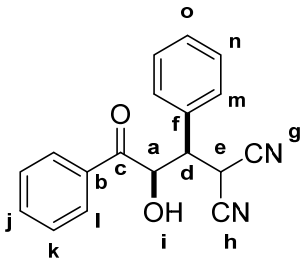
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.77 (1H, dd, J = 11.6, 2.7 Hz, d), 4.05 (1H, d, J = 6.0 Hz, i), 4.57 (1H, d, J = 11.6 Hz, e), 5.63 (1H, dd, J = 6.0, 2.7 Hz, a), 6.84 (2H, d, J = 7.4 Hz, m), 7.23 (2H, t, J = 7.4 Hz, n), 7.32 (1H, t, J = 7.4 Hz, o), 7.58 (2H, t, J = 7.5 Hz, k), 7.73 (1H, t, J = 7.5 Hz, j), 7.77 (2H, d, J = 7.5 Hz, l).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.1 (d), 50.7 (e), 72.2 (a), 111.5 (g or h), 112.3 (g or h), 128.1 , 128.4, 129.0, 129.4, 129.6, 130.9, 133.1, 134.9, 197.2 (c).

MS (EI) m/z 290(M^+,4), 225(10), 105(100), 77(24).

HRMS (EI) m/z calcd. for $C_{18}H_{14}N_2O_2$: 290.1055, found: 290.1050.

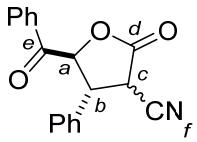
2-((1*R,2*S**)-2-hydroxy-3-oxo-1,3-diphenylpropyl)malononitrile** (**4b Minor**)



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.63 (1H, t, J = 6.5 Hz, d), 3.75 (1H, s, i), 4.53 (1H, d, J = 6.5 Hz, e), 5.44 (1H, d, J = 6.5 Hz, a), 7.18-7.94 (10H, m, Ar).

5-benzoyl-2-oxo-4-phenyltetrahydrofuran-3-carbonitrile (diastereomers mixture) (**5**)

The THF (1 mL) solution of **3i** (0.087g, 0.3 mmol) with 1M HCl (2 mL) was stirred at 25 ^{o}C for 1 h. After the reaction, the mixture was extracted with ether (5 mL x3), and the combined extracts were dried over sodium sulfate and concentrated. The yield of **5** was determined by ^{1}H NMR (0.061 g, 70%). The crude product was then purified by flash column chromatography eluted by Hexane/EtOAc with gradation mode changing from 9/1 to 5/5. The desired product was obtained at Hexane/EtOAc=5:5.



Clear wax

Rf= 0.69 (in hexane:ethyl acetate = 5:5)

IR (neat), 2257 cm^{-1} (CN), 1794,1693 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$, 400 MHz) (Major) δ 4.07 (1H, d, J = 10.9 Hz, c), 4.39 (1H, dd, J = 10.9, 8.5 Hz, b), 5.75 (1H, d, J = 8.5 Hz, a), 7.32-7.93 (10H, m, Ph).

(Minor) δ 4.10 (1H, dd, J = 1.2, 8.7 Hz, b'), 4.27 (1H, d, J = 8.7 Hz, c'), 6.04 (1H, d, J = 1.2 Hz, a'), 7.32-7.93 (10H, m, Ph).

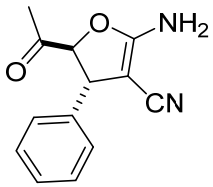
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 37.8 (b), 39.7 (b), 46.2 (c), 47.8 (c), 82.1 (a), 82.7 (a), 112.3 (f), 113.7 (f), 127.1, 127.3, 128.8, 129.0, 129.2, 129.3, 129.4, 129.6, 129.7, 129.9, 132.5, 133.7, 134.2, 134.8, 135.3, 135.5, 165.9 (d), 167.5 (d), 190.7 (e), 192.3 (e).

MS (CI) m/z 292(M^+＋1,100).

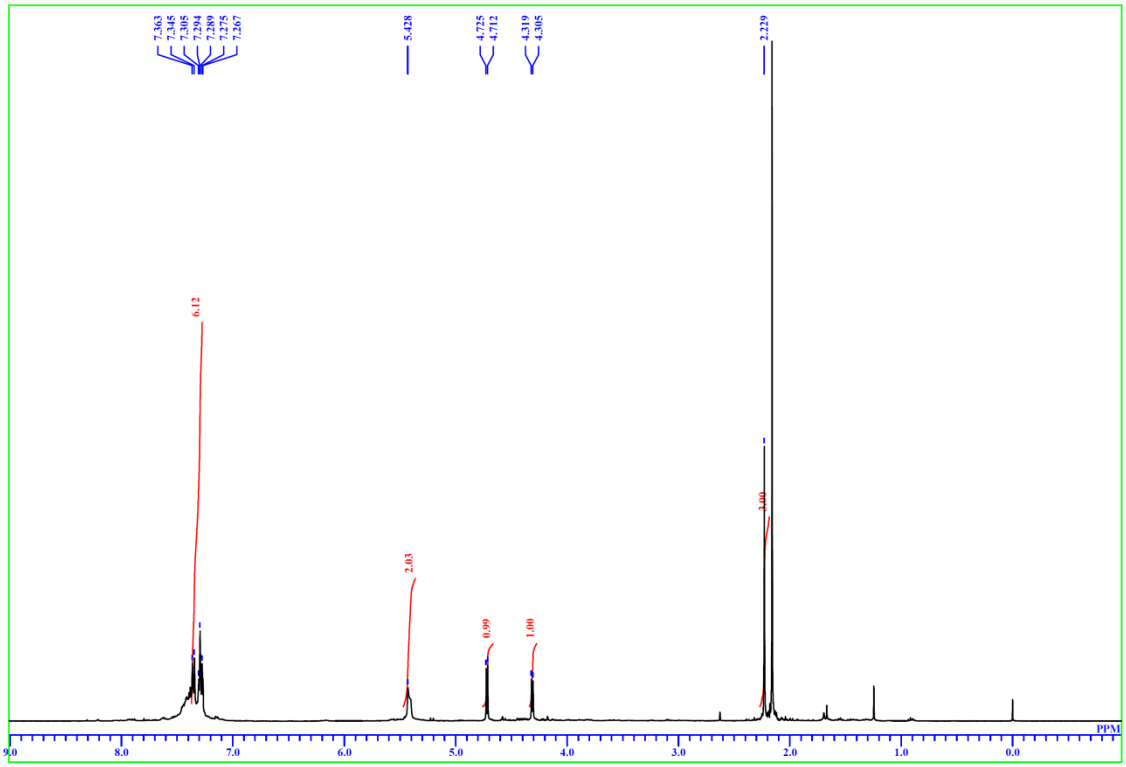
HRMS (CI) m/z calcd. for $C_{18}H_{14}NO_3$: 292.0974, found: 292.0976.

NMR Charts

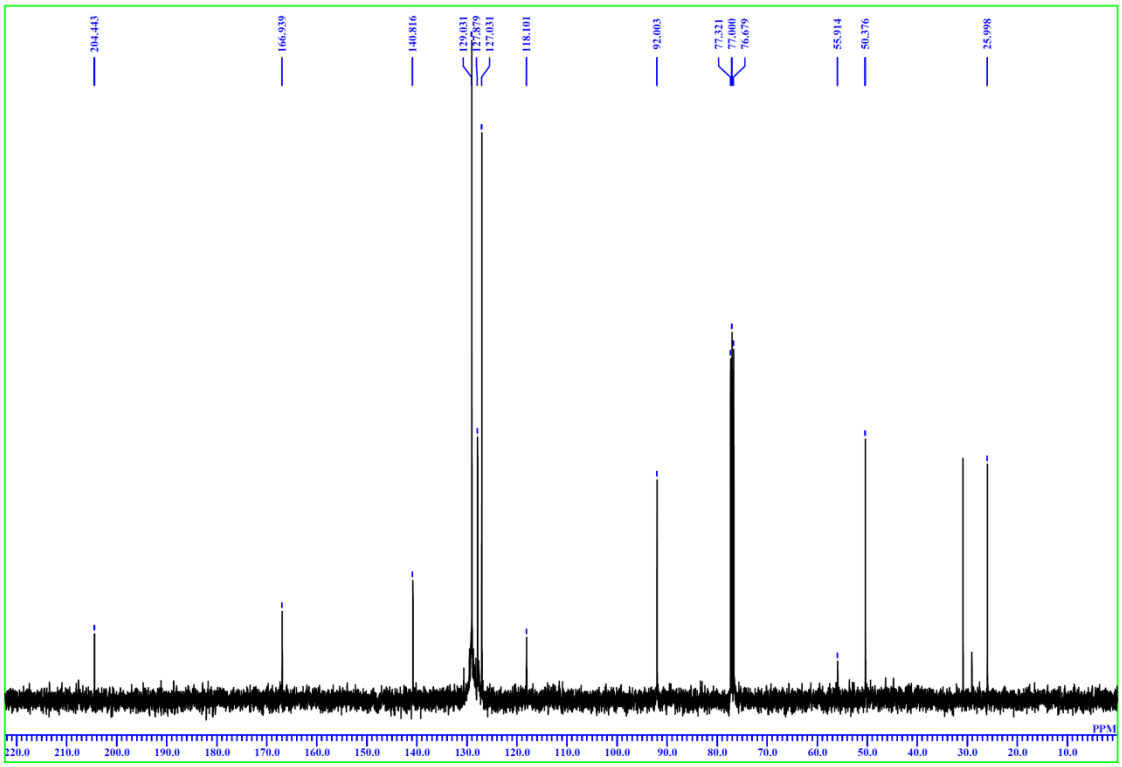
(*trans*-**3a**)



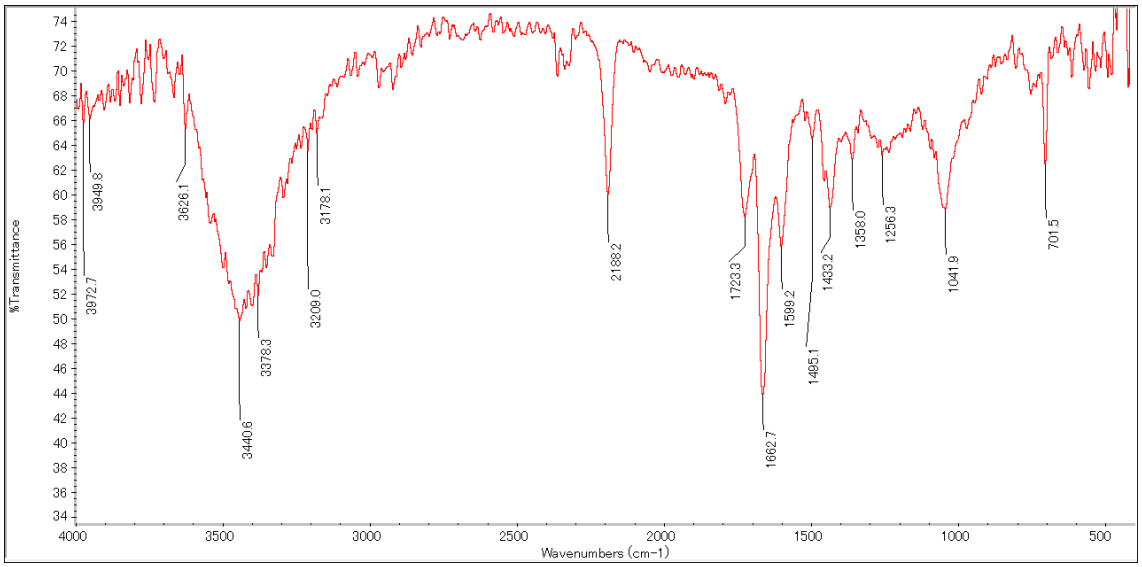
^{1}H NMR



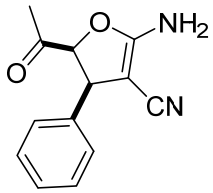
^{13}C NMR



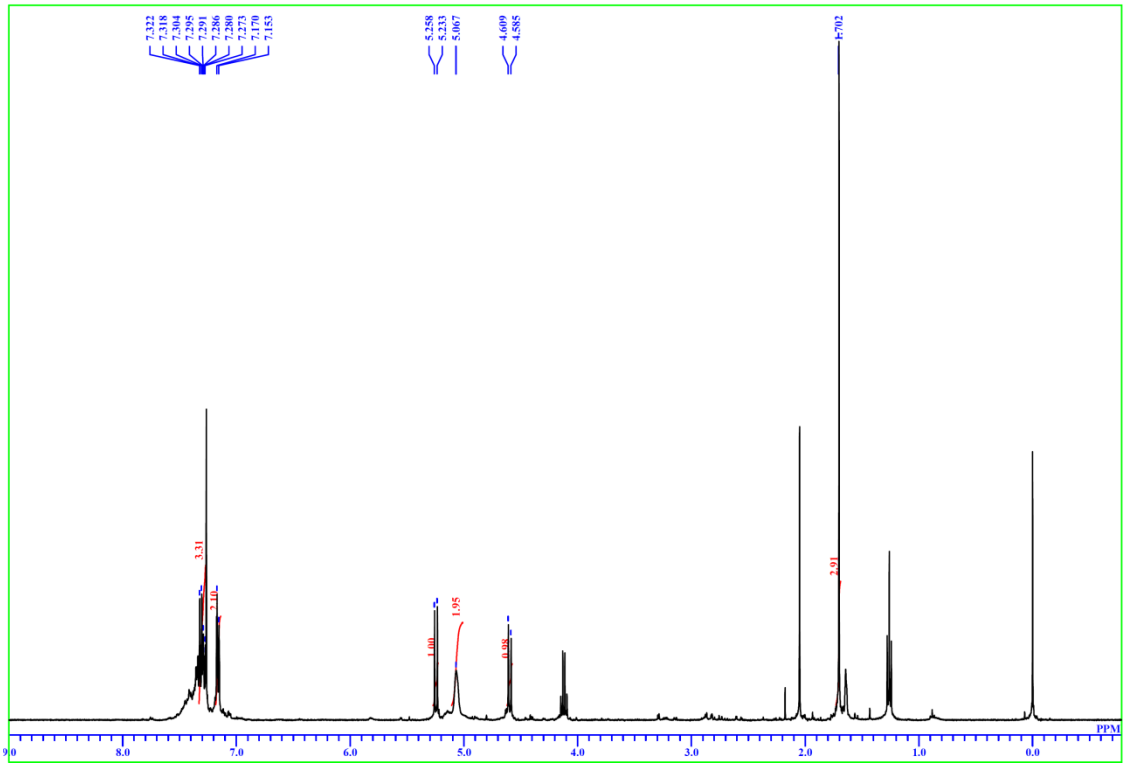
IR



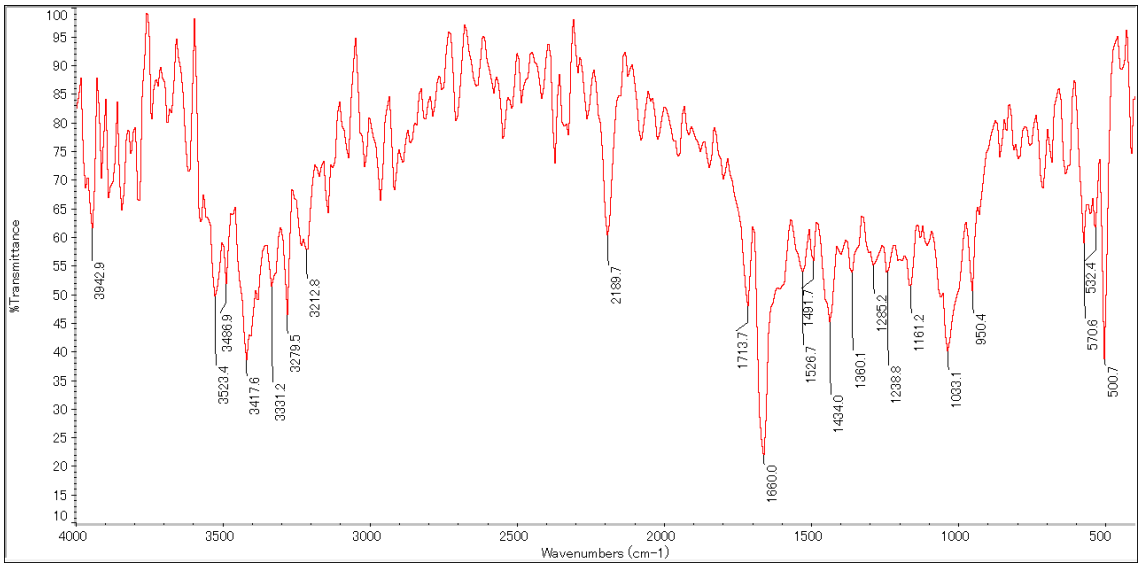
(*cis*-**3a**)



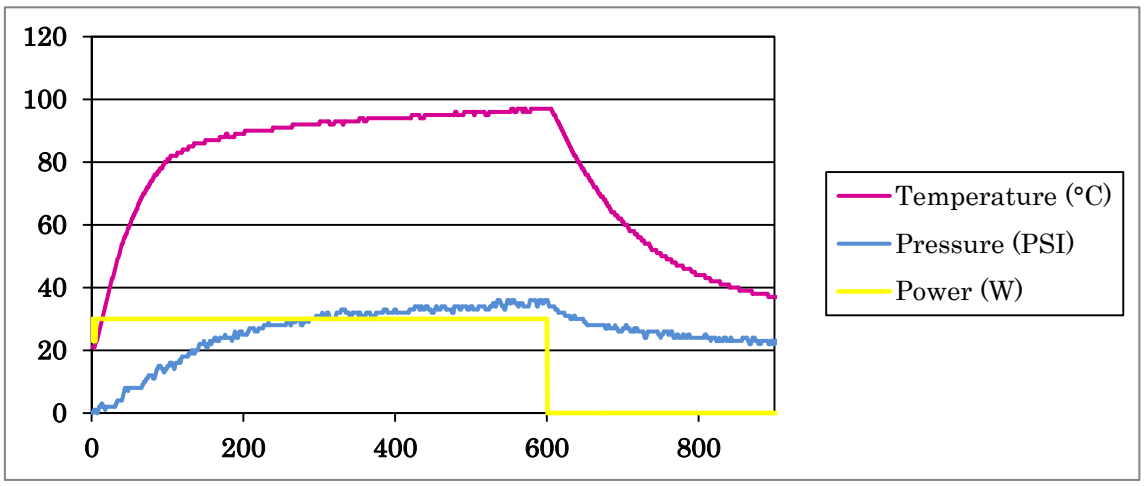
^{1}H NMR



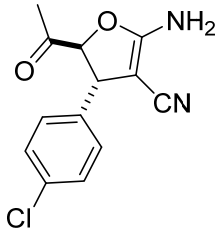
IR



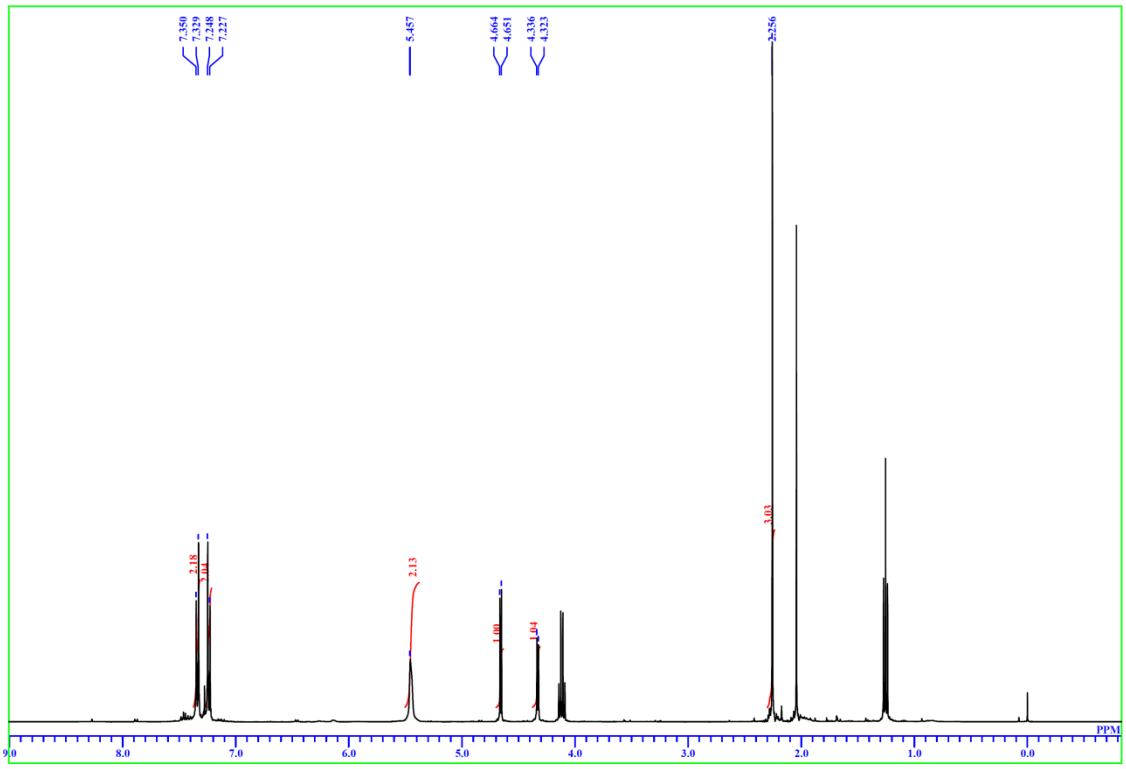
MW Profile (Table 1 entry 8, Table 2 entry 1)



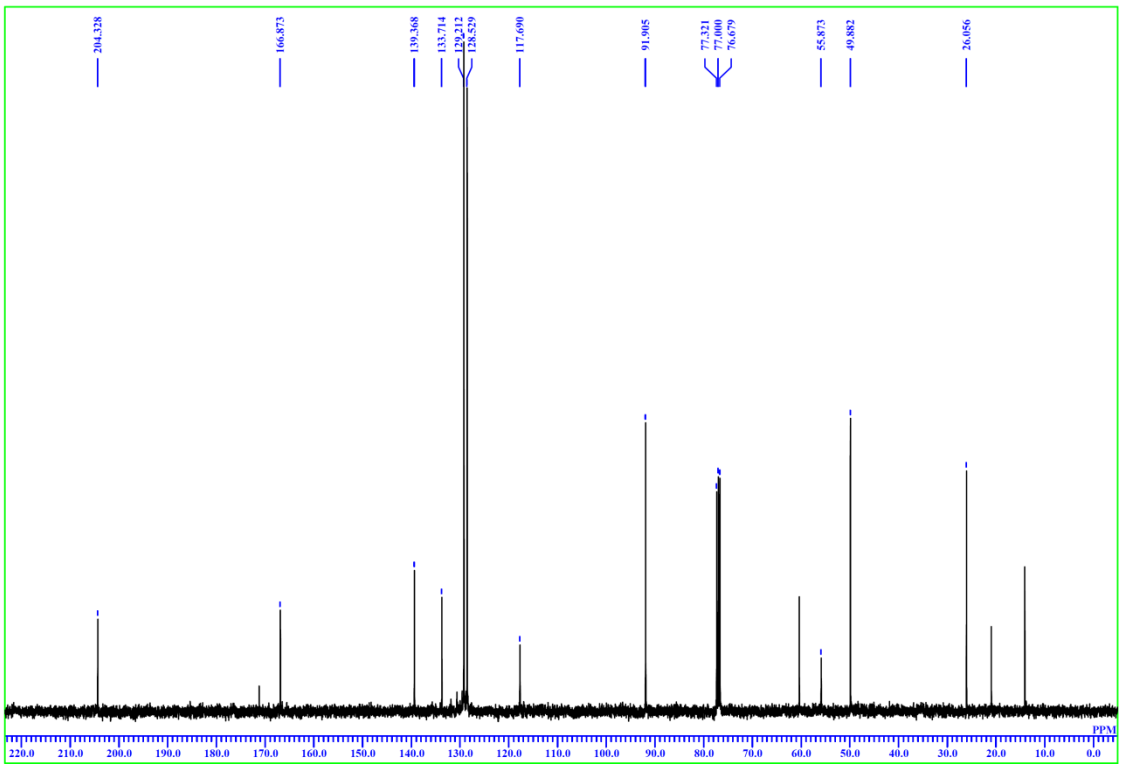
(*trans*-**3b**)



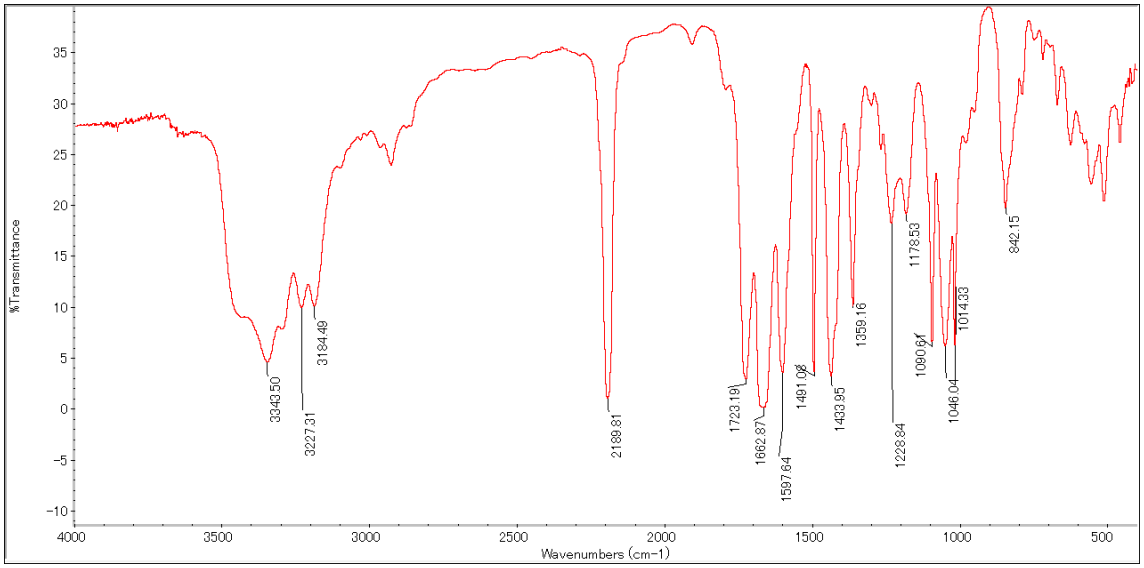
^{1}H NMR



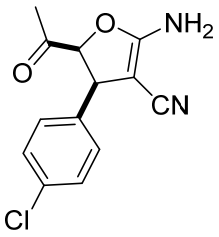
^{13}C NMR



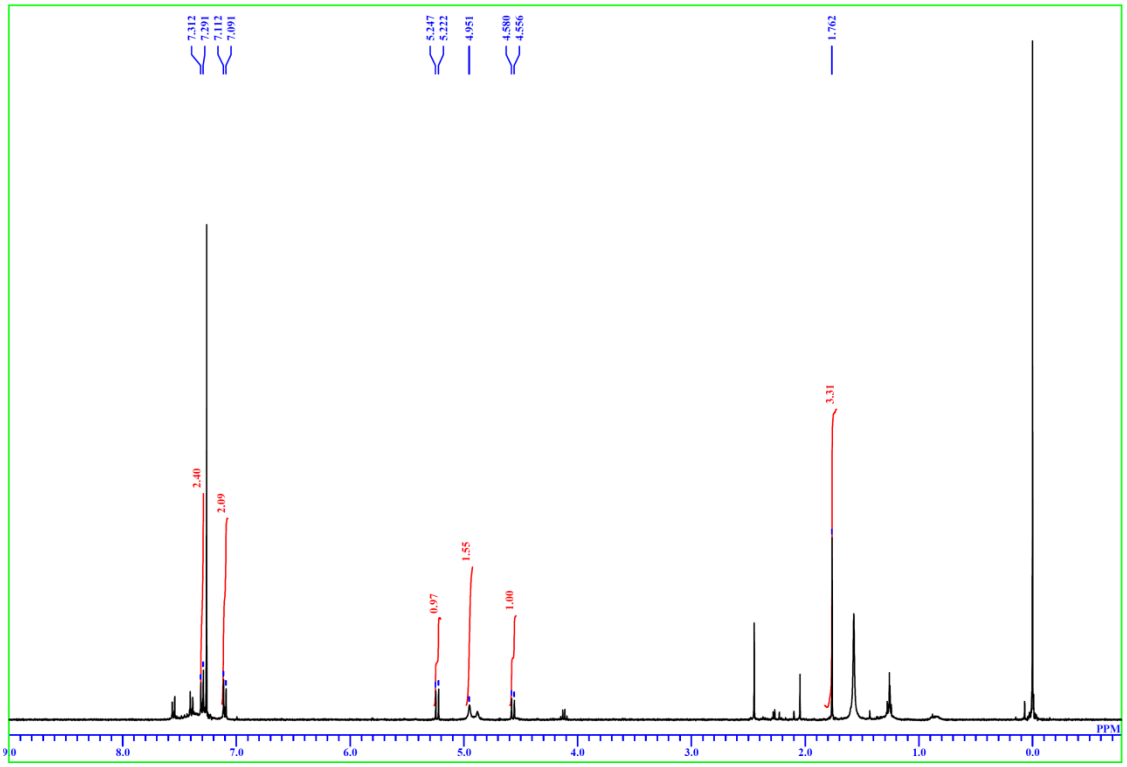
IR



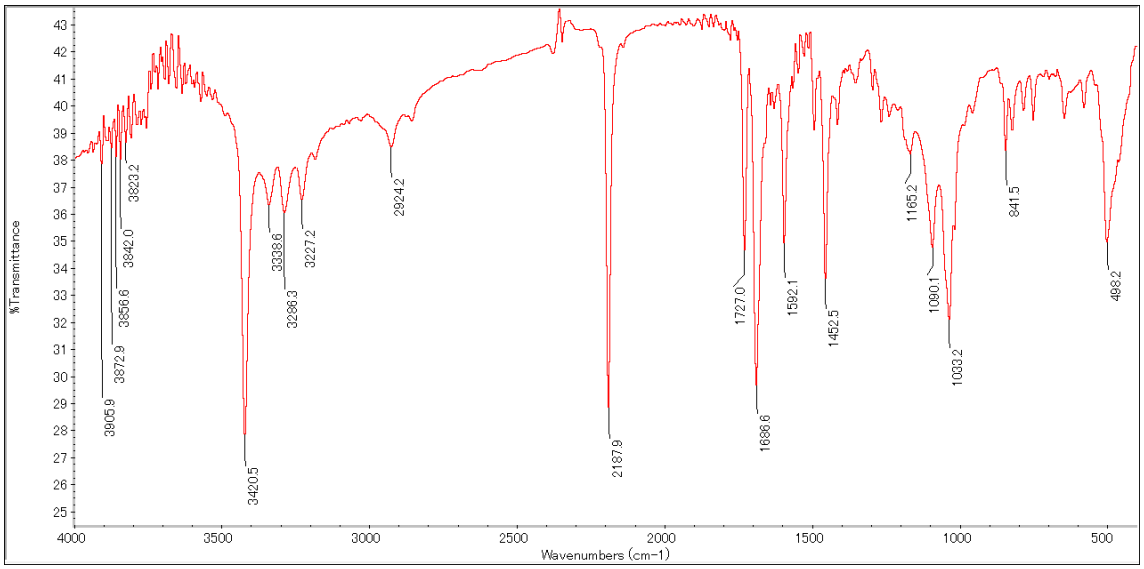
(*cis*-**3b**)



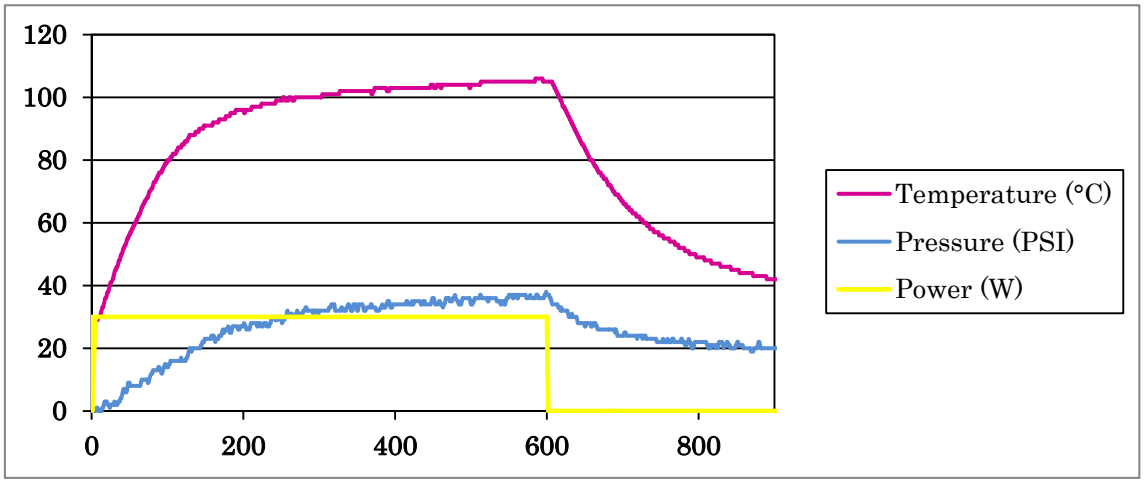
^{1}H NMR



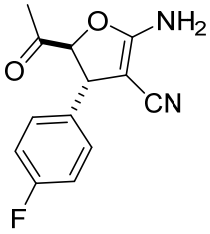
IR



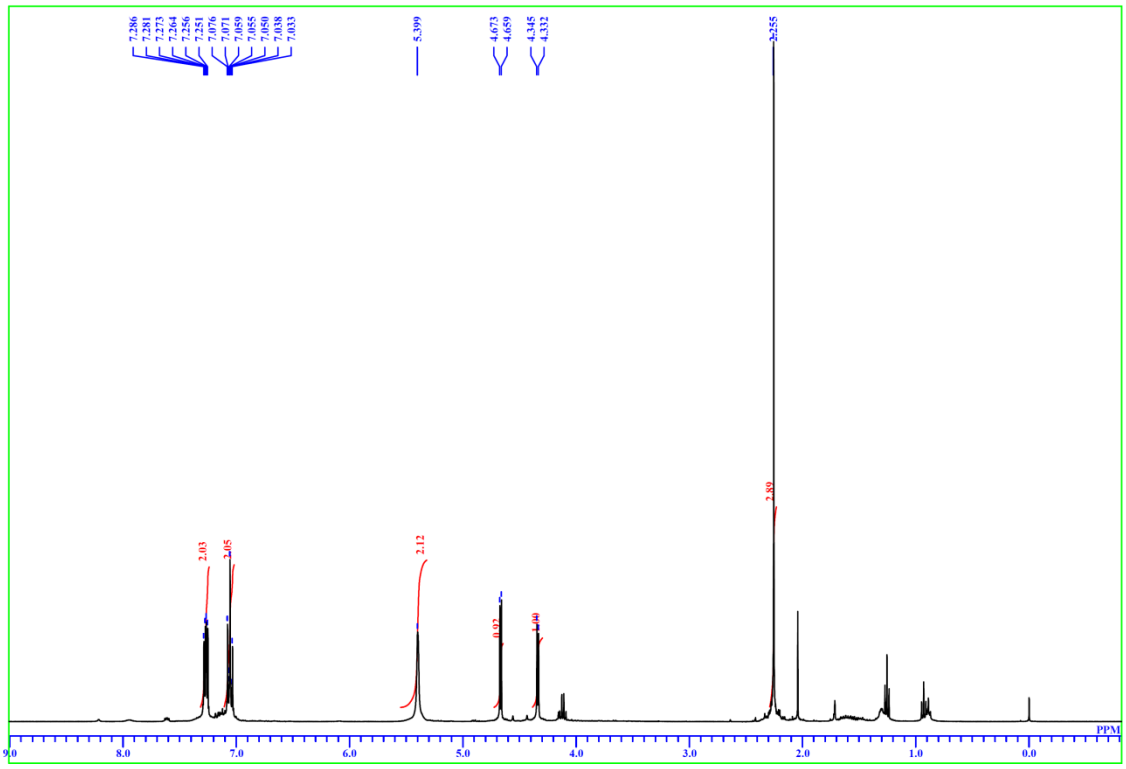
MW Profile (Table 2, entry 2)



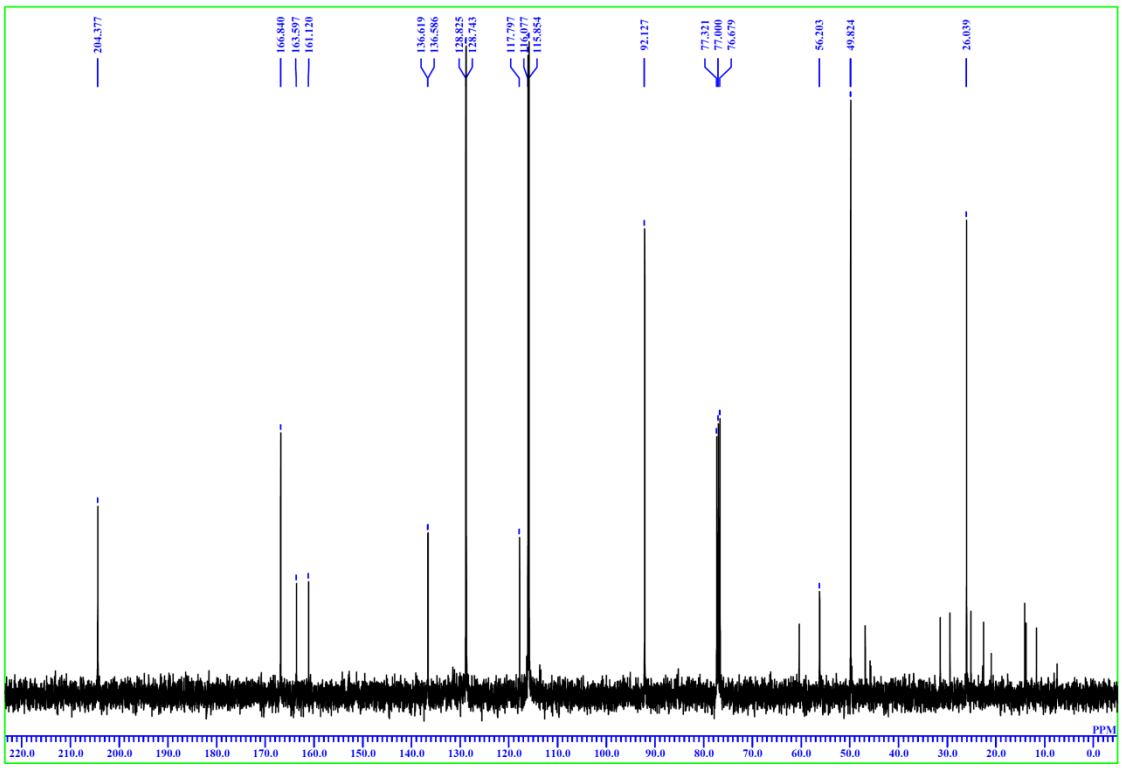
(*trans*-**3c**)



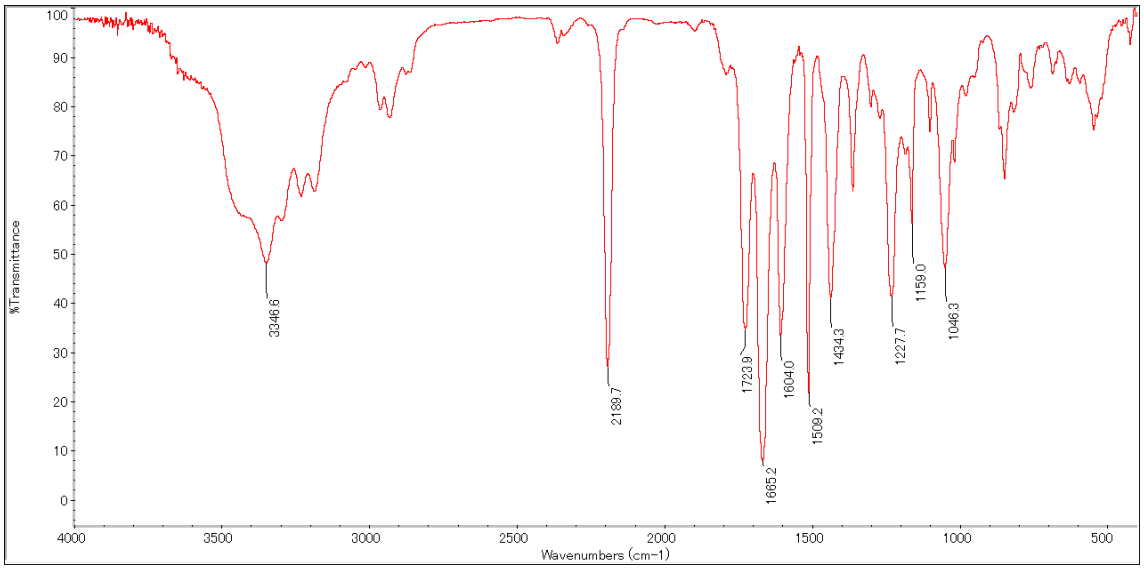
^{1}H NMR



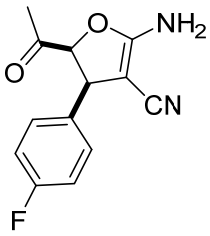
^{13}C NMR



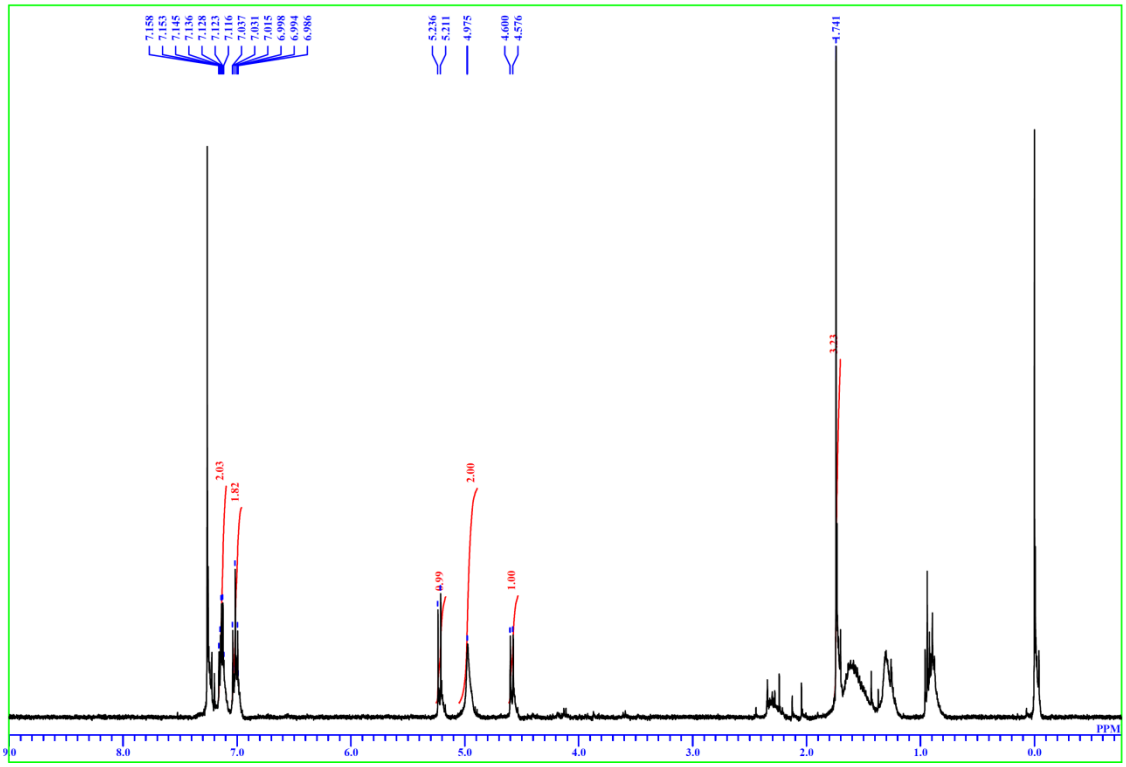
IR



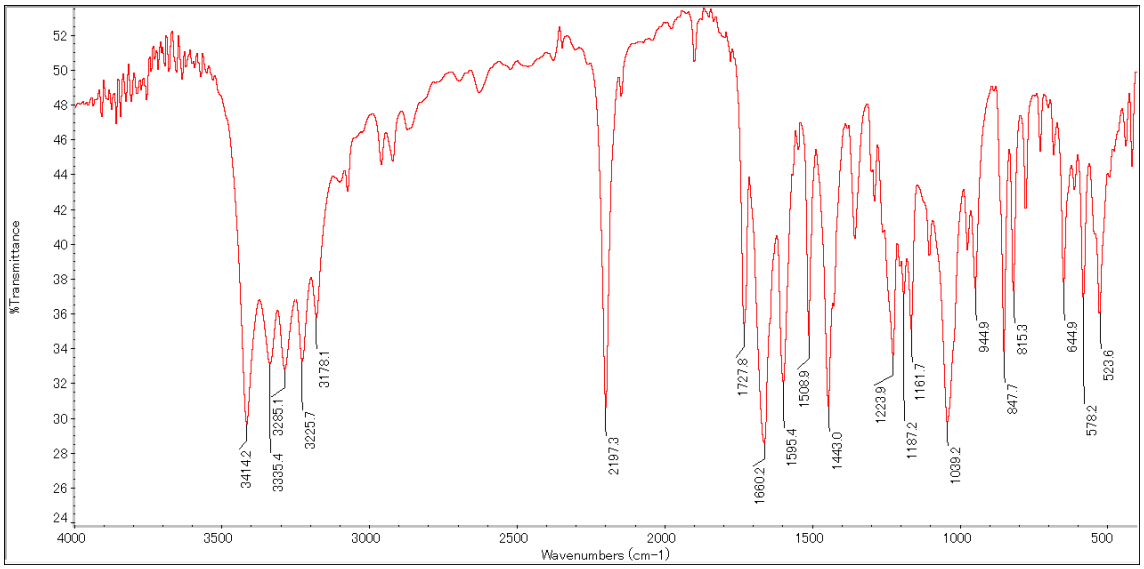
(*cis*-**3c**)



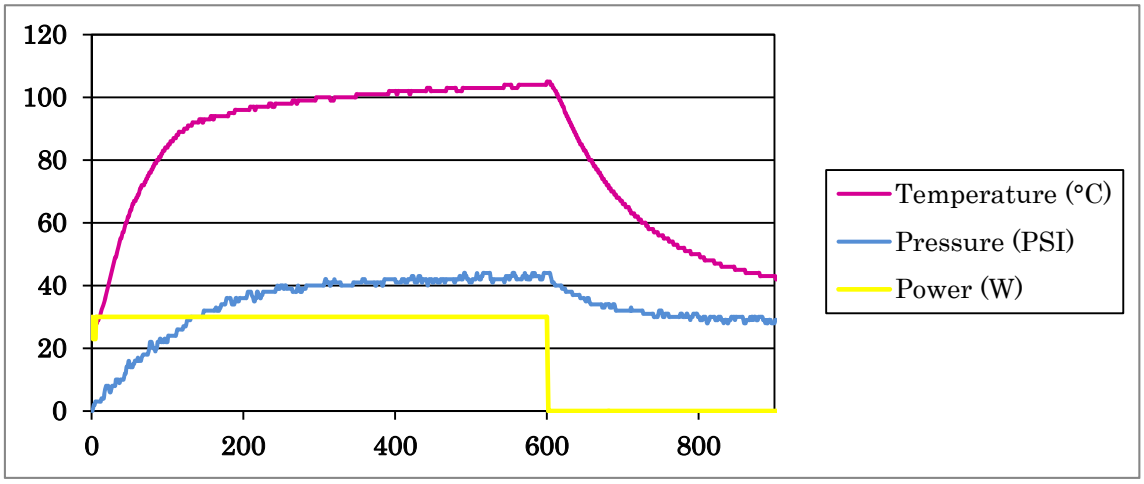
^{1}H NMR



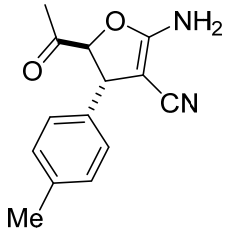
IR



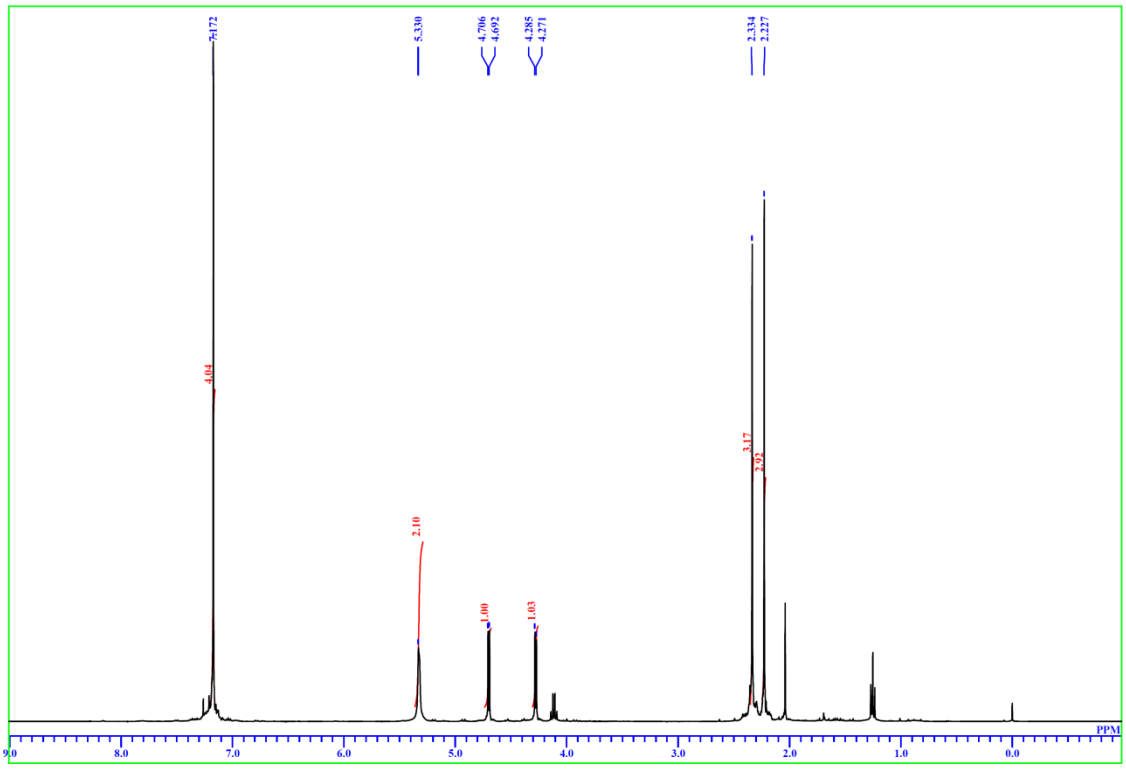
MW Profile (Table 2, entry 3)



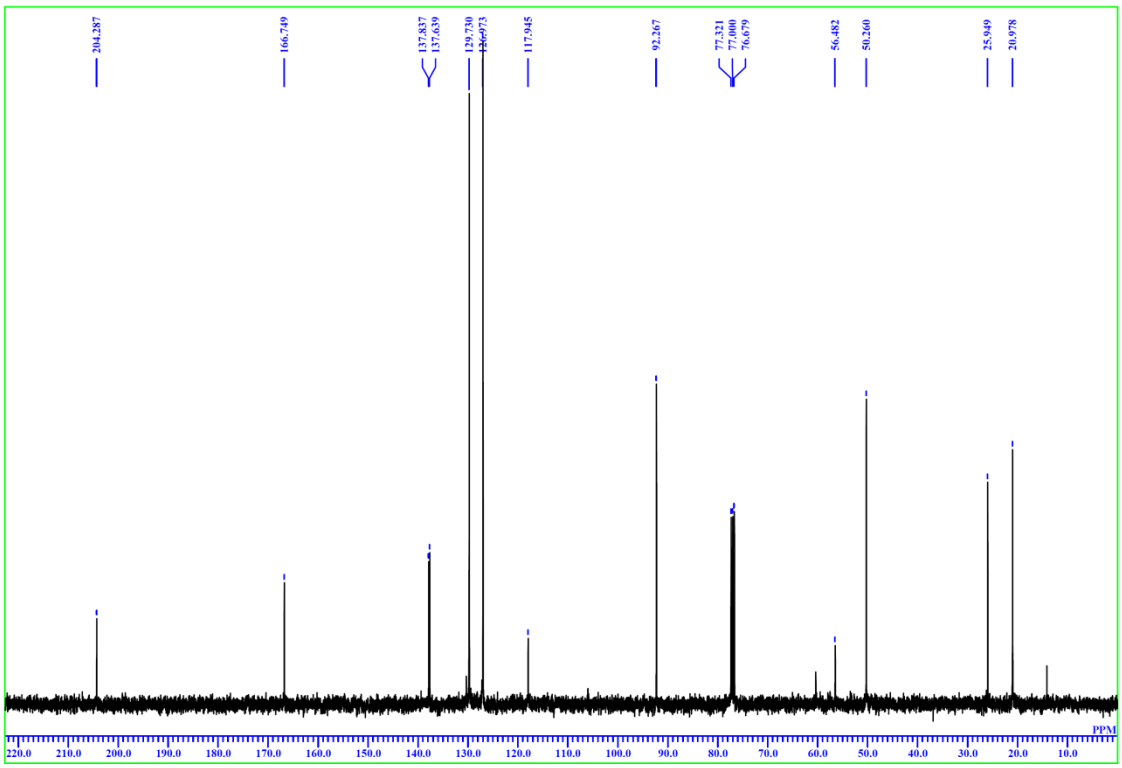
(*trans*-**3d**)



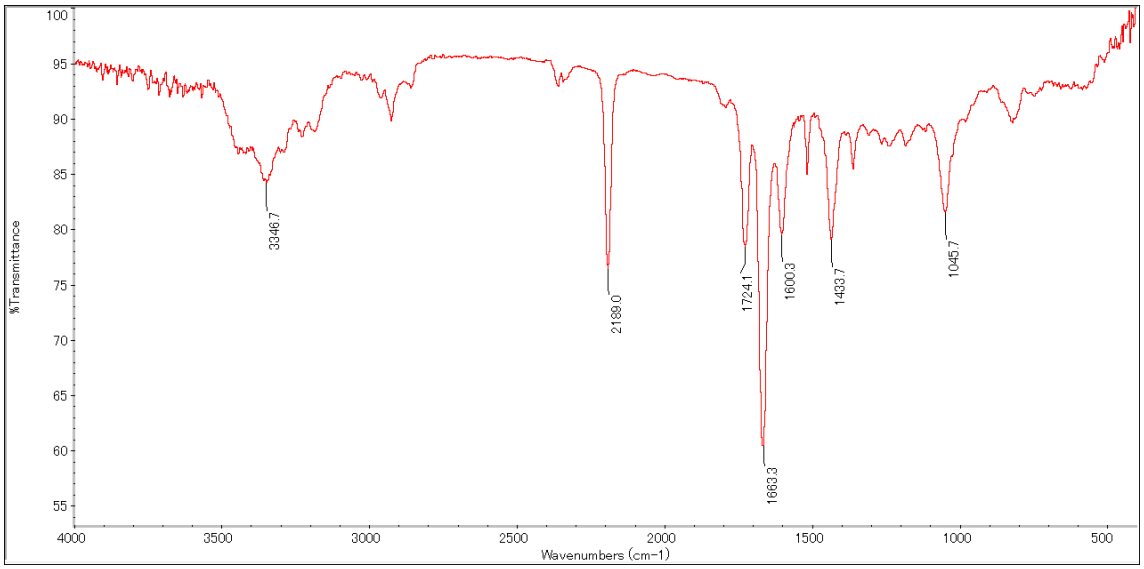
^{1}H NMR



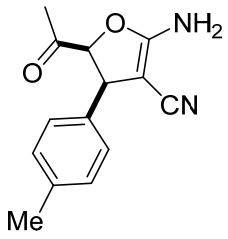
^{13}C NMR



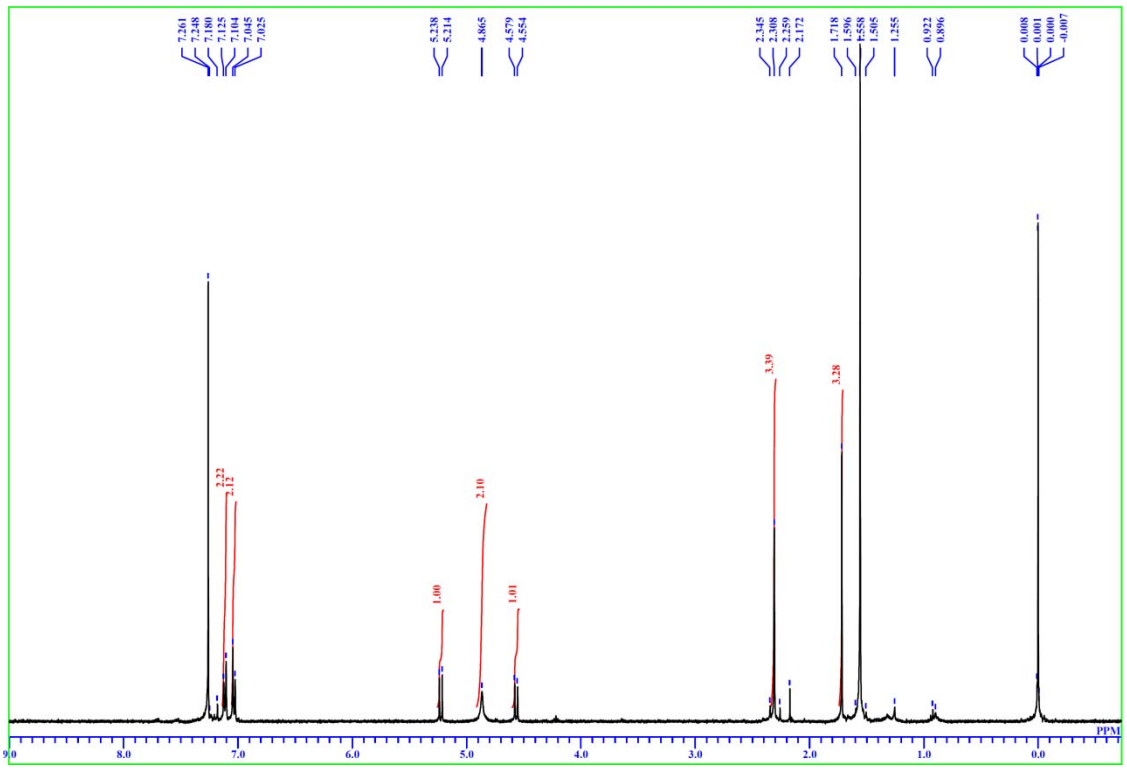
IR



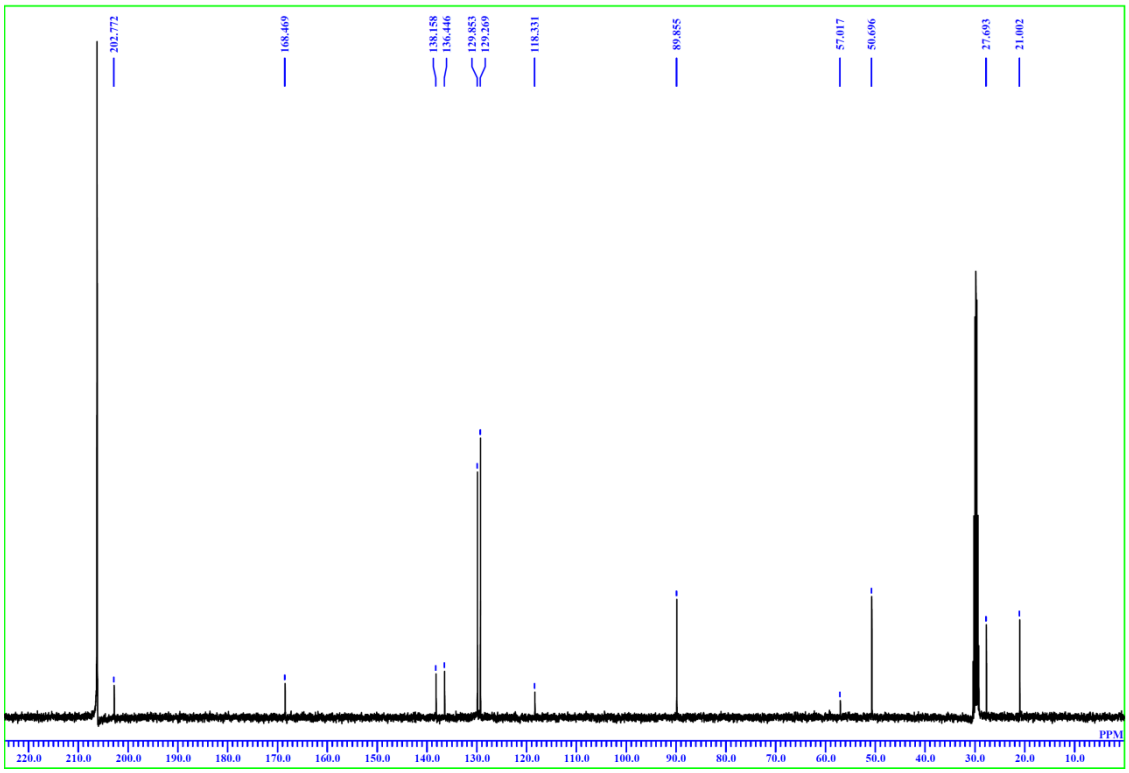
(*cis*-**3d**)



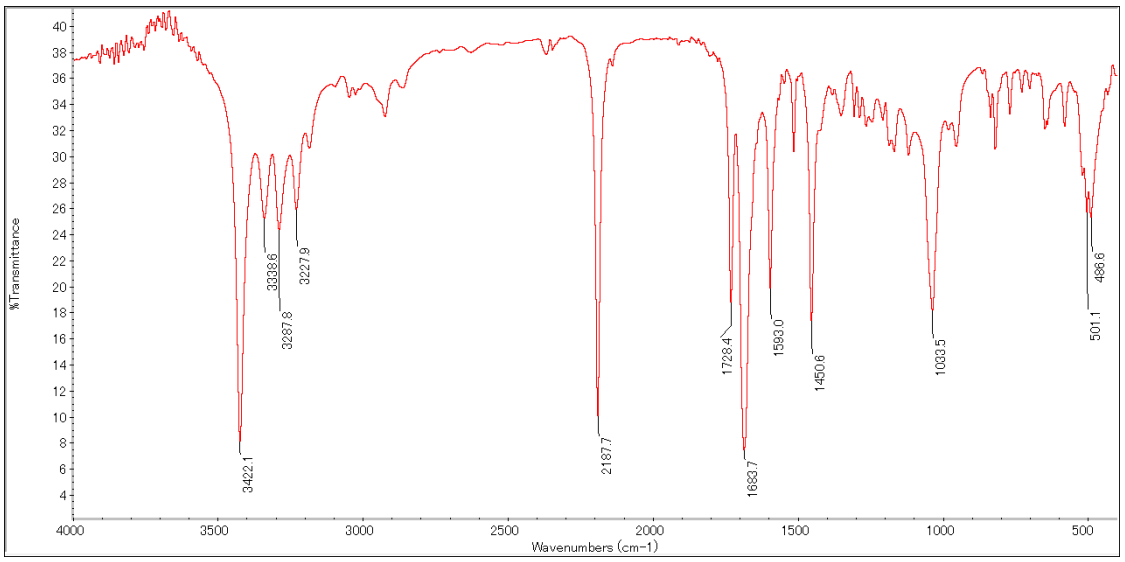
^{1}H NMR



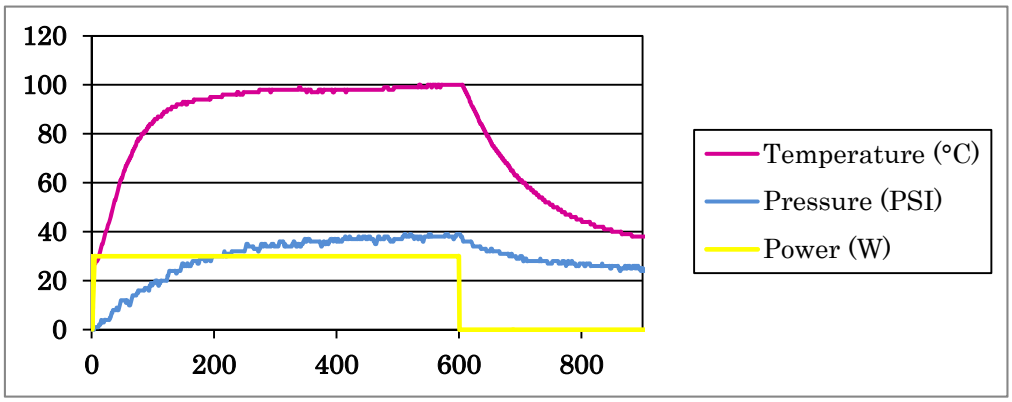
^{13}C NMR



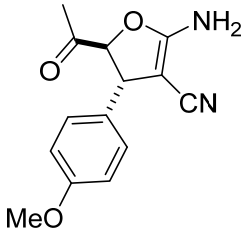
IR



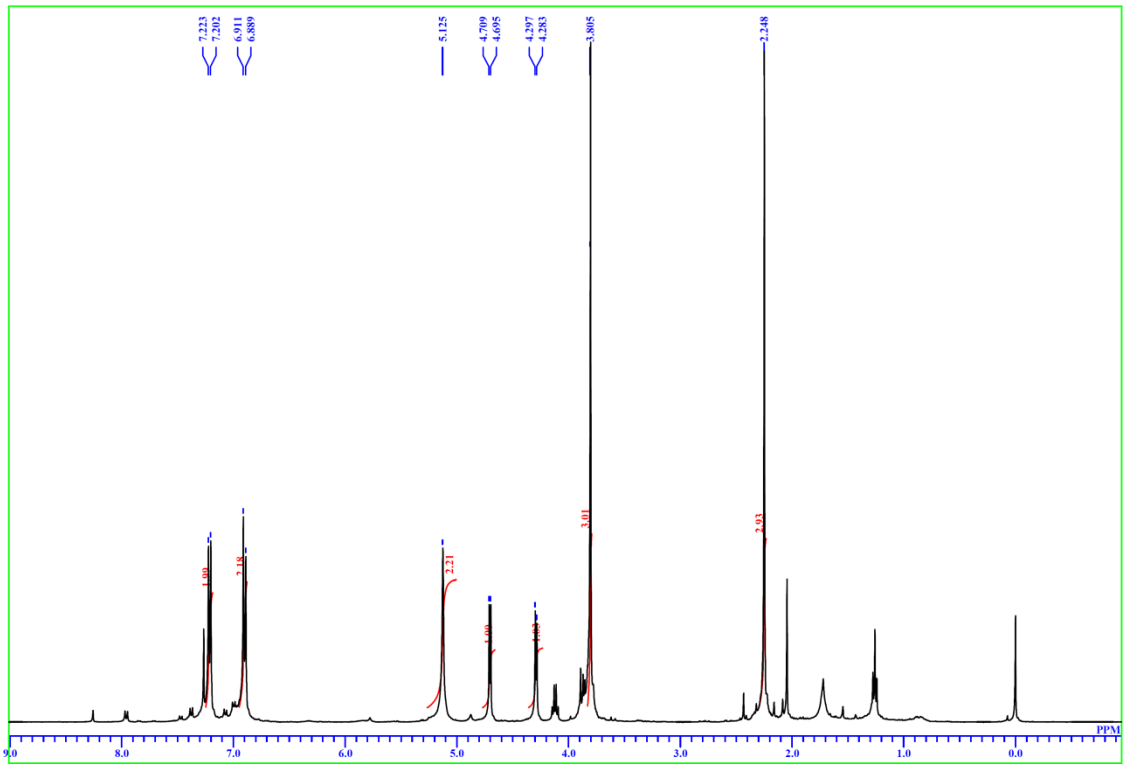
MW Profile (Table 2, entry 4)



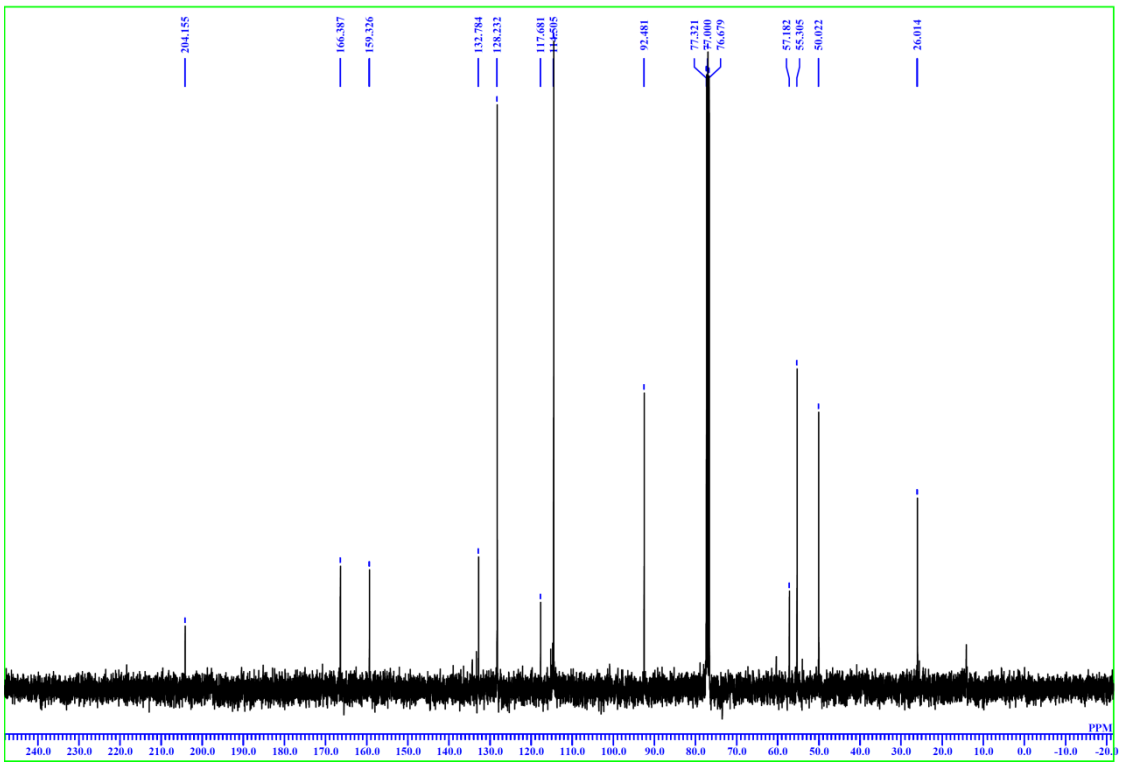
(*trans*-**3e**)



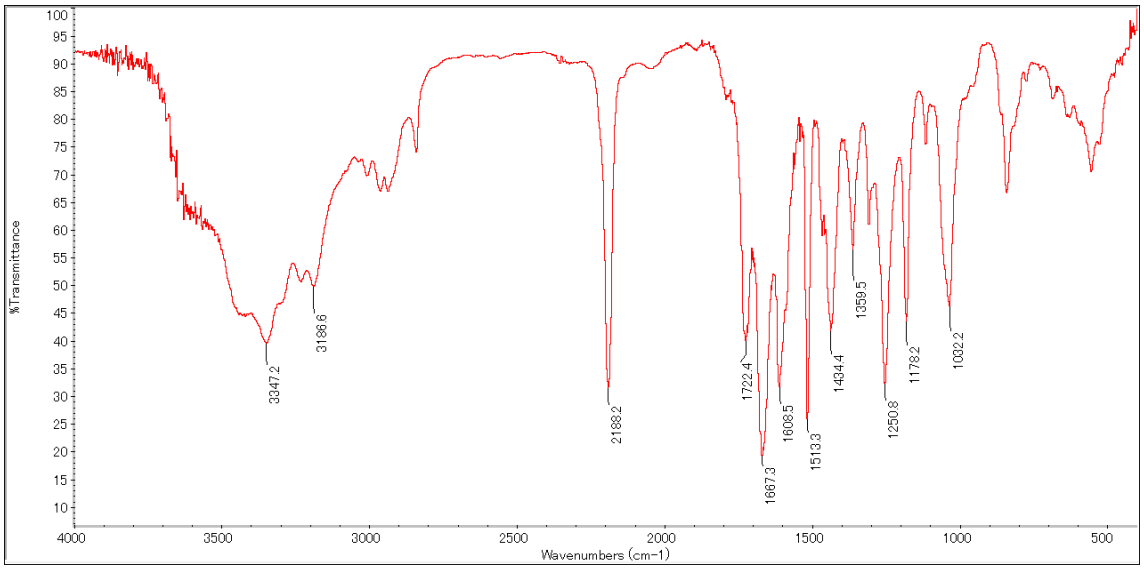
^{1}H NMR



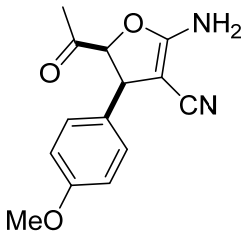
^{13}C NMR



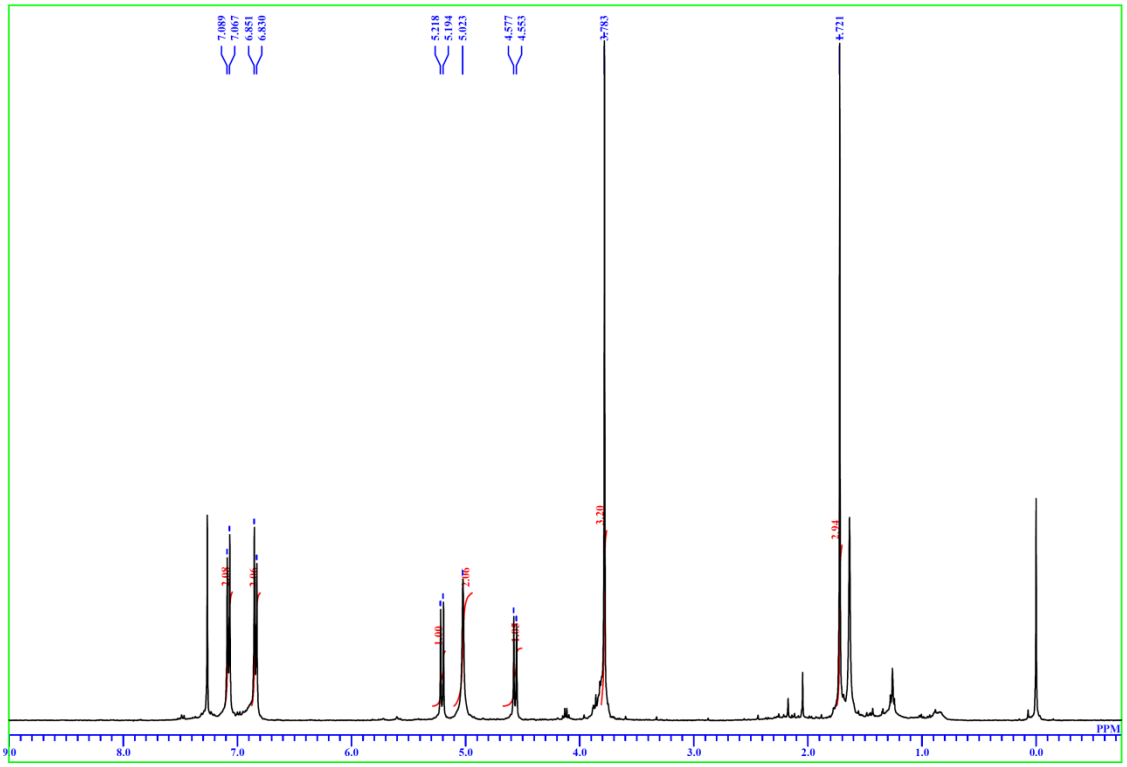
IR



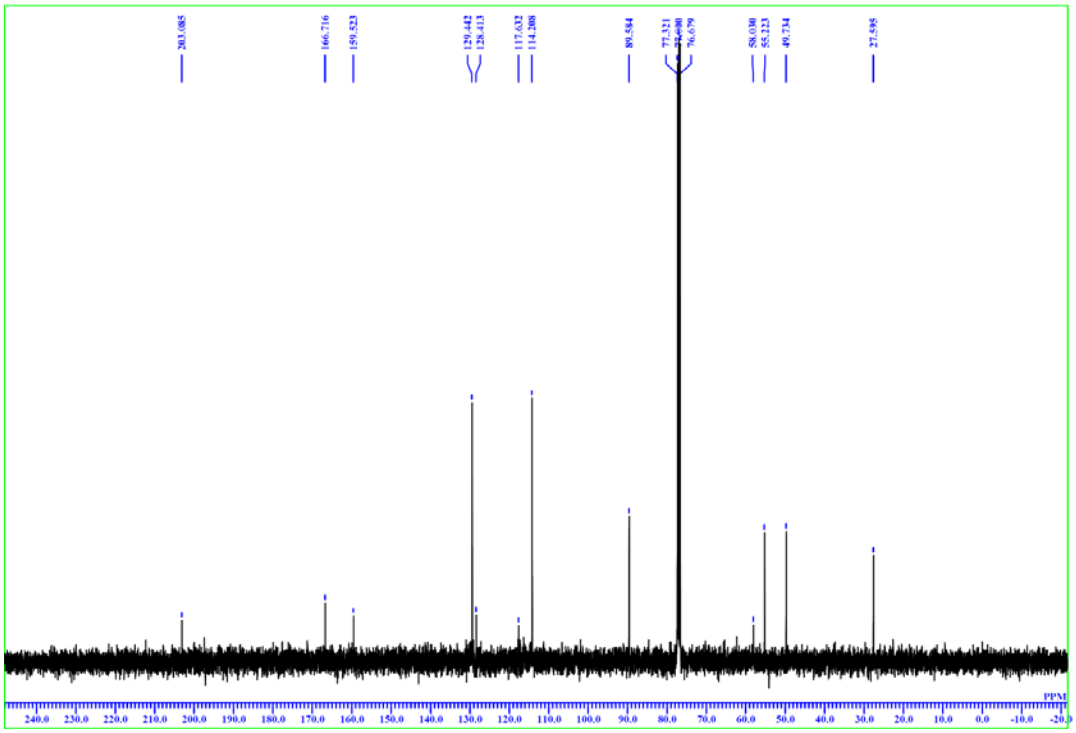
(*cis*-**3e**)



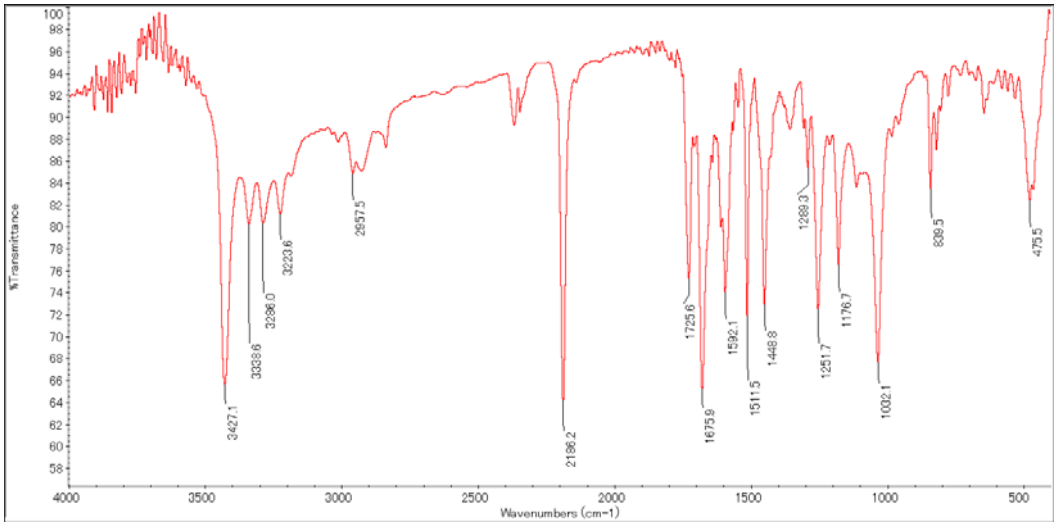
^{1}H NMR



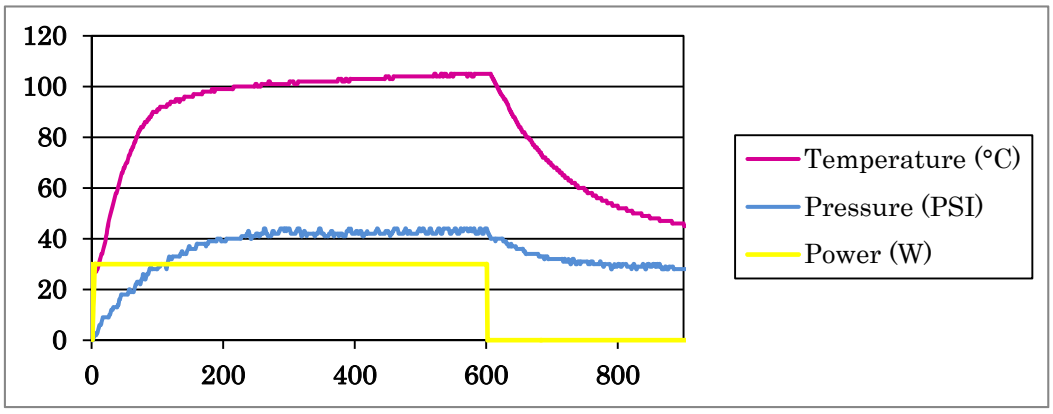
^{13}C NMR



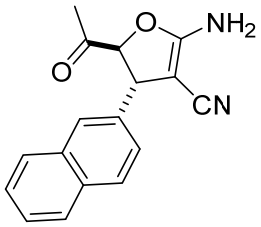
IR



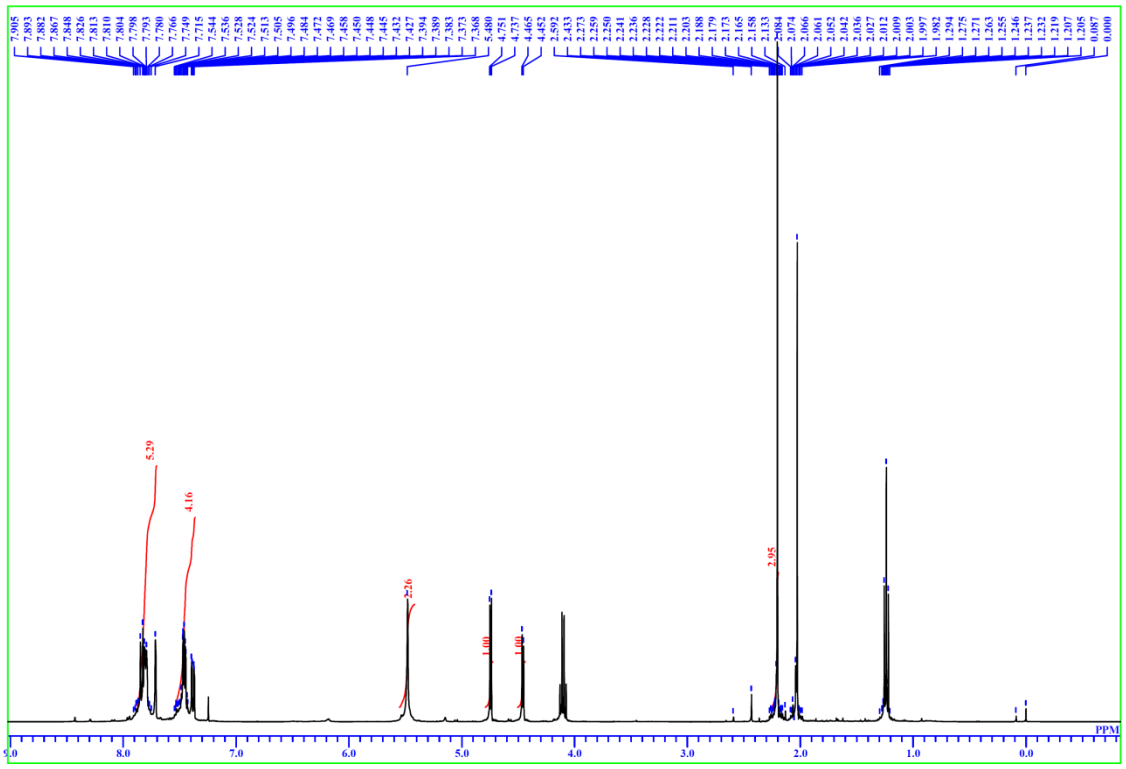
MW Profile (Table 2, entry 5)



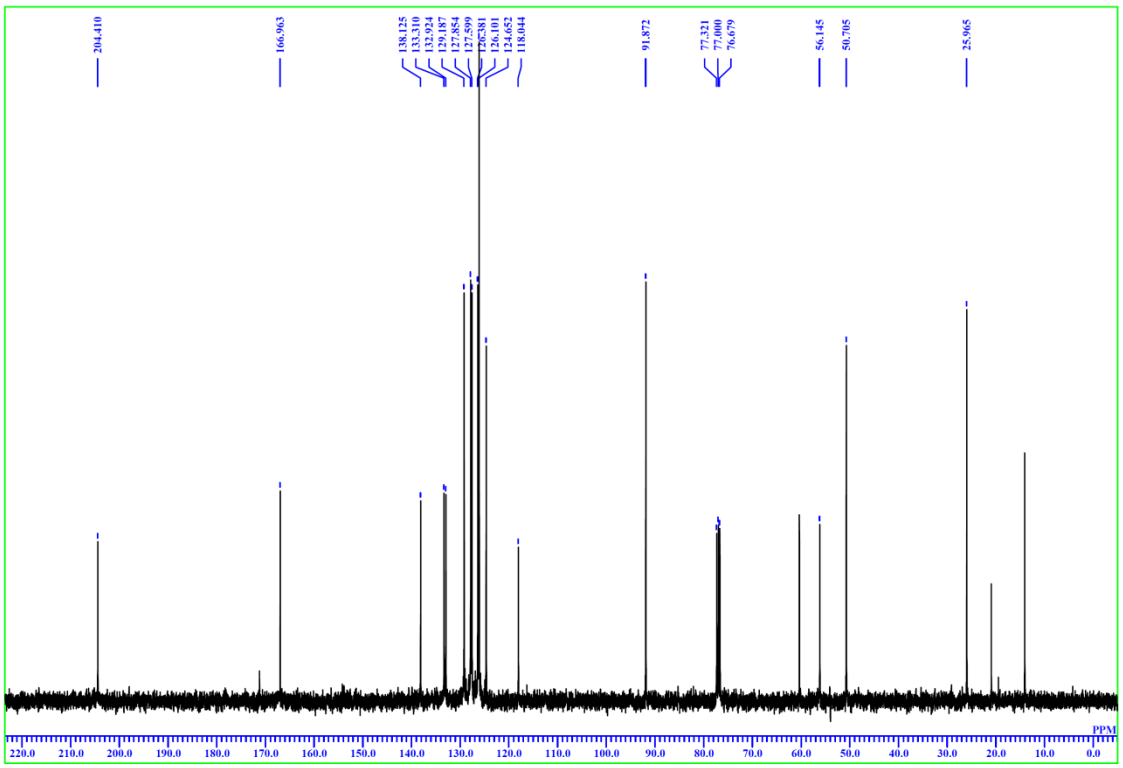
(*trans*-**3f**)



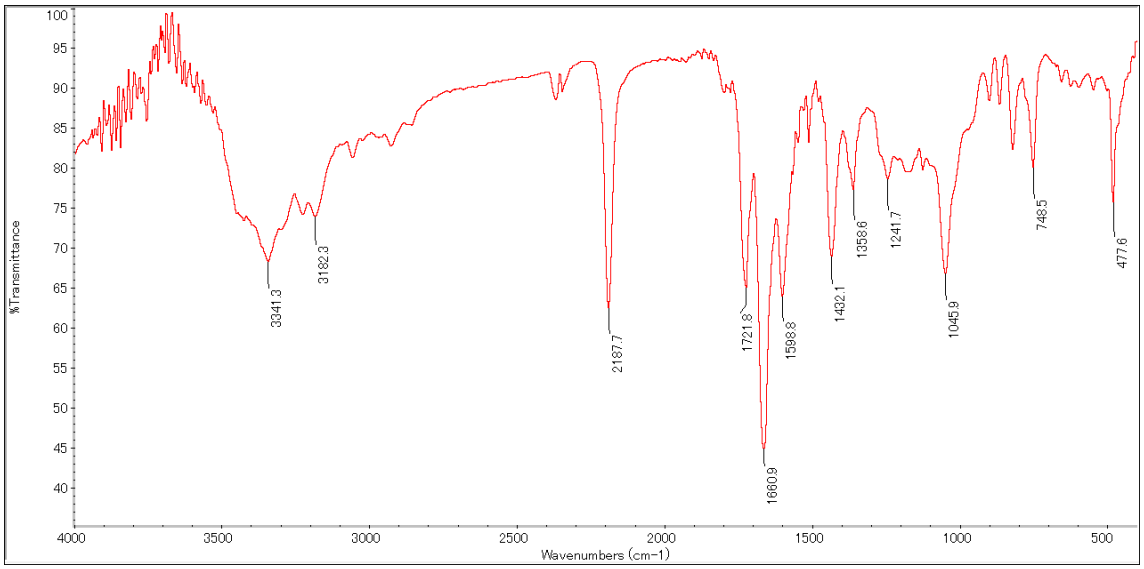
^{1}H NMR



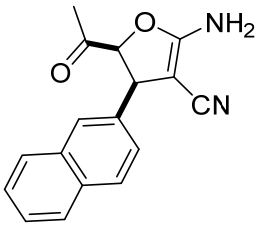
^{13}C NMR



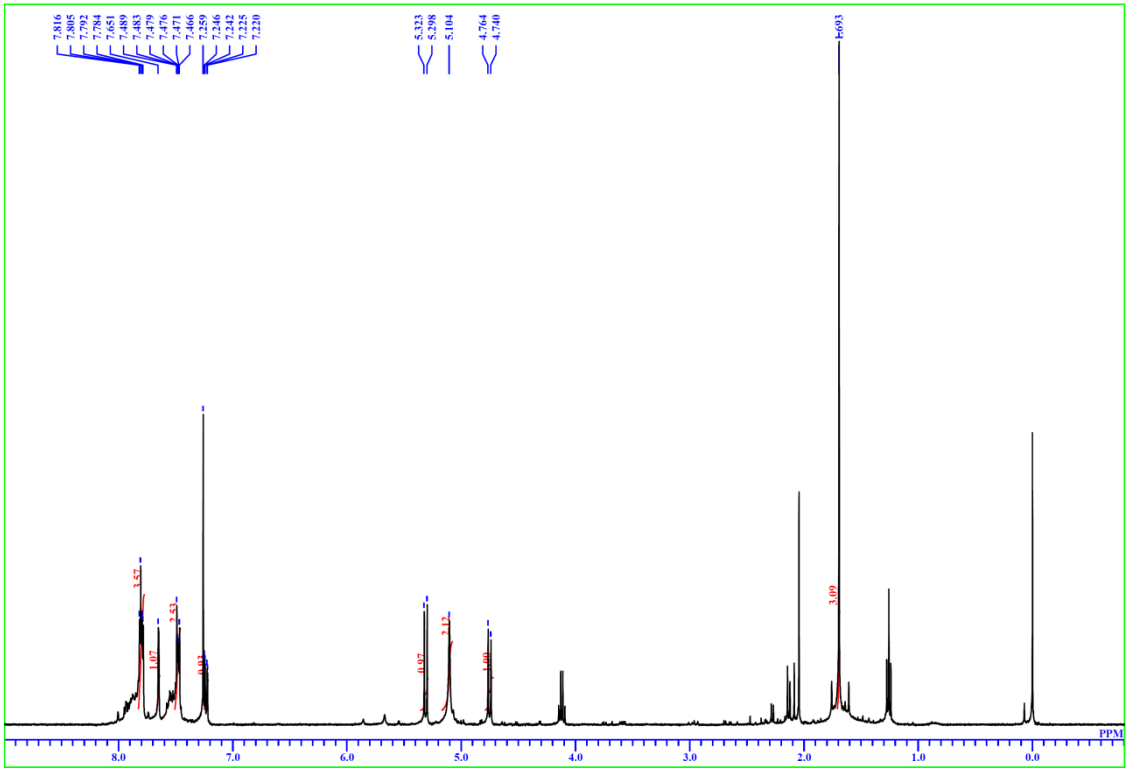
IR



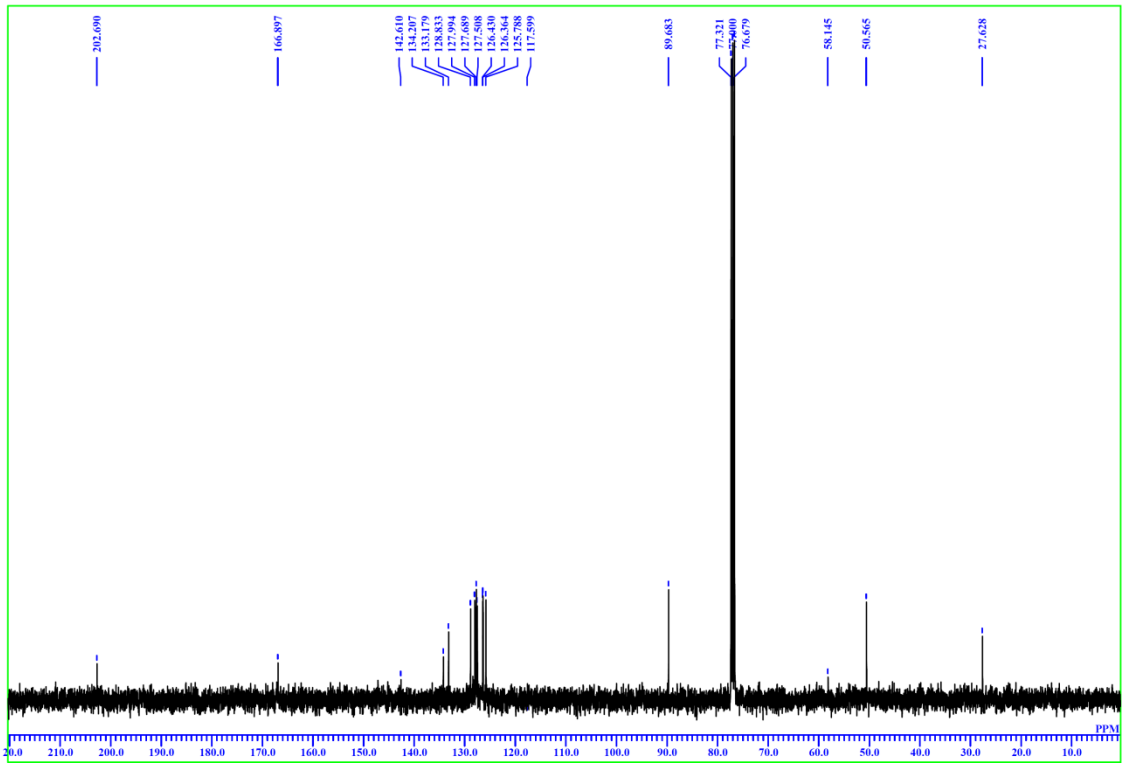
(*cis*-**3f**)



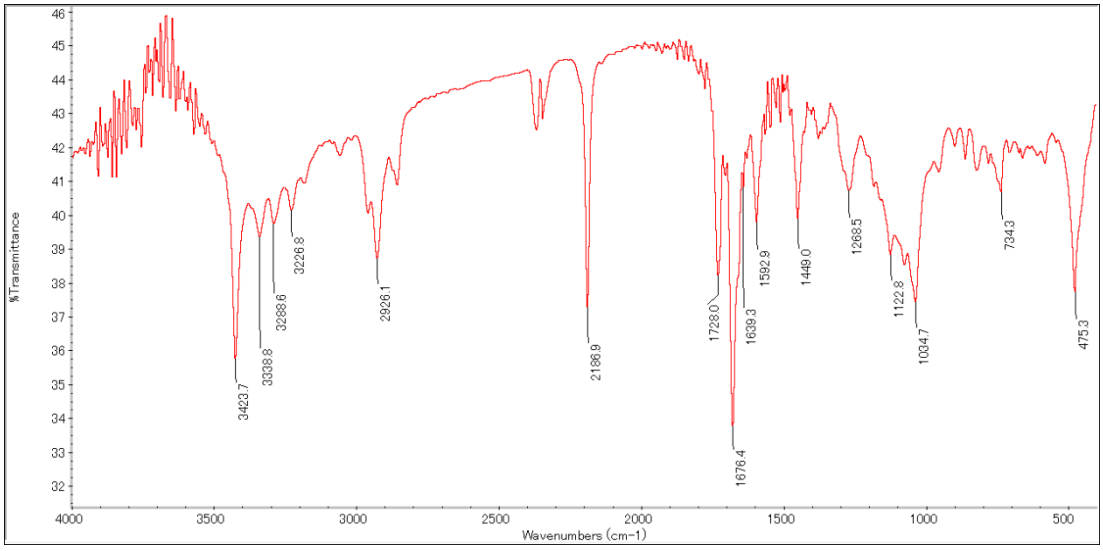
^{1}H NMR



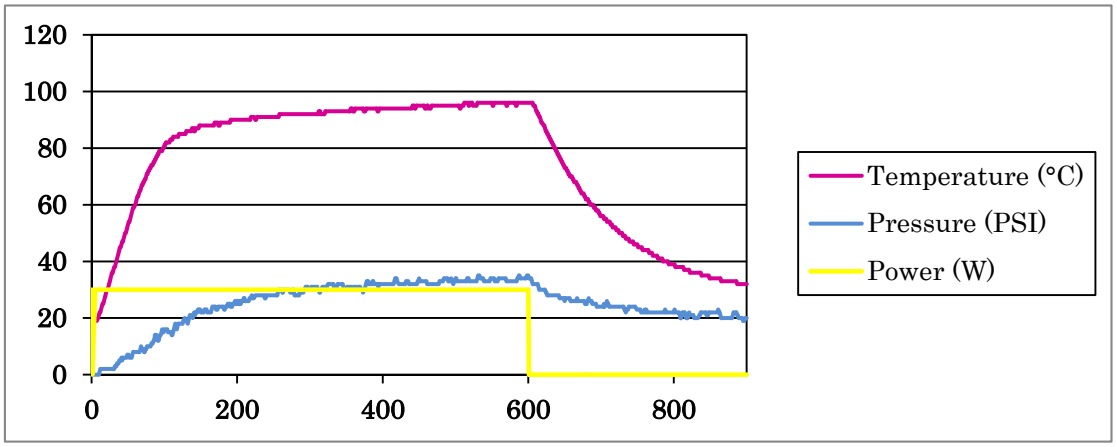
^{13}C NMR



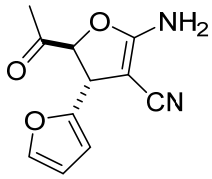
IR



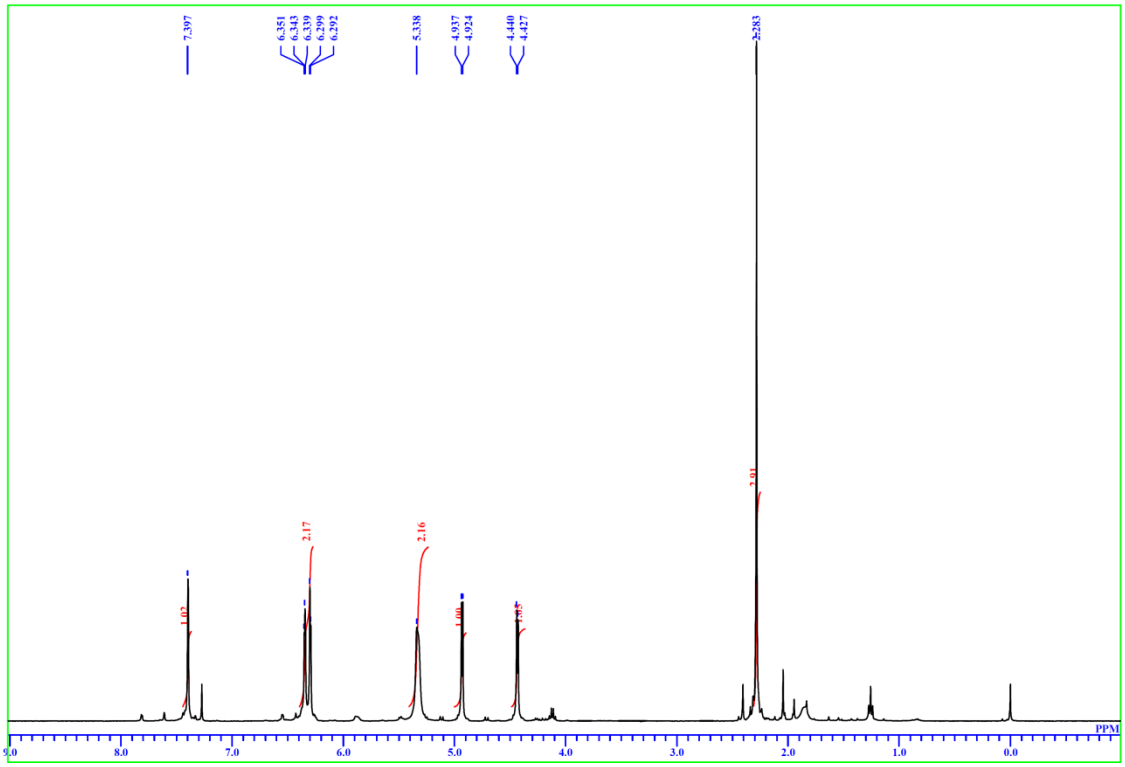
MW Profile (Table 2, entry 6)



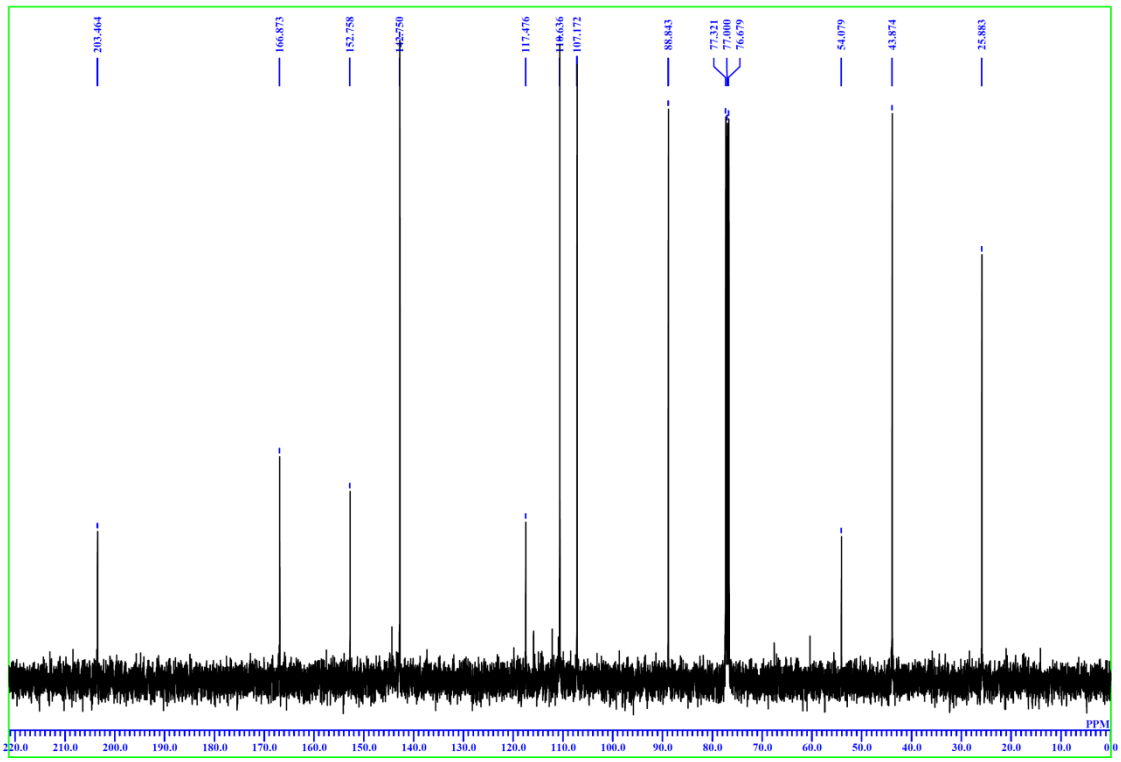
(*trans*-**3g**)



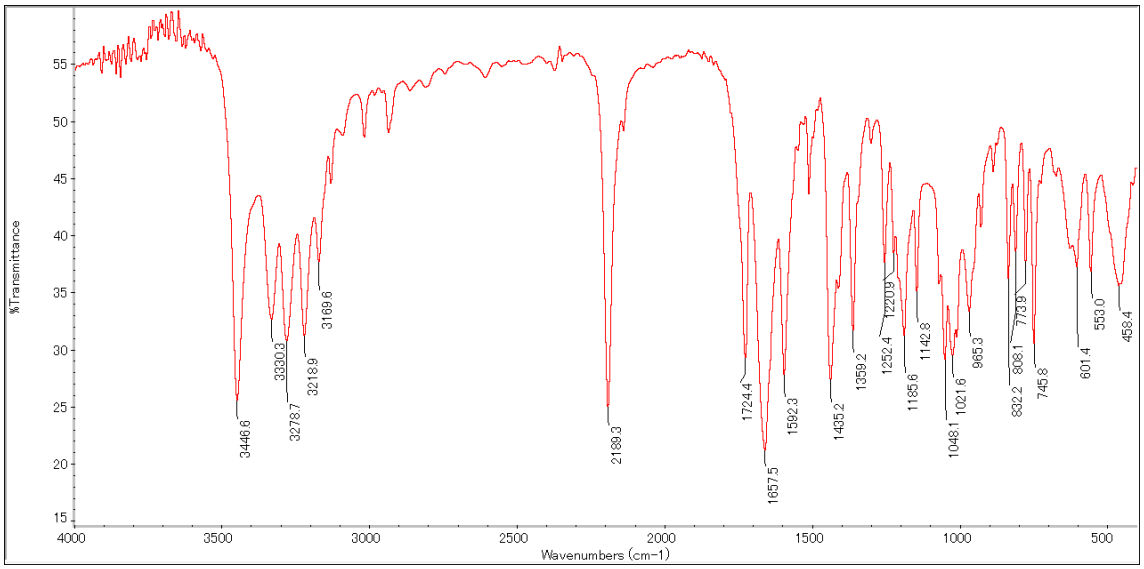
^{1}H NMR



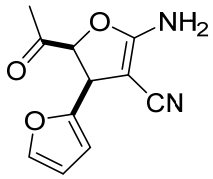
^{13}C NMR



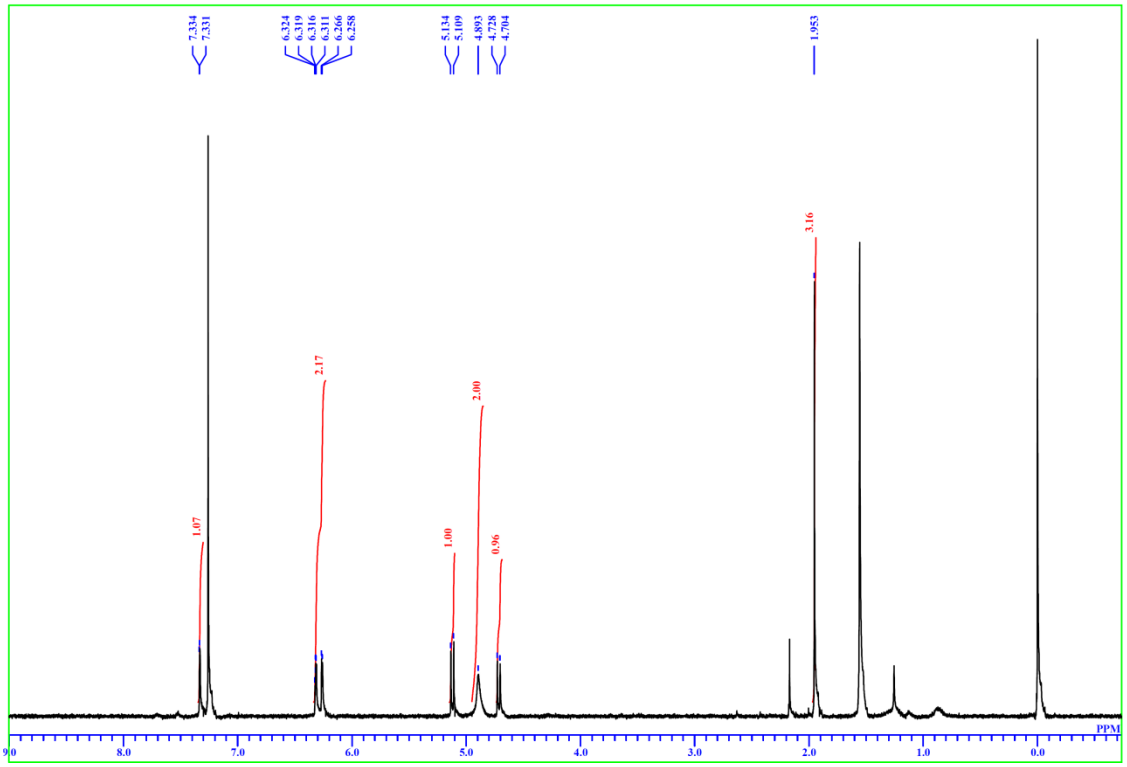
IR



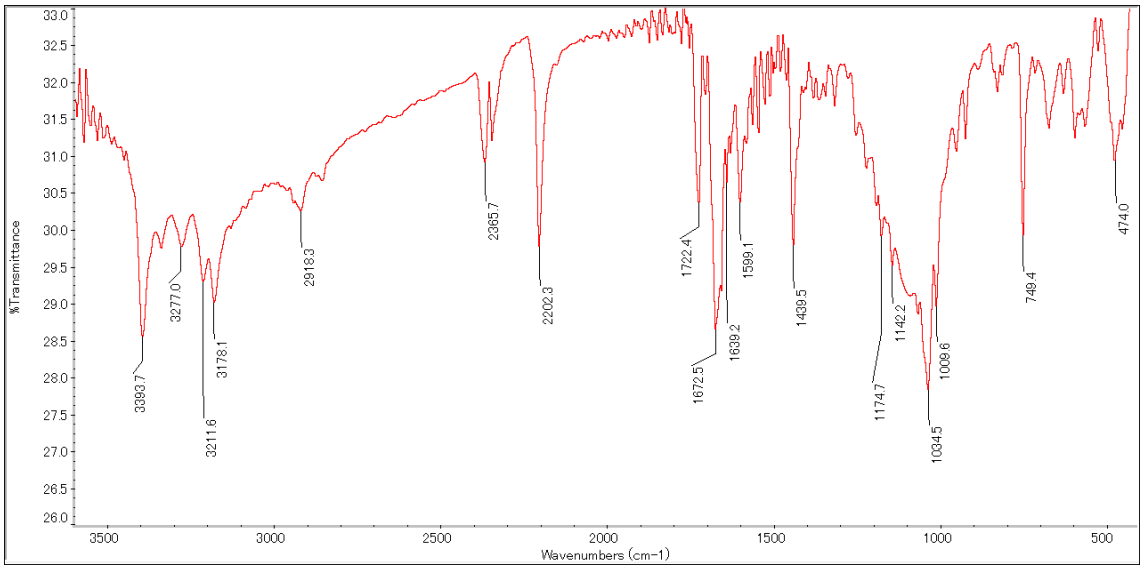
(*cis*-**3g**)



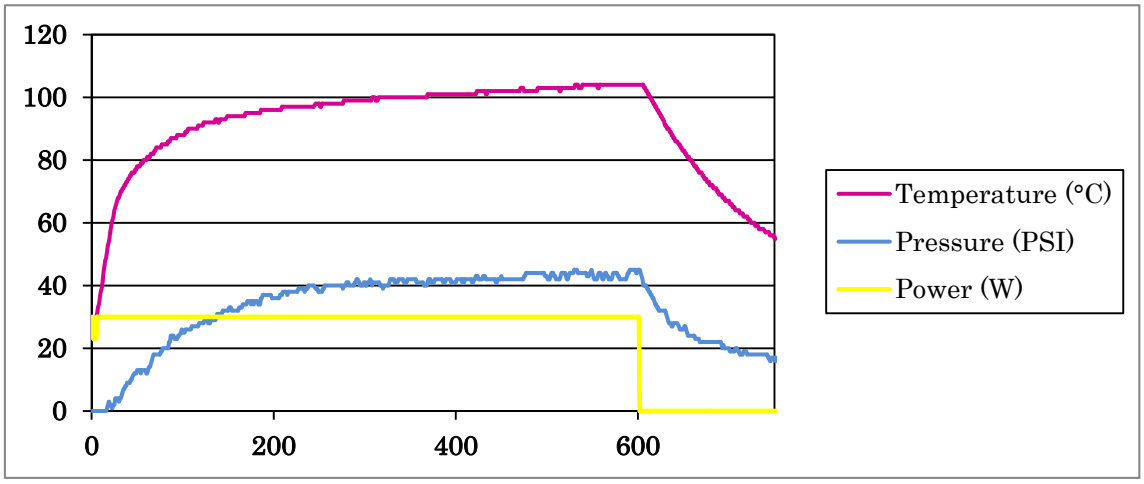
^{1}H NMR



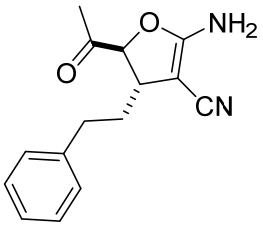
IR



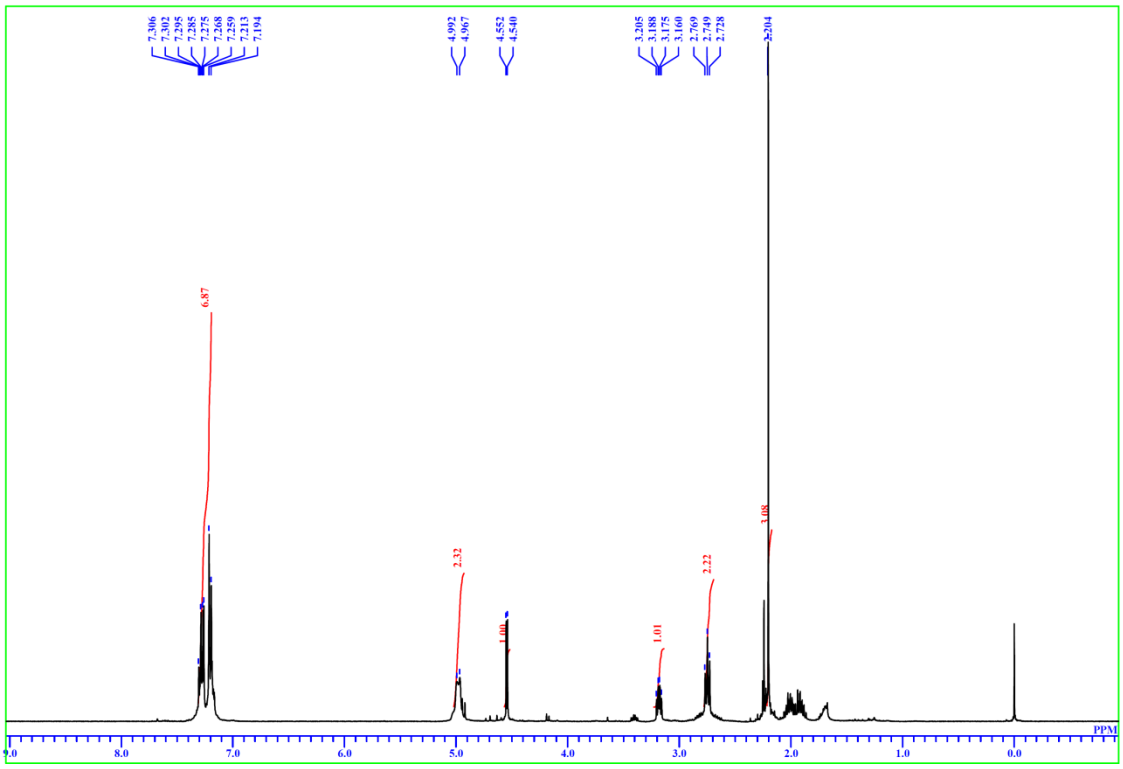
MW Profile (Table 2, entry 7)



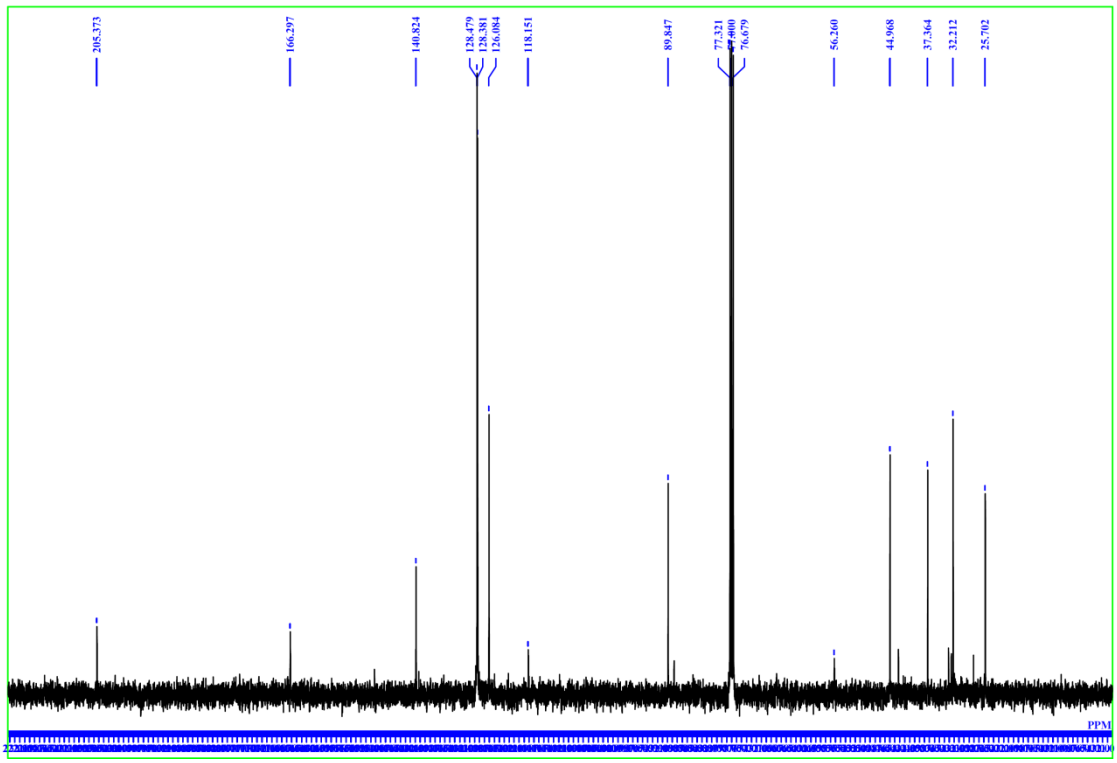
(*trans*-**3h**)



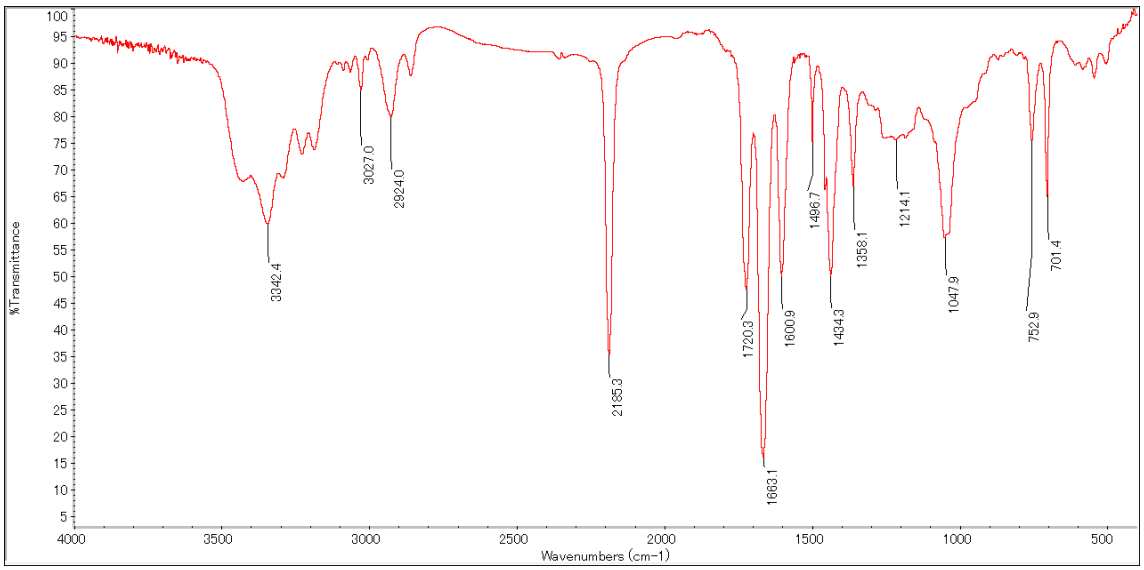
^{1}H NMR



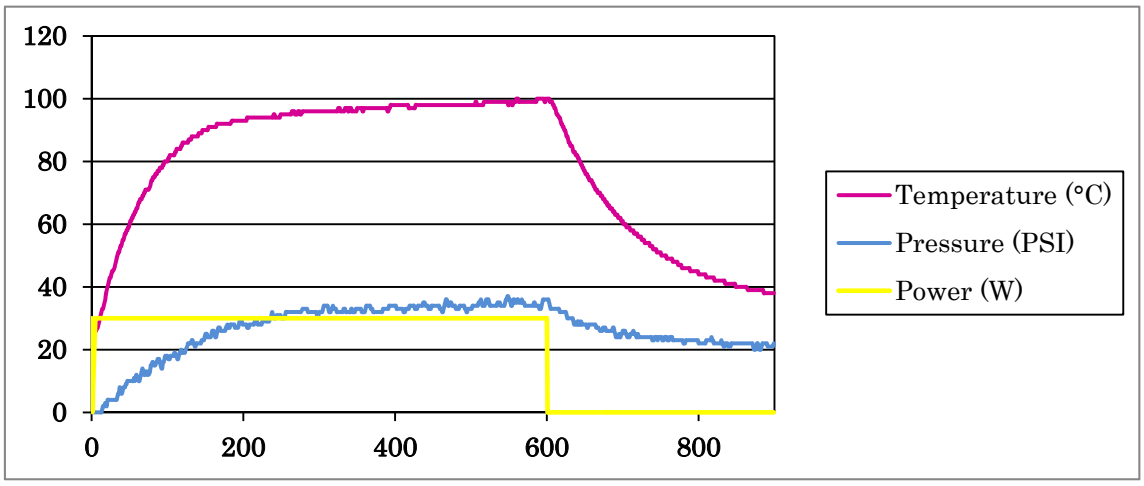
^{13}C NMR



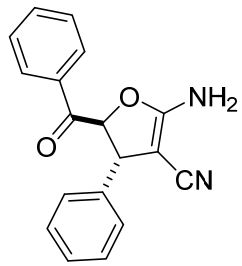
IR



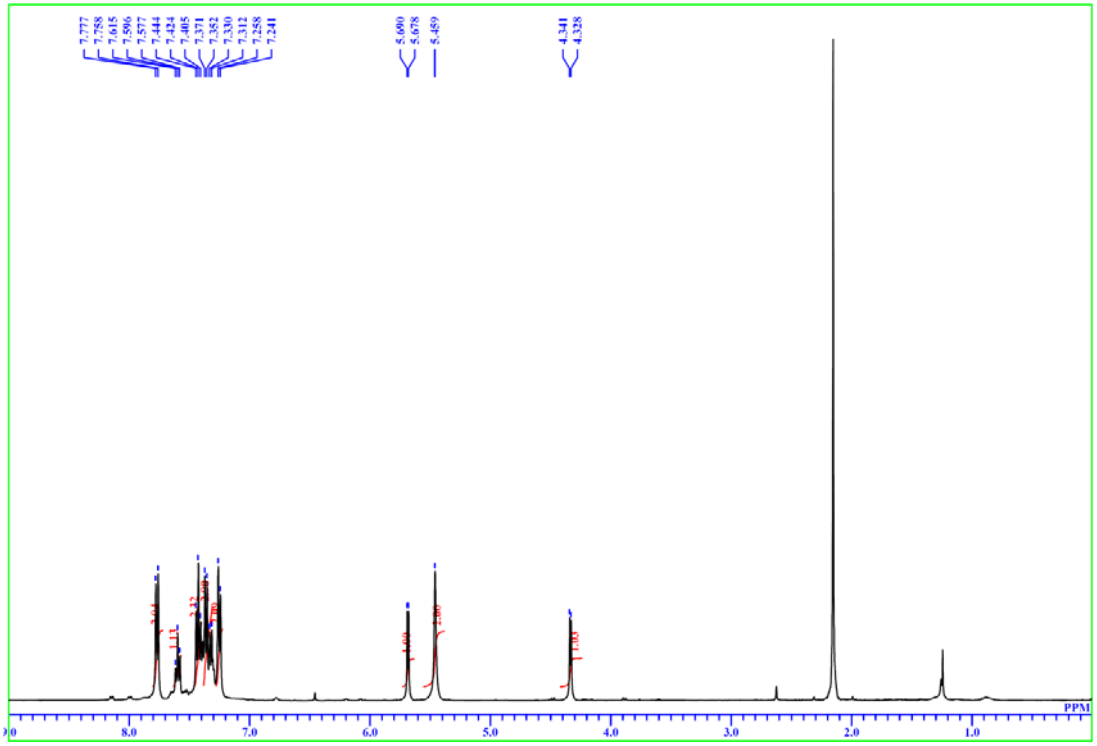
MW Profile (Table 2, entry 8)



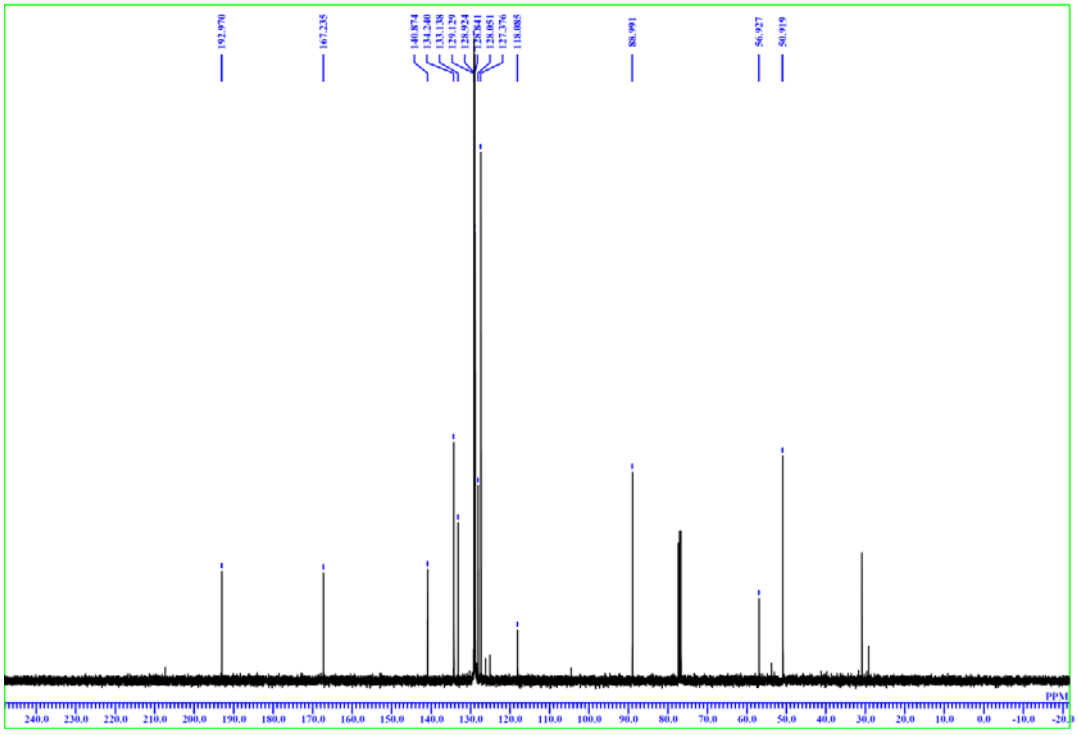
(*trans*-**3i**)



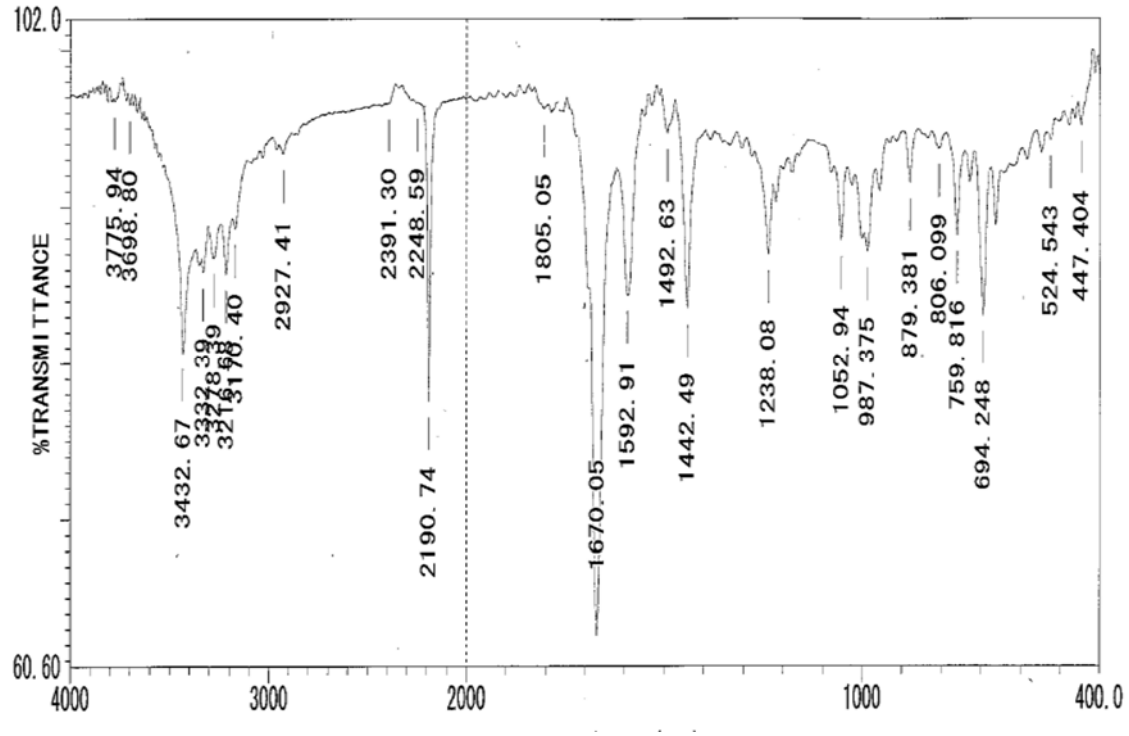
^{1}H NMR



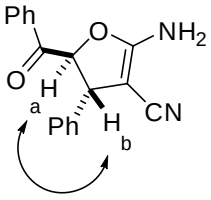
^{13}C NMR



IR

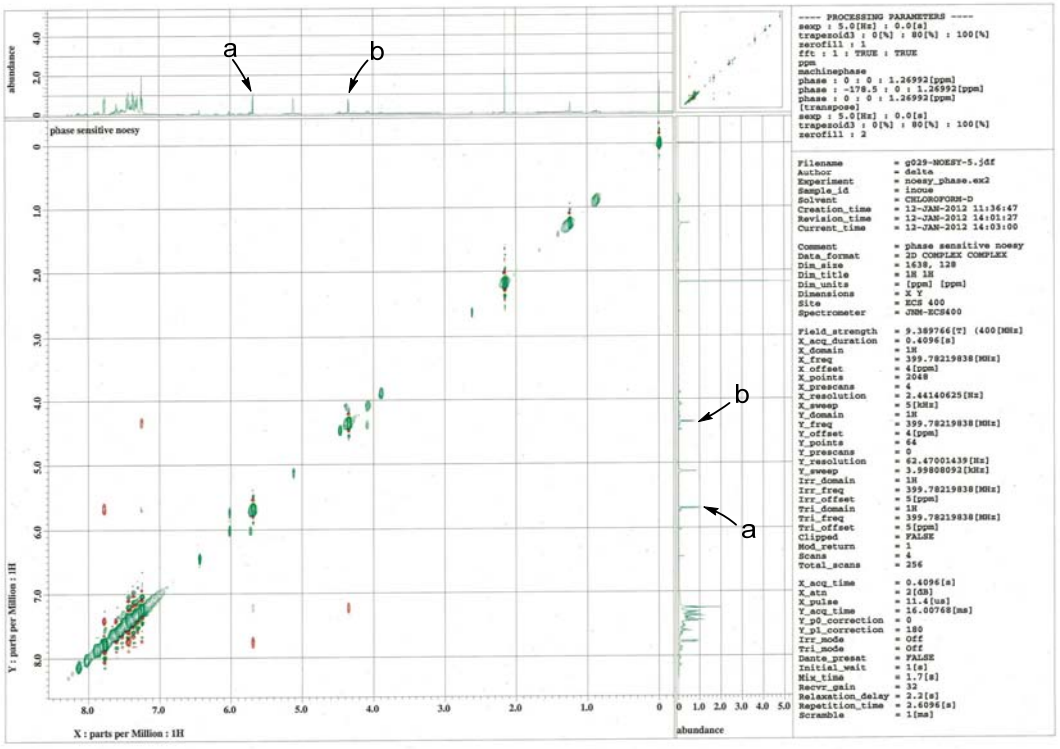


NOESY

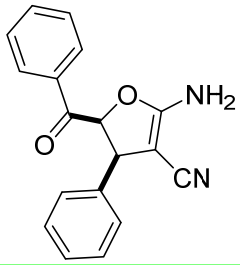


no *NOE*

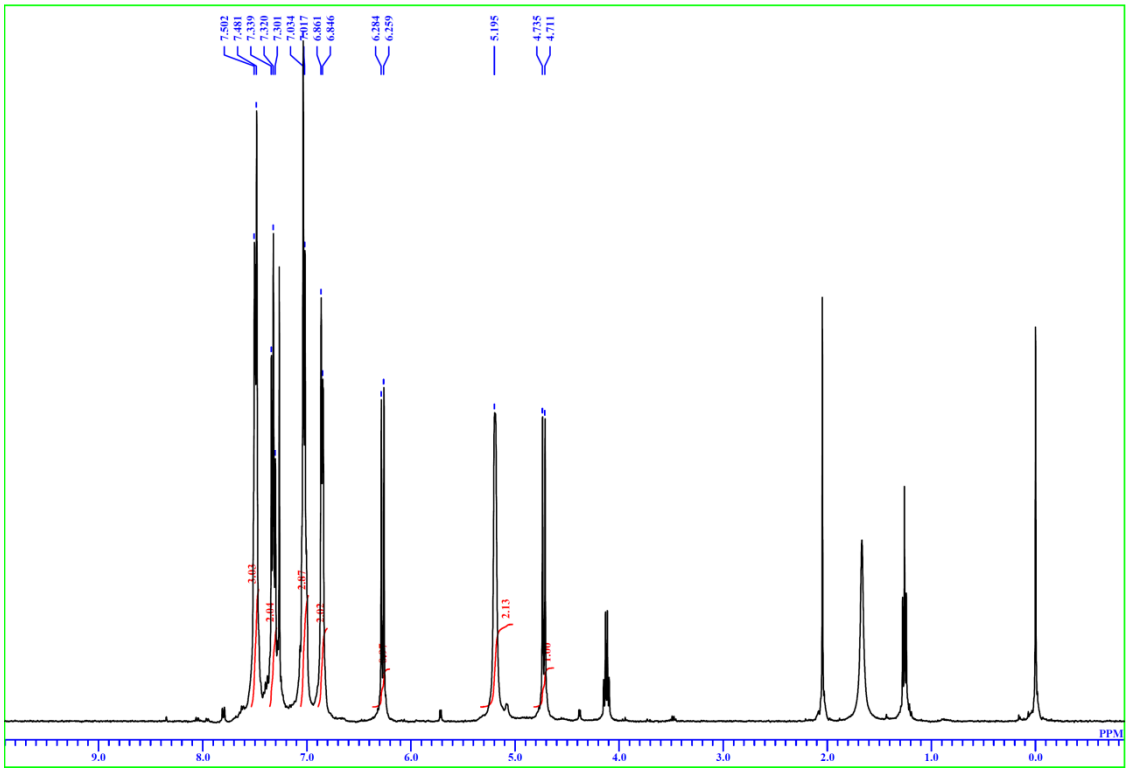
trans-**3i**



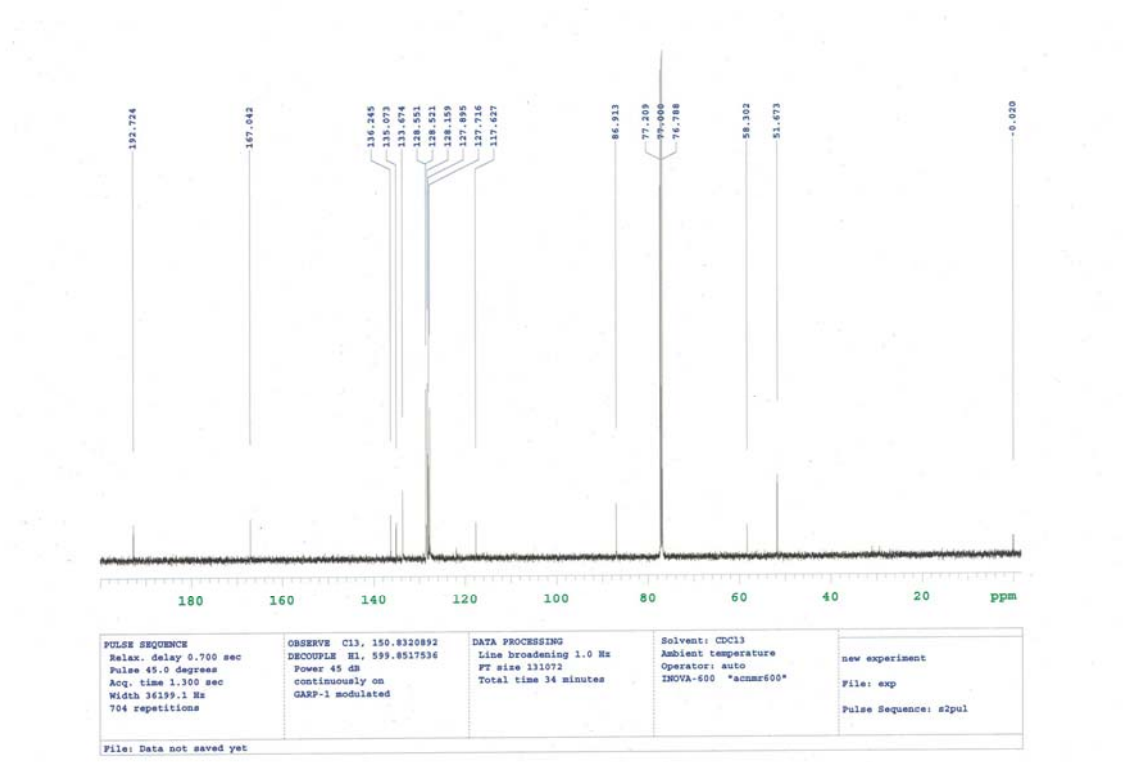
(*cis*-**3i**)



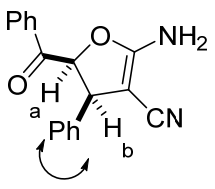
^{1}H NMR



^{13}C NMR

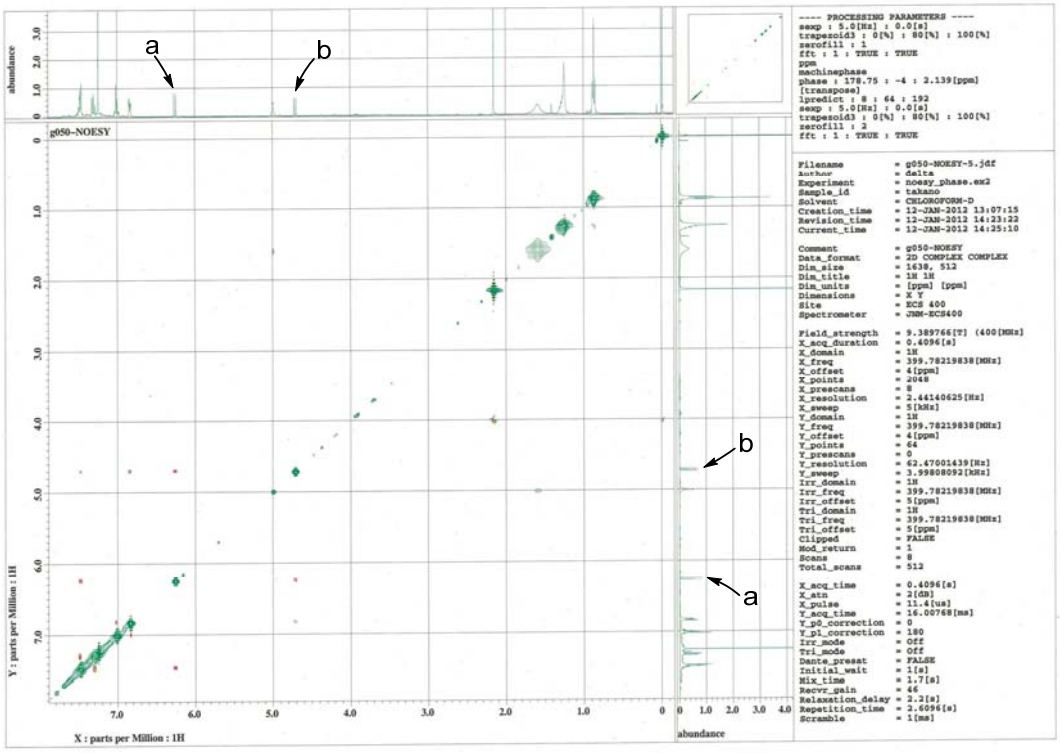


NOESY

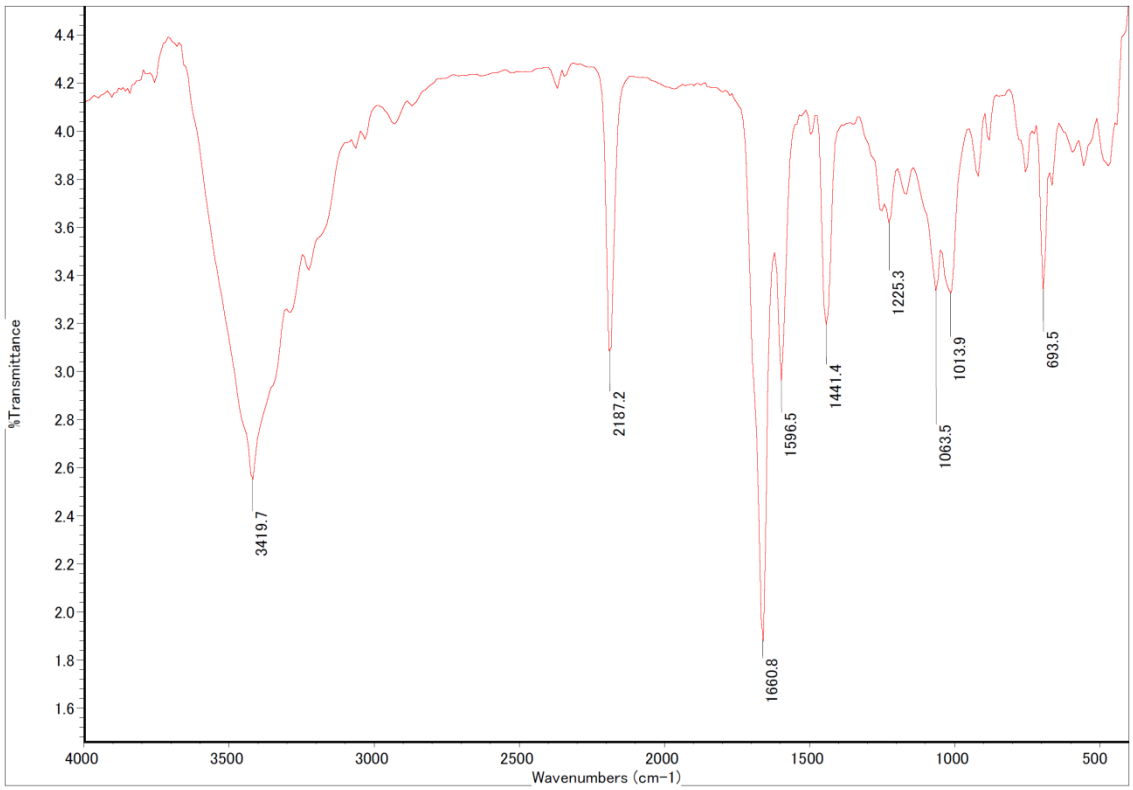


cis-**3i**

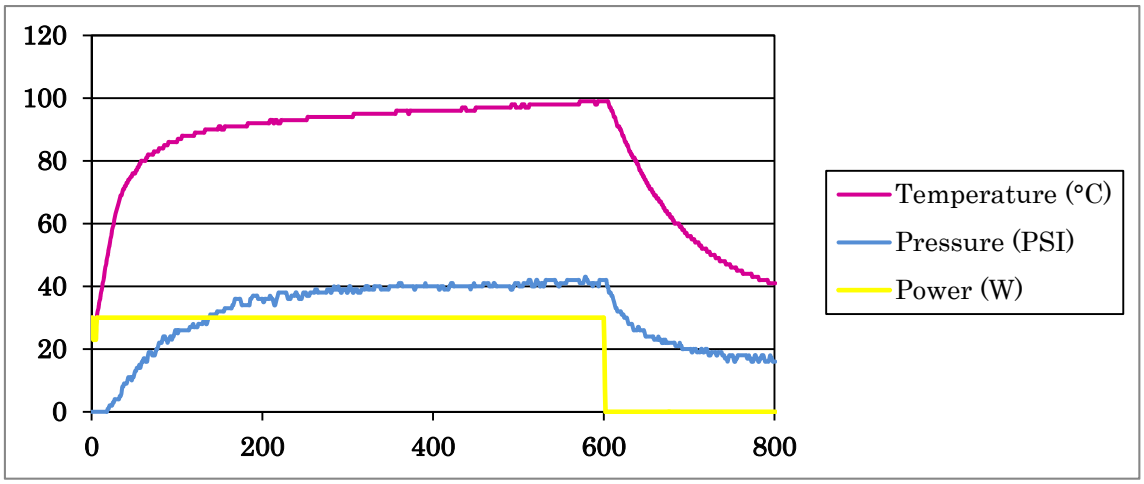
NOE



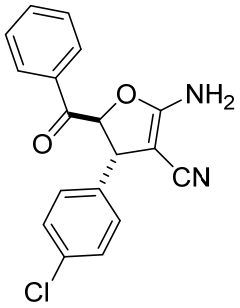
IR



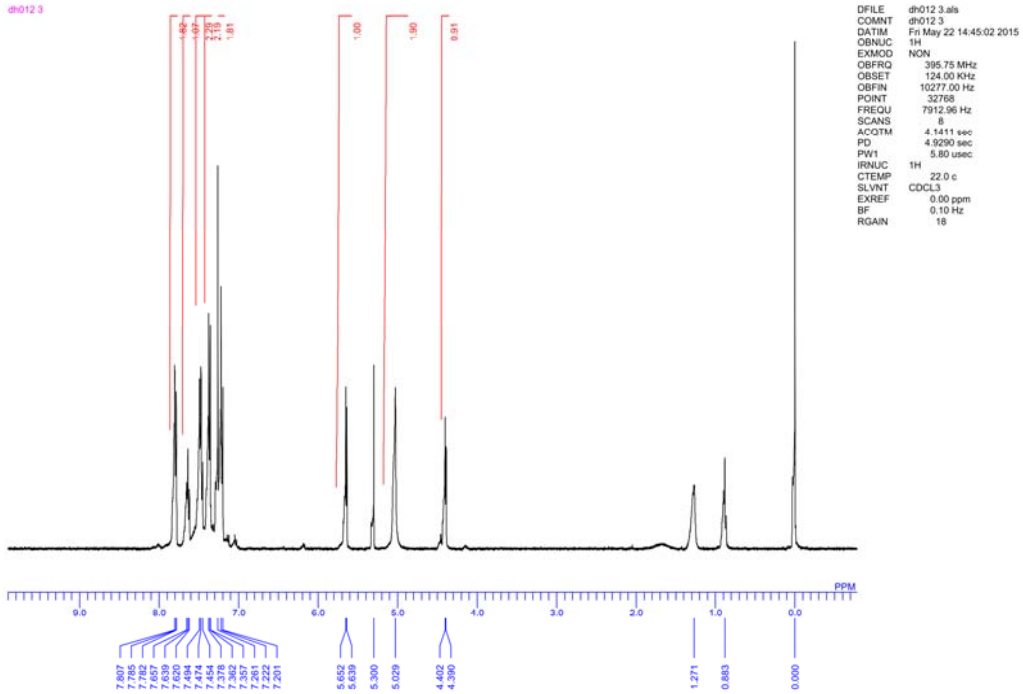
MW Profile (Table 2, entry 9)



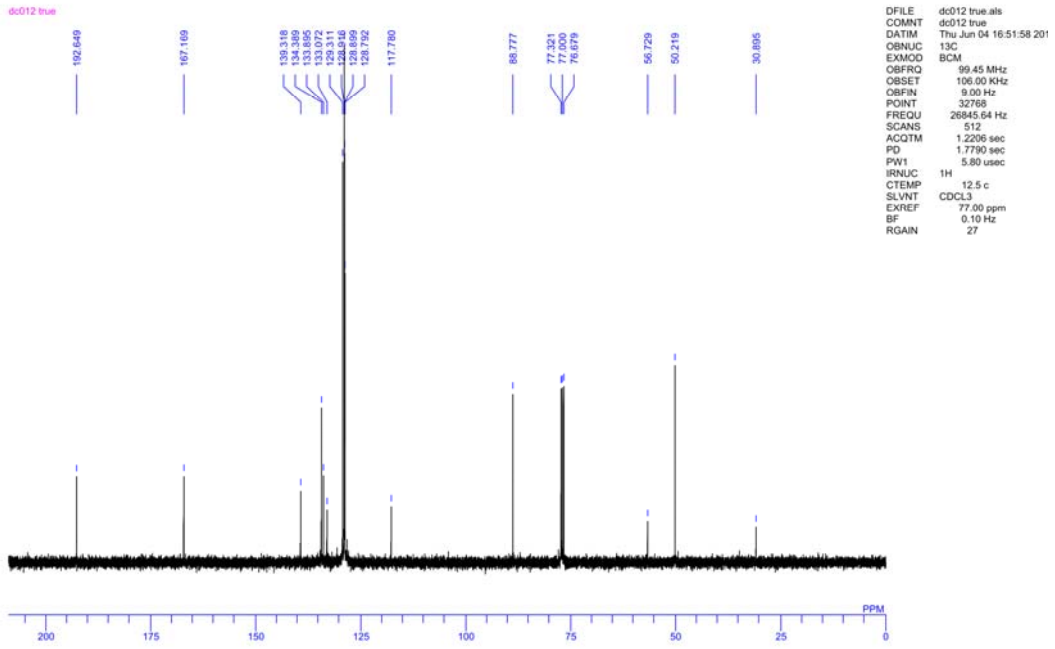
(*trans*-**3j**)



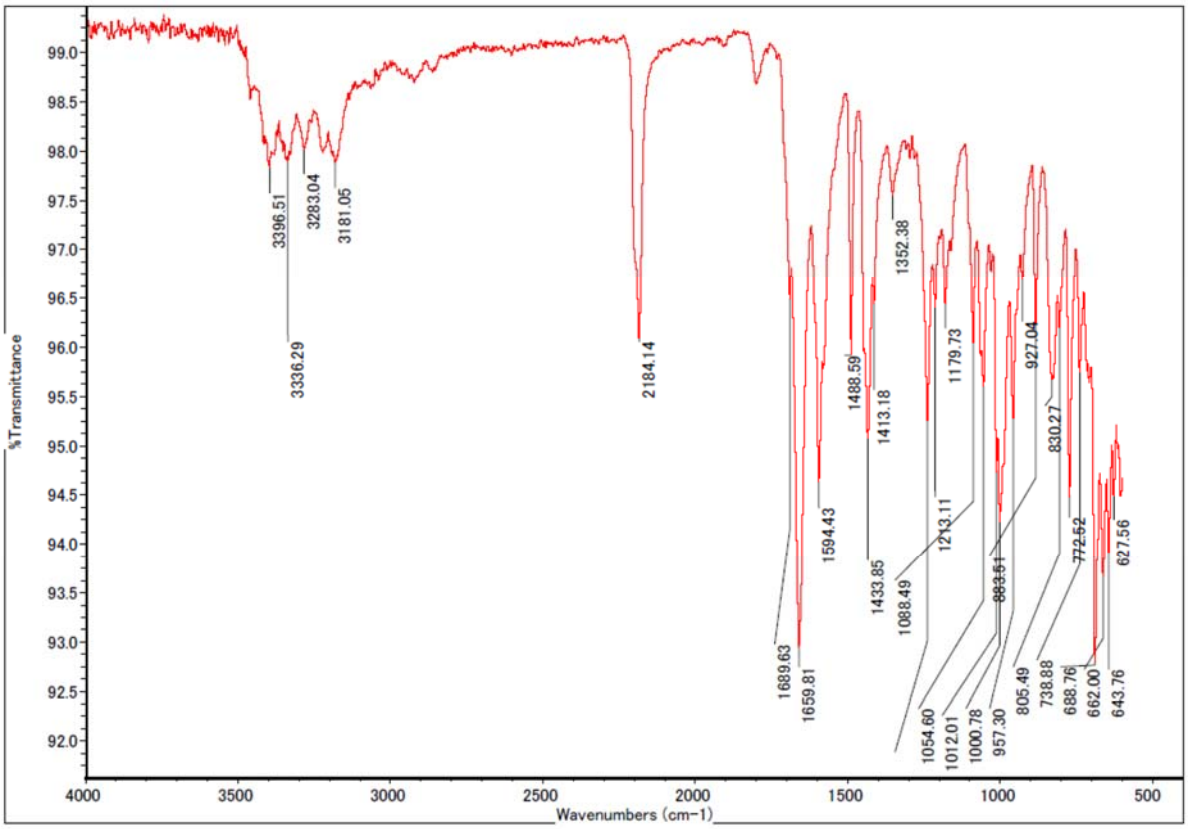
^{1}H NMR



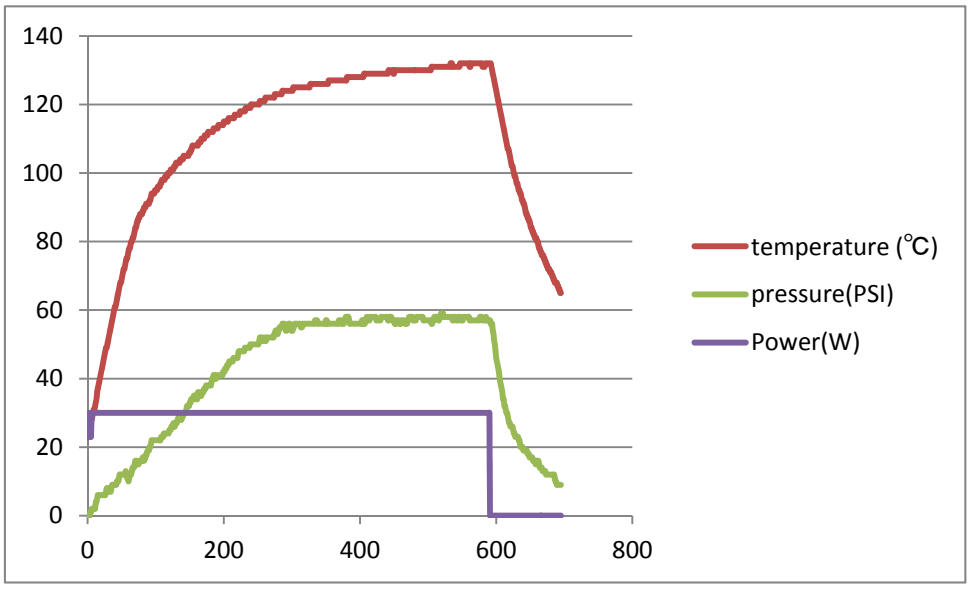
^{13}C NMR



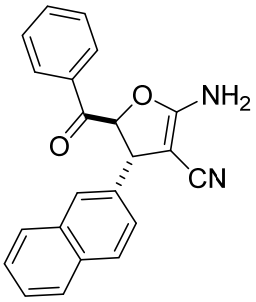
IR



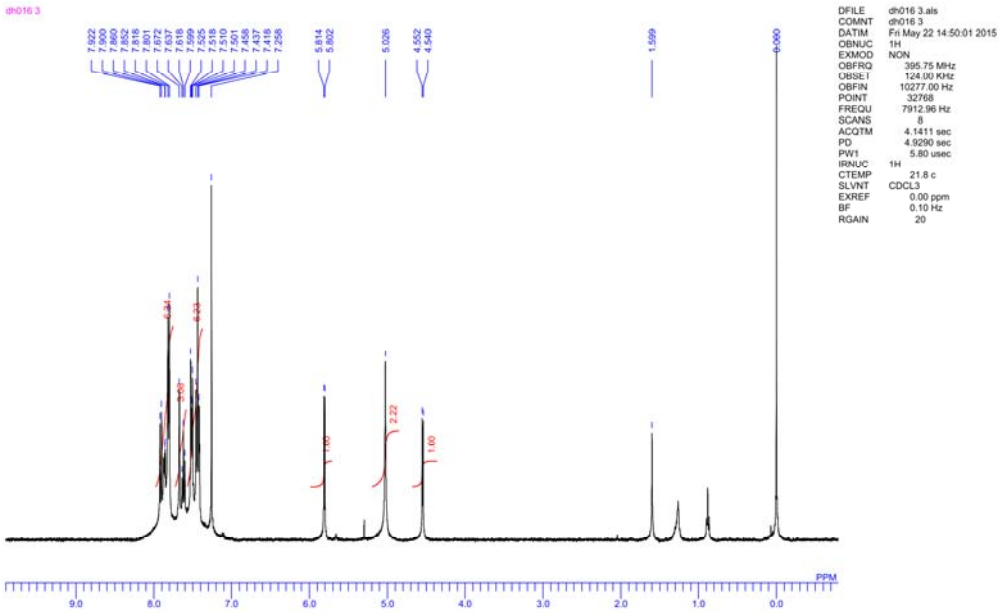
MW Profile (Table 2, entry 10)



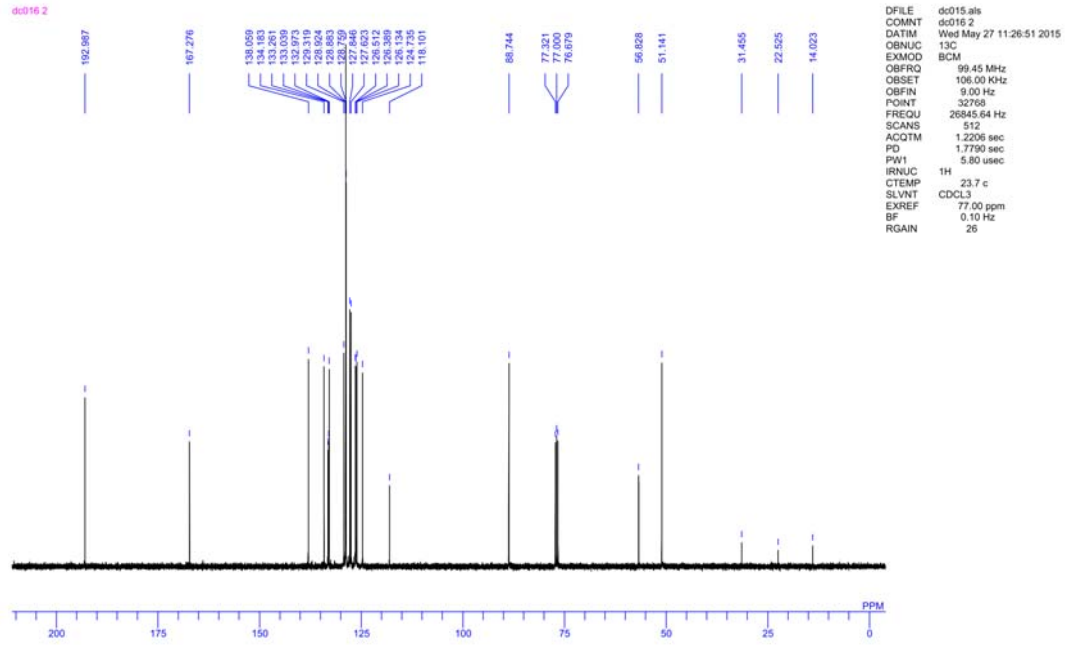
(*trans*-**3k**)



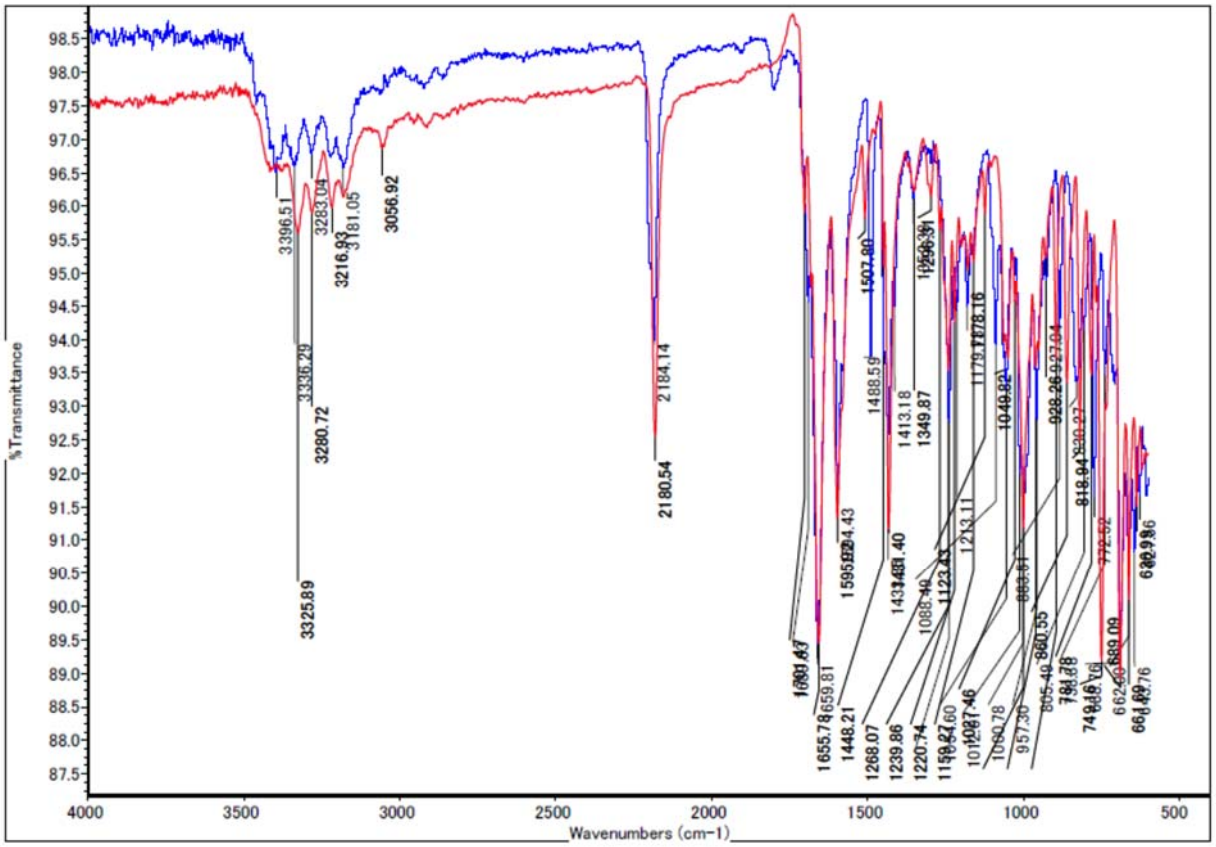
^{1}H NMR



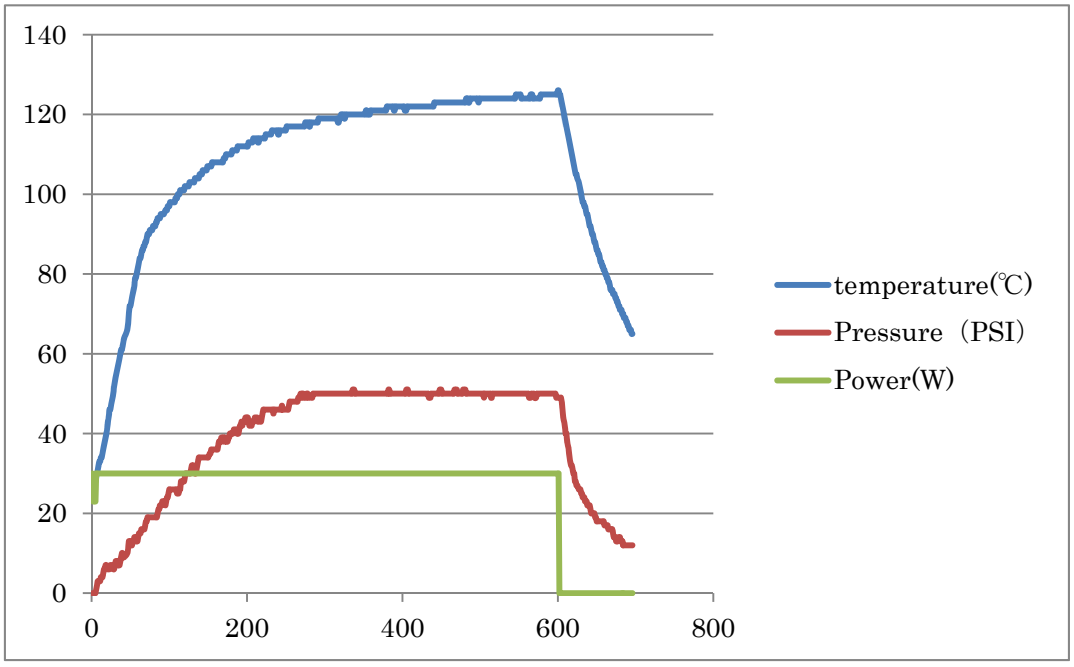
^{13}C NMR



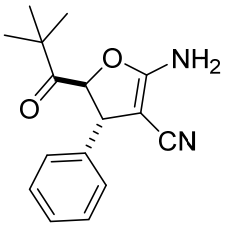
IR



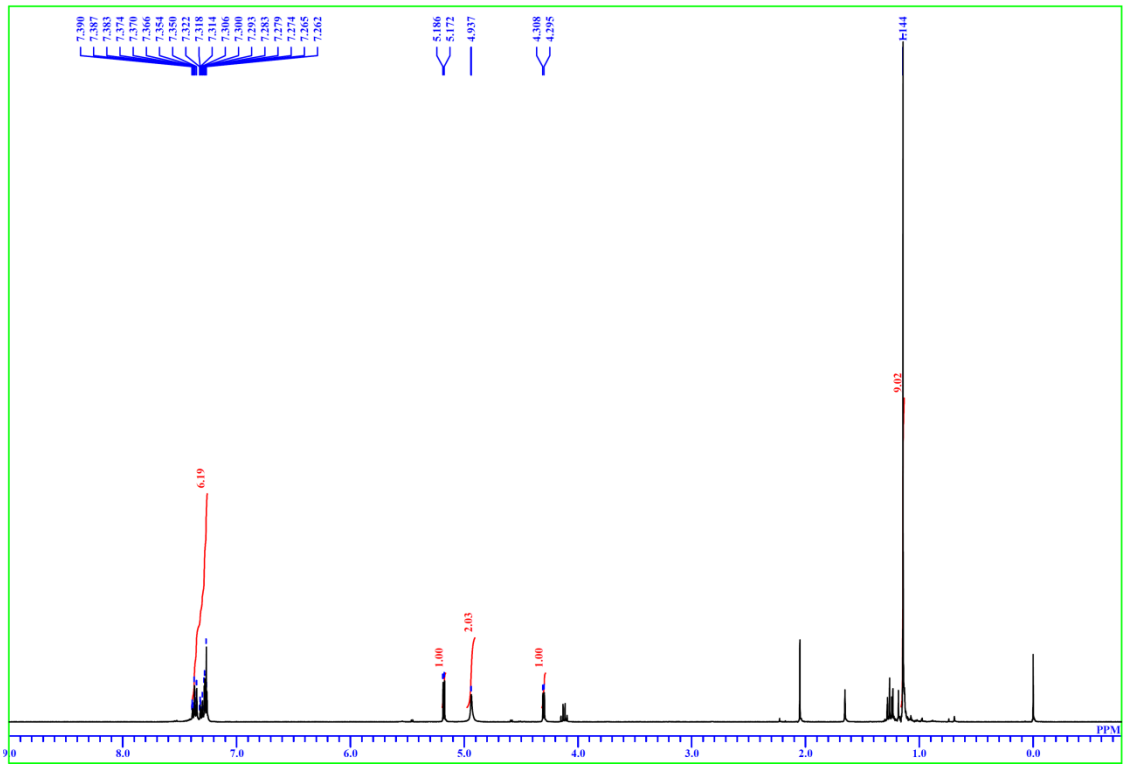
MW Profile (Table 2, entry 11)



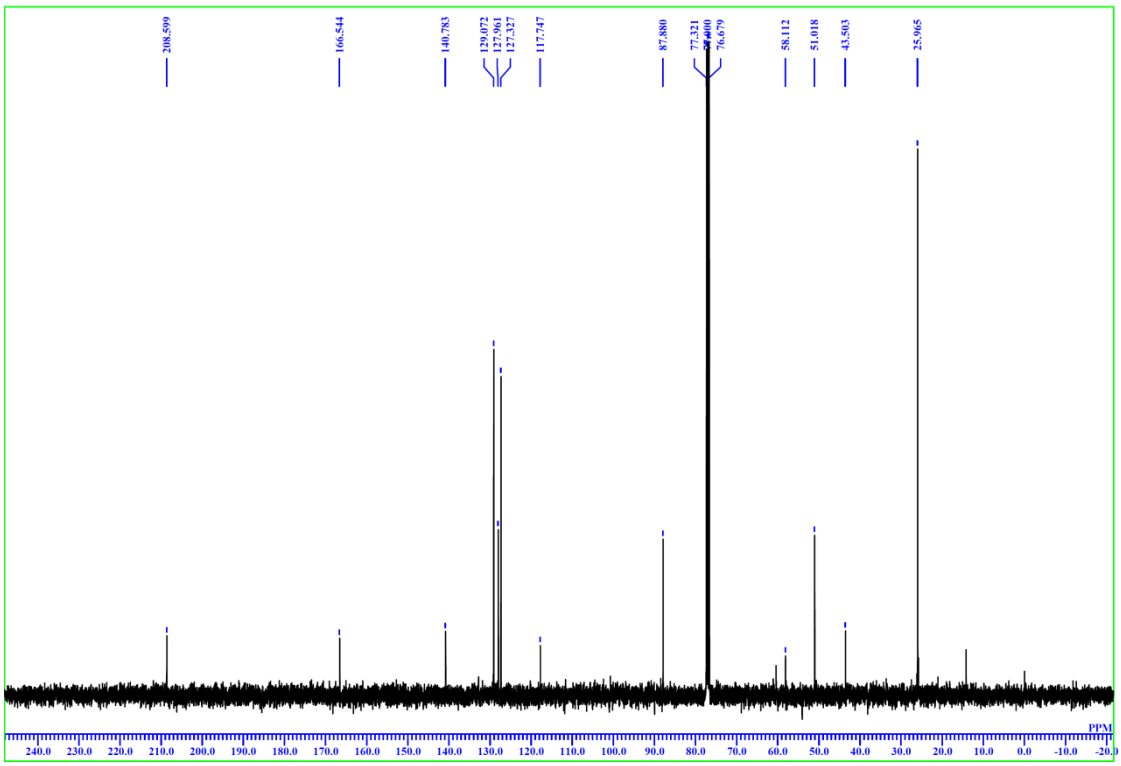
(*trans*-**3l**)



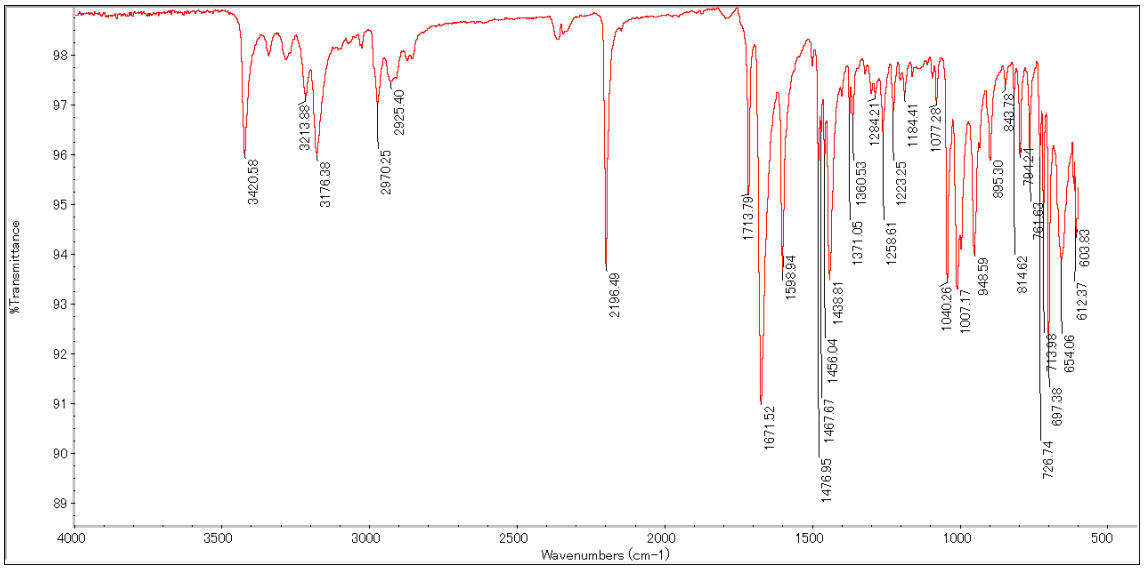
^{1}H NMR



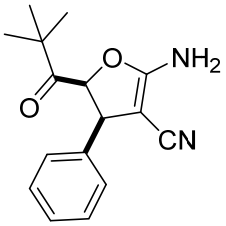
^{13}C NMR



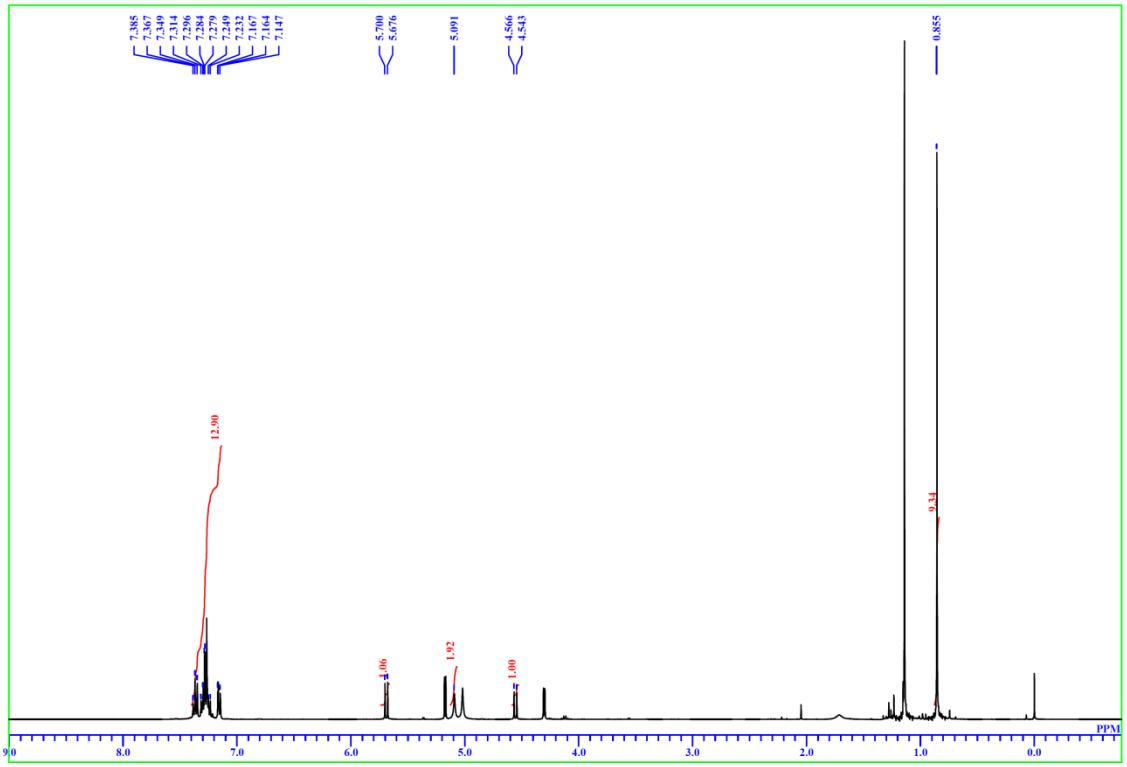
IR



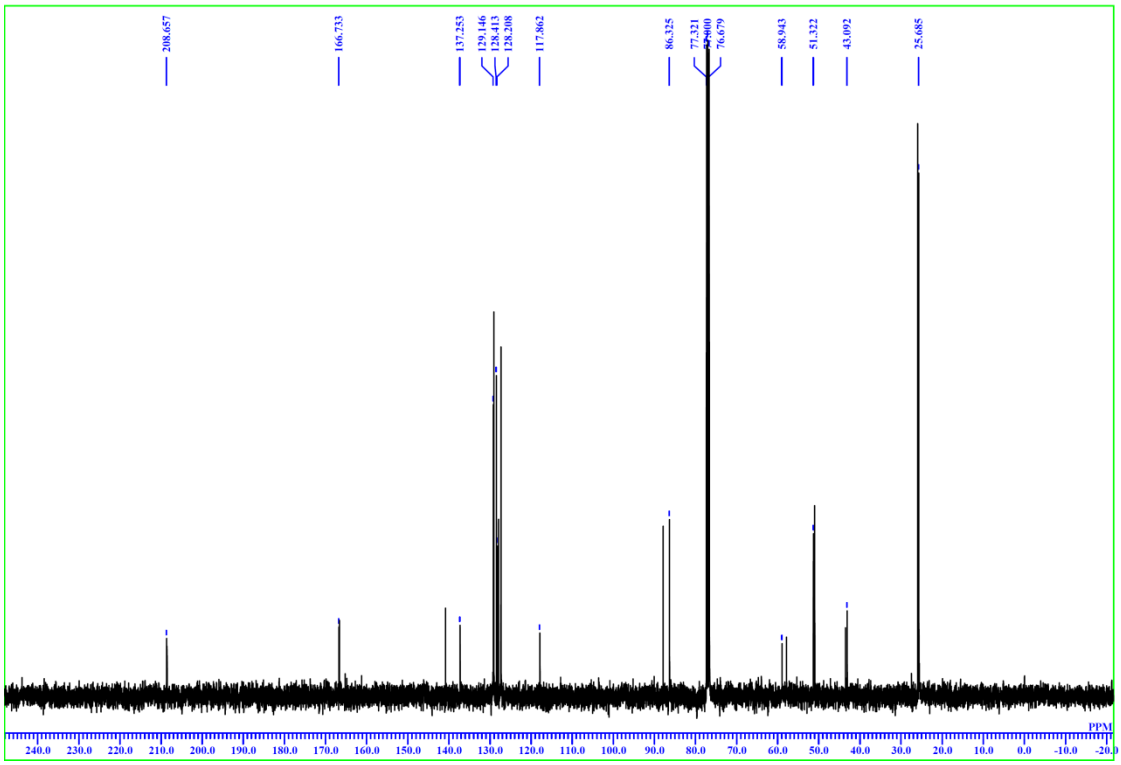
(*cis*-**3l**)



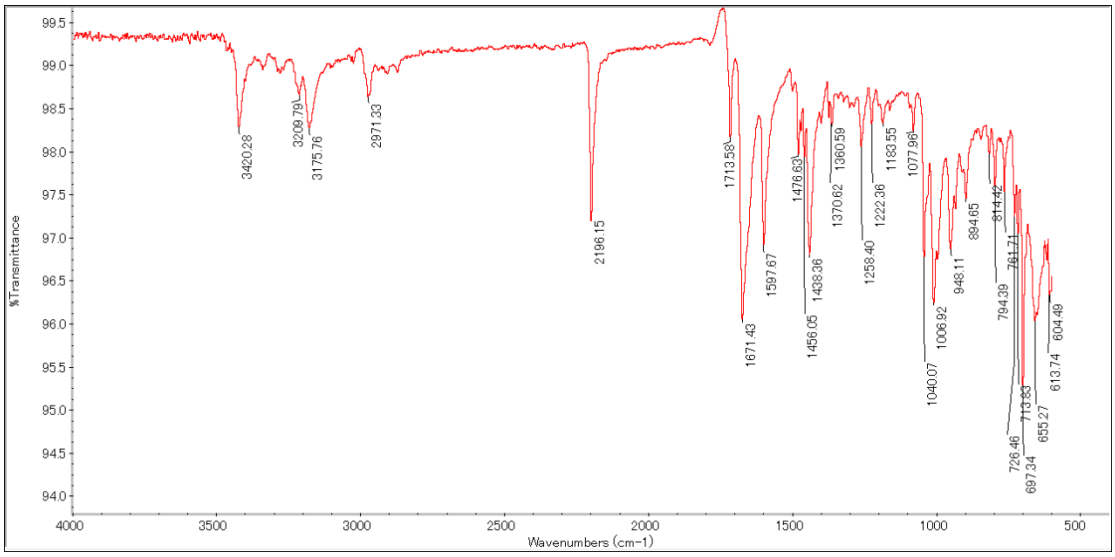
^{1}H NMR



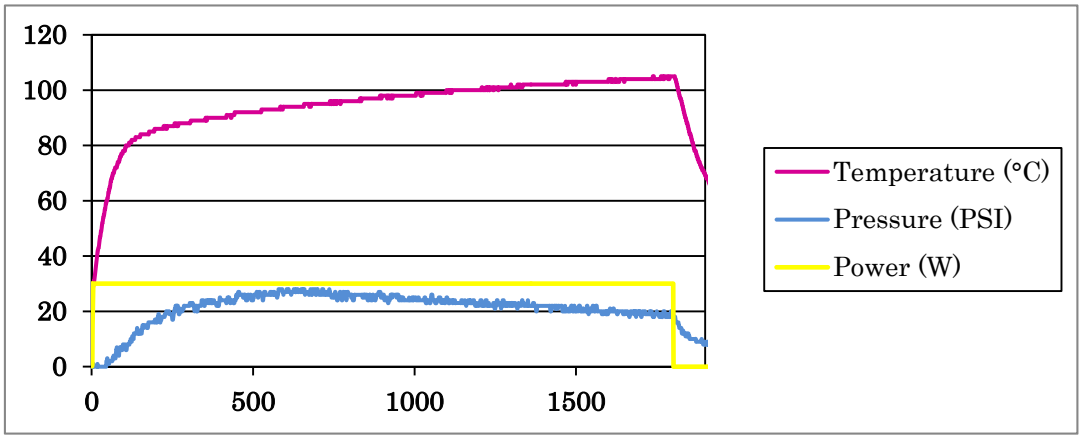
^{13}C NMR



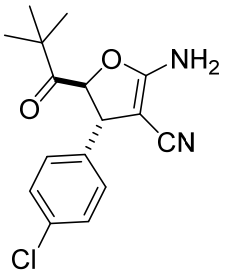
IR



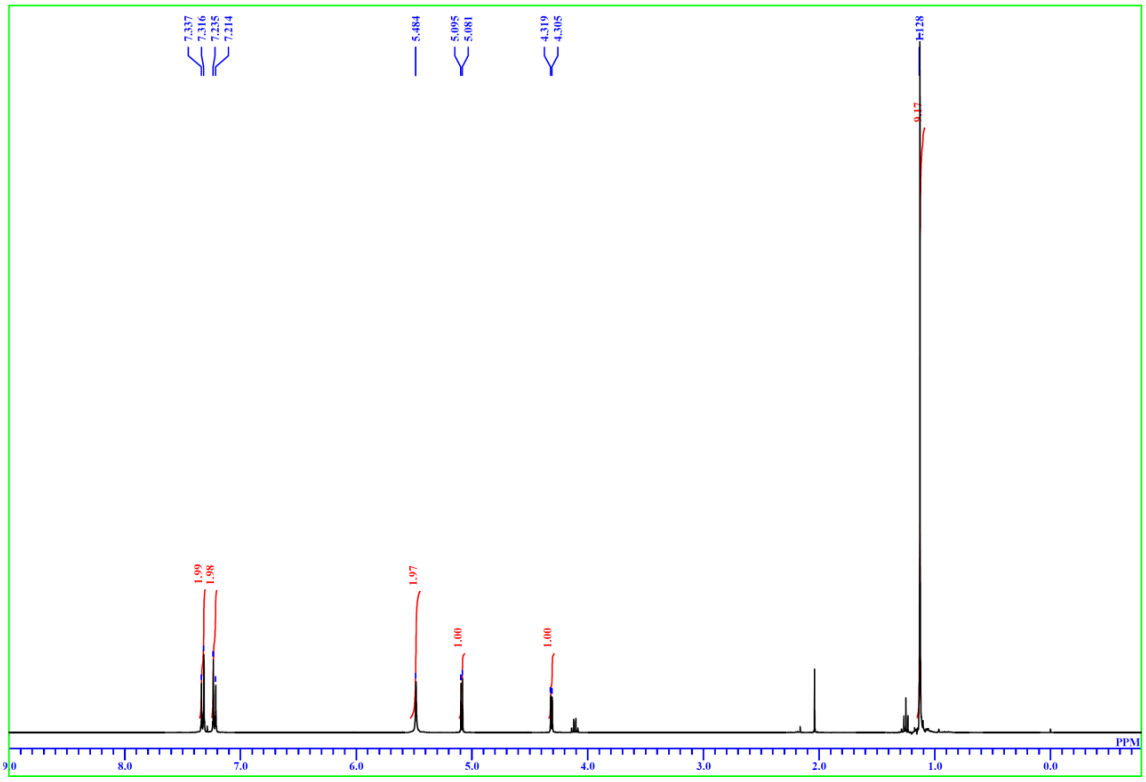
MW Profile (Table 2, entry 12)



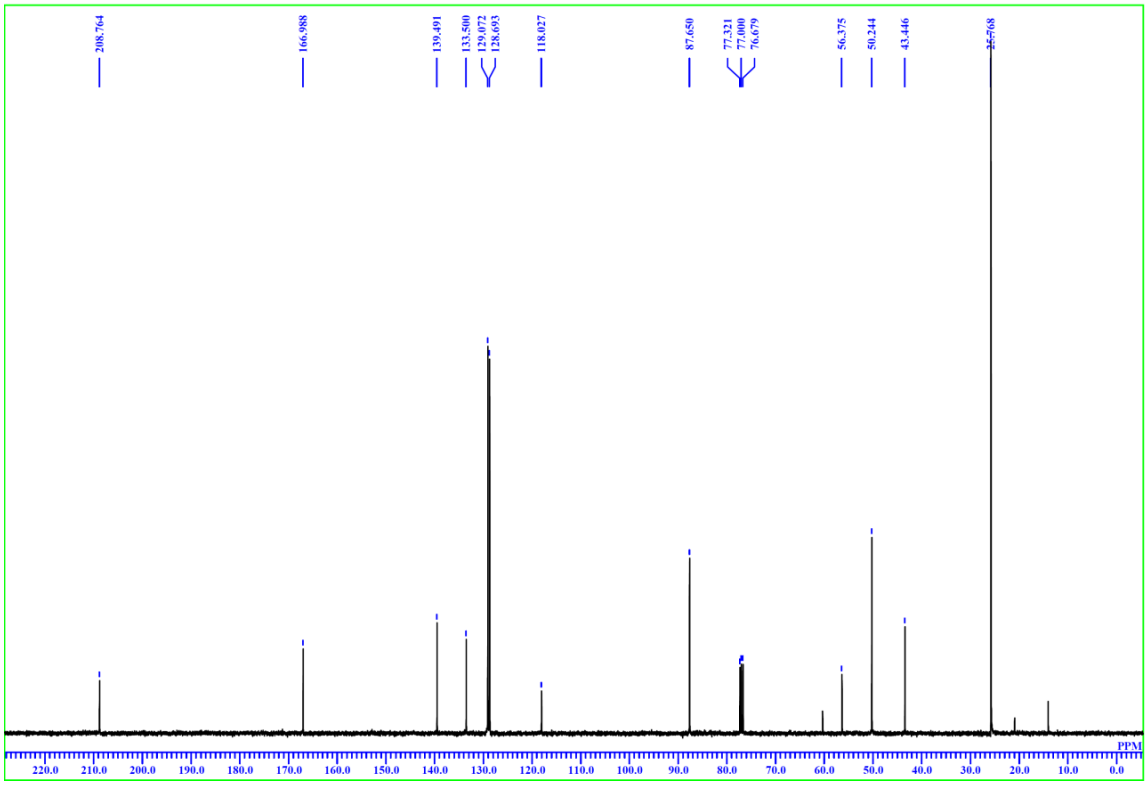
(*trans*-**3m**)



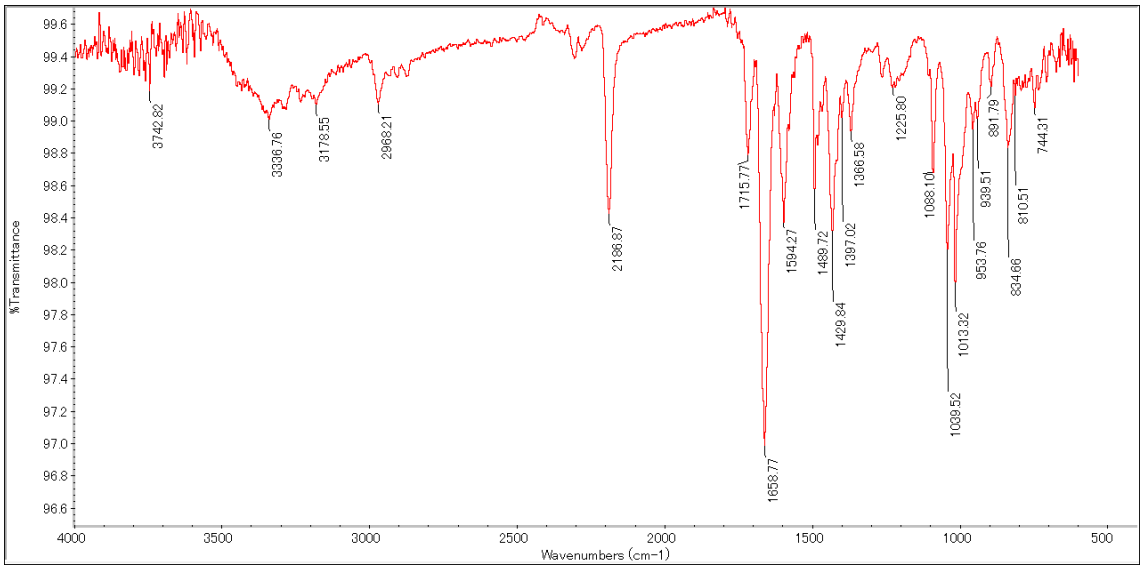
^{1}H NMR



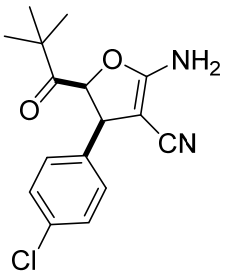
^{13}C NMR



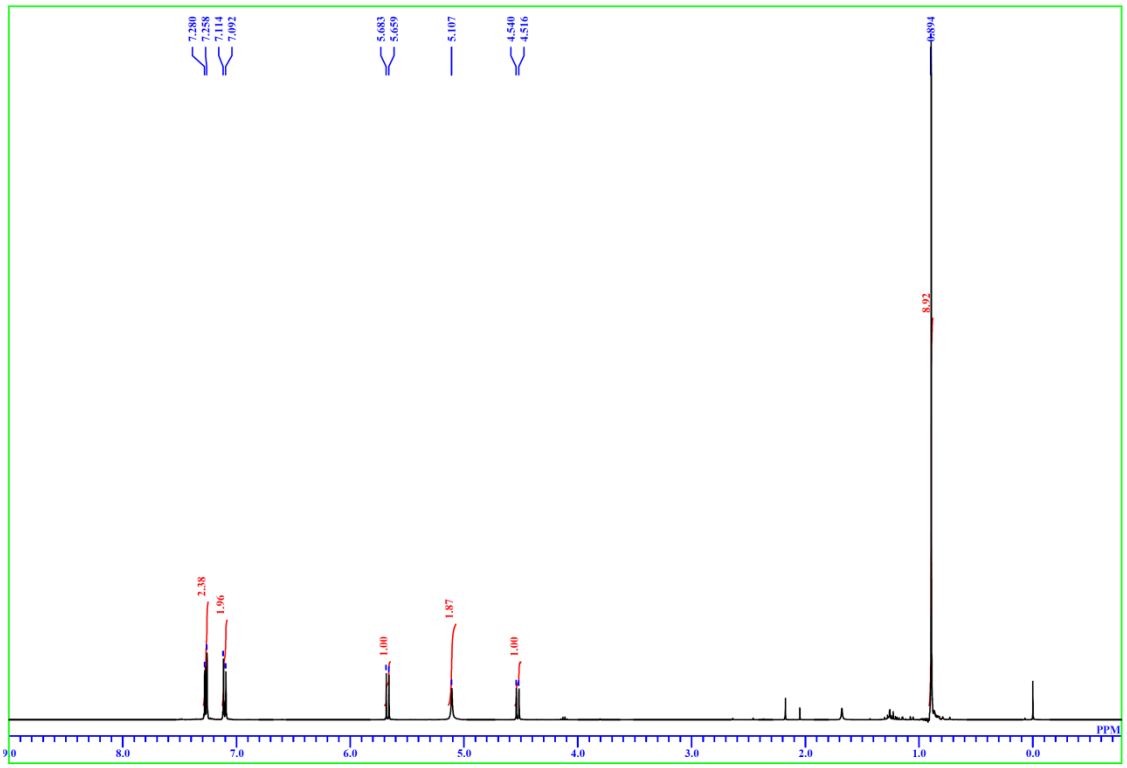
IR



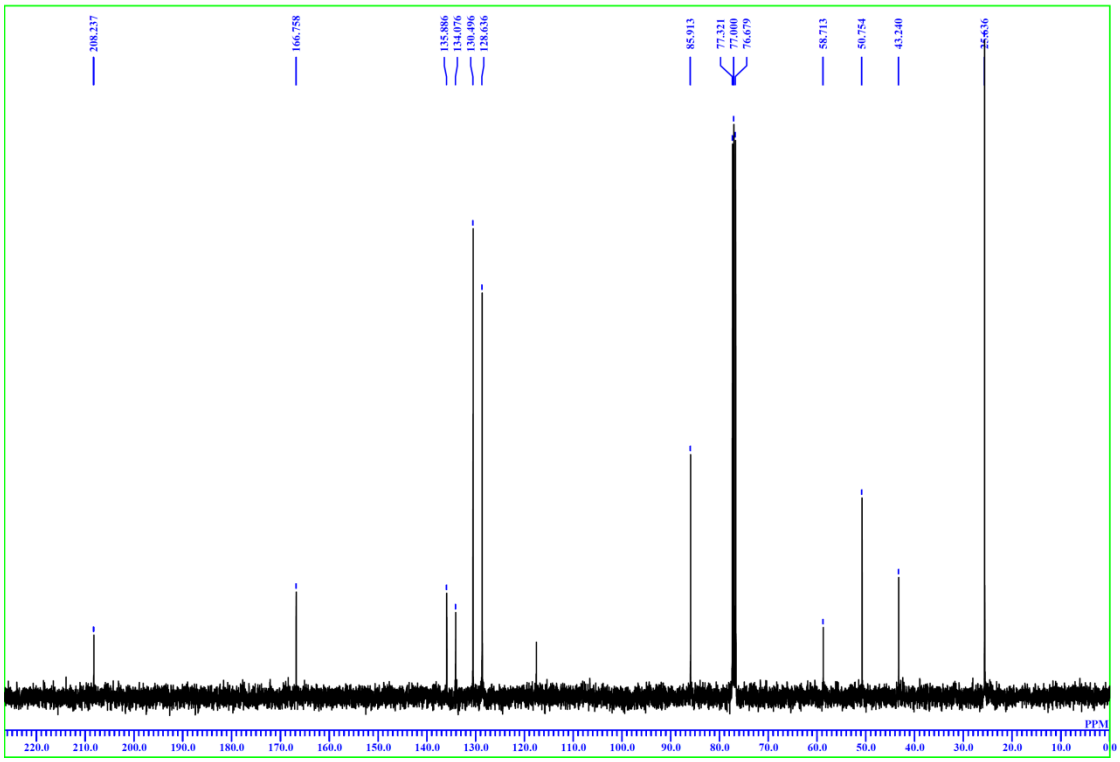
(*cis*-**3m**)



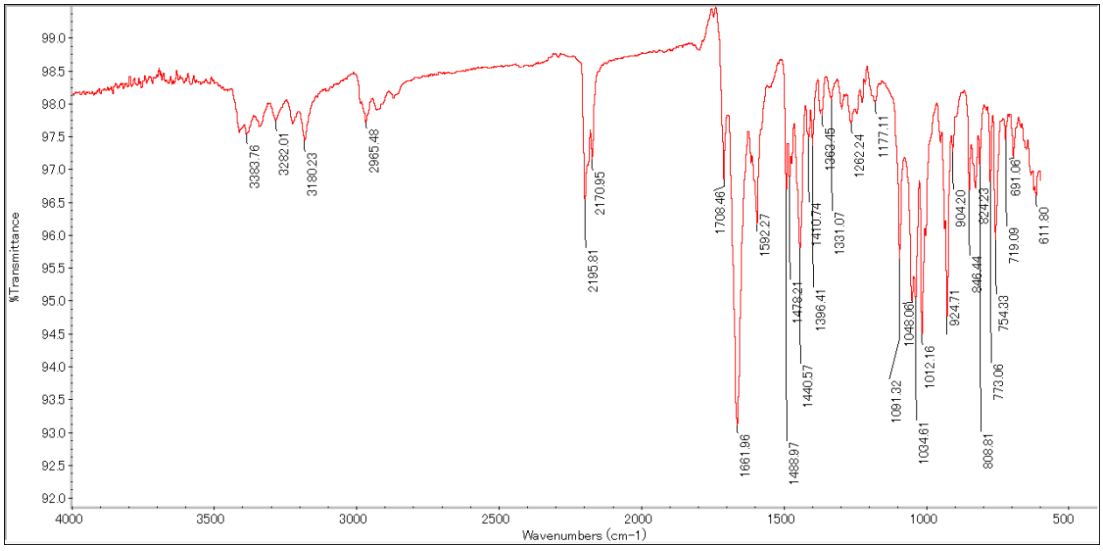
^{1}H NMR



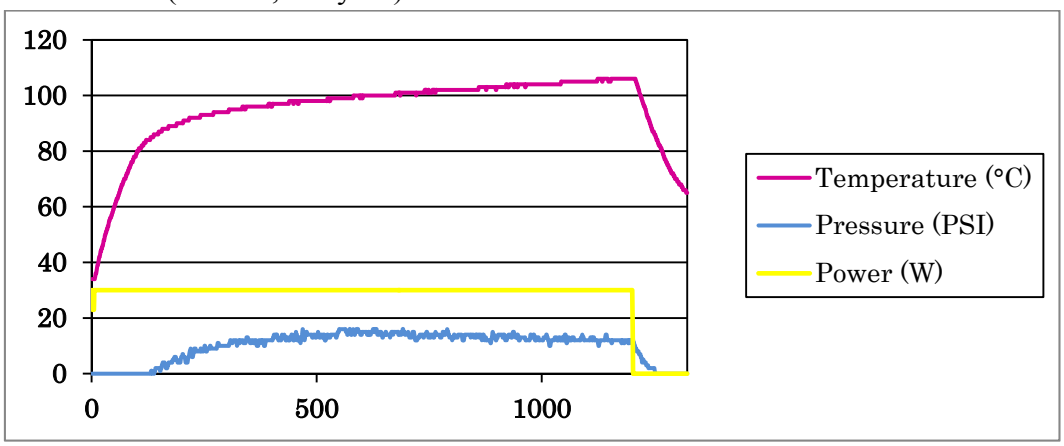
^{13}C NMR



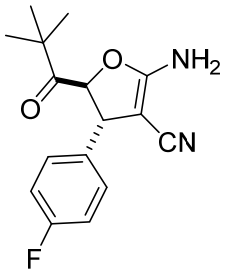
IR



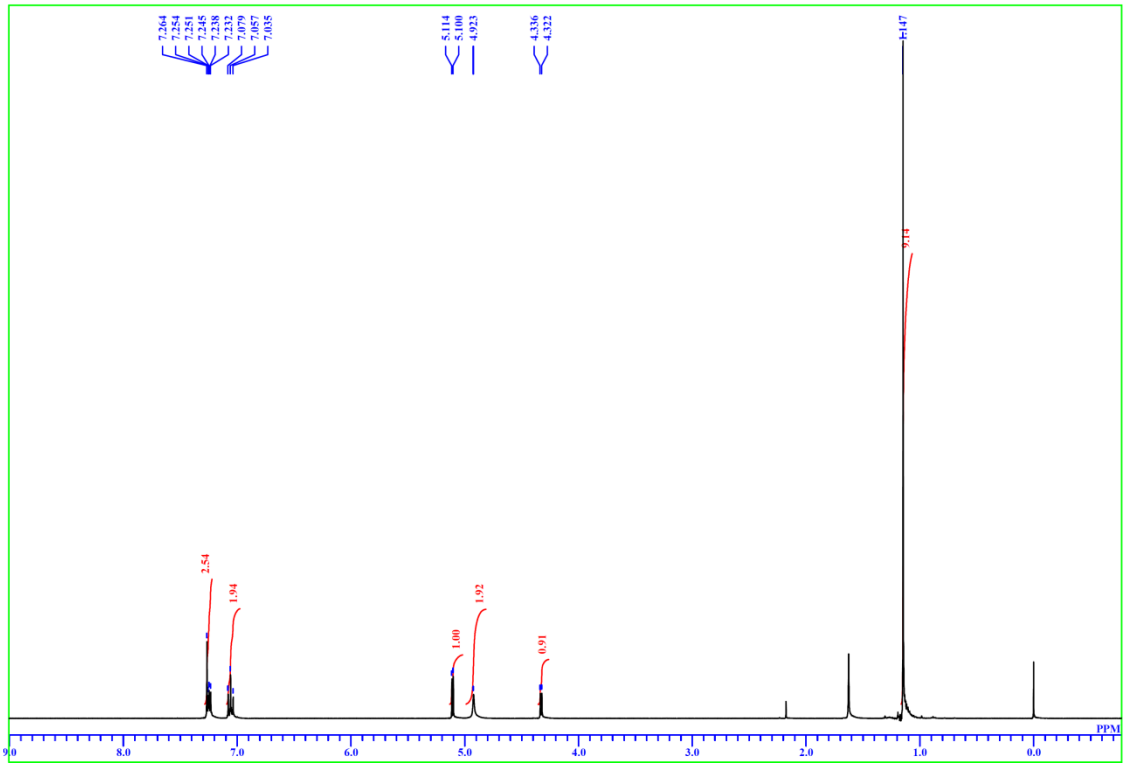
MW Profile (Table 2, entry 13)



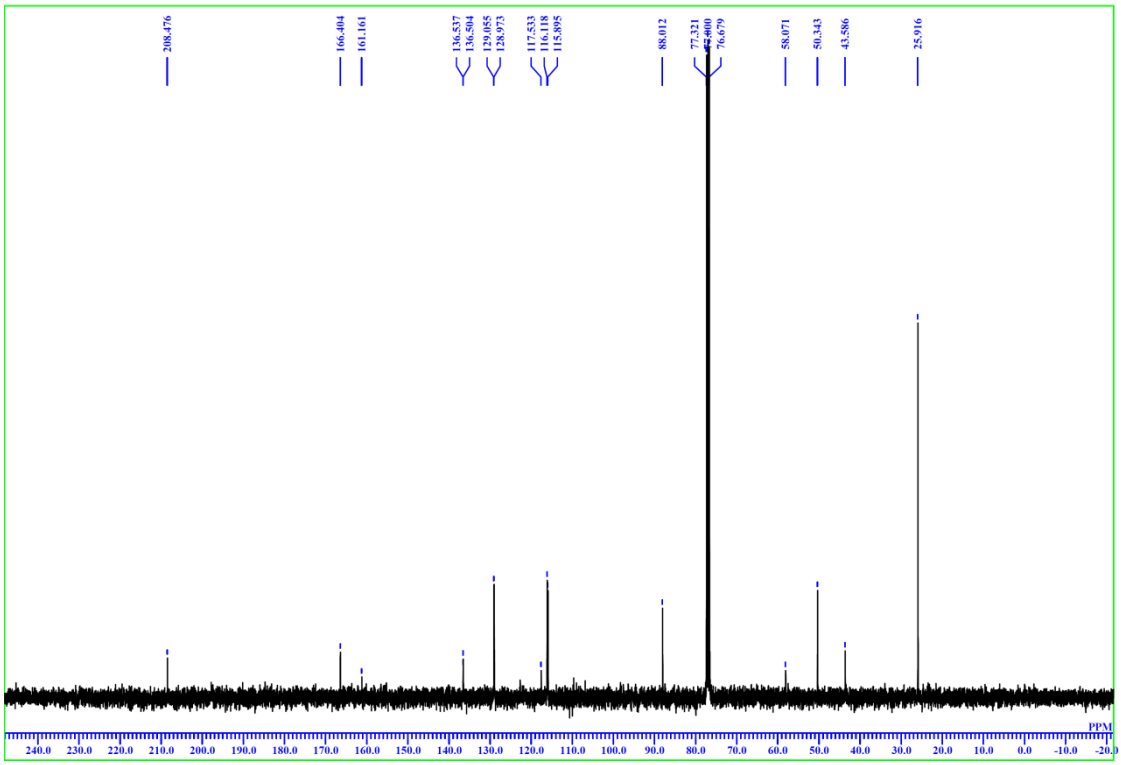
(*trans*-**3n**)



^{1}H NMR



^{13}C NMR



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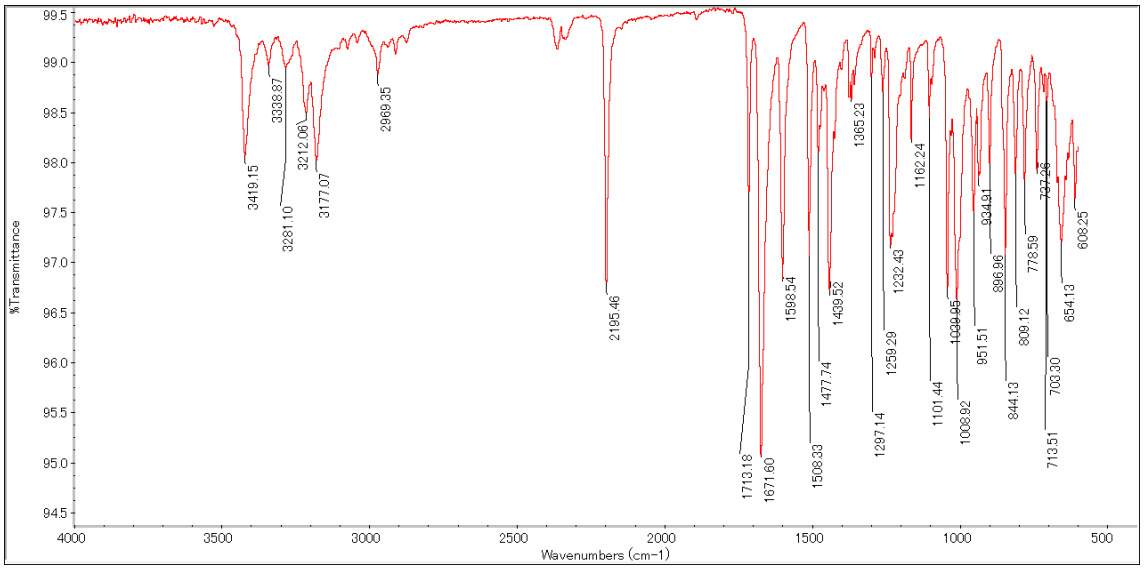
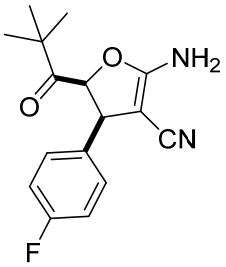
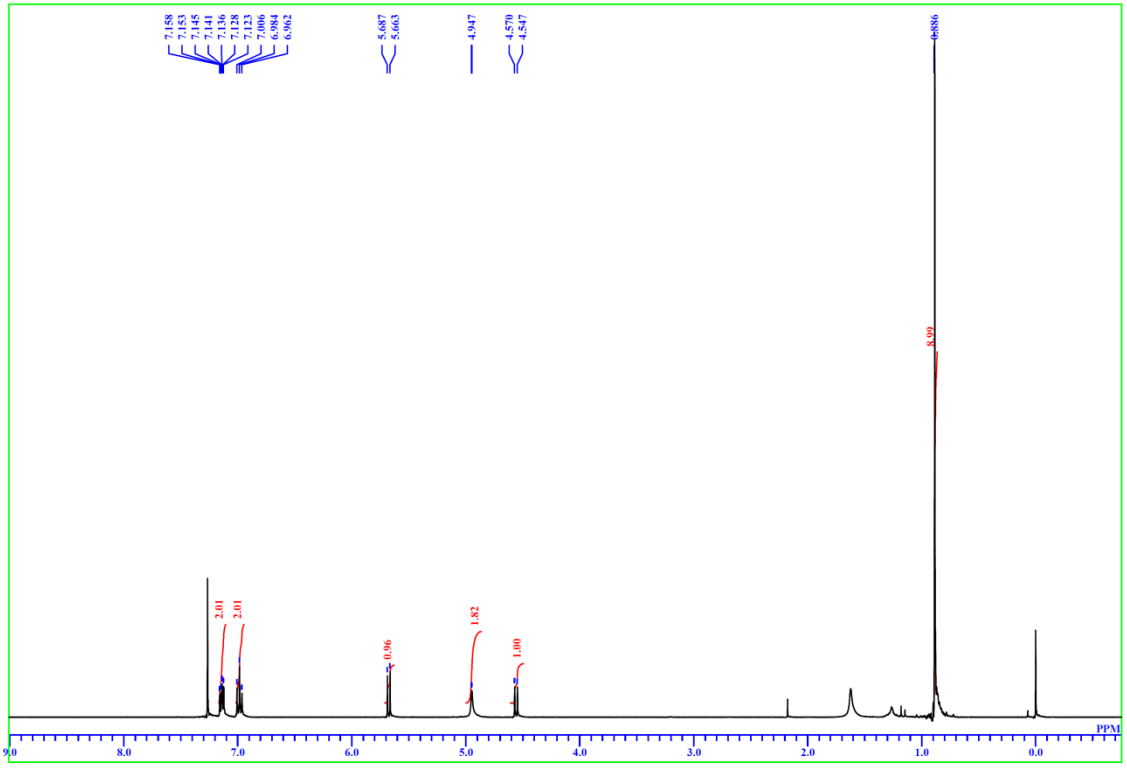


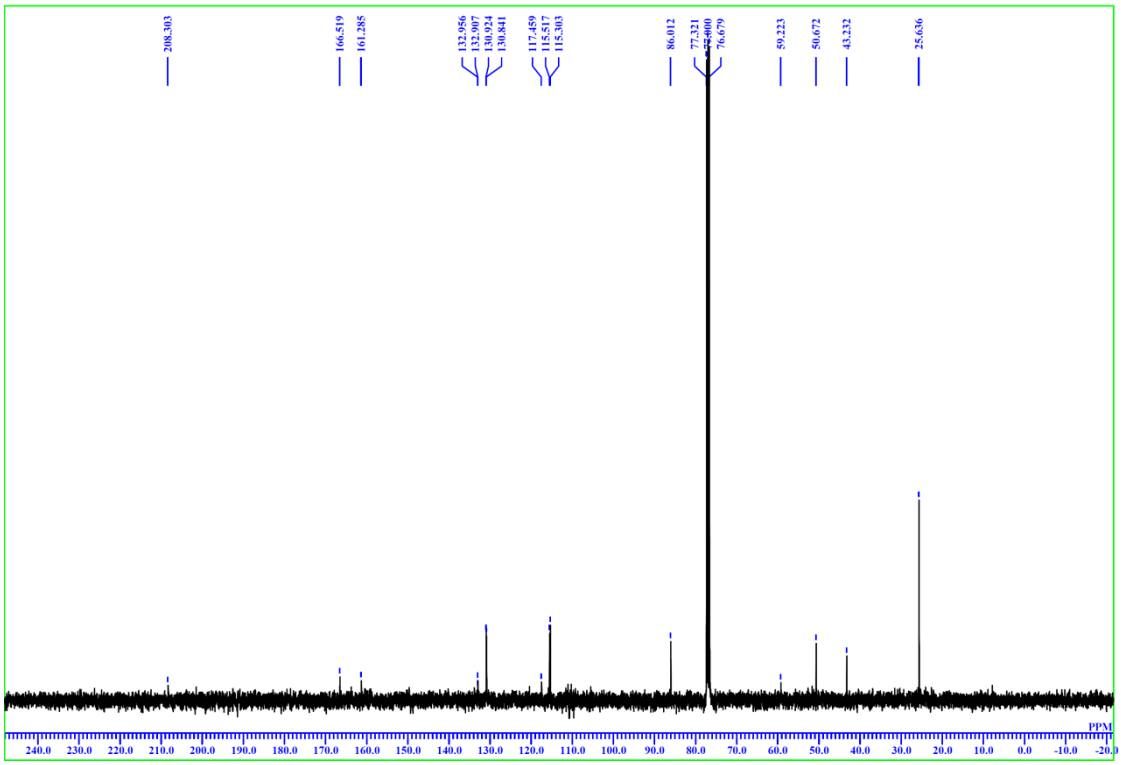
(*cis*-**3n**)



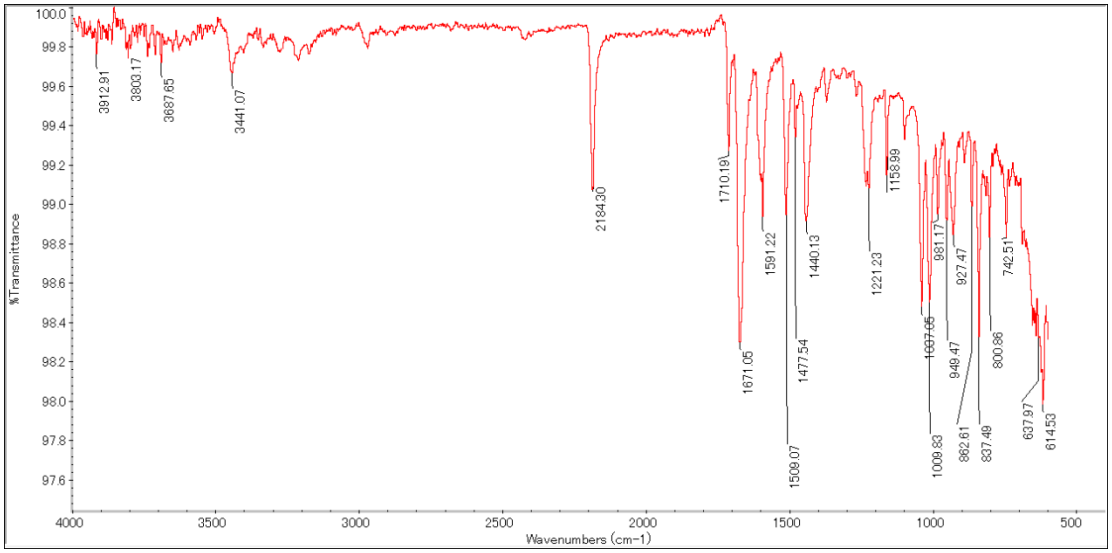
^{1}H NMR



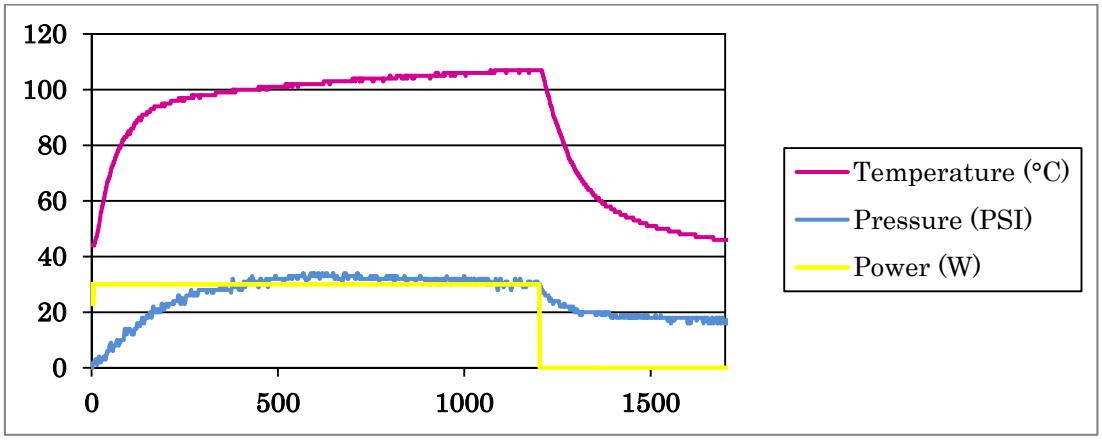
^{13}C NMR



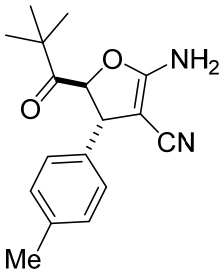
IR



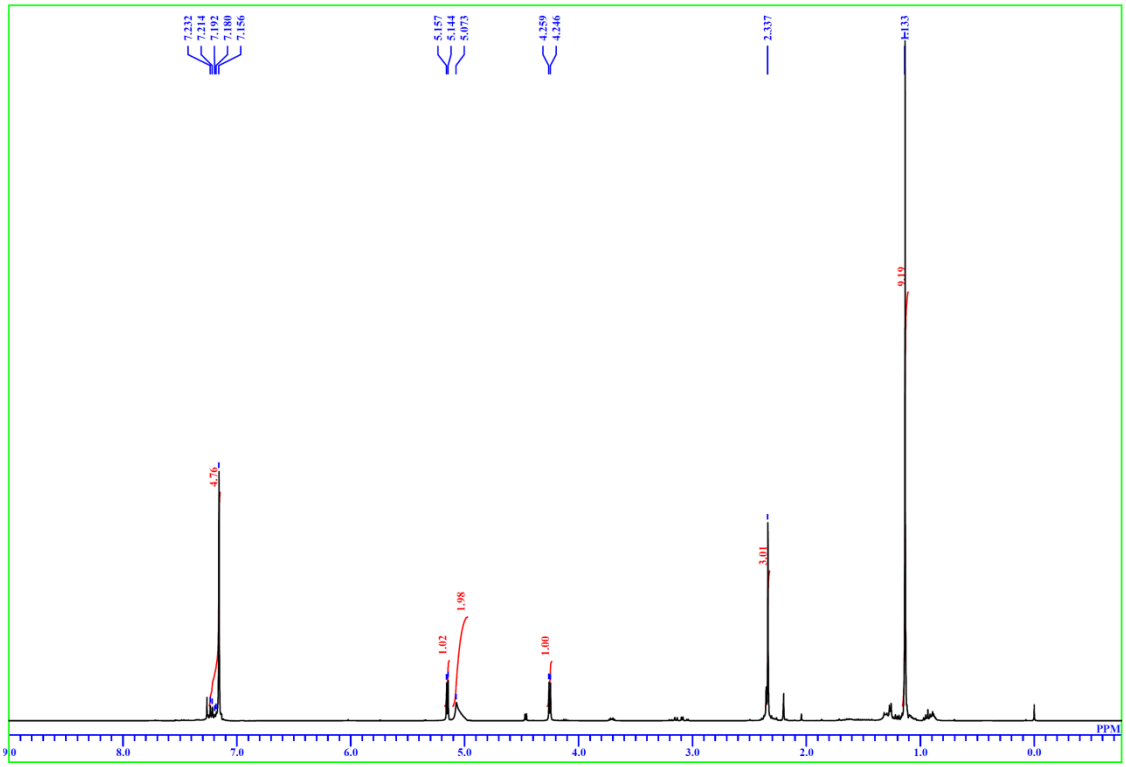
MW Profile (Table 2, entry 14)



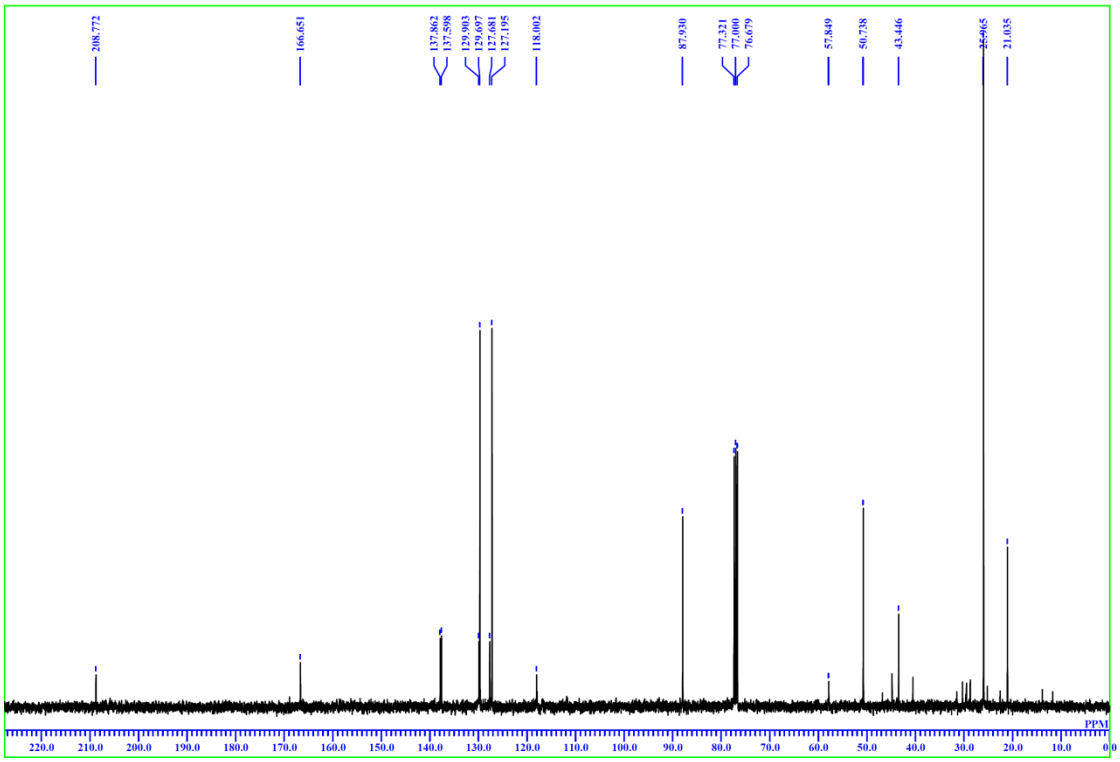
(*trans*-**3o**)



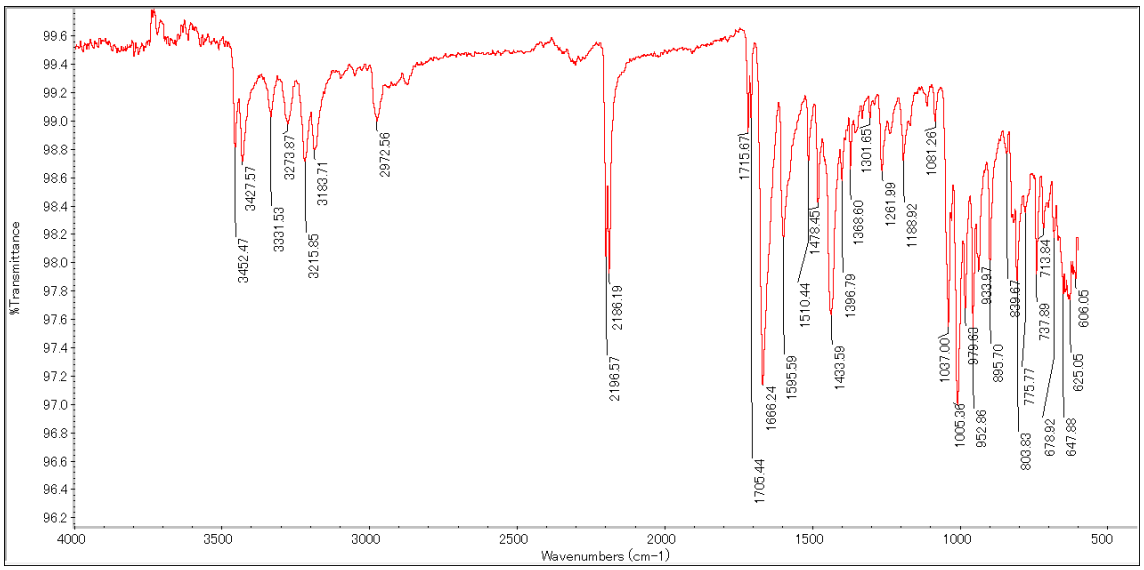
^{1}H NMR



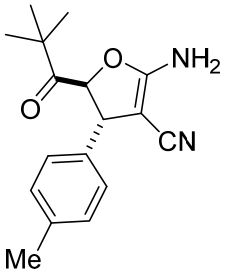
^{13}C NMR



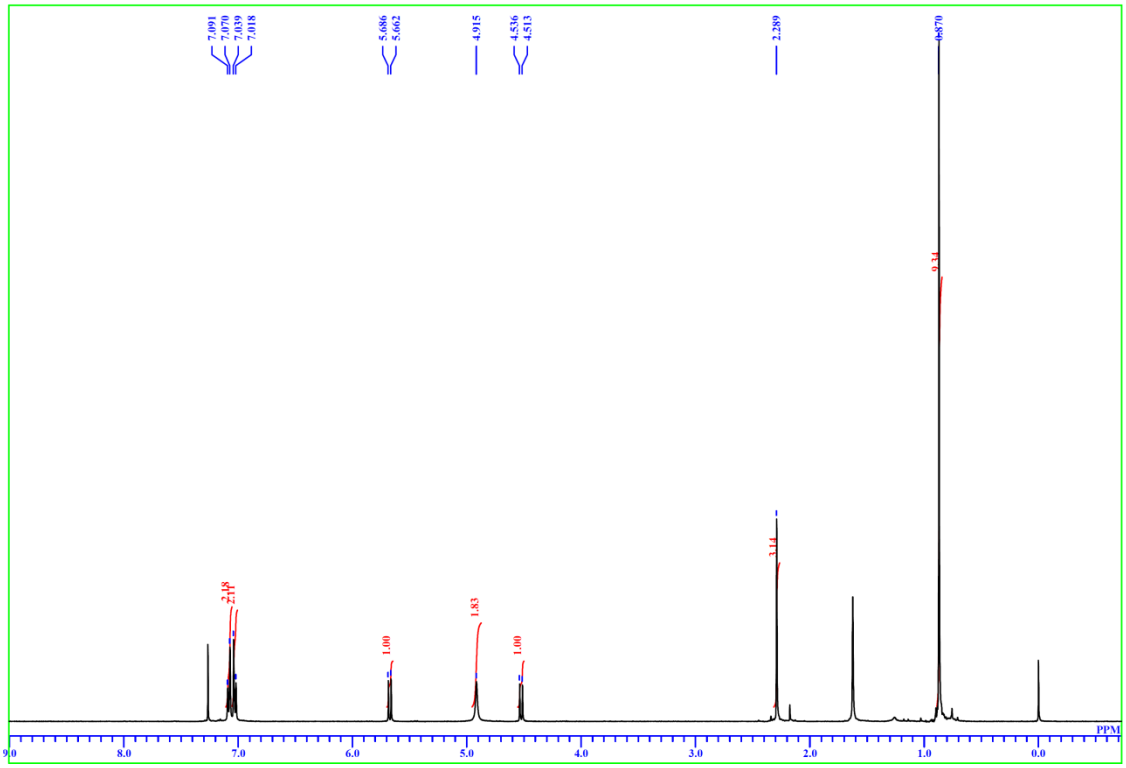
IR



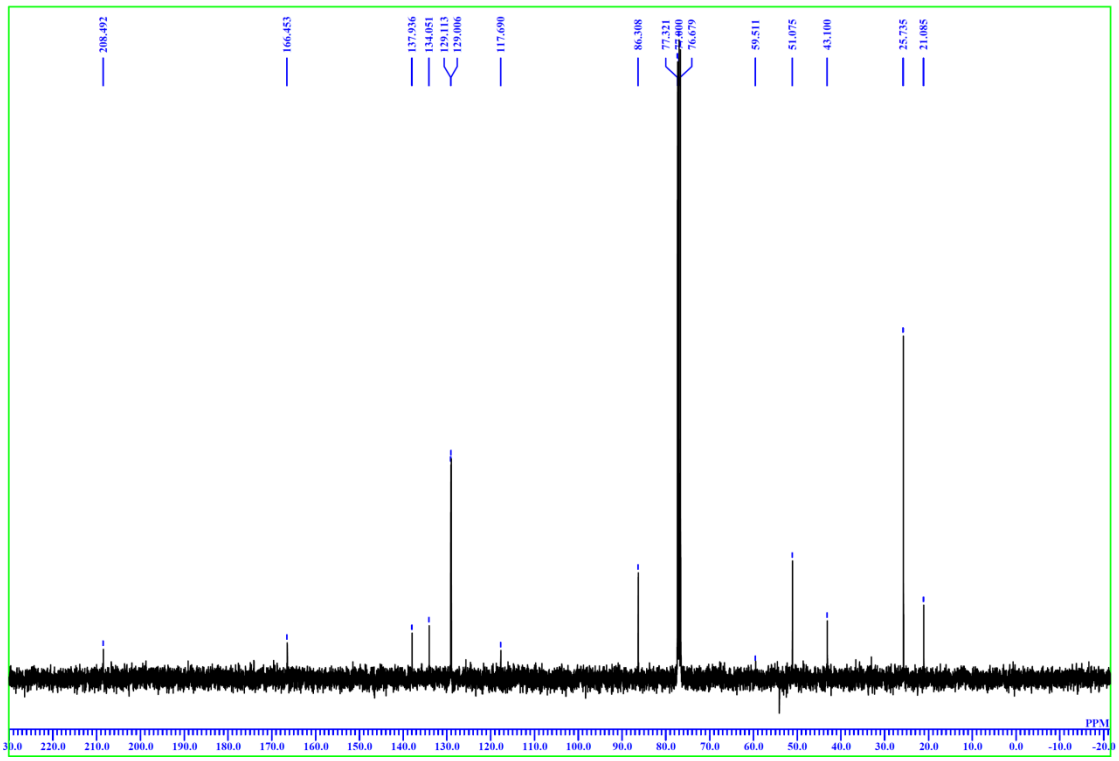
(*cis*-**3o**)



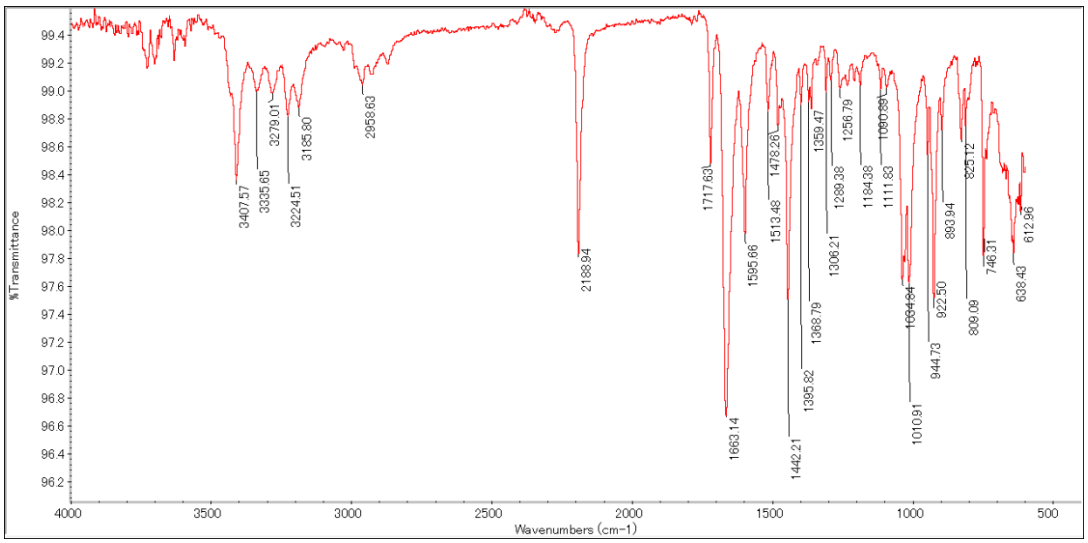
^{1}H NMR



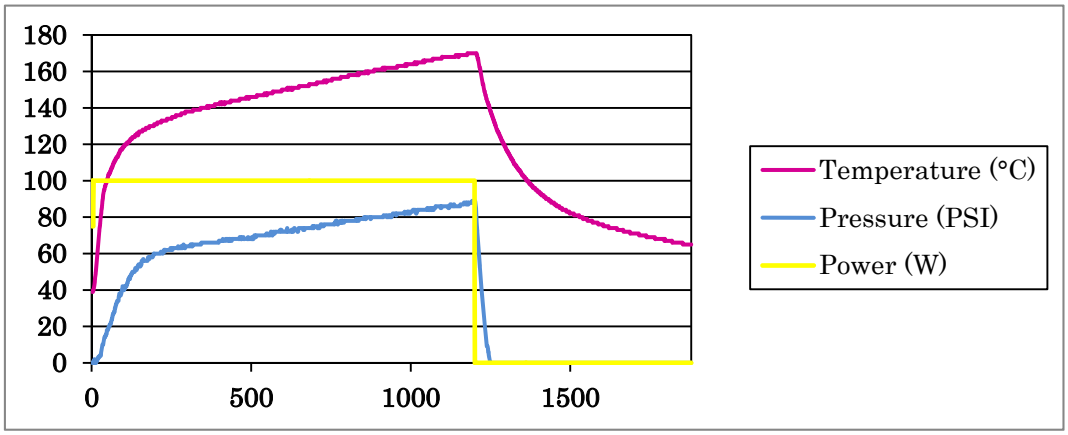
^{13}C NMR



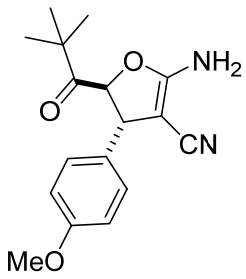
IR



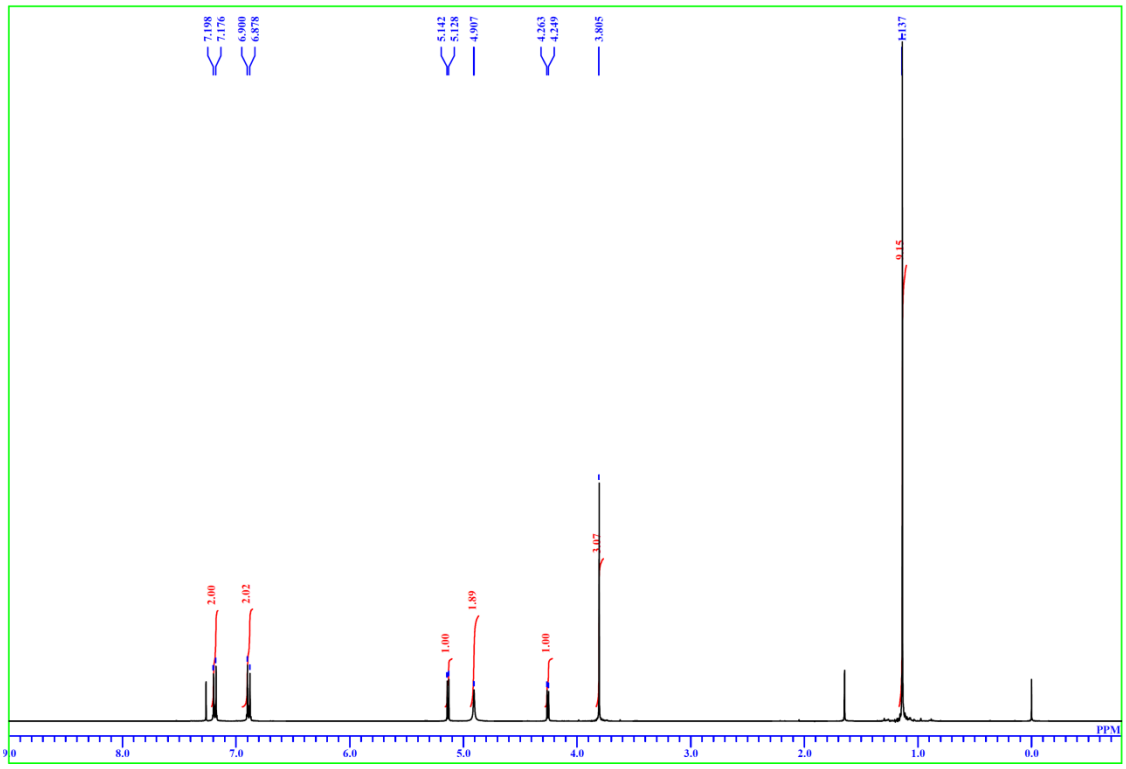
MW Profile (Table 2, entry 15)



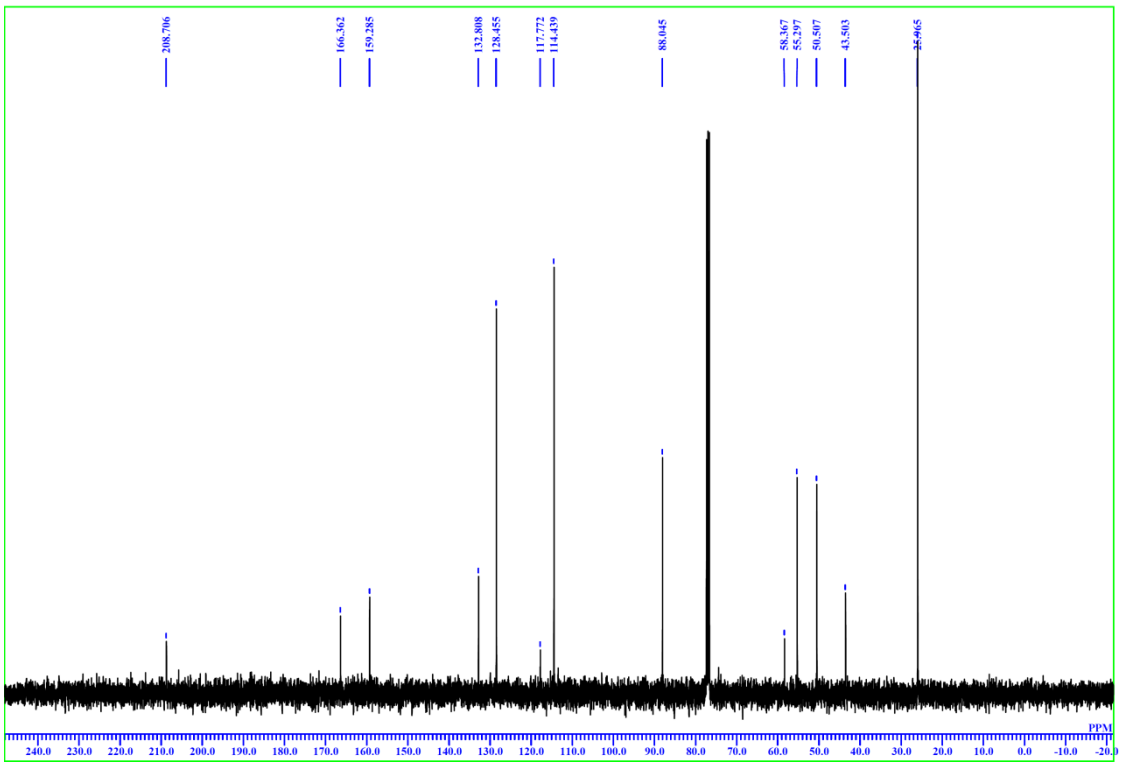
(*trans*-**3p**)



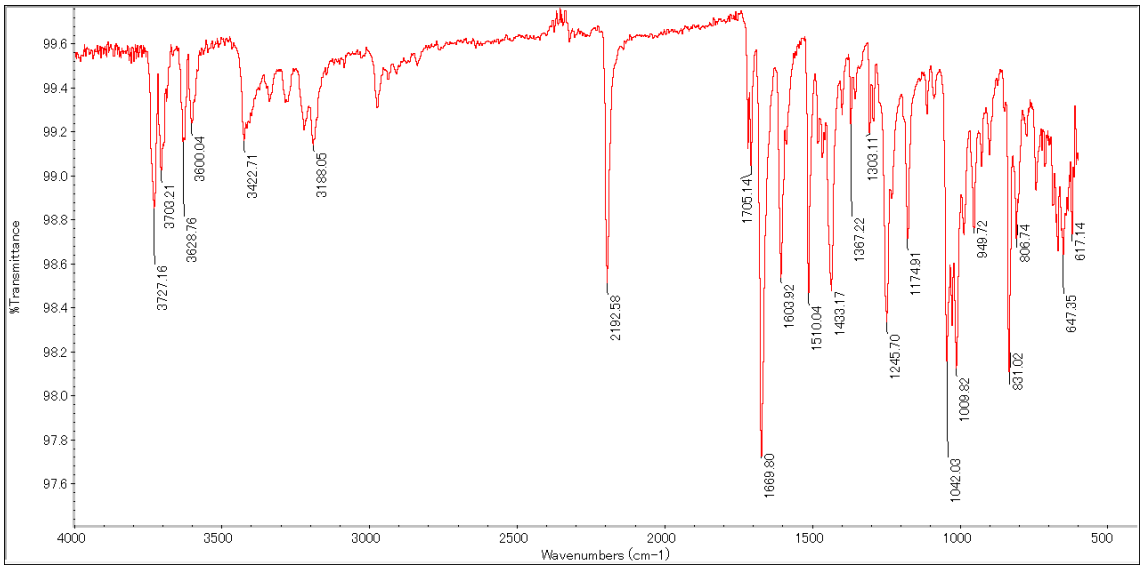
^{1}H NMR



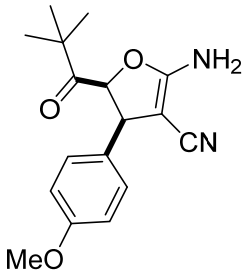
^{13}C NMR



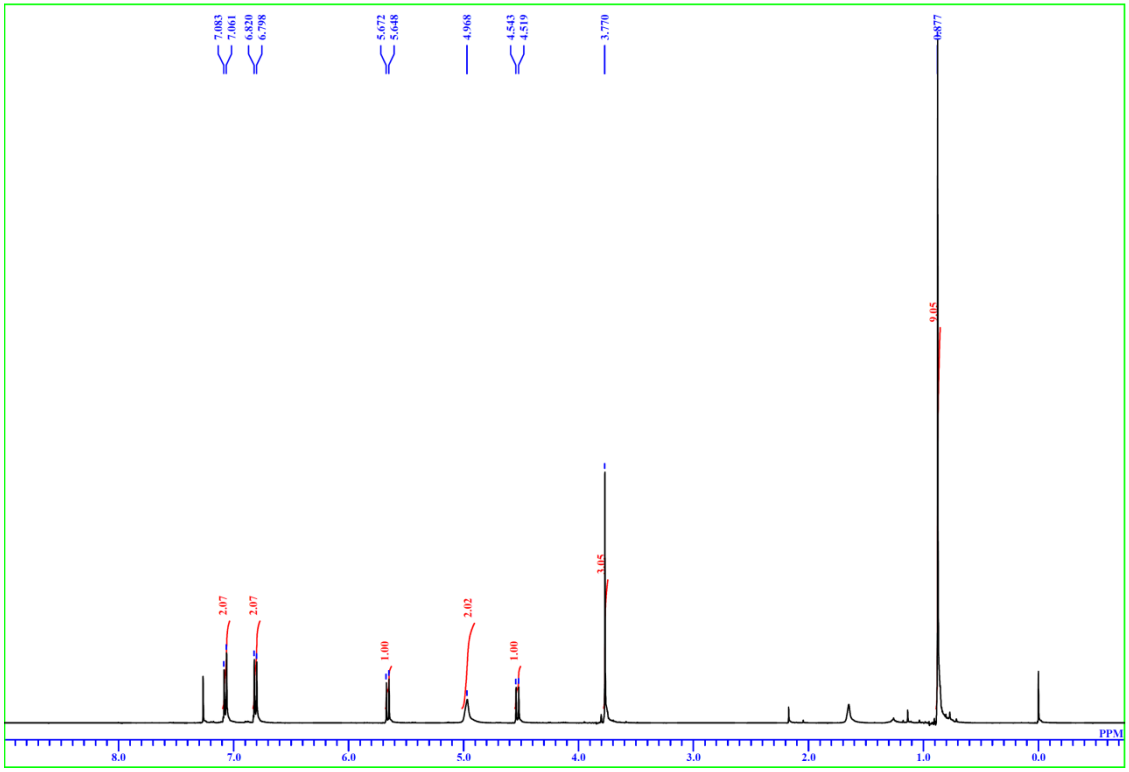
IR



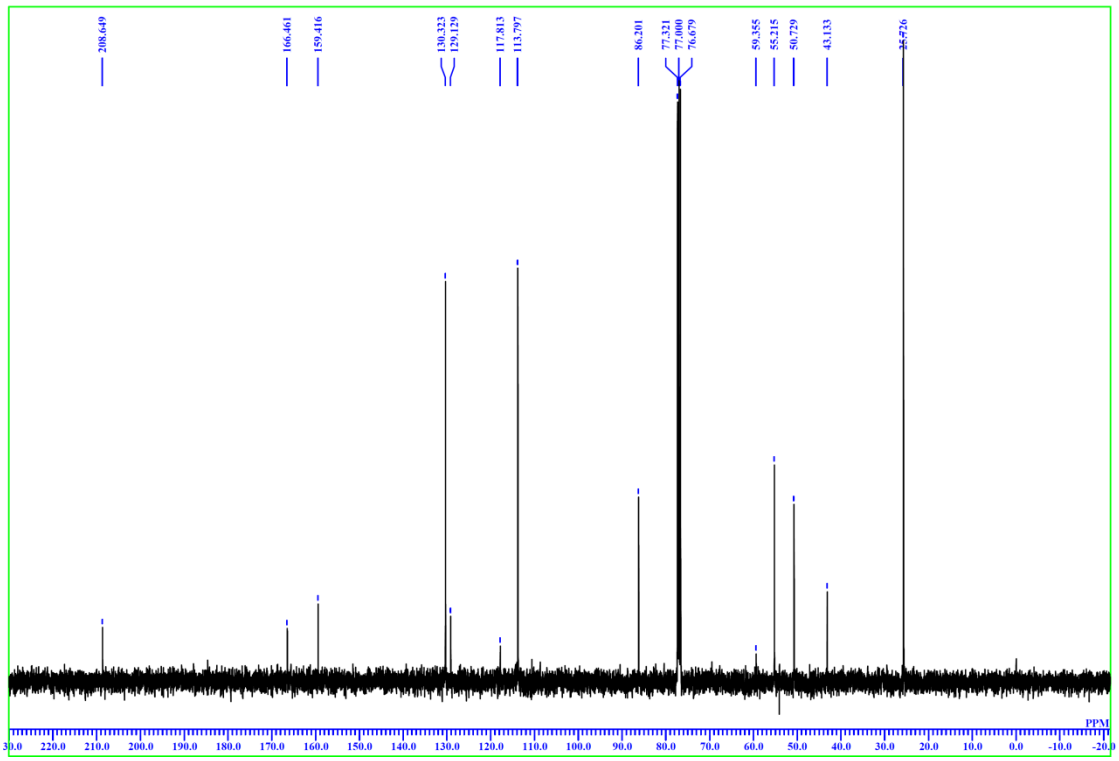
(*cis*-**3p**)



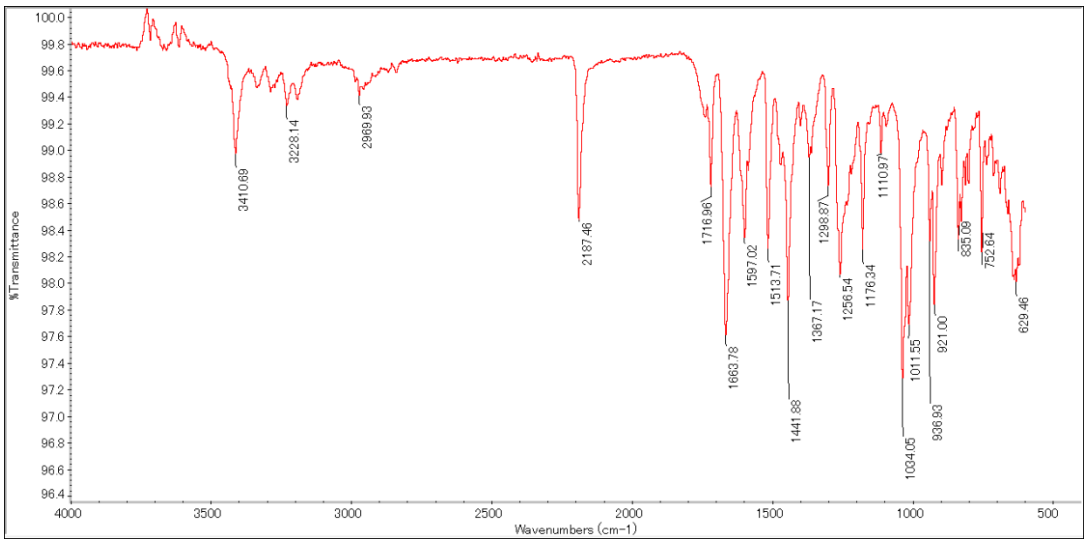
^{1}H NMR



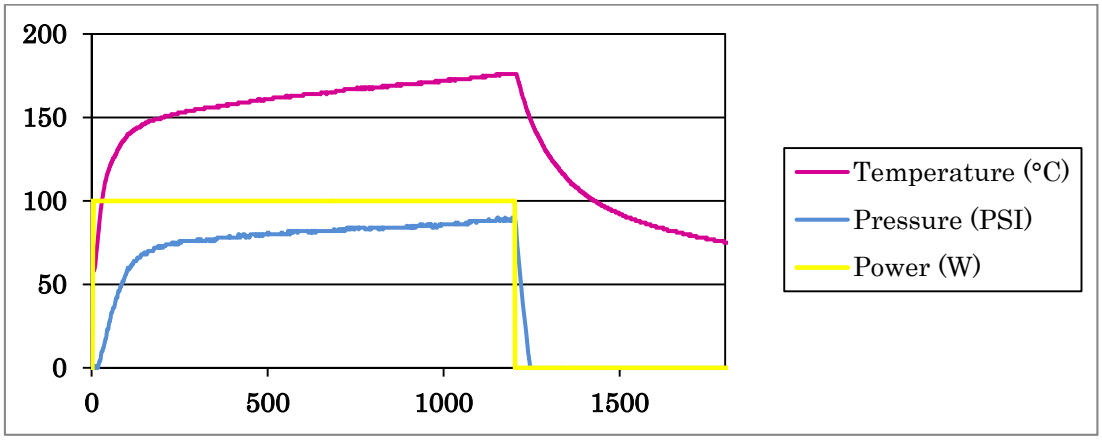
^{13}C NMR



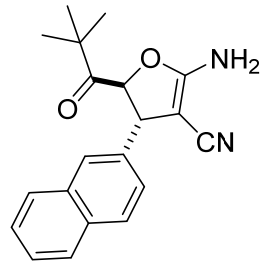
IR



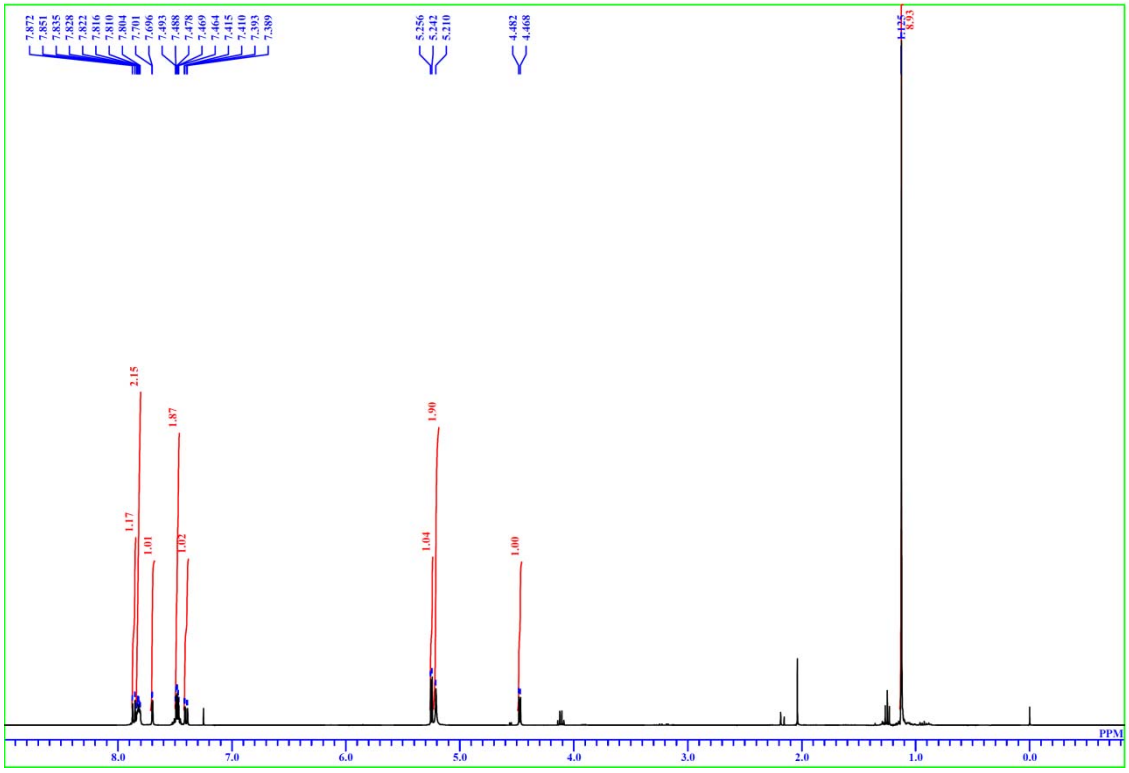
MW Profile (Table 2, entry 16)



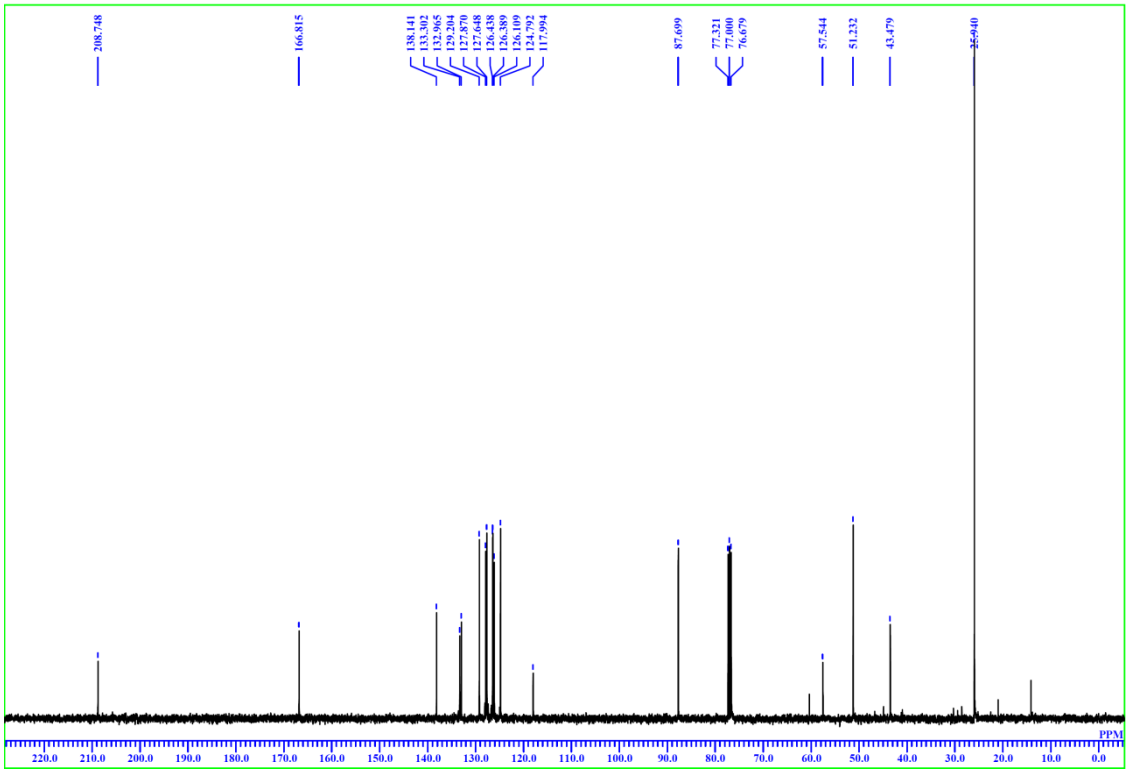
(*trans*-**3q**)



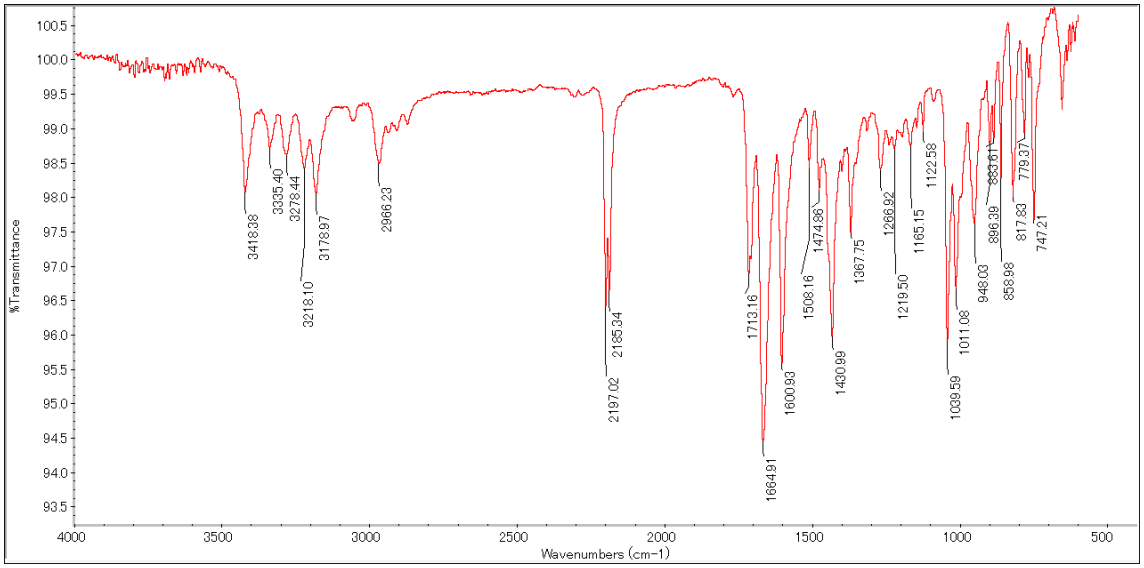
^{1}H NMR



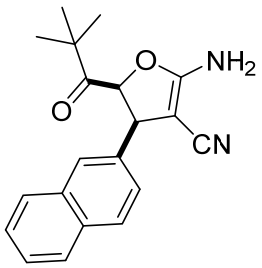
^{13}C NMR



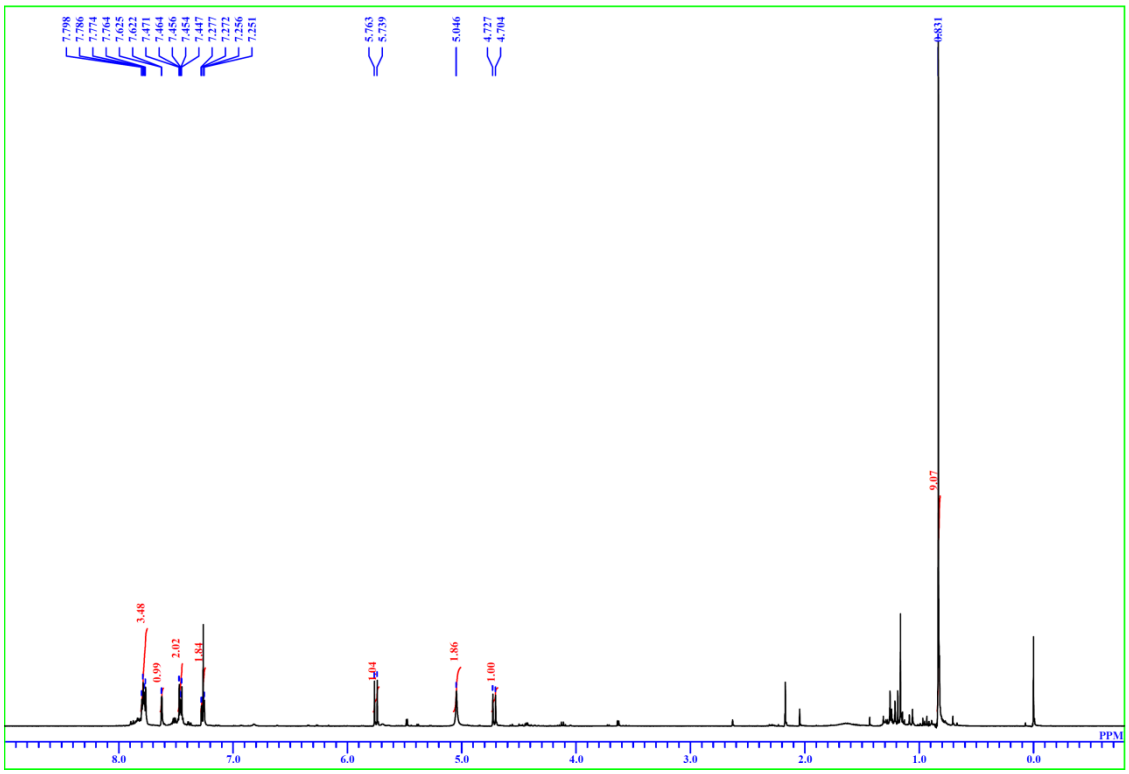
IR



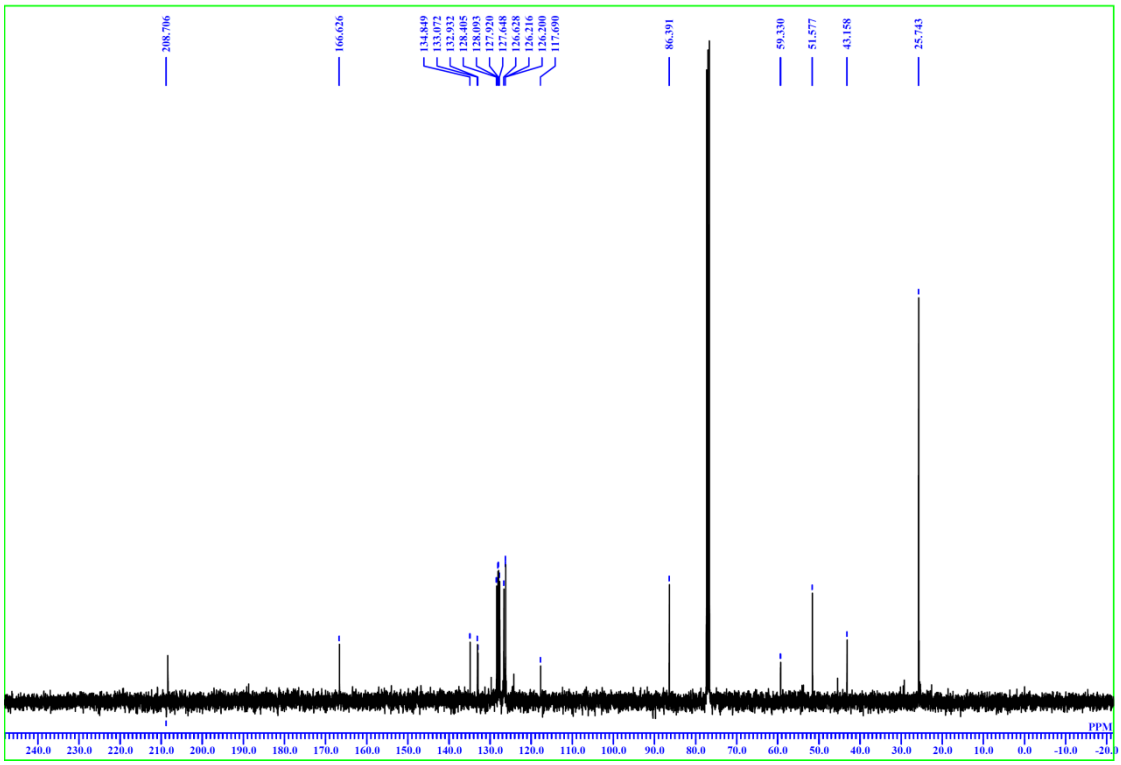
(*cis*-**3q**)



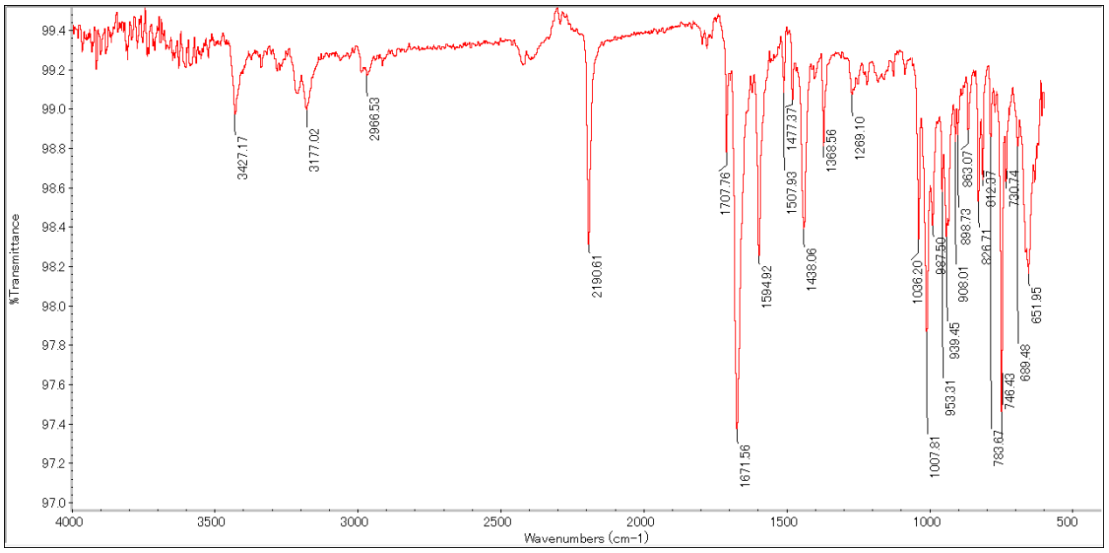
^{1}H NMR



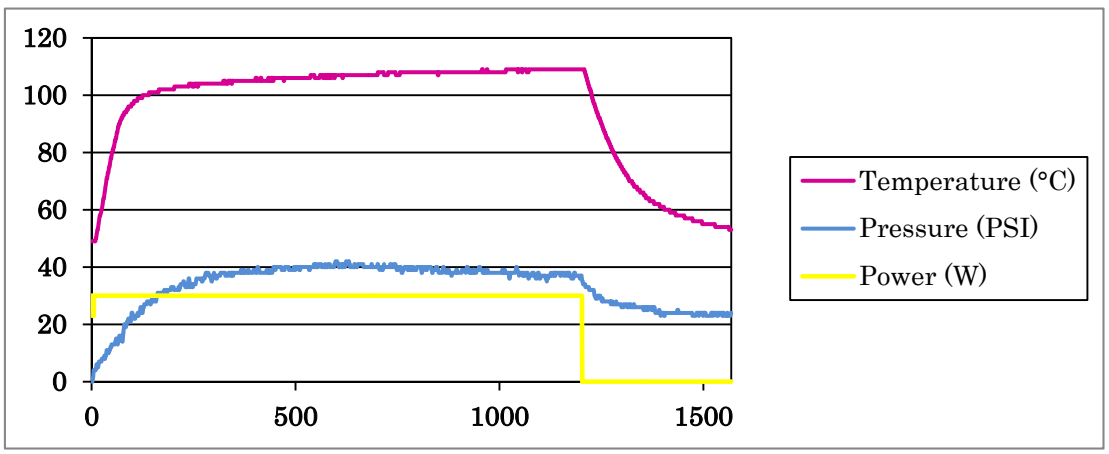
^{13}C NMR



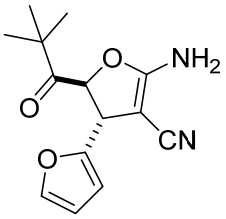
IR



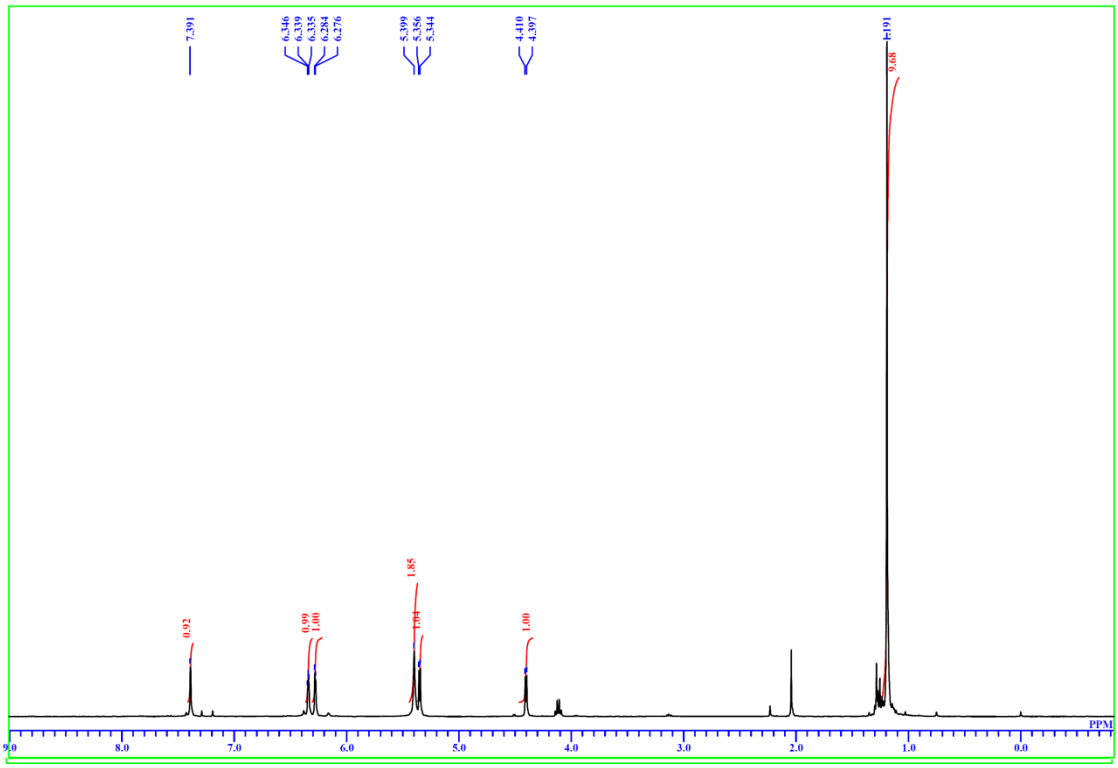
MW Profile (Table 2, entry 17)



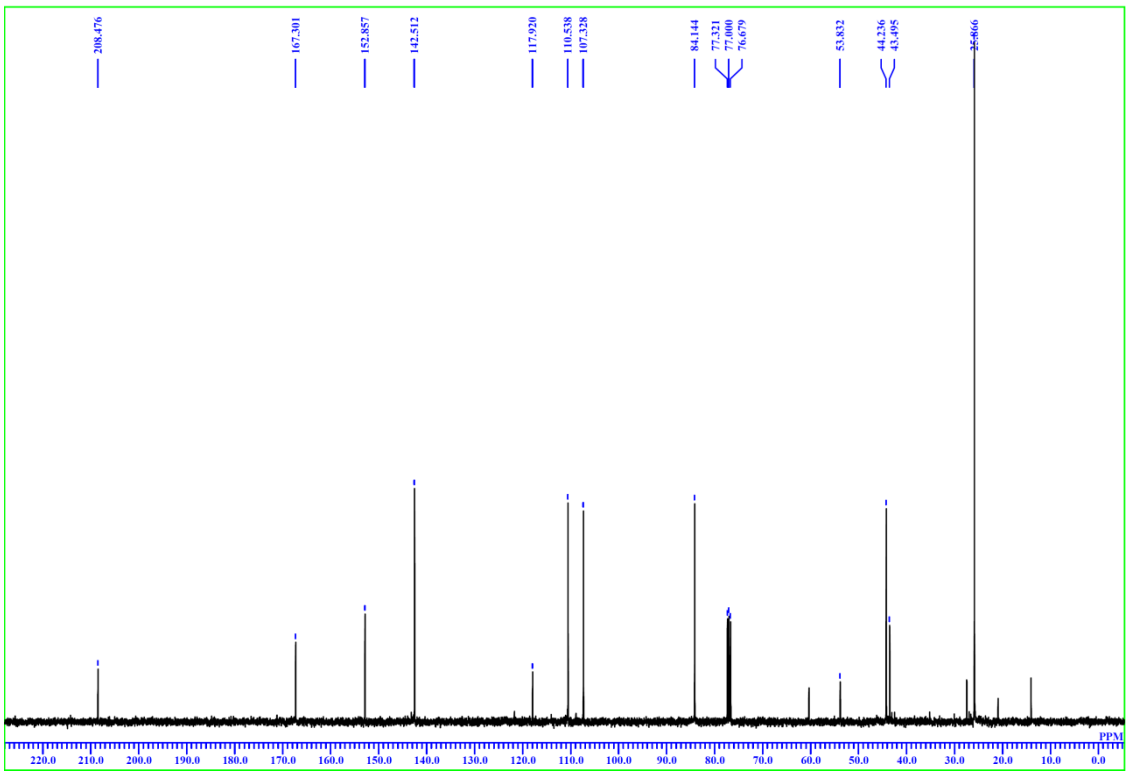
(*trans*-**3r**)



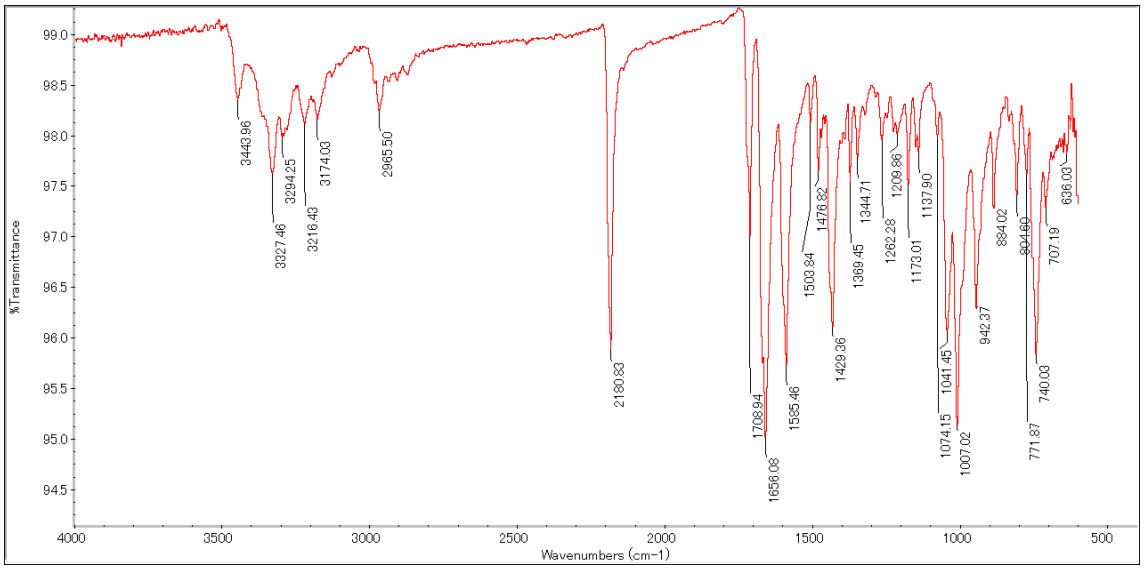
^{1}H NMR



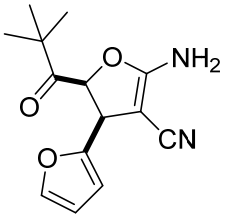
^{13}C NMR



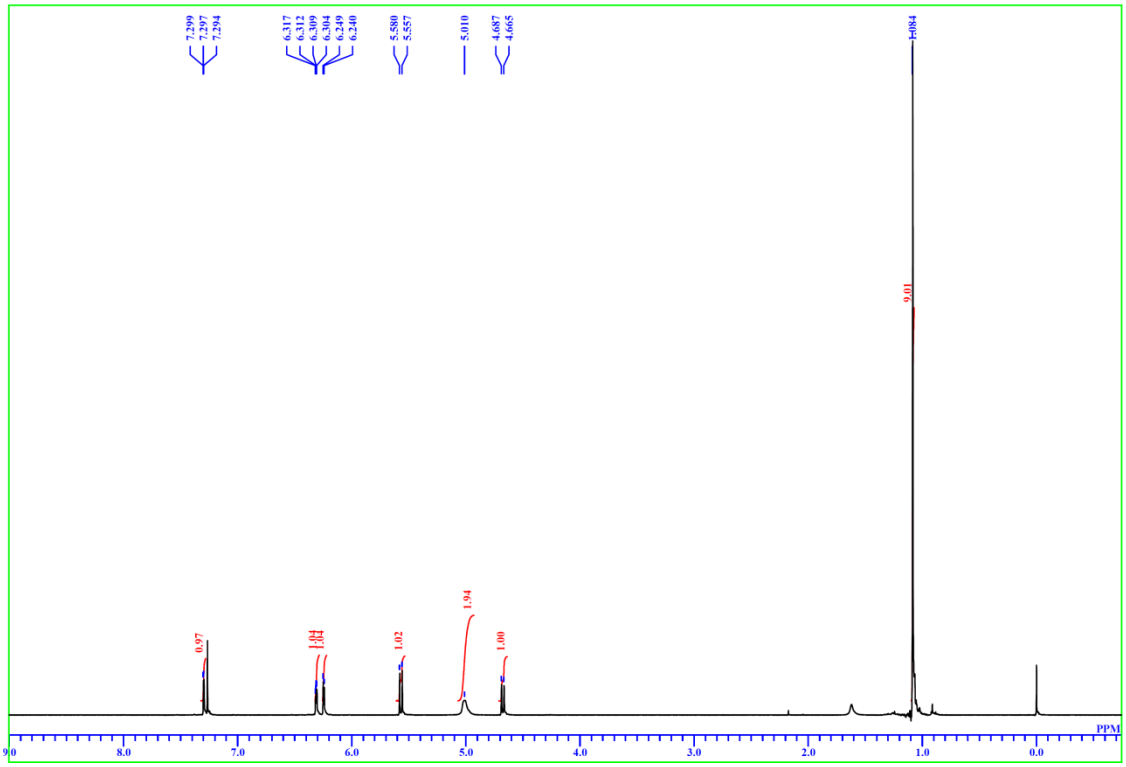
IR



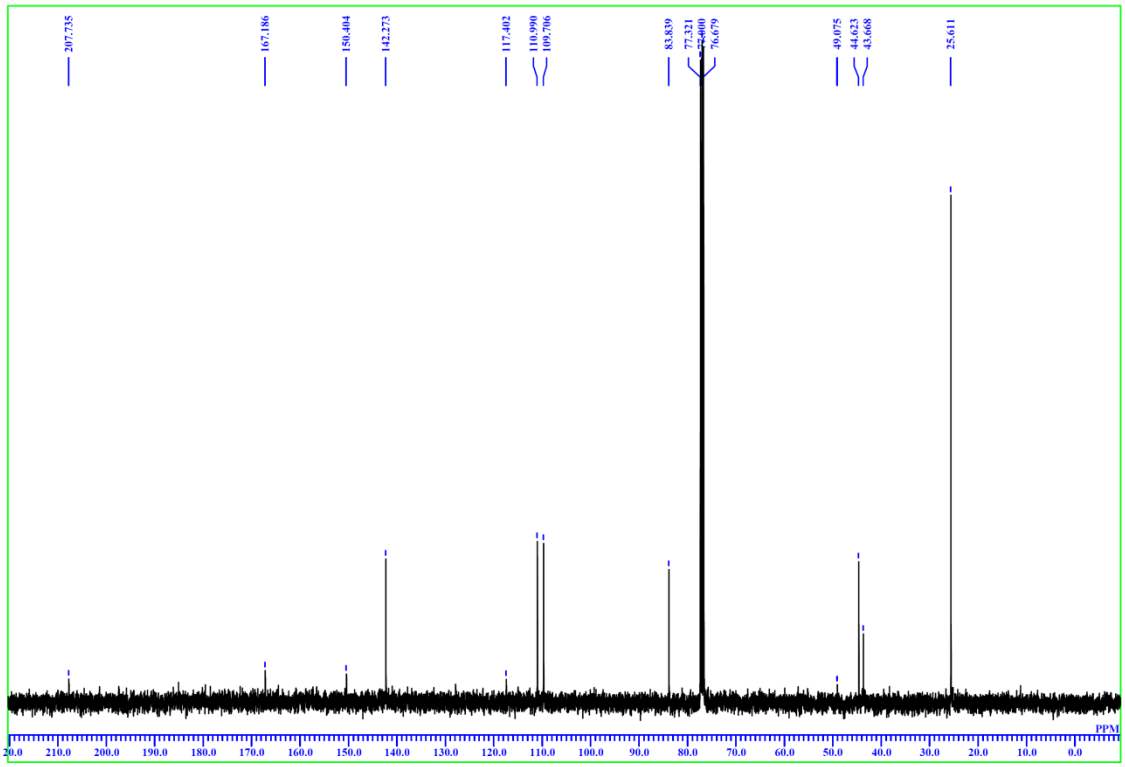
(*cis*-**3r**)



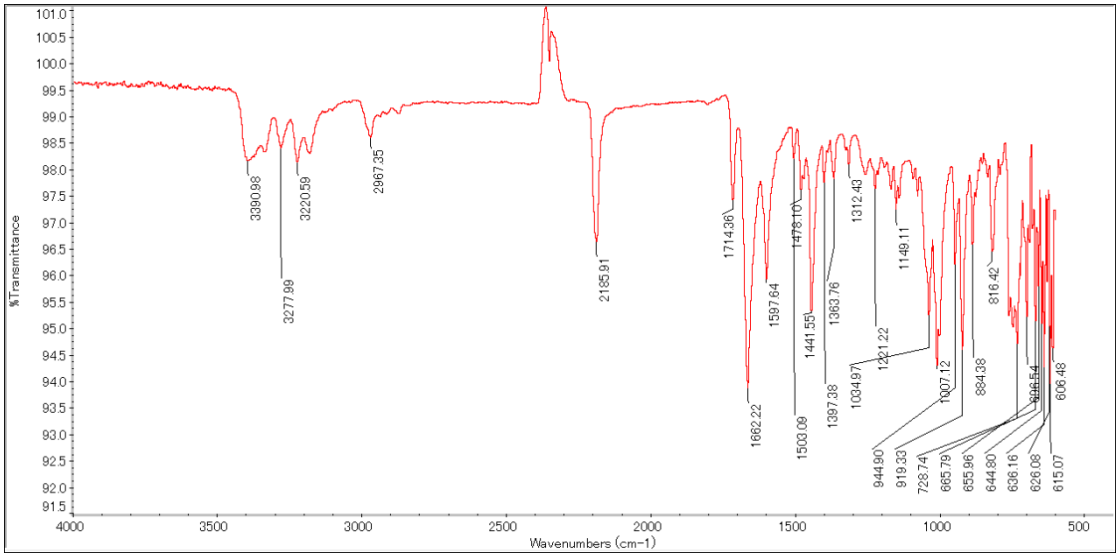
^{1}H NMR



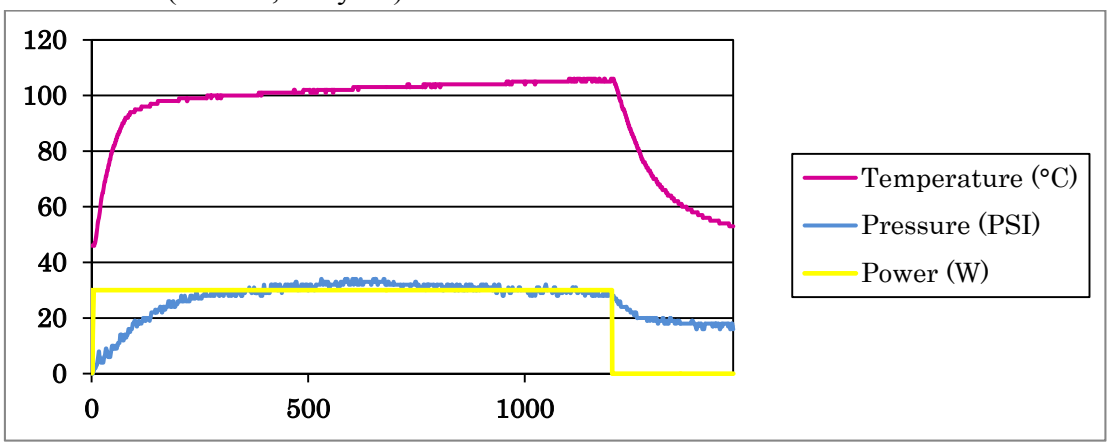
^{13}C NMR



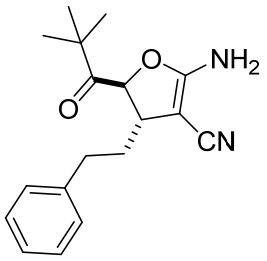
IR



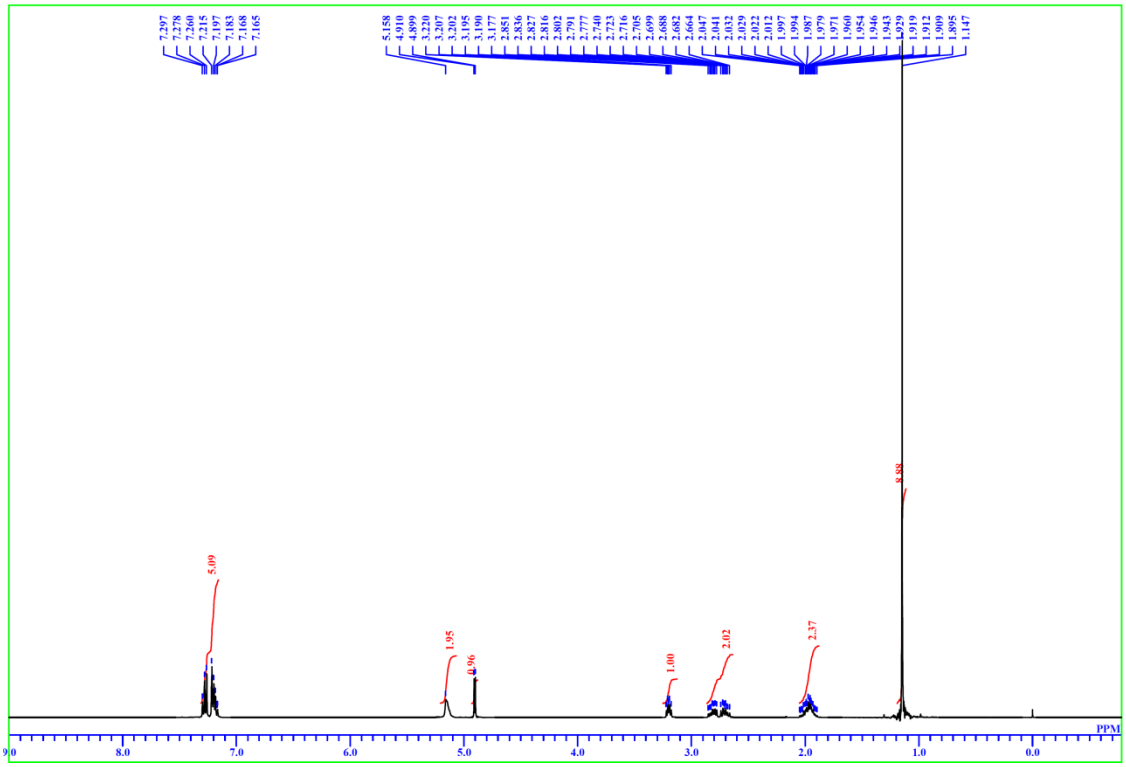
MW Profile (Table 2, entry 18)



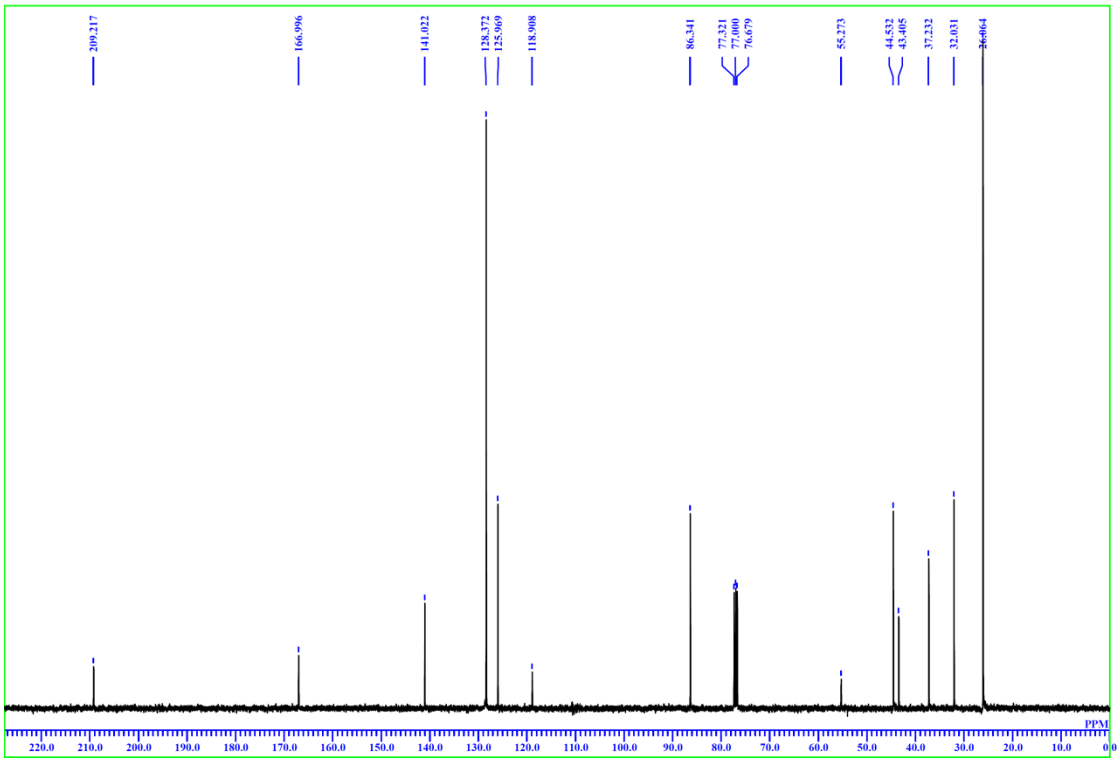
(*trans*-**3s**)



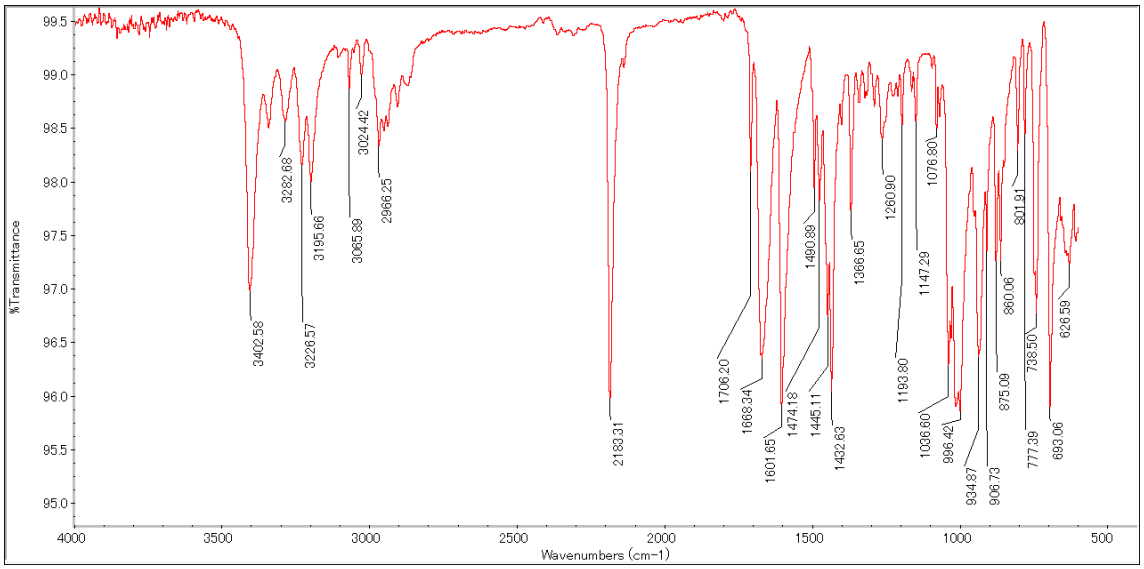
^{1}H NMR



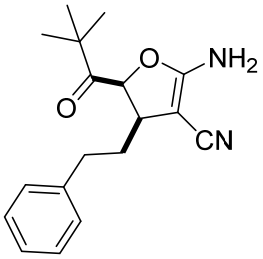
^{13}C NMR



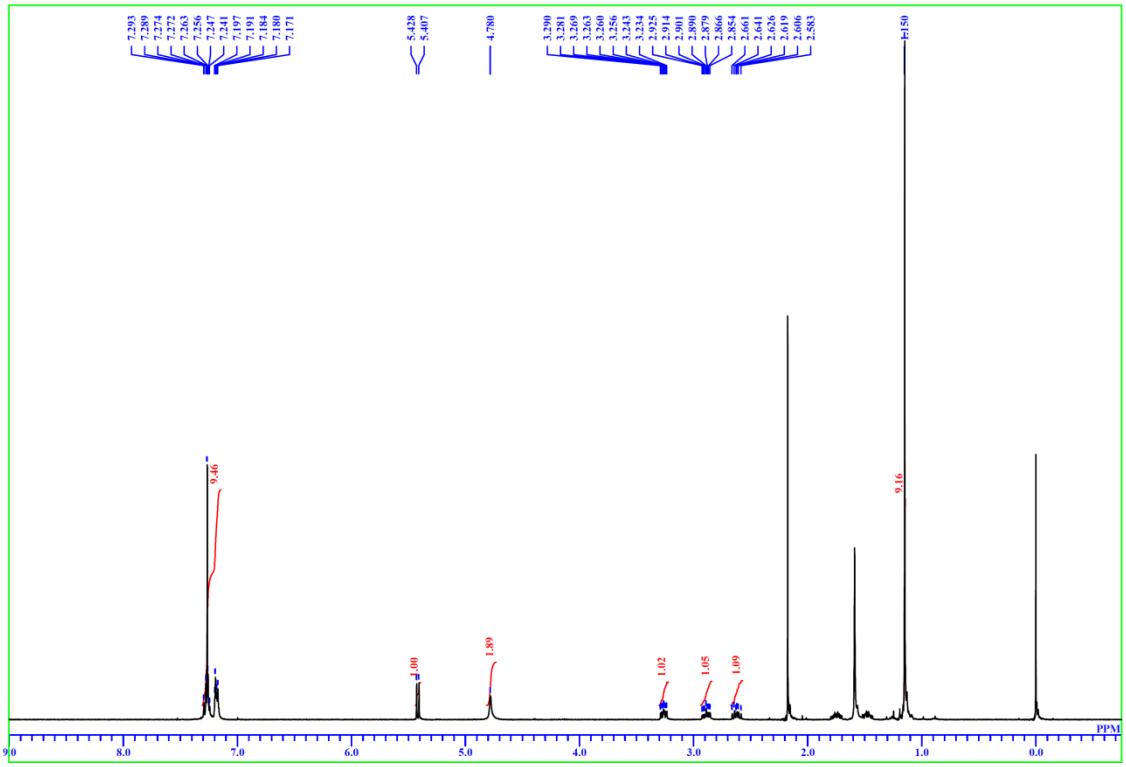
IR



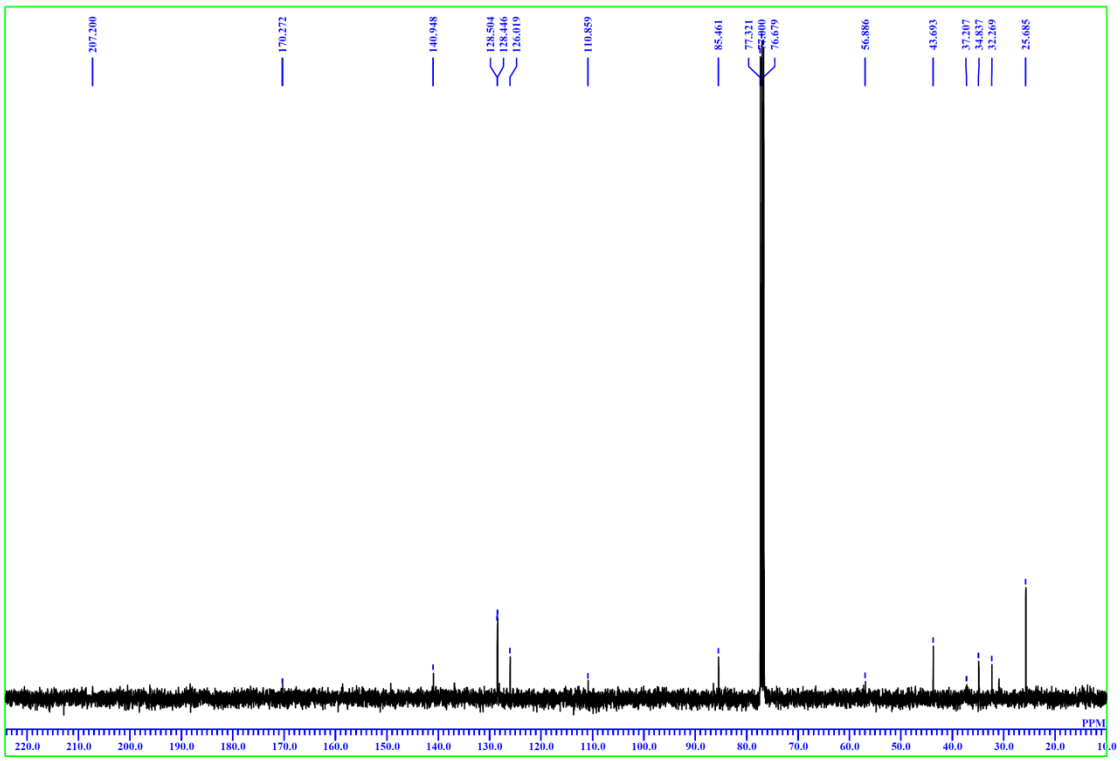
(*cis*-**3s**)



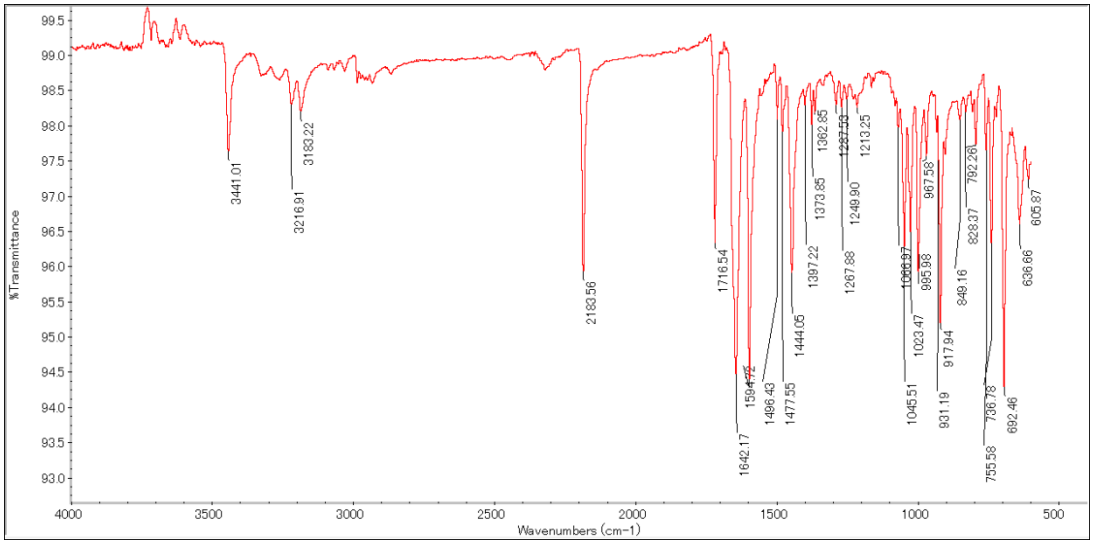
^{1}H NMR



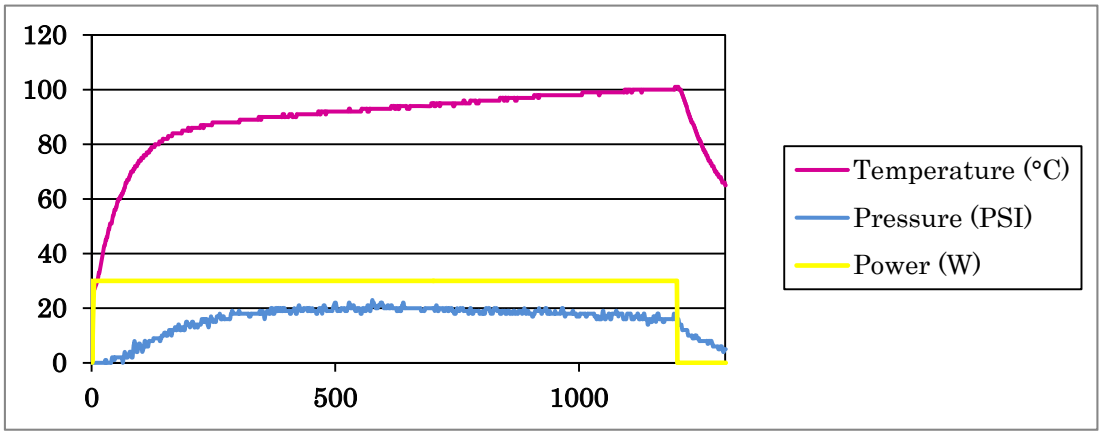
^{13}C NMR



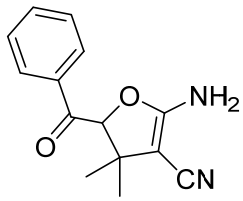
IR



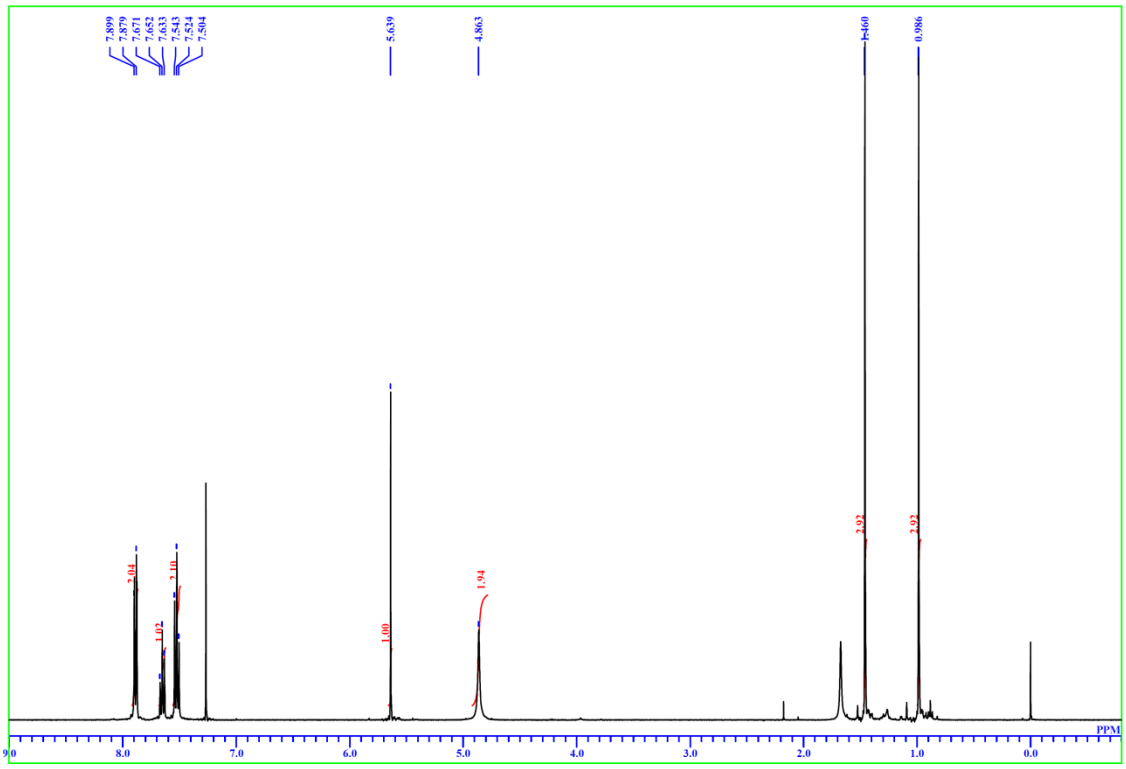
MW Profile (Table 2 entry 19)



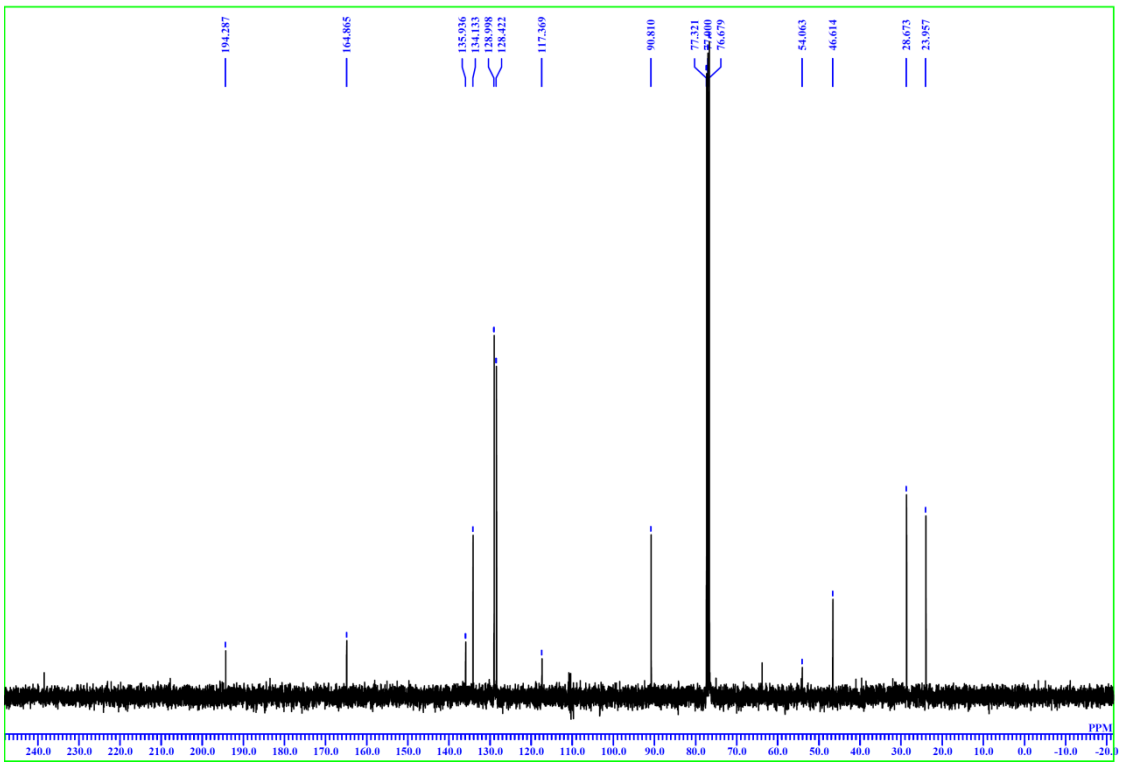
(3t)



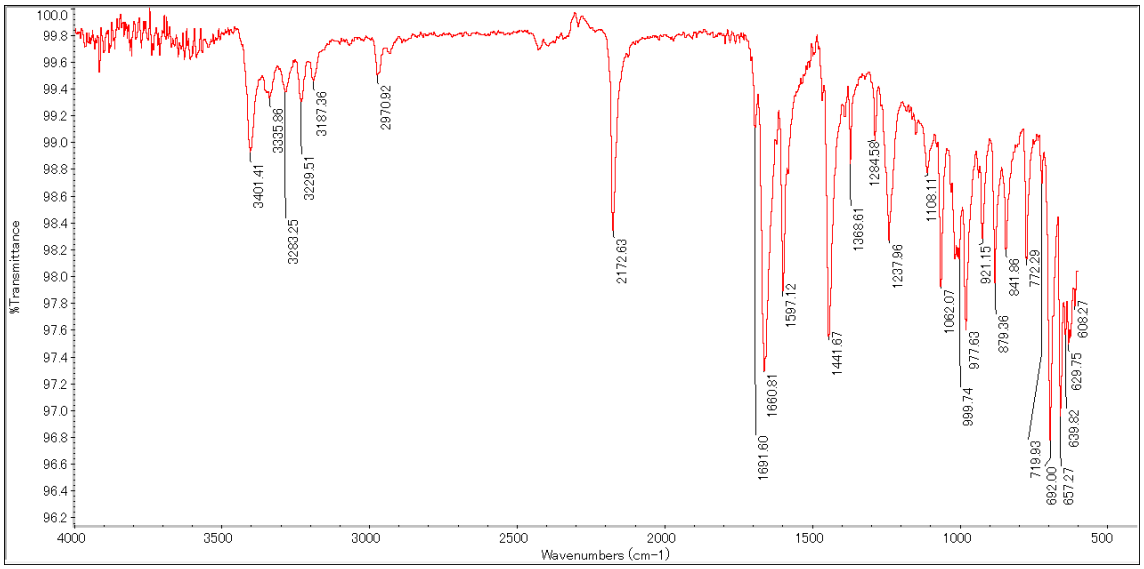
^{1}H NMR



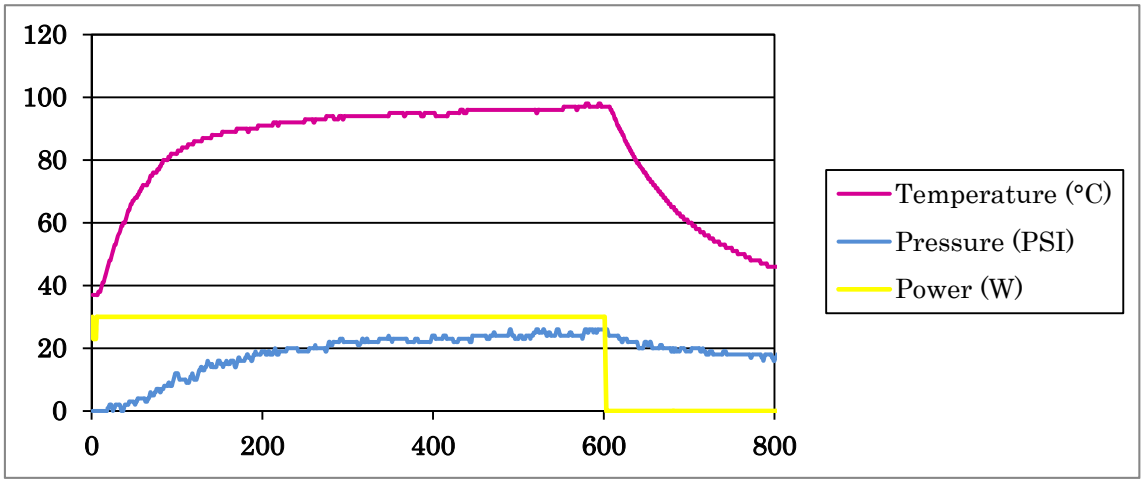
^{13}C NMR



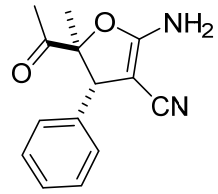
IR



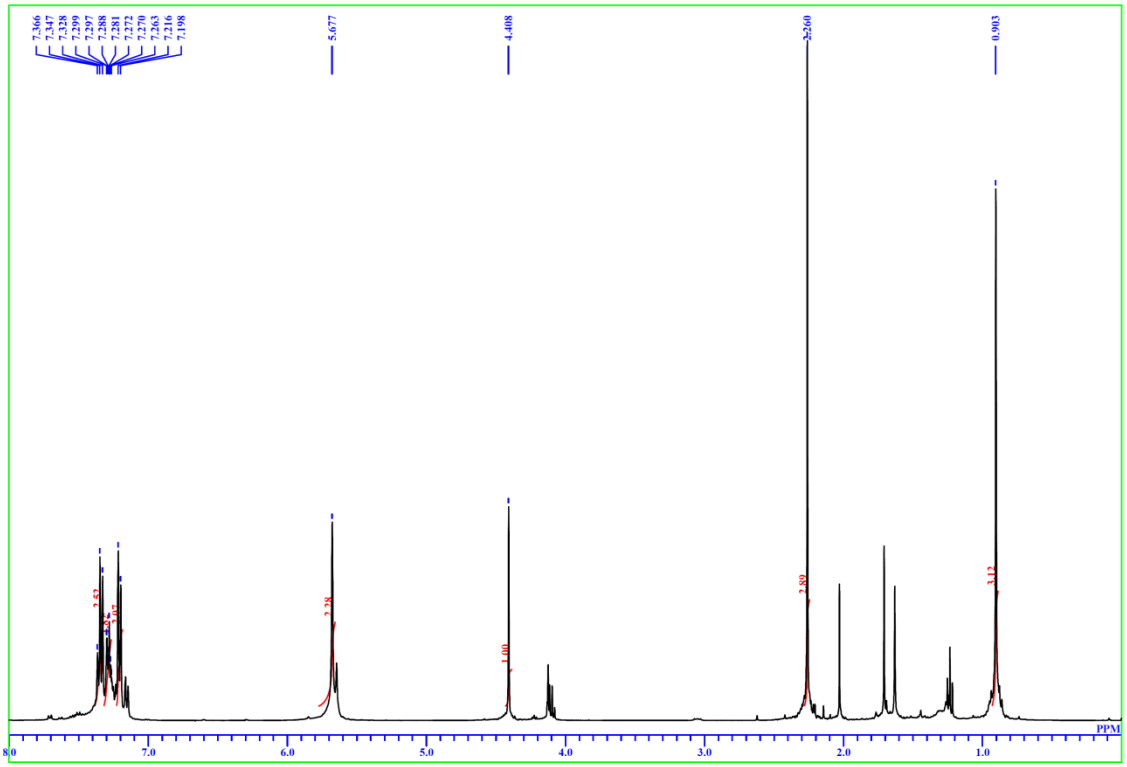
MW Profile (Scheme 1, eq.1)



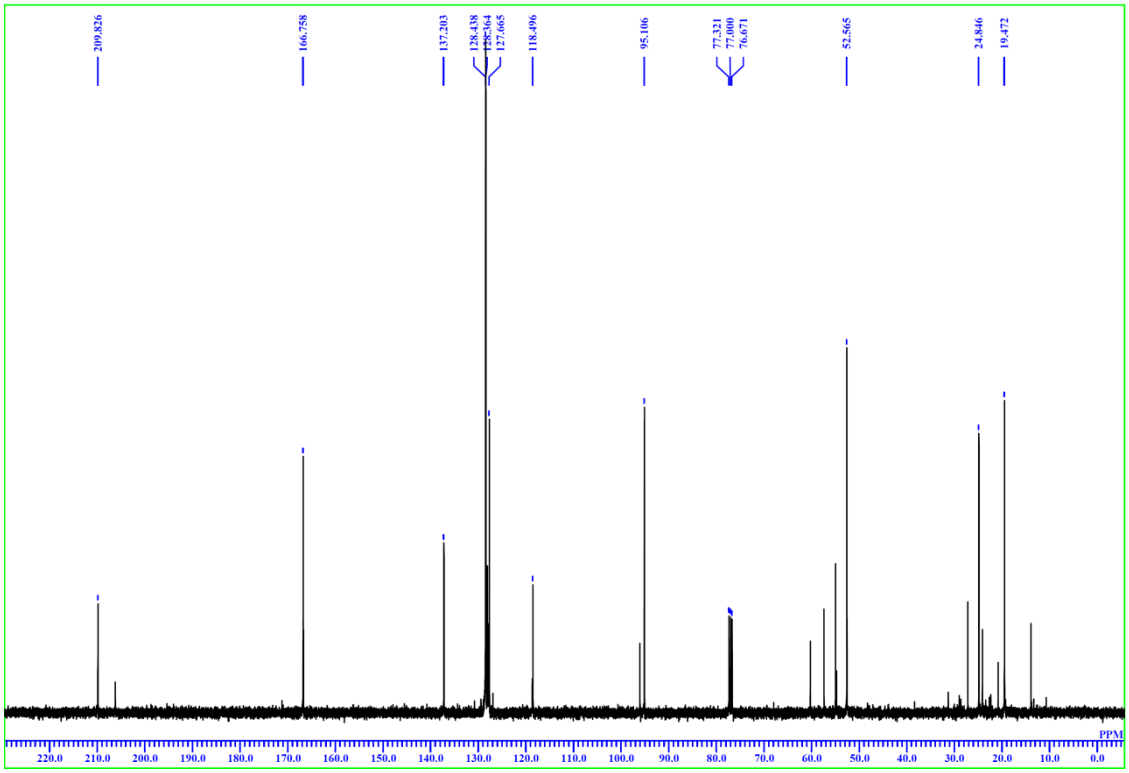
(*trans*-**3u**)



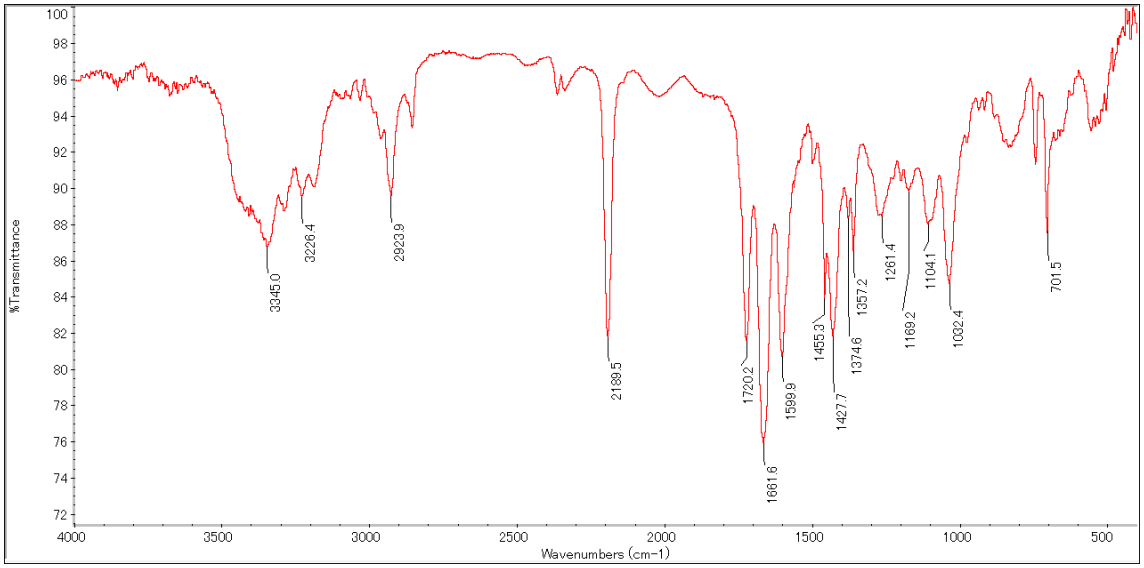
^{1}H NMR



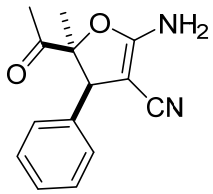
^{13}C NMR

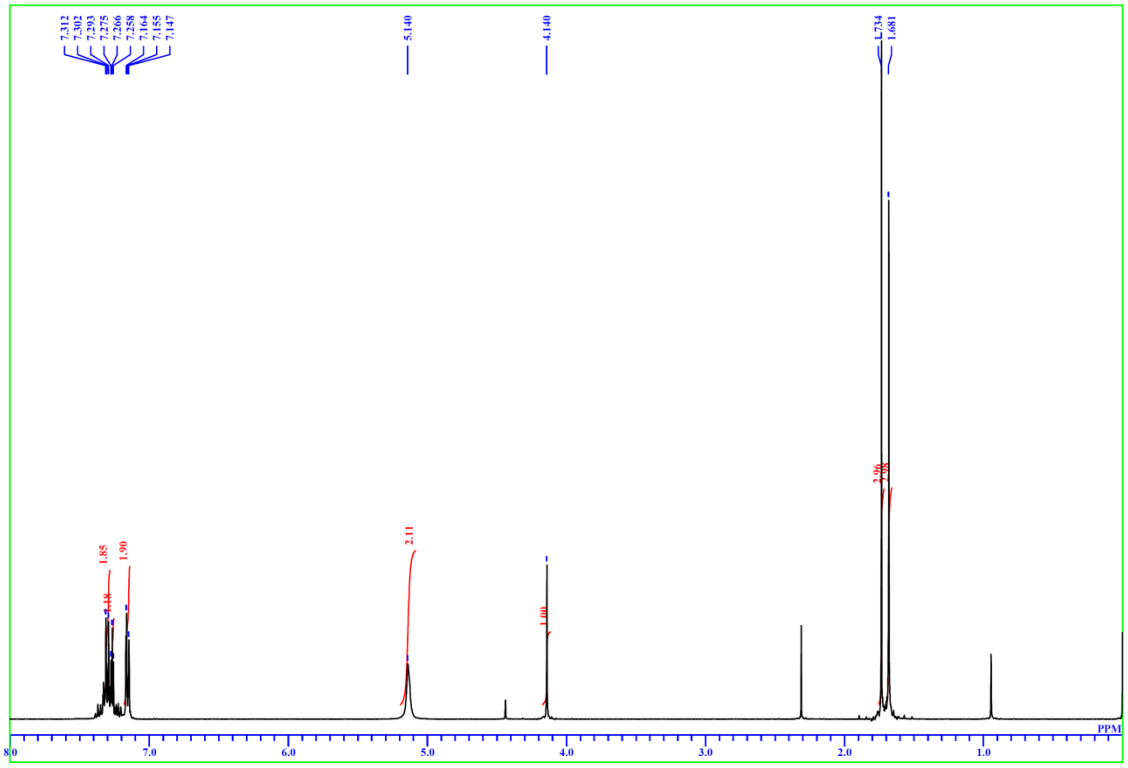


IR

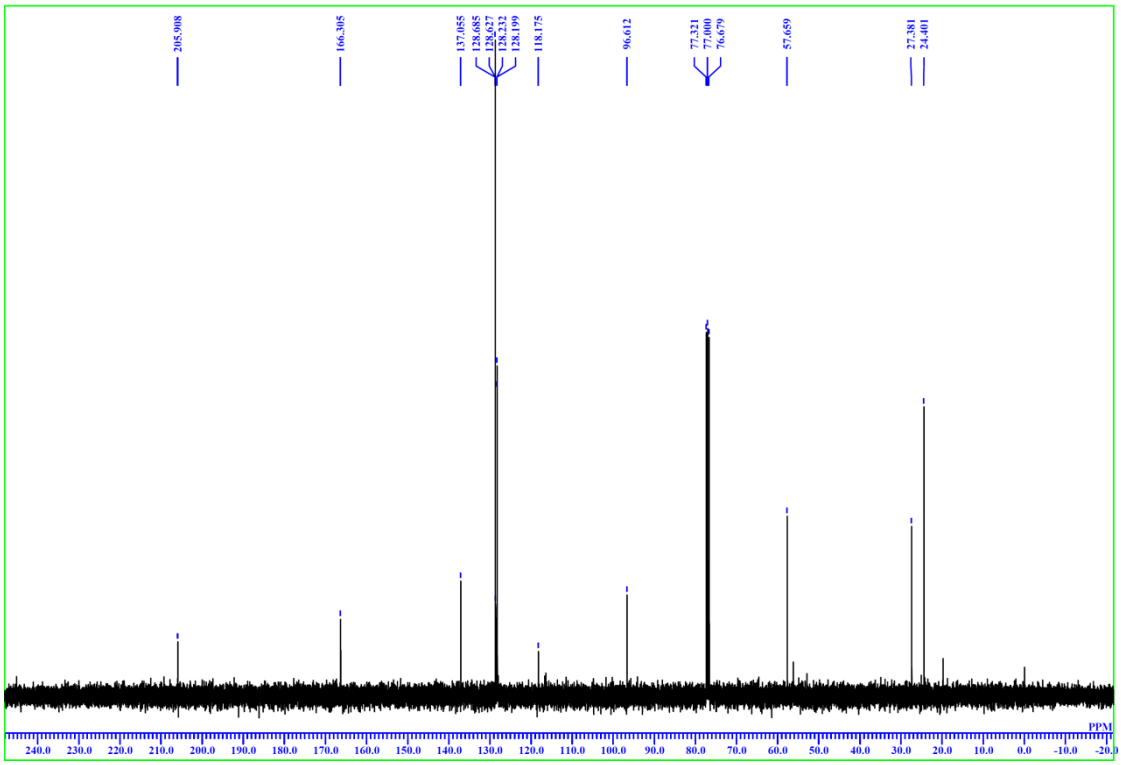

%Transmittance
Wavenumbers (cm-1)
3345.0
3226.4
2923.9
2189.5
1720.2
1661.6
1598.9
1455.3
1427.7
1374.6
1357.2
1261.4
1169.2
1104.1
1032.4
701.5

(*cis*-**3u**)


O
NH2
O
CN

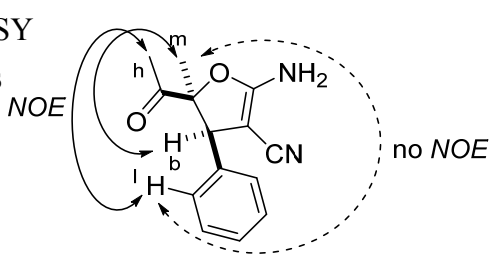

7.312
7.302
7.293
7.275
7.266
7.258
7.164
7.155
7.147
5.140
4.140
1.734
1.681
2.06
2.08
1.85
1.90
2.11
1.00
PPM

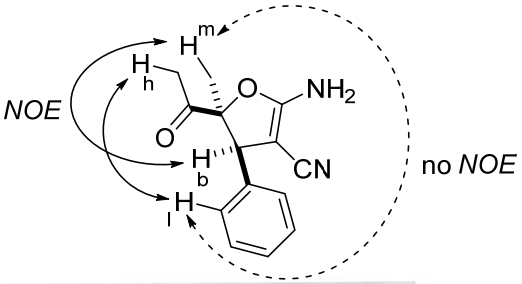
^{13}C NMR

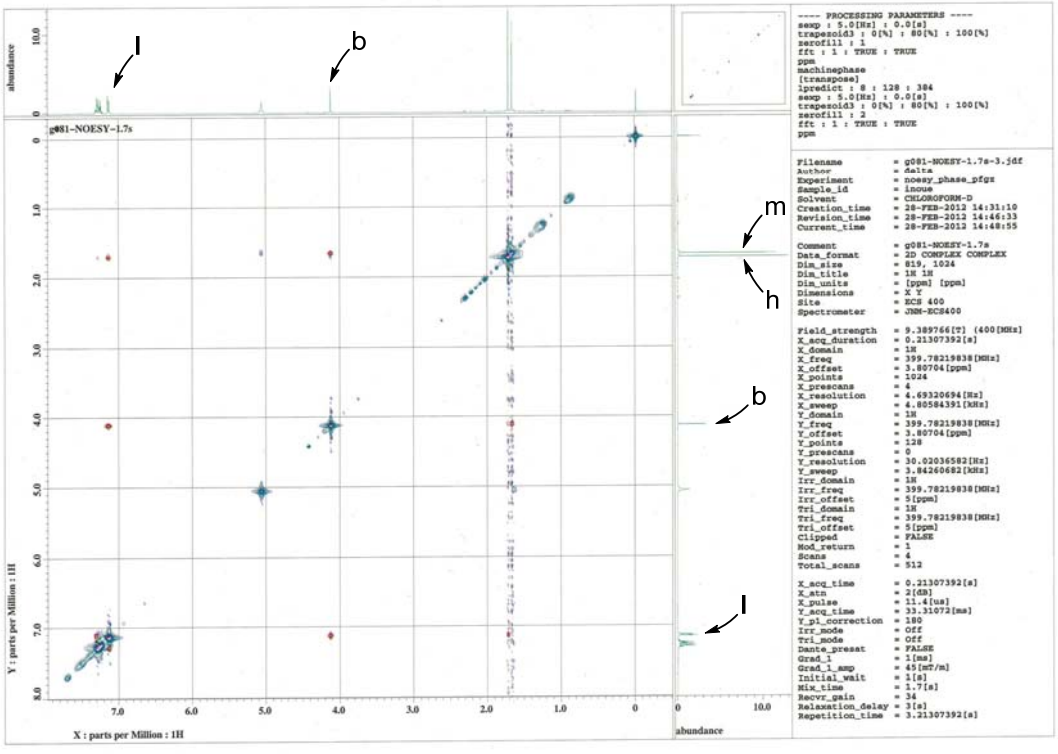


NOESY

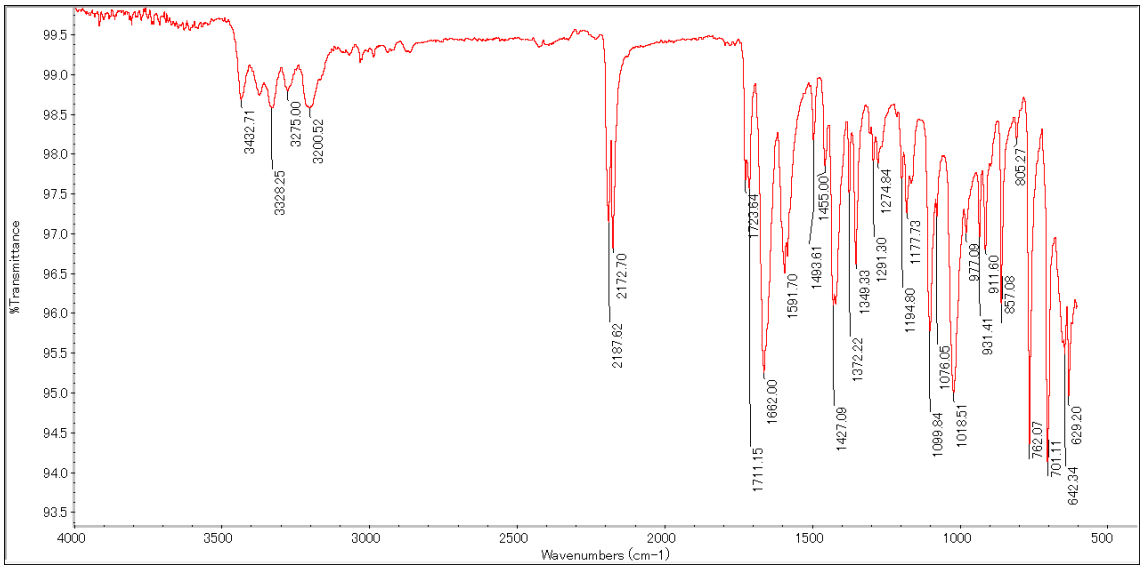
cis-**3s**



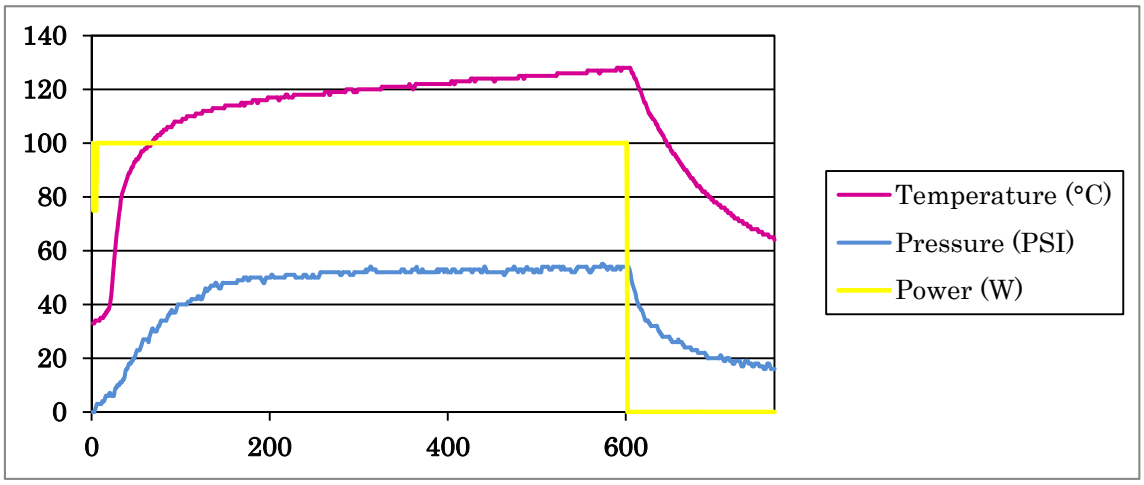




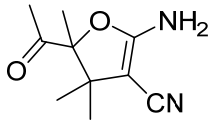
IR



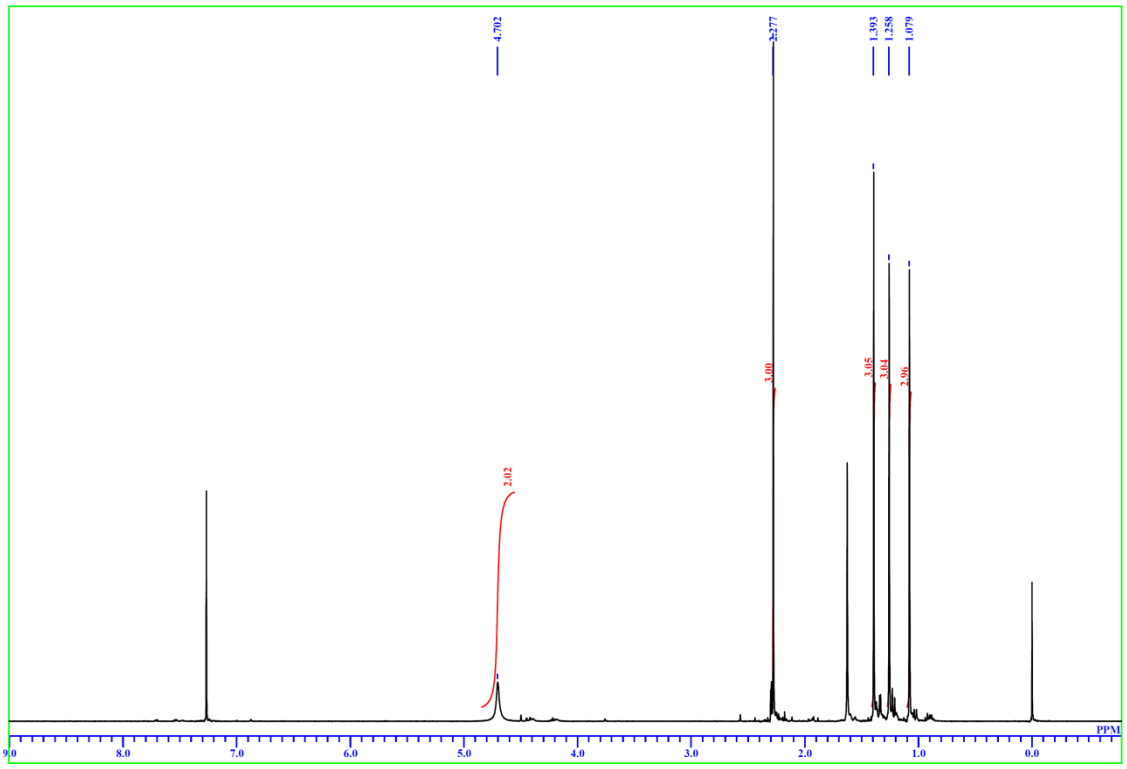
MW Profile (Scheme 1, eq 2)



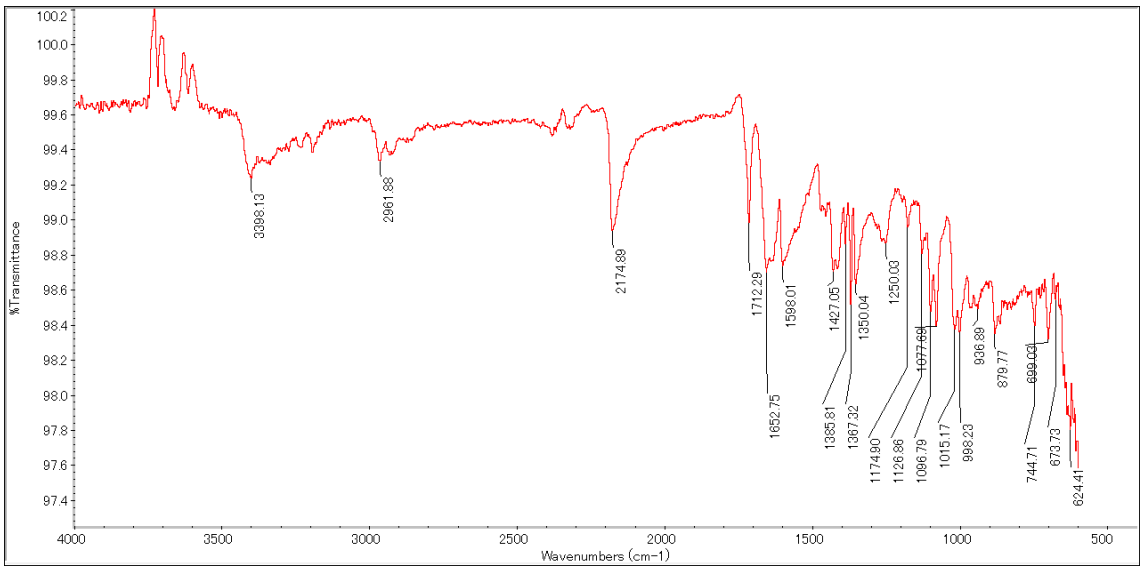
(3v)


O
NH2
O
CN

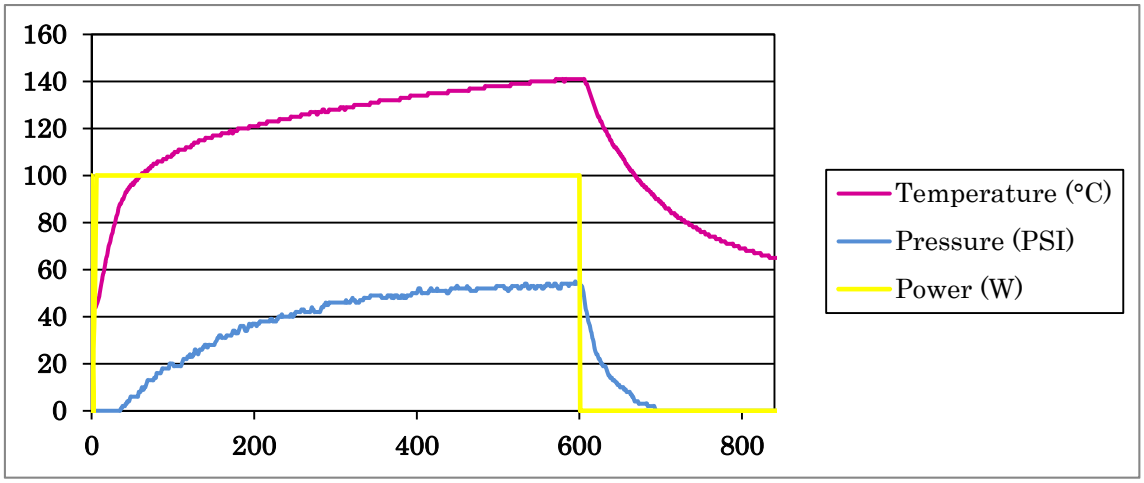
^{1}H NMR


4.702
2.277
1.393
1.258
1.079
3.00
3.05
3.04
2.96
2.02
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

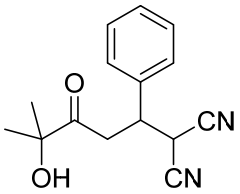
IR


%Transmittance
Wavenumbers (cm-1)
3398.13
2961.88
2174.89
1712.29
1652.75
1598.01
1427.05
1385.81
1367.32
1350.04
1250.03
1174.90
1126.86
1098.79
1077.69
1015.17
988.23
936.89
879.77
744.71
699.03
673.73
624.41

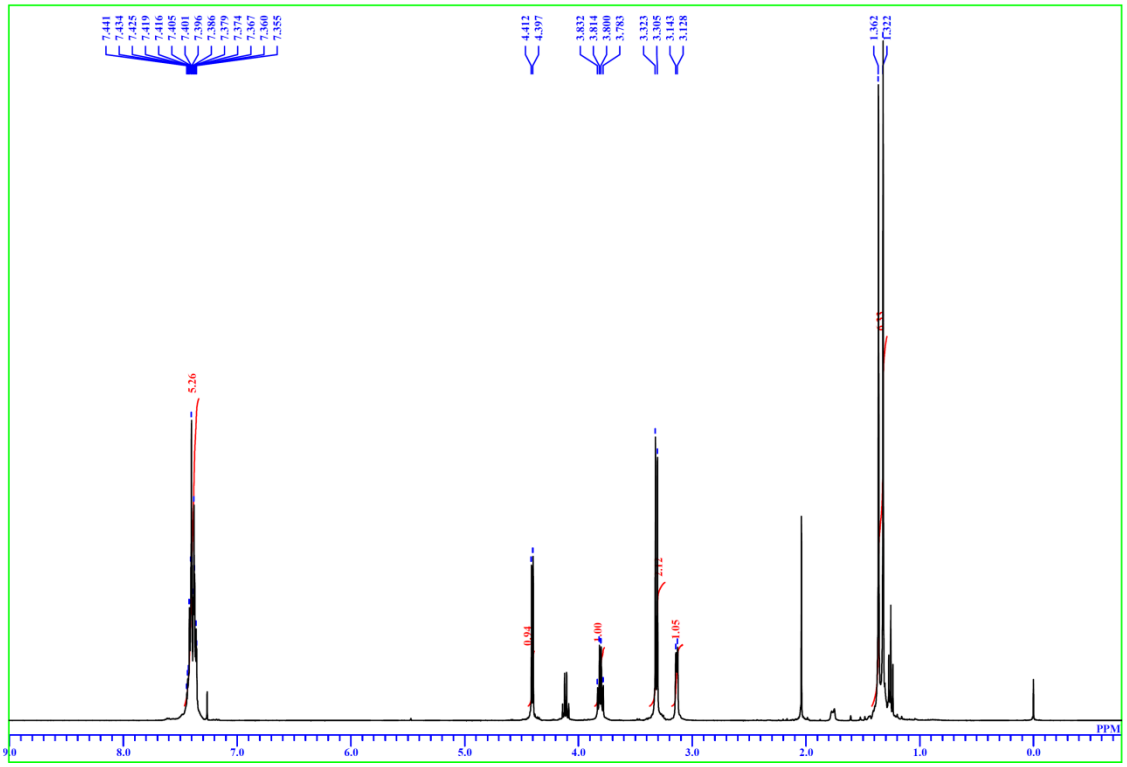
MW Profile (Scheme 1, eq.3)



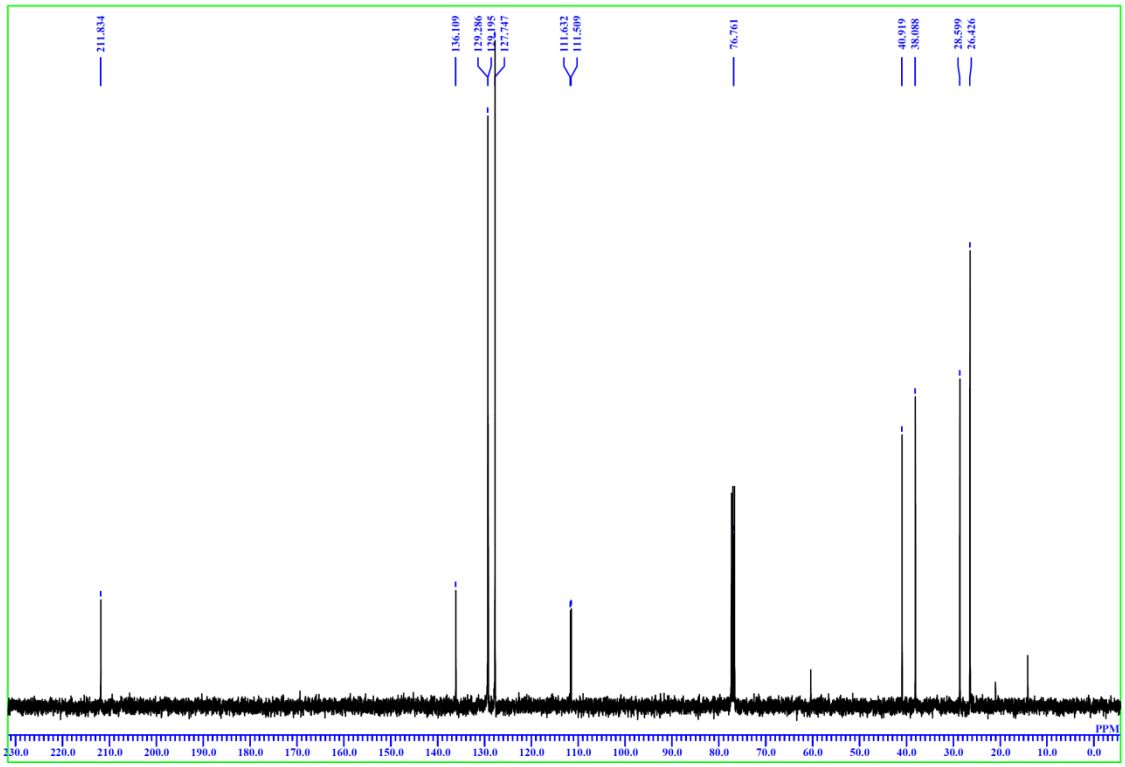
(4a)



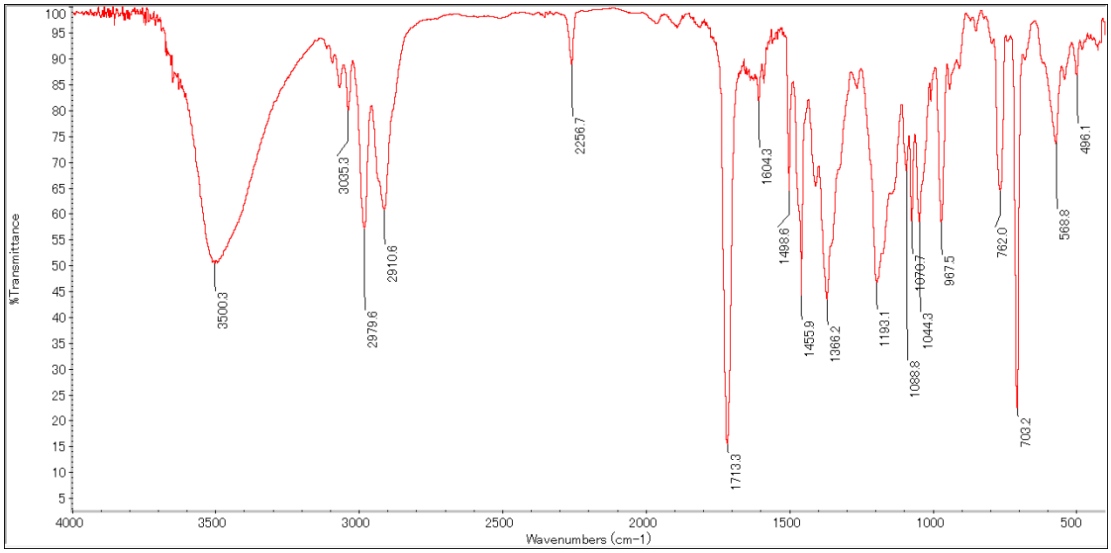
^{1}H NMR



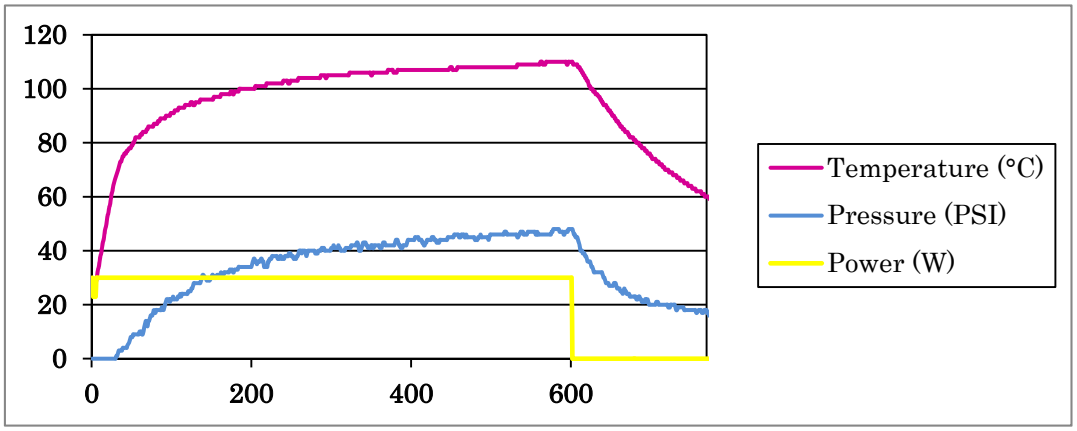
^{13}C NMR



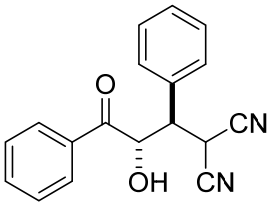
IR



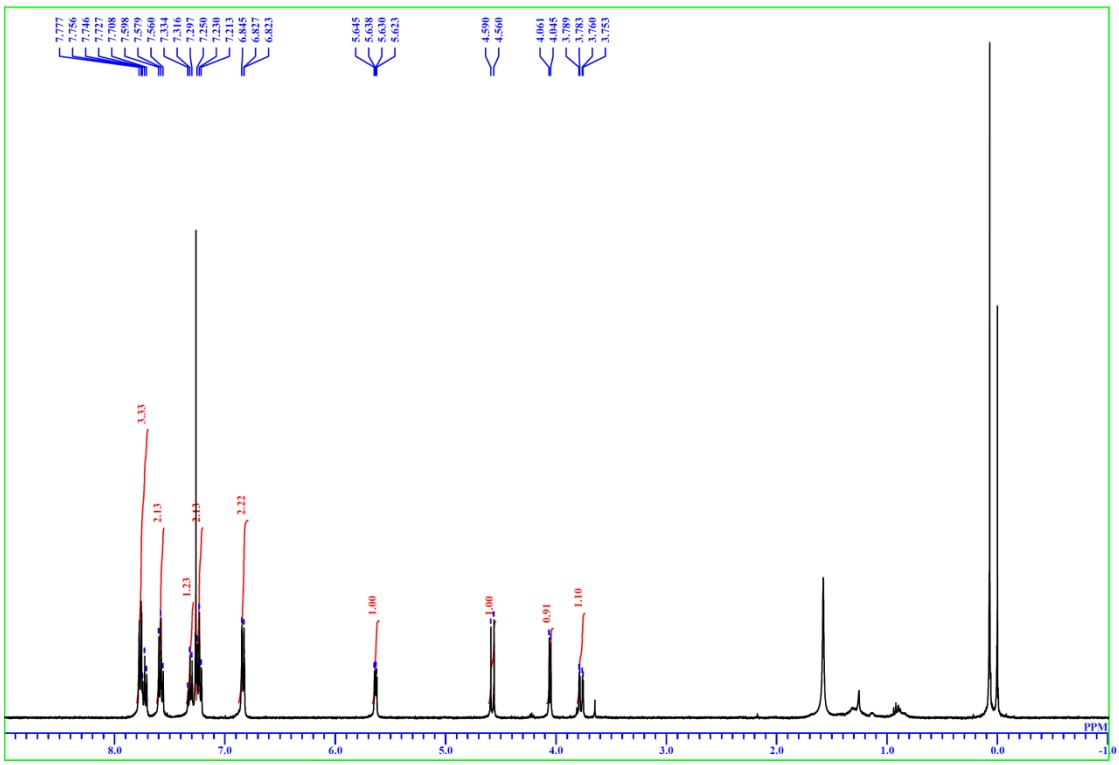
MW Profile (Scheme 2)



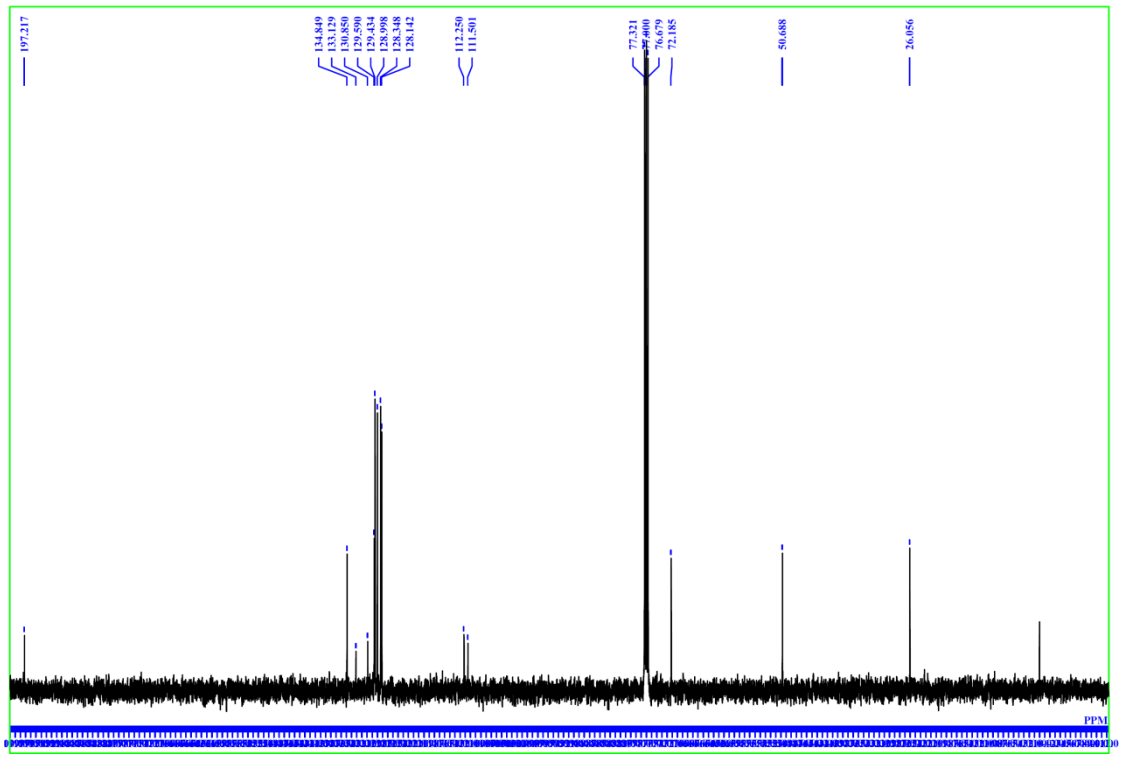
(4b Major)



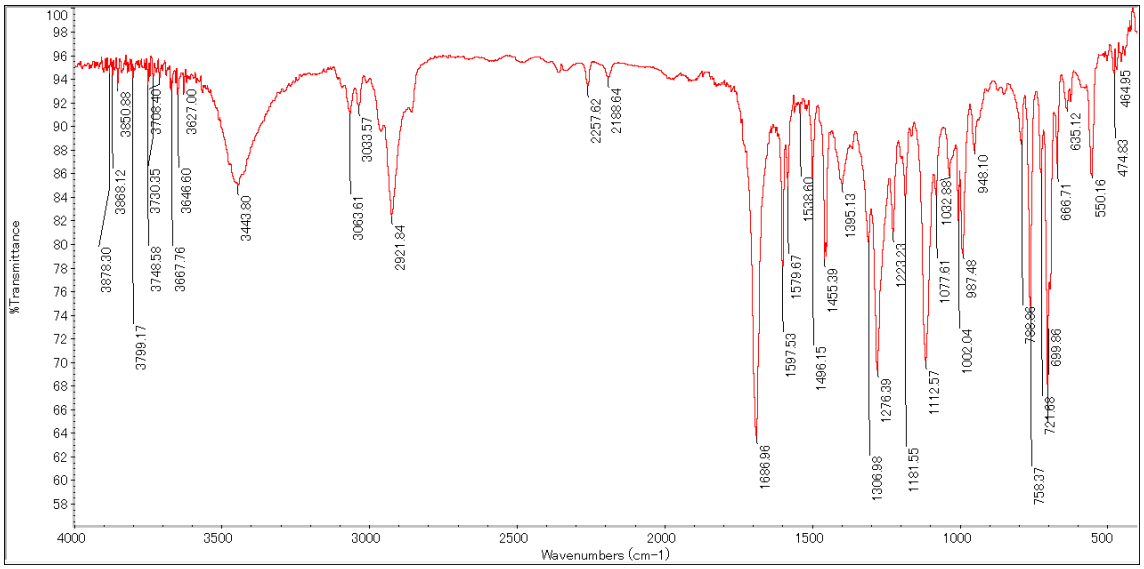
^{1}H NMR



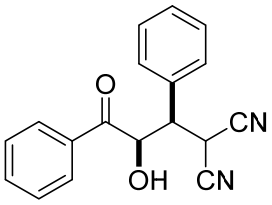
^{13}C NMR



IR

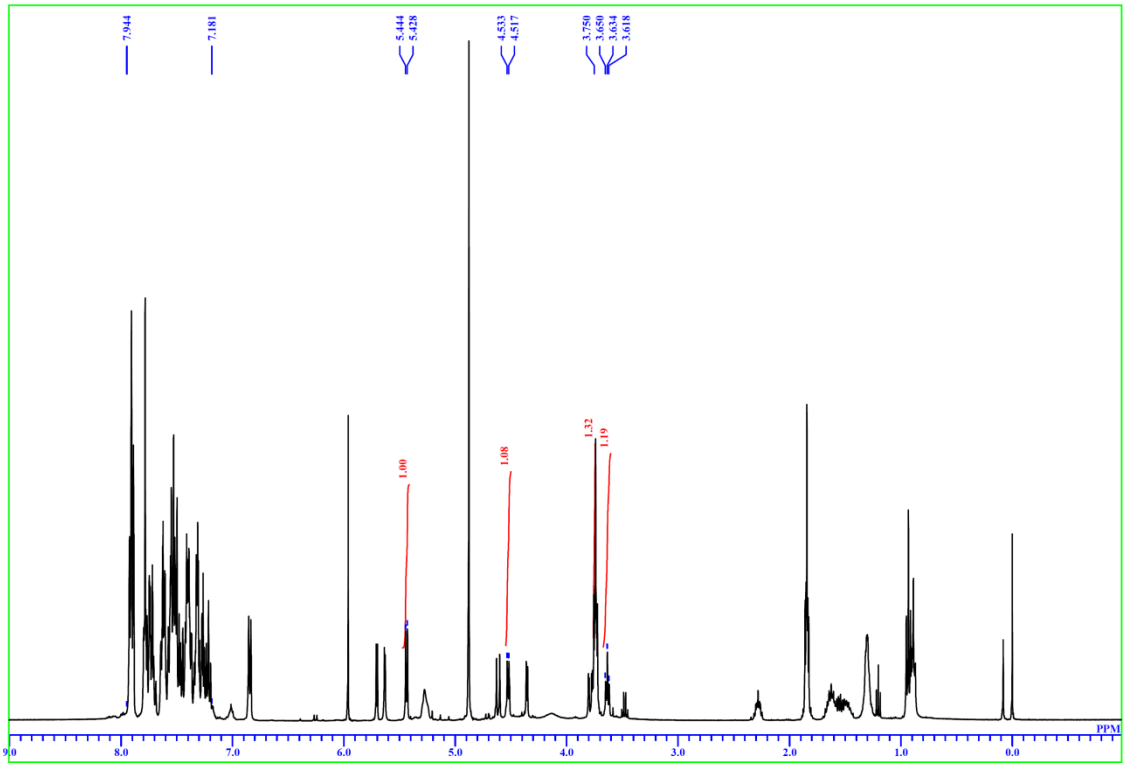


(4b Minor)

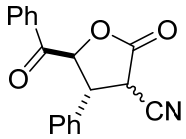


Diastereomer mixture

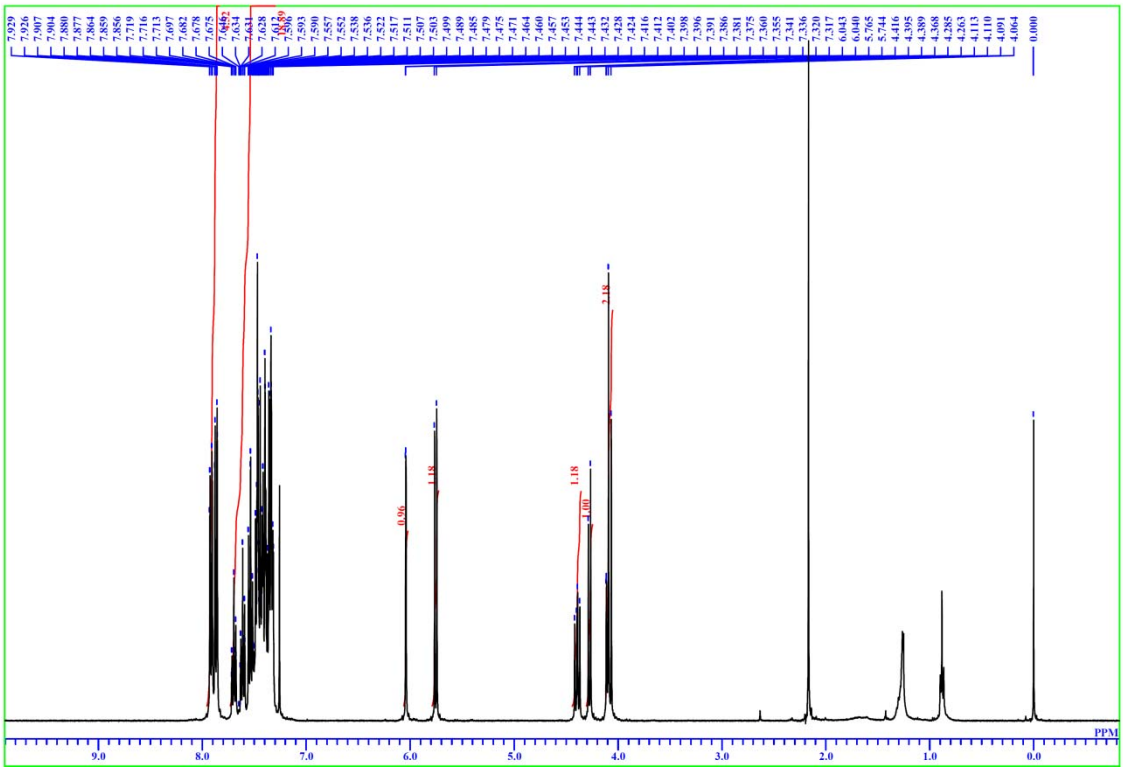
^{1}H NMR



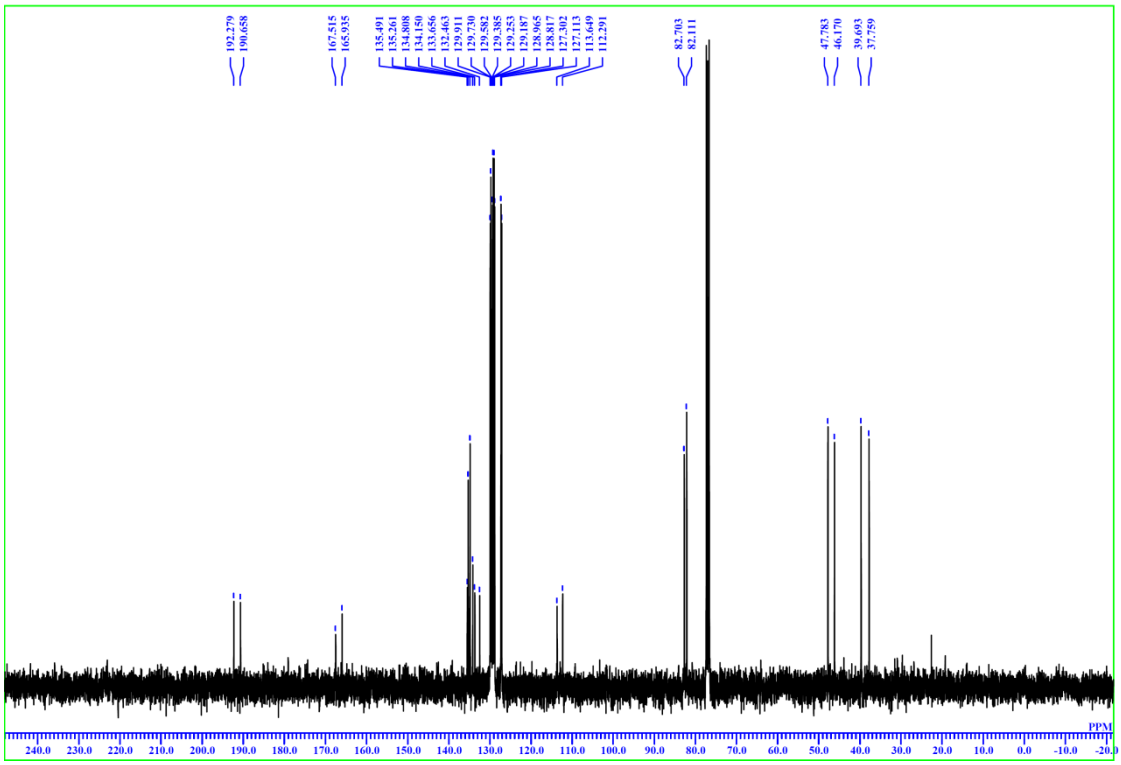
(5)



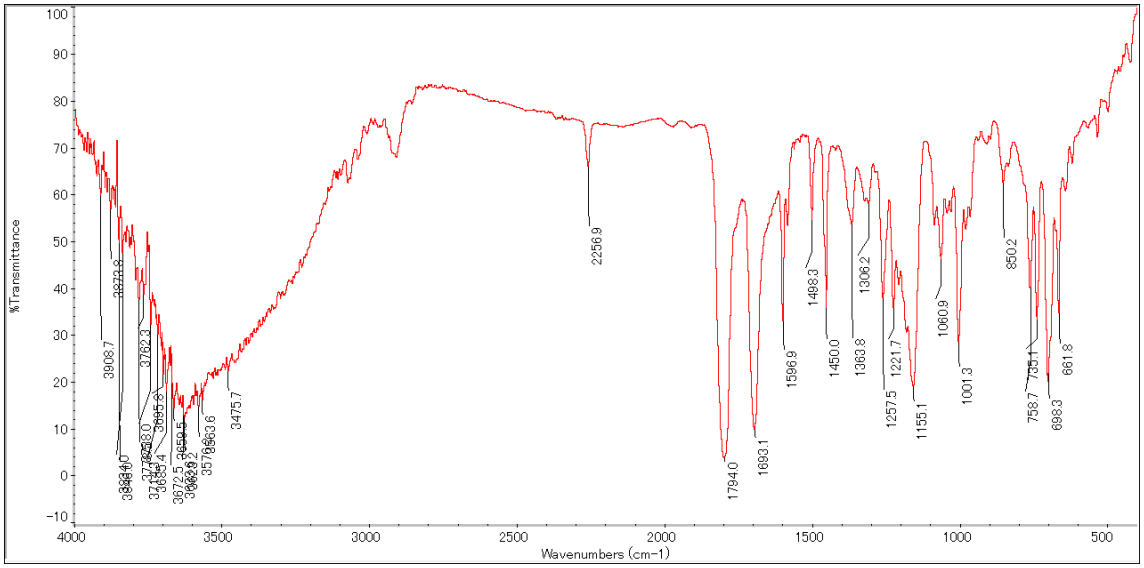
^{1}H NMR



^{13}C NMR



IR


%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
0
-10
4000
3500
3000
2500
2000
1500
1000
500
3908.7
3782.3
3475.7
2256.9
1940.0
1893.1
1596.9
1498.3
1450.0
1363.8
1306.2
1257.5
1221.7
1155.1
1060.9
1001.3
850.2
758.7
735.1
688.3
661.8