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Electronic Supplementary Information

Guanidine Cyclic Diimides and Their Polymers

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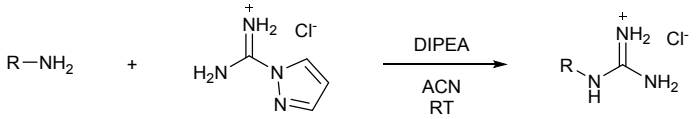
1. General Considerations

^{1}H-NMR spectra were recorded on Bruker (300 MHz) or Varian (500 MHz) spectrometer. ^{1}H chemical shifts were referenced from the chemical shifts of tetramethylsilane (for spectra recorded in $CDCl_3$; 0.00 ppm) or residual solvent peaks (for spectra recorded in D_2O; 4.79 ppm or DMSO-d_6; 2.50 ppm). ^{13}C-NMR spectra were recorded on Bruker (75 MHz) or Varian (125 MHz) spectrometer with complete proton decoupling. ^{13}C chemical shifts were referenced from the chemical shifts of $CDCl_3$ (77.16 ppm) or DMSO-d_6 (39.52 ppm). Two-dimensional NMR spectra were only recorded for compound **3aa** on Varian NMR System 500 MHz spectrometer. 2D ^{1}H-^{1}H homonuclear and ^{1}H-^{13}C heteronuclear experiments [2D correlated spectroscopy (COSY) and heteronuclear single quantum coherence (HSQC)] were performed. All spectral data were processed with the MestReNova (Version 6.0.2). Varian (500 MHz) spectrometer was used for degradation studies of GCDIs. Mass spectra (MS) were recorded on Agilent 6120 Quadrupole LCMS System using ESI-TOF (electronspray ionization-time of flight). ATR-FTIR spectra were recorded on Thermo Scientific NICOLET iS10 spectrometer. Melting points of the solid products were measured by Bibby Scientific IA9100 Digital Melting Point Apparatus. Gel permeation chromatography (GPC) was performed on Young Lin YL9100 GPC System equipped with Shodex GPC columns [K-803 (for chloroform) or KD-803 (for DMF + 0.1 wt% LiBr)]. Chloroform or 0.1 wt% LiBr solution in DMF was used as the mobile phase at a flow rate of 0.7 ml/min. The column was maintained at 50 °C. Samples were diluted in 5 mg/ml by mobile phase and filtered through a 0.20 μm PTFE filter before injection into the GPC. *N*,*N*-dimethylformamide (DMF), acetonitrile (ACN), dichloromethane (DCM), succinic anhydride, phthalic anhydride, glutaric anhydride, 1-hydroxybenzotriazole hydrate (HOBt), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl), butylamine, benzylamine, pyridine, trifluoroacetic acid (TFA) and potassium dideuterium phosphate were purchased from Sigma-Aldrich (USA). *N*,*N*-dimethylacetamide (DMAc), 1-methyl-2-pyrrolidinone (NMP), piperidine and 1*H*-pyrazole-1-carboxamidine hydrochloride were purchased from Alfa Aesar (USA). *N*,*N*-diisopropylethylamine (DIPEA), cyclohexylamine, *cis*-1,2-cyclohexanedicarboxylic anhydride, allylsuccinic anhydride, 4-bromophthalic anhydride, phenylsuccinic anhydride, 4,4'-biphthalic anhydride (BPDA), 3,3',4,4'-benzophenonetetracarboxylic dianhydride (BTDA), diisopropylcarbodiimide (DIC) and benzylmercaptan were purchased from TCI (Japan). Fmoc-Arg(Pbf)-OH was purchased from BeadTech (Korea). Acetic anhydride and triethylamine (TEA) were purchased from Samchun (Korea). Potassium carbonate anhydrous was purchased from Daejung (Korea). $CDCl_3$, D_2O, CD_3OD and DMSO-d_6 were purchased from BK Instruments (Korea). All reagents were used without further purification.

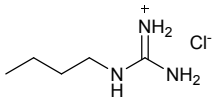
2. Synthetic Procedures

A. Preparation of Guanidine Substrates

- Preparation of **1a–1c**

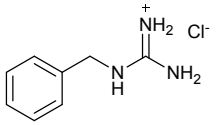


Butylguanidine hydrochloride (**1a**)



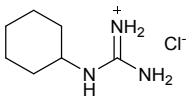
To a stirred solution of 1*H*-pyrazole-1-carboxamidine hydrochloride (2.73 g; 18.2 mmol; 1.00 equiv.) and DIPEA (3.53 ml; 20.1 mmol; 1.10 equiv.) in ACN (20 ml), butylamine (2.00 ml; 20.1 mmol; 1.10 equiv.) was added. The reaction mixture was stirred at ambient temperature for 26 h and concentrated under reduced pressure. The crude mixture was diluted with minimal amount of methanol, then excess amount of diethyl ether was added. Resulting gel was collected, washed with diethyl ether, and dried *in vacuo*. Orange gel (2.78g, 91%). ^{1}H NMR (500 MHz, D_2O): δ 3.16 (t, 2H), 1.54 (m, 2H), 1.35 (m, 2H), 0.89 (t, 3H). ^{13}C NMR (300 MHz, D_2O): δ 156.68, 40.92, 29.94, 19.19, 12.85. MS (ESI)$^+$ calculated for $C_5H_{14}N_3$ [M+H]$^+$: m/z 116.1, found 116.2.

Benzylguanidine hydrochloride (**1b**)



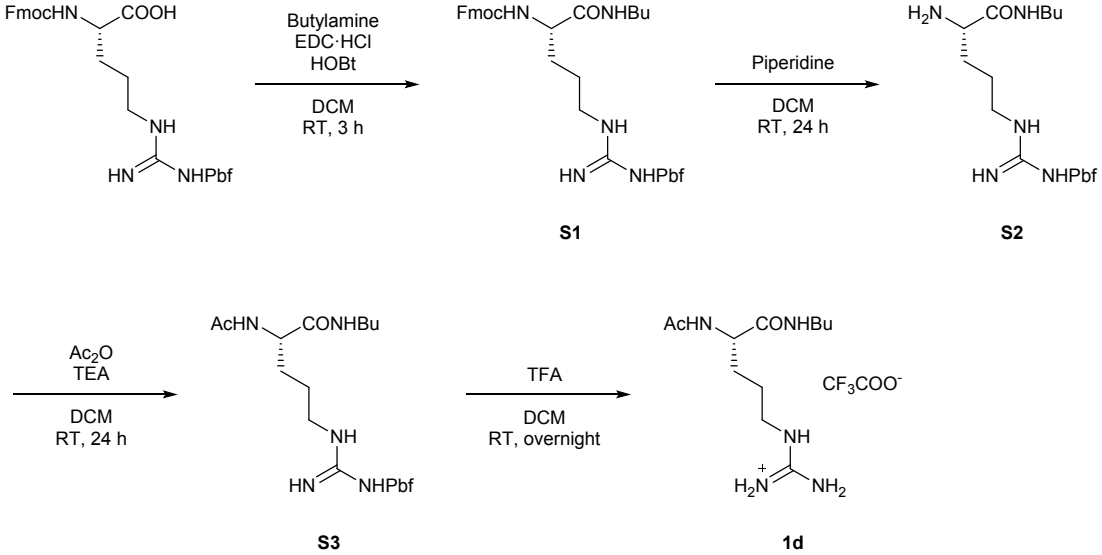
To a stirred solution of 1*H*-pyrazole-1-carboxamidine hydrochloride (2.00 g; 13.4 mmol; 1.00 equiv.) and DIPEA (2.47 ml; 14.0 mmol; 1.05 equiv.) in ACN (20 ml), benzylamine (1.55 ml; 14.0 mmol; 1.05 equiv.) was added. The reaction mixture was stirred at ambient temperature for 28 h and concentrated under reduced pressure. The crude mixture was diluted with minimal amount of methanol, then excess amount of diethyl ether was added. Resulting solid was collected, washed with diethyl ether, and dried *in vacuo*. Pale yellow solid (2.19 g, 88%). ^{1}H NMR (300 MHz, D_2O): δ 7.53-7.29 (m, 5H), 4.40 (s, 2H). ^{13}C NMR (300 MHz, D_2O): δ 156.80, 136.04, 128.96, 127.97, 126.96, 44.48. MS (ESI)$^+$ calculated for $C_5H_{14}N_3$ [M+H]$^+$: m/z 150.1, found 150.2.

Cyclohexylguanidine hydrochloride (**1c**)

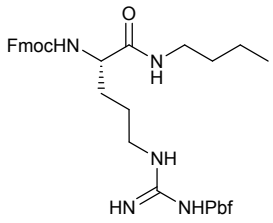


To a stirred solution of 1*H*-pyrazole-1-carboxamidine hydrochloride (500 mg; 3.34 mmol; 1.00 equiv.) and DIPEA (0.620 ml; 3.51 mmol; 1.05 equiv.) in ACN (10 ml), cyclohexylamine (0.410 ml; 3.51 mmol; 1.05 equiv.) was added. The reaction mixture was stirred at ambient temperature for 28 h and concentrated under reduced pressure. The crude mixture was diluted with minimal amount of methanol, then excess amount of diethyl ether was added. Resulting solid was collected, washed with diethyl ether, and dried *in vacuo*. Pale yellow solid (508 mg, 86%). ^{1}H NMR (300 MHz, D_2O): δ 3.34 (m, 1H), 2.02-1.83 (m, 2H), 1.81-1.65 (m, 2H), 1.65-1.53 (m, 1H), 1.45-1.09 (m, 5H). ^{13}C NMR (300 MHz, D_2O): δ 155.60, 50.53, 31.85, 24.66, 24.04. MS (ESI)$^+$ calculated for $C_5H_{14}N_3$ [M+H]$^+$: m/z 142.1, found 142.2.

- Preparation of **1d**



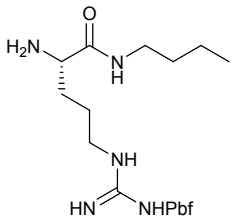
Synthesis of Fmoc-Arg(Pbf)-NH-(*n*-Bu) (**S1**)



To a stirred solution of Fmoc-Arg(Pbf)-OH (2.00 g; 3.08 mmol; 1.20 equiv.), EDC·HCl (709 mg; 3.70 mmol; 1.20 equiv.), and HOBt (500 mg; 3.70 mmol; 1.20 equiv.) in 20 ml of DCM, butylamine (0.360 ml; 3.70 mmol; 1.20 equiv.) was added. The reaction mixture was stirred at ambient temperature for 3 h and concentrated under reduced pressure. The reaction mixture was diluted with 50 ml of ethyl acetate and 50 ml of saturated aq. NH_4Cl. The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, 10:1 hexane/ethyl acetate → 1:2 hexane/ethyl acetate) and pale yellow solid was yielded (1.92 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, 2H), 7.50 (m, 2H), 7.33 (m, 2H), 7.20 (m, 2H), 7.12 (brs, 1H), 6.50-6.13 (brs, 1H), 6.42 (brs, 2H), 6.23 (m, 1H), 4.36-4.16 (m, 3H), 4.08 (t, 1H), 3.25 (m, 2H), 3.14 (m, 2H), 2.85 (s, 2H), 2.57 (s, 3H), 2.48 (s, 3H), 2.04 (s, 3H), 1.83 (m, 1H), 1.70 (m, 1H), 1.57 (m, 2H), 1.39 (m, 8H), 1.24 (m, 2H), 0.81 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 172.25, 158.93, 156.64, 143.83, 143.76, 141.25, 138.38, 132.65, 132.27, 127.78, 127.12, 125.21, 124.80, 120.01, 117.71, 85.51, 67.21, 54.67, 47.07, 43.24, 40.38, 39.49, 31.43, 30.26, 28.61, 25.74, 20.11, 19.42, 18.07, 13.80, 12.55. MS (ESI)$^+$ calculated for $C_{38}H_{50}N_5O_6S$ $[M+H]^+$: m/z 704.4, found 704.2.

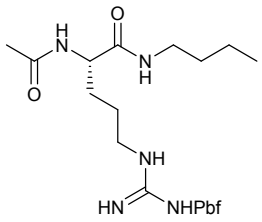
Synthesis of H-Arg(Pbf)-NH-(*n*-Bu) (**S2**)



To a stirred solution of Fmoc-Arg(Pbf)-NH-(*n*-Bu) (1.50 g; 2.13 mmol; 1.00 equiv.) in DCM (20 ml), piperidine (1.05 ml; 10.5 mmol; 5.00 equiv.) was added. The reaction mixture was stirred at ambient temperature for 24 h and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, ethyl acetate → 4:1 ethyl acetate/methanol) and pale yellow solid was yielded (907 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 6.75 (s, 1H), 6.52 (s, 2H), 5.61-4.62 (brs, 2H), 3.85 (m, 1H), 3.34-3.06 (m, 4H), 2.94 (s, 2H), 2.55 (s, 3H), 2.48 (s, 3H), 2.07 (s, 3H), 1.91 (m, 1H), 1.81 (m, 1H), 1.68 (m, 2H), 1.45 (m, 8H), 1.30 (m, 2H), 0.87 (t, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 172.20, 158.91, 156.74, 138.34, 132.65, 132.26, 124.78, 117.67, 86.54, 53.85, 43.32, 40.39, 39.50, 31.39, 30.72, 28.70, 25.37, 20.20, 19.42, 18.08, 13.84, 12.57. MS (ESI)$^+$ calculated for $C_{23}H_{40}N_5O_4S$ $[M+H]^+$: m/z 482.3, found 482.2.

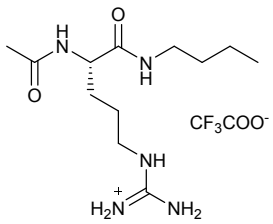
Synthesis of Ac-Arg(Pbf)-NH-(*n*-Bu) (**S3**)



To a stirred solution of H-Arg(Pbf)-NH-(*n*-Bu) (500 mg; 1.04 mmol; 1.00 equiv.) in DCM (10 ml), acetic anhydride (0.120 ml; 1.25 mmol; 1.20 equiv.) and TEA (0.170 ml; 1.25 mmol; 1.20 equiv.) was added. The reaction mixture was stirred at ambient temperature for 24 h and concentrated under reduced pressure. The reaction mixture was diluted with 50 ml of ethyl acetate and 50 ml of saturated aq. NH_4Cl. The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, dichloromethane → 19:1 dichloromethane/methanol) and white solid was yielded (415 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.12 (s, 1H), 6.38 (s, 3H), 4.45 (m, 1H), 3.26 (m, 2H), 3.17 (m, 2H), 2.95 (s, 2H), 2.57 (s, 3H), 2.50 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H), 1.83 (m, 1H), 1.70 (m, 1H), 1.59 (m, 2H), 1.46 (m, 8H), 1.29 (m, 2H), 0.87 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 172.07, 171.12, 159.00, 156.70, 138.44, 132.74, 132.35, 124.86, 117.77, 86.60, 53.14, 43.38, 40.73, 39.52, 31.50, 30.36, 28.74, 25.76, 23.27, 20.19, 19.43, 18.09, 13.86, 12.61. MS (ESI)$^+$ calculated for $C_{25}H_{42}N_5O_5S$ $[M+H]^+$: m/z 524.3, found 524.2.

Synthesis of Ac-Arg-NH-(*n*-Bu)·TFA (**1d**)



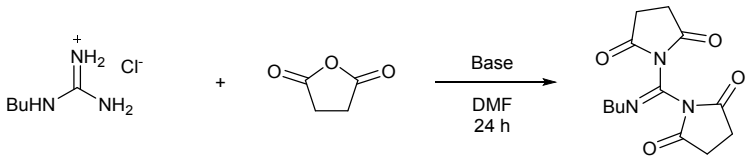
To a stirred solution of Ac-Arg(Pbf)-NH-(*n*-Bu) (200 mg; 0.382 mmol) in DCM (2.5 ml), TFA (2.5 ml) was added. The reaction mixture was stirred at ambient temperature for overnight and concentrated under reduced pressure. The crude mixture was diluted with 30 ml of deionized water, washed with 30 ml of DCM three times and the aqueous layer was lyophilized. After lyophilizing, the product was further washed with diethyl ether, dried *in vacuo* and orange-colored solid was yielded (142 mg, 96%).

^{1}H NMR (300 MHz, D_2O): δ 4.18 (t, 1H), 3.19 (m, 4H), 2.02 (s, 3H), 1.74 (m, 2H), 1.63 (m, 2H), 1.45 (m, 2H), 1.29 (m, 2H), 0.86 (t, 3H). ^{13}C NMR (500 MHz, D_2O): δ 174.17, 173.49, 156.66, 53.80, 40.41, 38.96, 30.36, 28.15, 24.34, 21.57, 19.24, 12.85. MS (ESI)$^+$ calculated for $C_{12}H_{26}N_5O_2$ $[M+H]^+$: m/z 272.2, found 272.2.

B. Initial Optimization for Preparation of GCDI **3aa**

To a stirred solution of butylguanidine hydrochloride (**1a**) (100 mg; 0.659 mmol) and succinic anhydride in DMF (5 ml), base was added. The reaction mixture was further stirred at various temperatures for 24 h and concentrated under reduced pressure. The crude mixture was diluted with 50 ml of ethyl acetate and 50 ml of aqueous HCl (0.01 M). The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, hexane/ethyl acetate).

Table S1. Initial optimization studies



1a **2a** **3aa**

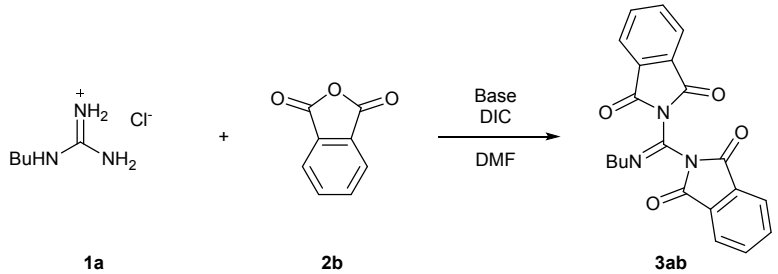
Entry	Base	equiv. of base	equiv. of anhydride	Temperature	Yield[a]
1	TEA	1.00	2.00	RT	10%
2	DIPEA	1.00	2.00	RT	11%
3	Pyridine	1.00	2.00	RT	-
4	K_2CO_3	1.00	2.00	RT	15% (15%)[b]
5	K_2CO_3	1.00	2.00	30 °C	16%
6	K_2CO_3	1.00	2.00	40 °C	15%
7	K_2CO_3	1.00	2.00	70 °C	-
8	K_2CO_3	2.00	2.00	30 °C	-
9	K_2CO_3	3.00	2.00	30 °C	-
10	K_2CO_3	1.00	4.00	30 °C	51%
11	K_2CO_3	1.00	6.00	30 °C	75%
12	K_2CO_3	1.00	8.00	30 °C	85%
13	TEA	15.0	5.00	RT	37%
14	-	-	6.00	RT	-

[a]Isolated yields are given unless otherwise noted. [b]^{1}H-NMR yield.

C. Optimization for Preparation of GCDI **3ab** with Stoichiometric Amount of Phthalic Anhydride

To a flame-dried RBF, butylguanidine hydrochloride (**1a**) (152 mg; 1.00 mmol; 1.00 equiv.) and phthalic anhydride (299 mg; 2.00 mmol; 2.00 equiv.) was added, then the RBF was flushed with Ar. DMF (3 ml), base (10.0 mmol; 10.0 equiv.), and DIC was added, then the reaction mixture was stirred at various temperatures for indicated reaction time under Ar atmosphere. The crude mixture was concentrated under reduced pressure, diluted with 50 ml of ethyl acetate and 50 ml of aqueous HCl (0.01 M). The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The yield was determined by ^{1}H-NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

Table S2. Further optimization studies using stoichiometric amount of anhydrides



1a **2b** **3ab**

Entry	Base	equiv. of DIC	Temperature	Reaction time	Yield[a]
1	TEA	10.0	70 °C	5 h	94%
2	TEA	3.00	70 °C	5 h	87%
3	TEA	4.00	70 °C	5 h	88%
4	TEA	5.00	70 °C	5 h	93% (90%)[b]
5	TEA	5.00	70 °C	1 h	82%
6	TEA	5.00	70 °C	2 h	90%
7	TEA	5.00	RT	10 h	65%
8	TEA	5.00	RT	24 h	79%
9	TEA	5.00	RT	48 h	78%
10	TEA	5.00	50 °C	5 h	80%
11	DIPEA	5.00	50 °C	5 h	92%
12	DIPEA[c]	5.00[d]	50 °C	5 h	85%

[a]^{1}H-NMR yields are given unless otherwise noted. [b]Isolated yield. [c]15.0 equiv. [d]EDC·HCl was used instead of DIC.

D. General Procedures for GCDI Preparation

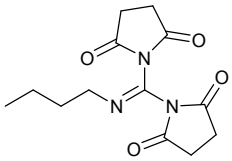
- General Procedure A

To a mixture of guanidine salt (0.659 mmol; 1.00 equiv.), acid anhydride (3.96 mmol; 6.00 equiv.) and K_2CO_3 (0.659 mmol; 1.00 equiv.), DMF (5 ml) was added. The reaction mixture was stirred at 30 °C for 24 h and concentrated under reduced pressure. The crude mixture was diluted with 50 ml of ethyl acetate and 50 ml of aqueous HCl (0.01 M). The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, hexane/ethyl acetate).

- General Procedure B

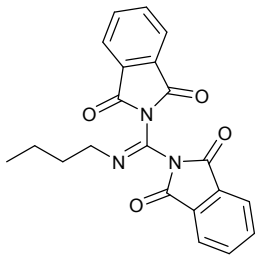
To a flame-dried RBF, guanidine salt (1.00 mmol; 1.00 equiv.), acid anhydride (2.00 mmol; 2.00 equiv.) and EDC·HCl (978 mg; 5.00 mmol; 5.00 equiv.) was added, then the RBF was flushed with Ar. DMF (3 ml) and DIPEA (2.58 ml; 15.0 mmol; 15.0 equiv.), was added, then the reaction mixture was stirred at 50 °C for 5 h under Ar atmosphere. The crude mixture was concentrated under reduced pressure, diluted with 50 ml of ethyl acetate and 50 ml of aqueous HCl (0.01 M). The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

1,1'-((butylimino)methylene)bis(pyrrolidine-2,5-dione) (**3aa**)



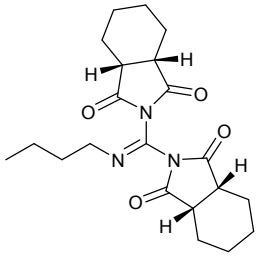
3aa was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 1:2 hexane/ethyl acetate, pale yellow solid, 138 mg, 75%) or B (pale brown solid, 131 mg, 47%). mp: 102–103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45 (t, 2H), 2.84 (s, 4H), 2.77 (s, 4H), 1.71 (m, 2H), 1.42 (m, 2H), 0.92 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.95, 173.50, 128.24, 51.29, 32.19, 28.52, 28.20, 20.41, 13.85. FTIR (ATR): 2957, 2939, 2873, 1797, 1728, 1674, 1466, 1428, 1321, 1265, 1201, 1147, 1078, 1006, 863, 818, 699 cm^{-1}. MS (ESI)$^+$ calculated for $C_{13}H_{18}N_3O_4$ $[M+H]^+$: m/z 280.1, found 280.2.

2,2'-((butylimino)methylene)bis(isoindoline-1,3-dione) (**3ab**)



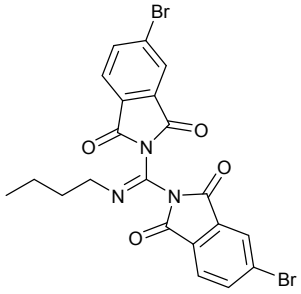
3ab was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 2:1 hexane/ethyl acetate, white solid, 120 mg, 48%) or B (pale brown solid, 320 mg, 85%). mp: 154–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (m, 2H), 7.88 (m, 2H), 7.82 (m, 2H), 7.77 (m, 2H), 3.63 (t, 2H), 1.79 (m, 2H), 1.49 (m, 2H), 0.95 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 165.21, 164.91, 135.15, 135.02, 131.52, 131.31, 128.13, 124.58, 124.32, 51.49, 32.52, 20.47, 13.91. FTIR (ATR): 2957, 2933, 2870, 1793, 1727, 1671, 1468, 1310, 1124, 1051, 886, 794, 755, 710, 656 cm^{-1}. MS (ESI)$^+$ calculated for $C_{21}H_{18}N_3O_4$ $[M+H]^+$: m/z 376.1, found 376.2.

(3aR,3a'R,7aS,7a'S)-2,2'-((butylimino)methylene)bis(hexahydro-1*H*-isoindole-1,3(2*H*)-dione) (**3ac**)



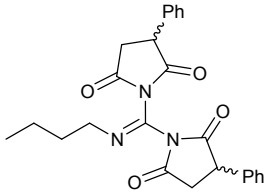
3ac was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 2:1 hexane/ethyl acetate, white solid, 213 mg, 83%) or B (orange solid, 341 mg, 88%). mp: 116–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41 (t, 2H), 2.99 (m, 2H), 2.92 (m, 2H), 1.96-1.76 (m, 8H), 1.70 (m, 2H), 1.57-1.34 (m, 10H), 0.91 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 176.28, 175.91, 128.70, 51.11, 40.36, 40.23, 32.19, 23.90, 23.77, 22.10, 20.39, 13.81. FTIR (ATR): 2936, 2860, 1799, 1726, 1673, 1451, 1314, 1204, 1158, 1137, 1085, 894, 816 cm^{-1}. MS (ESI)$^{+}$ calculated for $C_{21}H_{30}N_3O_4$ $[M+H]^{+}$: m/z 388.2, found 388.2.

2,2'-((butylimino)methylene)bis(5-bromoisoindoline-1,3-dione) (**3ad**)



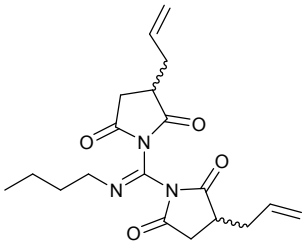
3ad was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 3:1 hexane/ethyl acetate, pale yellow solid, 120 mg, 34%) or B (brown solid, 456 mg, 86%). mp: 65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.00 (s, 1H), 7.94 (d, 1H), 7.90 (d, 1H), 7.80 (d, 1H), 7.76 (d, 1H), 3.60 (t, 2H), 1.77 (m, 2H), 1.48 (m, 2H), 0.94 (t, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.35, 164.06, 163.81, 163.51, 138.31, 138.22, 132.94, 132.74, 130.39, 130.20, 129.87, 129.67, 127.92, 127.63, 127.36, 125.94, 125.70, 51.55, 32.40, 20.43, 13.89. FTIR (ATR): 2958, 2933, 2870, 1789, 1733, 1673, 1603, 1462, 1419, 1348, 1309, 1172, 1142, 1101, 1050, 903, 844, 765, 730, 661 cm^{-1}. MS (ESI)$^{+}$ calculated for $C_{21}H_{16}Br_2N_3O_4$ $[M+H]^{+}$: m/z 532.0, 534.0, 536.0, found 532.0, 533.8, 536.0.

1,1'-((butylimino)methylene)bis(3-phenylpyrrolidine-2,5-dione) (**3ae**)



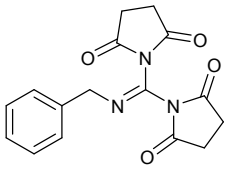
3ae was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 3:1 hexane/ethyl acetate, yellow solid, 208 mg, 73%) or B (brown solid, 192 mg, 45%). The product was obtained as a mixture of inseparable diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) (diastereomeric mixture): δ 7.51-7.07 (m, 10H), 4.14 (t, 1H), 4.05 (t, 1H), 3.49 (m, 2H), 3.29 (m, 2H), 2.91 (m, 2H), 1.72 (m, 2H), 1.41 (m, 2H), 0.91 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 175.03, 174.83, 174.43, 174.27, 172.71, 172.57, 172.38, 172.23, 136.60, 136.57, 136.19, 136.18, 129.43, 129.40, 129.34, 128.39, 128.31, 128.22, 128.16, 127.94, 127.89, 127.86, 127.80, 51.39, 51.37, 46.45, 46.03, 45.97, 37.46, 37.38, 37.31, 37.26, 32.16, 32.15, 20.39, 13.81. FTIR (ATR): 2958, 2934, 2872, 1794, 1731, 1675, 1603, 1498, 1455, 1319, 1237, 1202, 1172, 765, 749, 699 cm^{-1}. MS (ESI)$^{+}$ calculated for $C_{25}H_{26}N_3O_4$ $[M+H]^{+}$: m/z 432.2, found 432.2.

1,1'-((butylimino)methylene)bis(3-allylpyrrolidine-2,5-dione) (**3af**)



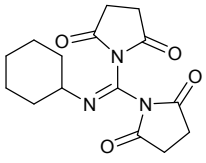
3af was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 2:1 hexane/ethyl acetate, yellow oil, 202 mg, 85%) or B (brown oil, 303 mg, 85%). The product was obtained as a mixture of inseparable diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) (diastereomeric mixture): δ 5.73 (m, 2H), 5.27-5.03 (m, 4H), 3.43 (m, 2H), 3.06 (m, 1H), 2.97 (m, 1H), 2.94-2.79 (m, 2H), 2.67-2.32 (m, 6H), 1.70 (m, 2H), 1.41 (m, 2H), 0.91 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 176.13, 176.09, 175.65, 175.61, 173.10, 172.68, 133.27, 132.93, 128.15, 119.25, 118.92, 51.24, 39.70, 39.25, 35.01, 34.92, 33.58, 33.46, 32.11, 20.34, 13.77. FTIR (ATR): 2958, 2934, 2873, 1785, 1722, 1675, 1642, 1440, 1416, 1319, 1202, 1148, 1079, 1006, 916, 751, 688 cm^{-1}. MS (ESI)$^{+}$ calculated for $C_{19}H_{26}N_3O_4$ $[M+H]^{+}$: m/z 360.2, found 360.2.

1,1'-((benzylimino)methylene)bis(pyrrolidine-2,5-dione) (**3ba**)



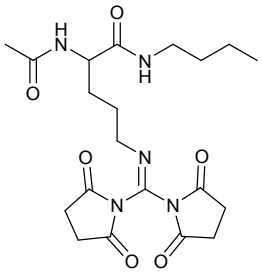
3ba was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 1:2 hexane/ethyl acetate, white solid, 126 mg, 61%) or B (pale brown solid, 214 mg, 68%). mp: 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.20 (m, 5H), 4.72 (s, 2H), 2.78 (s, 4H), 2.77 (s, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.98, 173.52, 137.80, 129.69, 128.64, 127.52, 127.21, 54.50, 28.49, 28.20. FTIR (ATR): 1798, 1729, 1673, 1497, 1454, 1427, 1372, 1320, 1265, 1196, 1144, 1068, 1005, 847, 817, 747, 700 cm^{-1}. MS (ESI)$^{+}$ calculated for $C_{21}H_{18}N_3O_4$ $[M+H]^{+}$: m/z 314.1, found 314.2.

1,1'-((cyclohexylimino)methylene)bis(pyrrolidine-2,5-dione) (**3ca**)



3ca was prepared following general procedure A (purification by 10:1 hexane/ethyl acetate → 1:2 hexane/ethyl acetate, white solid, 76.5 mg, 38%) or B (pale brown solid, 181 mg, 59%). mp: 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (m, 1H), 2.85 (s, 4H), 2.76 (s, 4H), 1.89-1.70 (m, 4H), 1.69-1.46 (m, 3H), 1.41-1.17 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.91, 173.88, 126.18, 60.17, 33.23, 28.48, 28.12, 25.48, 24.09. FTIR (ATR): 2934, 2857, 1798, 1730, 1672, 1451, 1428, 1358, 1321, 1261, 1200, 1153, 1085, 1004, 950, 849, 817, 749, 701 cm^{-1}. MS (ESI)$^{+}$ calculated for $C_{21}H_{18}N_3O_4$ $[M+H]^{+}$: m/z 306.2, found 306.2.

E. Preparation of **3da**

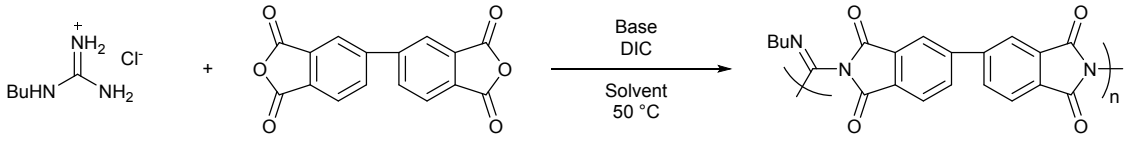


To a mixture of **1d** (126 mg; 0.343 mmol; 1.00 equiv.), succinic anhydride (208 mg; 2.06 mmol; 6.00 equiv.), and K_2CO_3 (47.6 mg; 0.343 mmol; 1.00 equiv.), DMF (3 ml) was added. The reaction mixture was stirred at 30 °C for 24 h and concentrated under reduced pressure. The crude mixture was diluted with 30 ml of ethyl acetate and 30 ml of aqueous HCl (0.01 M) and the organic layer was further washed with 30 ml of brine twice. Residual water was removed with anhydrous $MgSO_4$. The product was purified by flash column chromatography (SiO_2, ethyl acetate → 2:1 ethyl acetate/acetone) and white solid was yielded (33.7 mg, 23%). mp: 149–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (s, 1H), 6.32 (m, 1H), 4.09 (m, 1H), 3.59 (m, 2H), 3.25 (m, 1H), 3.19 (m, 1H), 3.09-2.75 (brs, 4H), 2.81 (s, 4H), 2.03 (m, 2H), 1.95 (s, 3H), 1.63 (m, 2H), 1.50 (m, 2H), 1.37 (m, 2H), 0.92 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 174.16, 172.17, 170.06, 129.83, 49.87, 49.27, 39.48, 31.44, 29.56, 28.94, 28.39, 24.10, 23.45, 20.08, 13.89. FTIR (ATR): 3379, 3300, 2956, 2927, 2856, 1797, 1732, 1649, 1545, 1429, 1369, 1324, 1265, 1203, 1149, 1080, 1005, 817, 701 cm^{-1}. MS (ESI)$^+$ calculated for $C_{20}H_{30}N_5O_6$ $[M+H]^+$: m/z 436.2, $C_{20}H_{29}N_5NaO_6$ $[M+Na]^+$: 458.2, found 436.2, 458.2.

F. Preparation of poly(GCDI) **5aa** under Various Conditions

To a flame-dried vial, butylguanidine hydrochloride (152 mg; 1.00 mmol; 1.00 equiv.) and BPDA (300 mg; 1.00 mmol; 1.00 equiv.) was added, then the vial was flushed with Ar. Solvent (3 ml), base (10.0 mmol; 10.0 equiv.), and DIC was added, then the reaction mixture was stirred at 50 °C under Ar atmosphere. The crude mixture was poured into 40 ml of ACN. Then, resulting precipitate was collected, washed with ACN, and dried *in vacuo*.

Table S3. Preparation of **5aa** under various conditions



1a 1.00 mmol + **4a** 1.00 mmol → **5a**

Entry	Base (equiv.)	equiv. of DIC	Solvent (ml)	Reaction time	Yield[a]	M_n[b]	M_w[b]	M_w/M_n[b]	DP[c]
1	TEA (10.0)	5.00	DMF (3.00 ml)	5 h	40%	2,880	3,580	1.24	7.71
2	DIPEA (10.0)	5.00	DMF (3.00 ml)	5 h	71%	4,250	5,550	1.30	11.4
3	DIPEA (10.0)	5.00	DMF (3.00 ml)	12 h	76%	4,420	5,980	1.35	11.8
4	DIPEA (10.0)	10.0	DMF (3.00 ml)	5 h	83%	4,050	5,860	1.44	10.8
5	DIPEA (10.0)	5.00	DMAc (3.00 ml)	5 h	62%	2,760	3,380	1.23	7.39
6	DIPEA (10.0)	5.00	NMP (3.00 ml)	5 h	67%	3,620	4,910	1.36	9.70
7	DIPEA (1.10)	5.00	DMF (3.00 ml)	5 h	92%	2,250	2,920	1.30	6.03
8	DIPEA (1.10)	5.00	DMF (1.50 ml)	5 h	96%	3,280	4,490	1.37	8.78
9	DIPEA (1.10)	5.00	DMF (1.00 ml)	5 h	97%	3,910	5,550	1.42	10.5
10	DIPEA (1.10)	5.00	DMF (1.00 ml)	20 h	96%	10,300	18,100	1.75	27.6

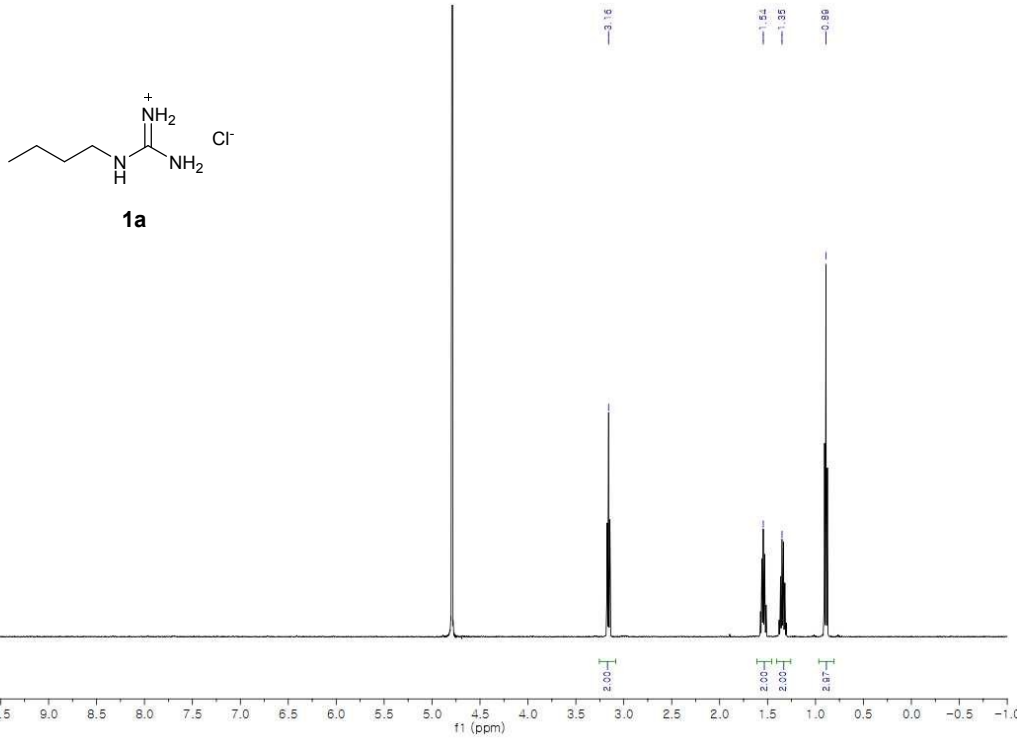
[a]Isolated yields. [b]Determined by gel permeation chromatography (GPC) in chloroform eluent. [c]Degree of polymerization.

G. General Procedure for Poly(GCDI) Preparation

To a flame-dried vial, guanidine salt (1.00 mmol; 1.00 equiv.) and dianhydride (1.00 mmol; 1.00 equiv.) was added, then the vial was flushed with Ar. DMF (1.00 ml), DIPEA (0.189 ml; 1.10 mmol; 1.10 equiv.), and DIC (0.785 ml; 5.00 mmol; 5.00 equiv.) was added, then the reaction mixture was stirred at 50 °C for 20 h under Ar atmosphere. The crude mixture was filtered and poured into 80 ml of ACN. Then, resulting precipitate was collected, washed with ACN, and dried *in vacuo*.

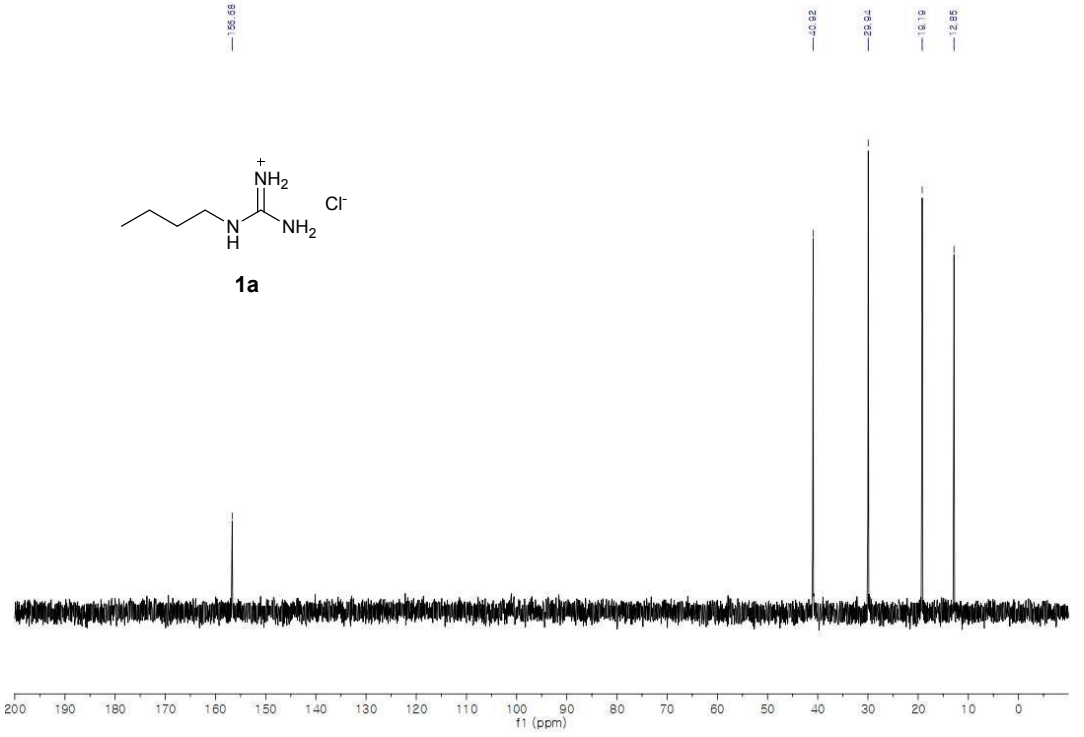
3. NMR Spectra of Compounds

^{1}H NMR (500 MHz, D_2O)



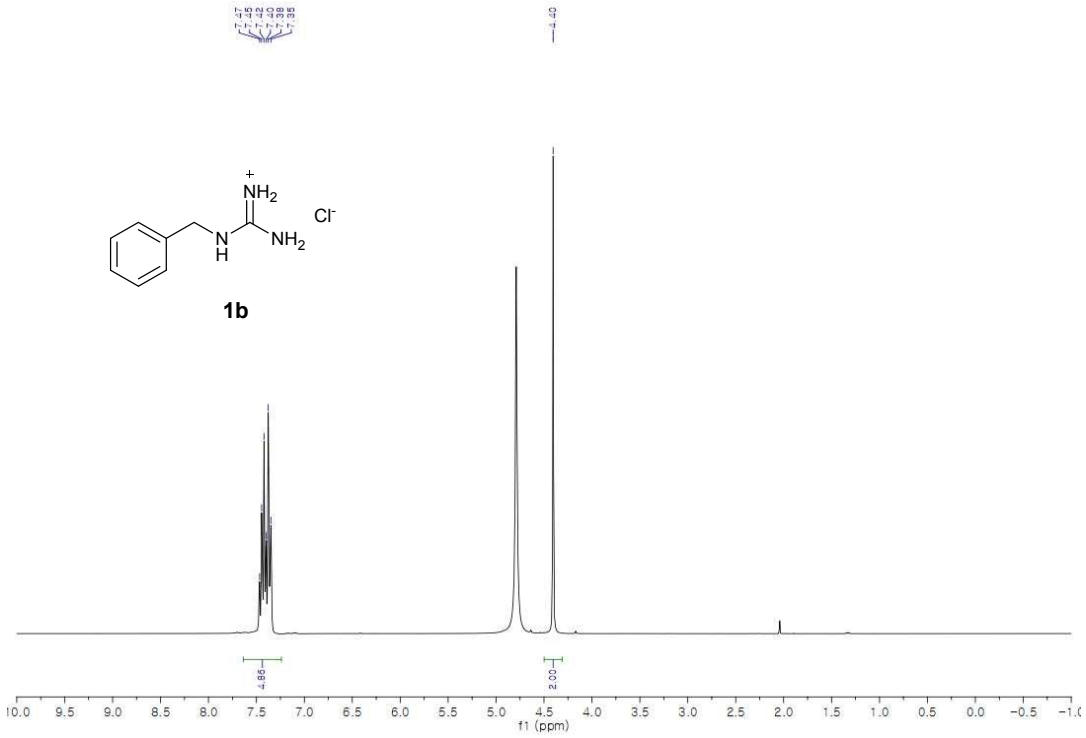
1a

^{13}C NMR (75 MHz, D_2O)

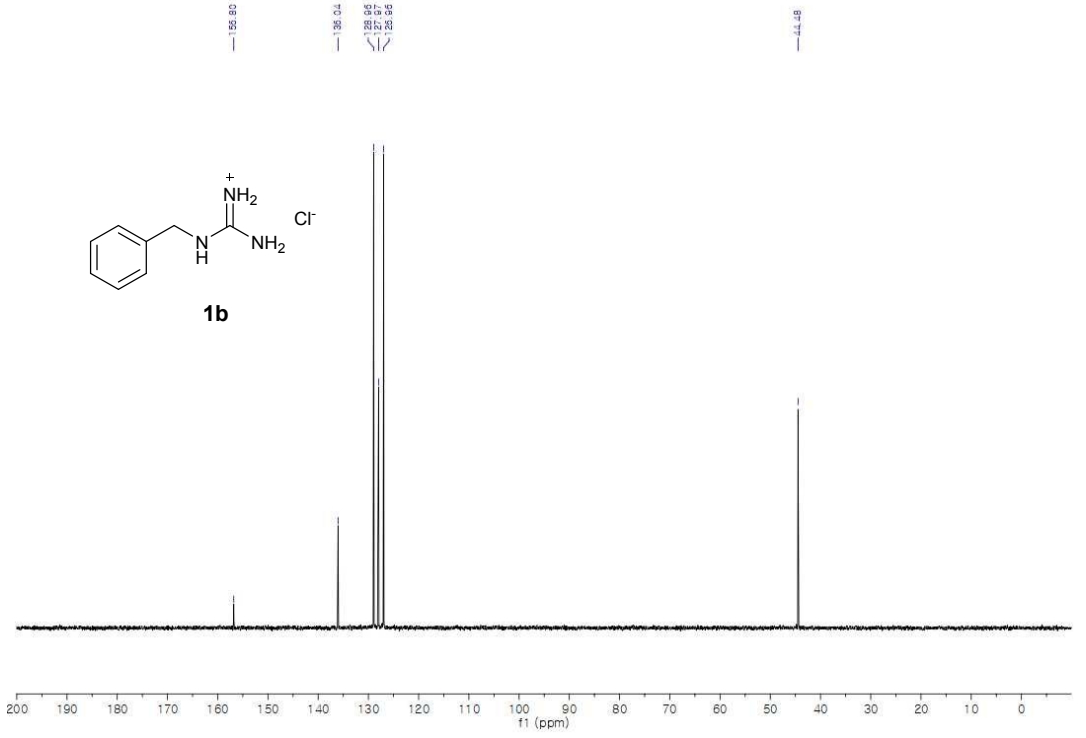


1a

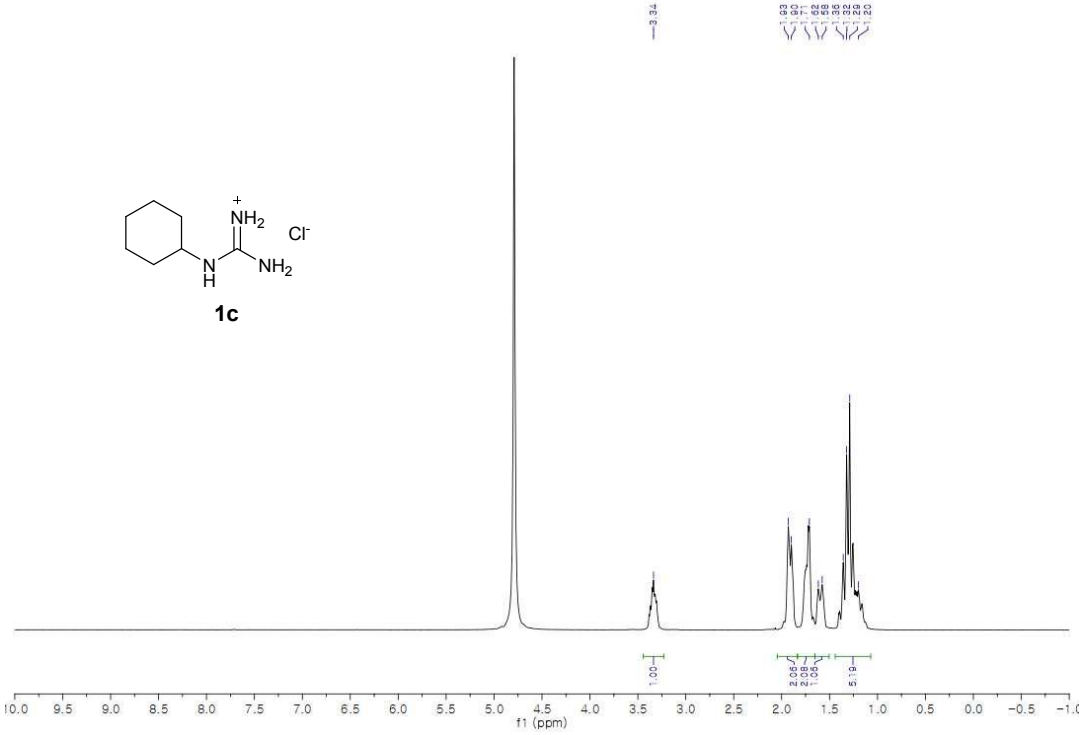
^{1}H NMR (300 MHz, D_2O)



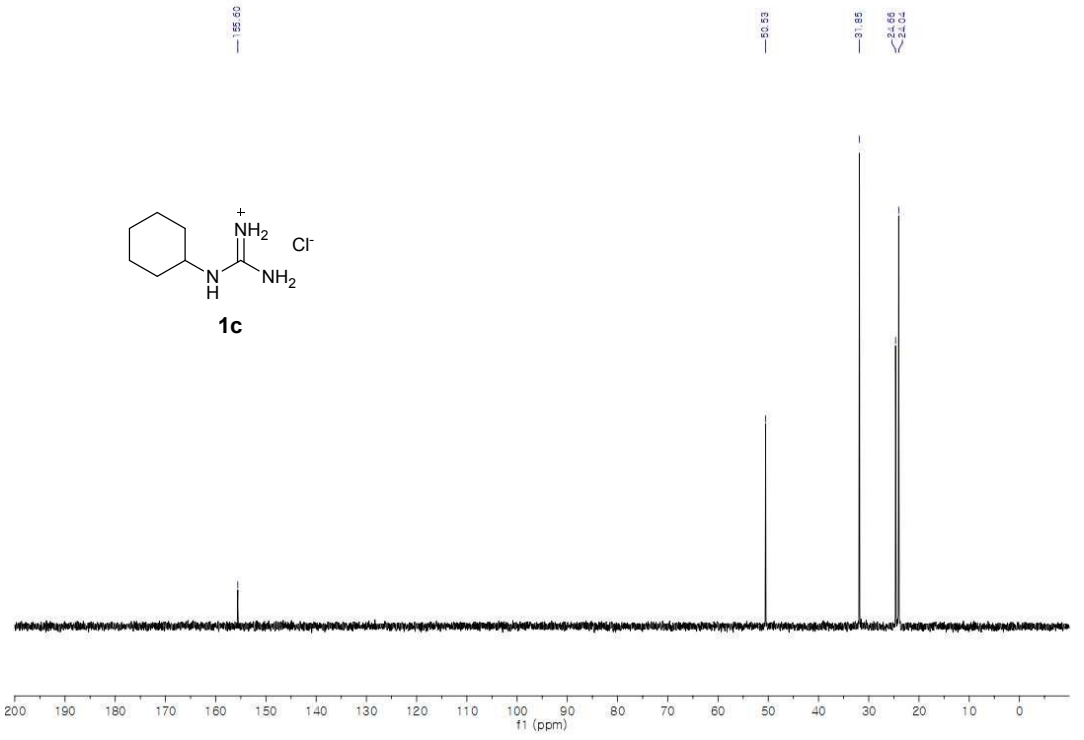
^{13}C NMR (75 MHz, D_2O)



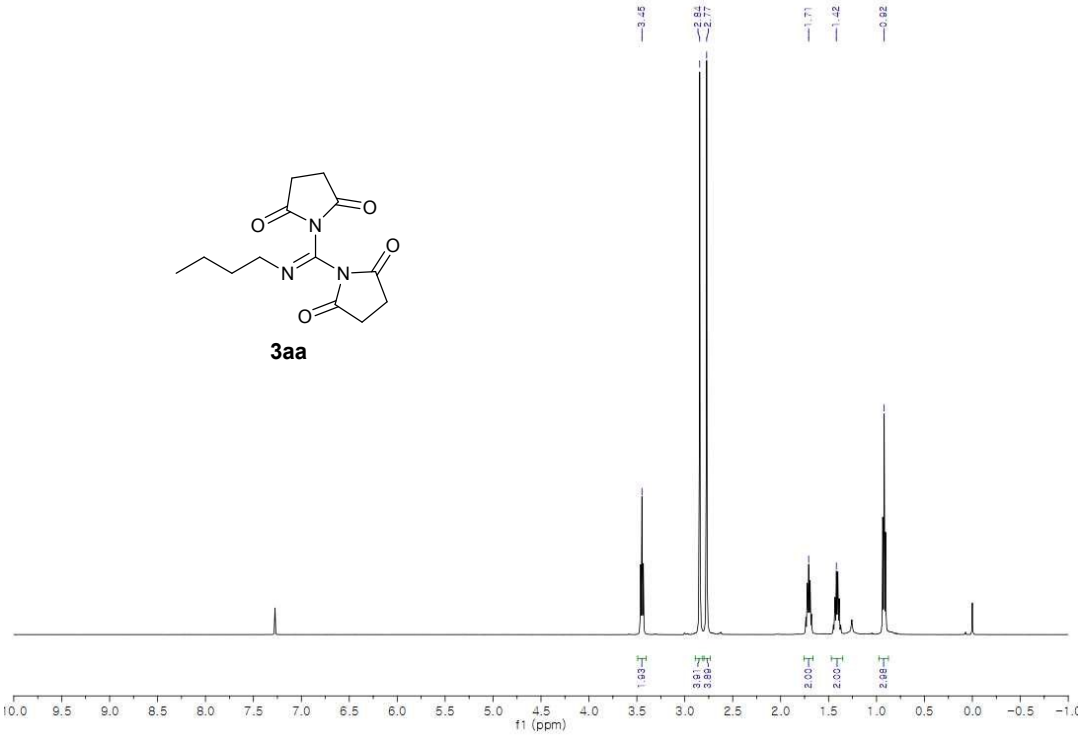
^{1}H NMR (300 MHz, D_2O)



^{13}C NMR (75 MHz, D_2O)

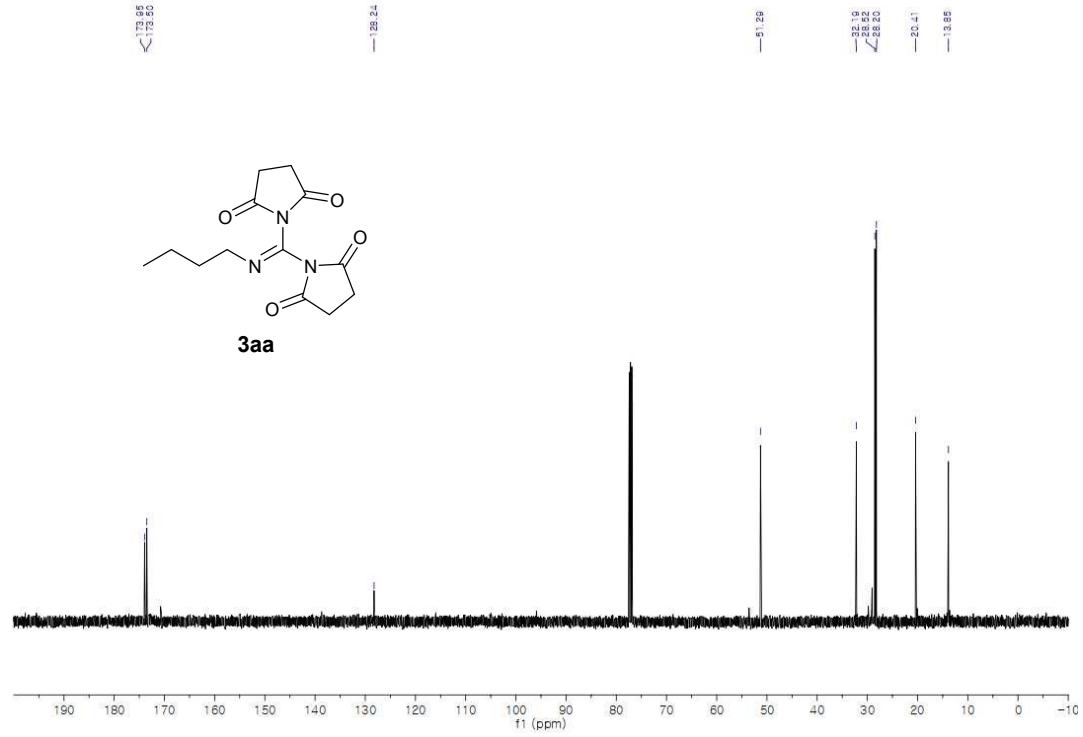


^{1}H NMR (500 MHz, $CDCl_3$)



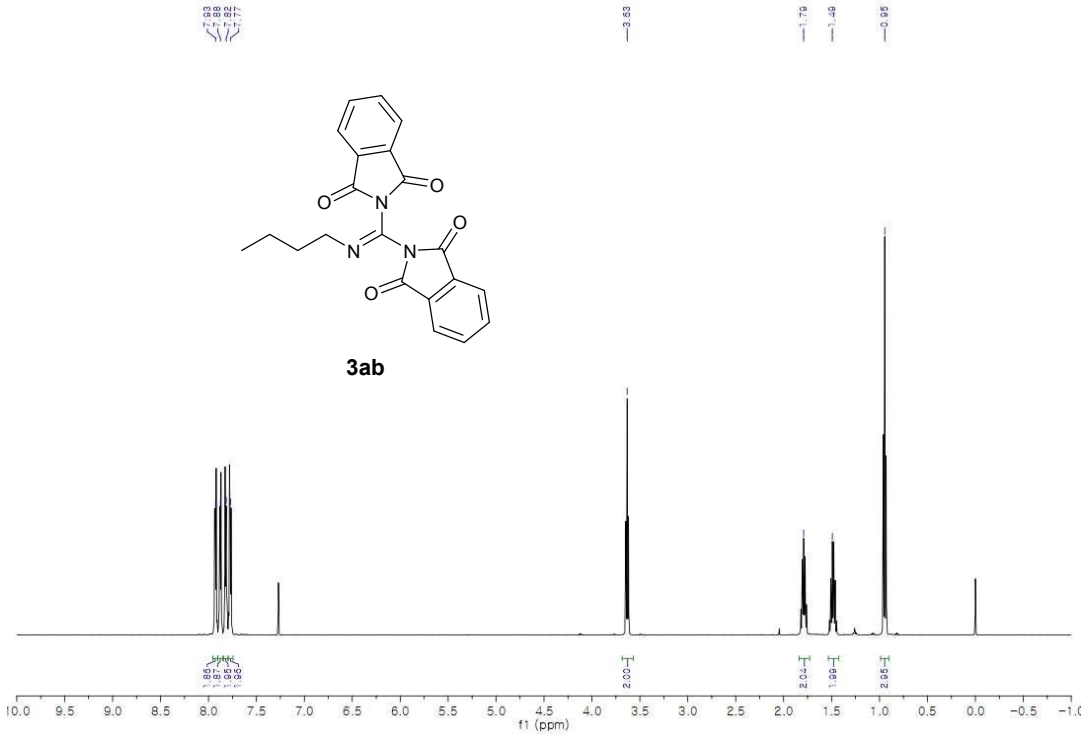
3aa

^{13}C NMR (125 MHz, $CDCl_3$)



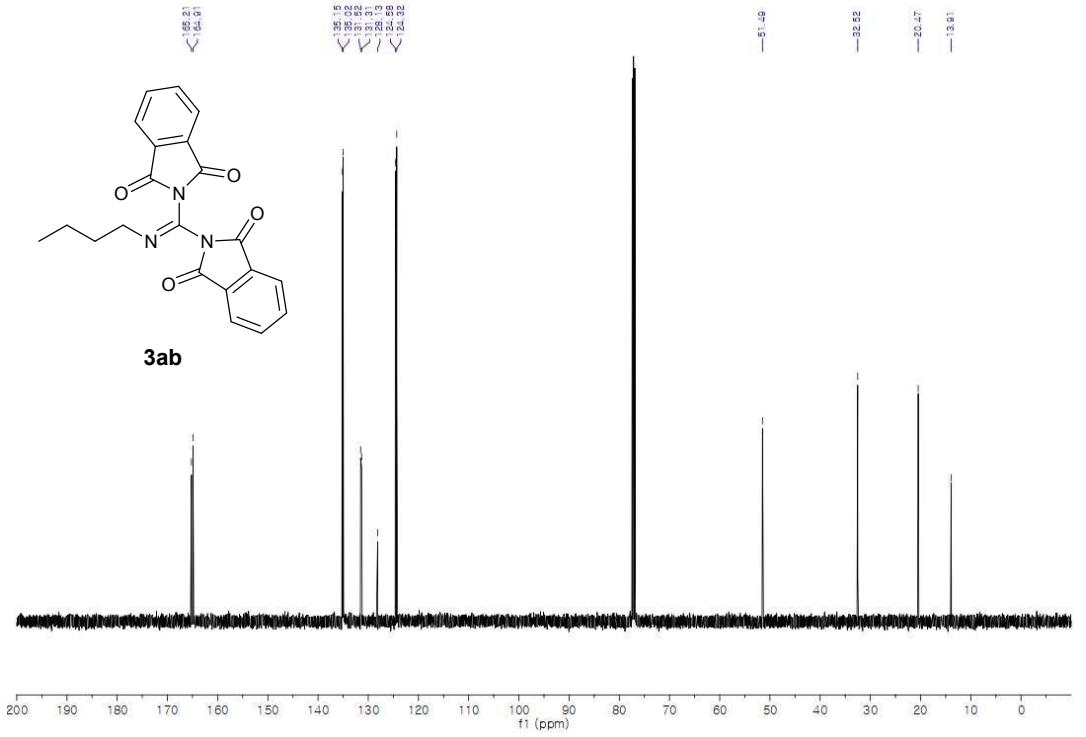
3aa

^{1}H NMR (500 MHz, $CDCl_3$)



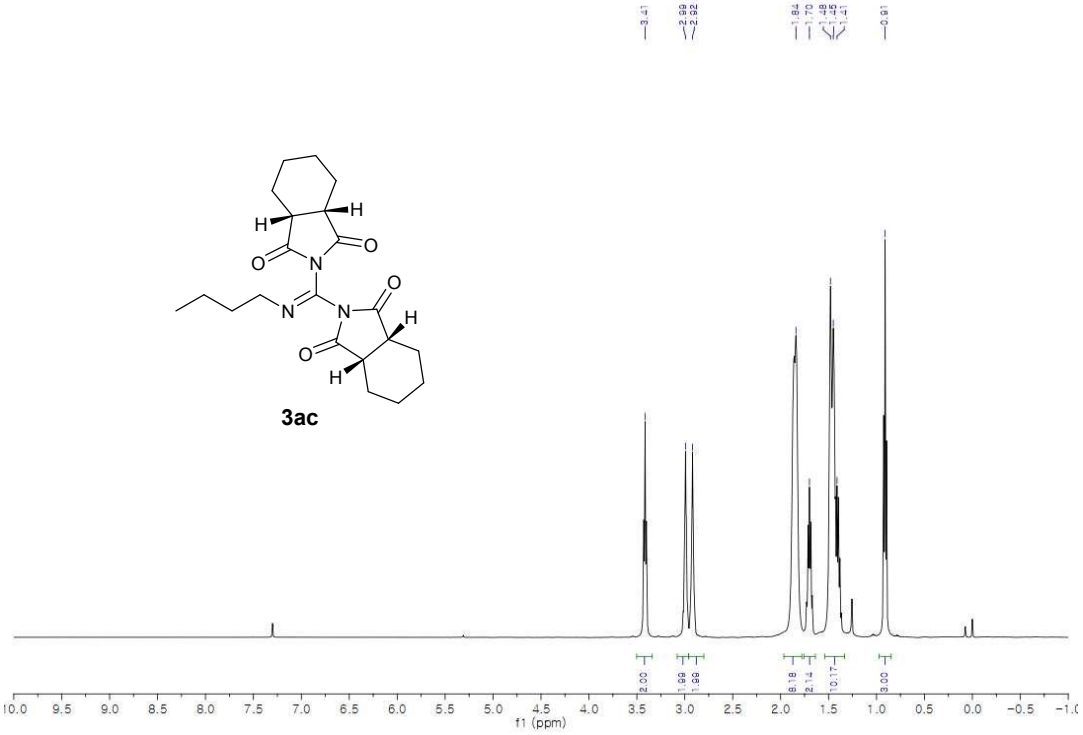
3ab

^{13}C NMR (125 MHz, $CDCl_3$)

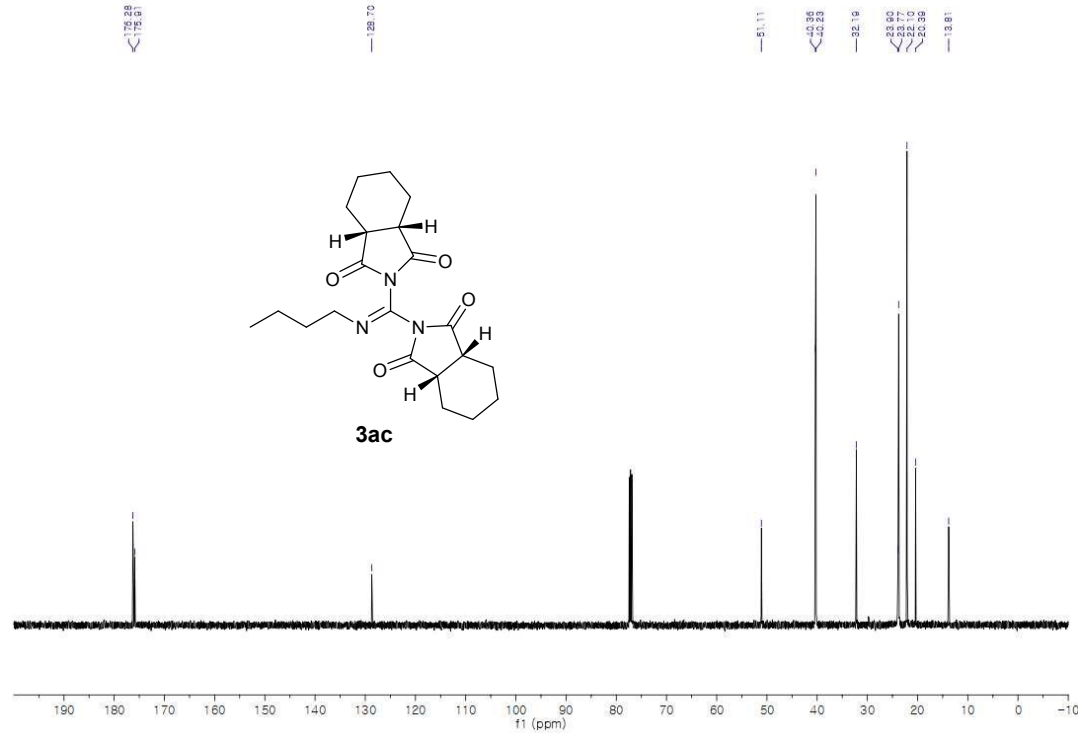


3ab

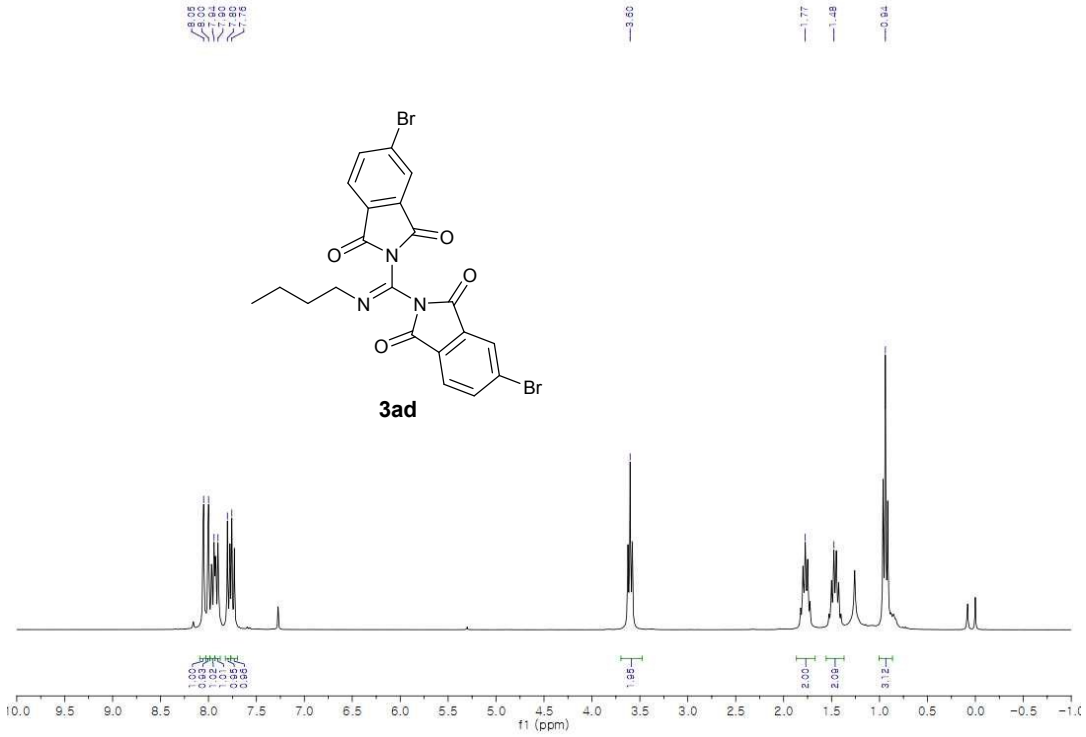
^{1}H NMR (500 MHz, $CDCl_3$)



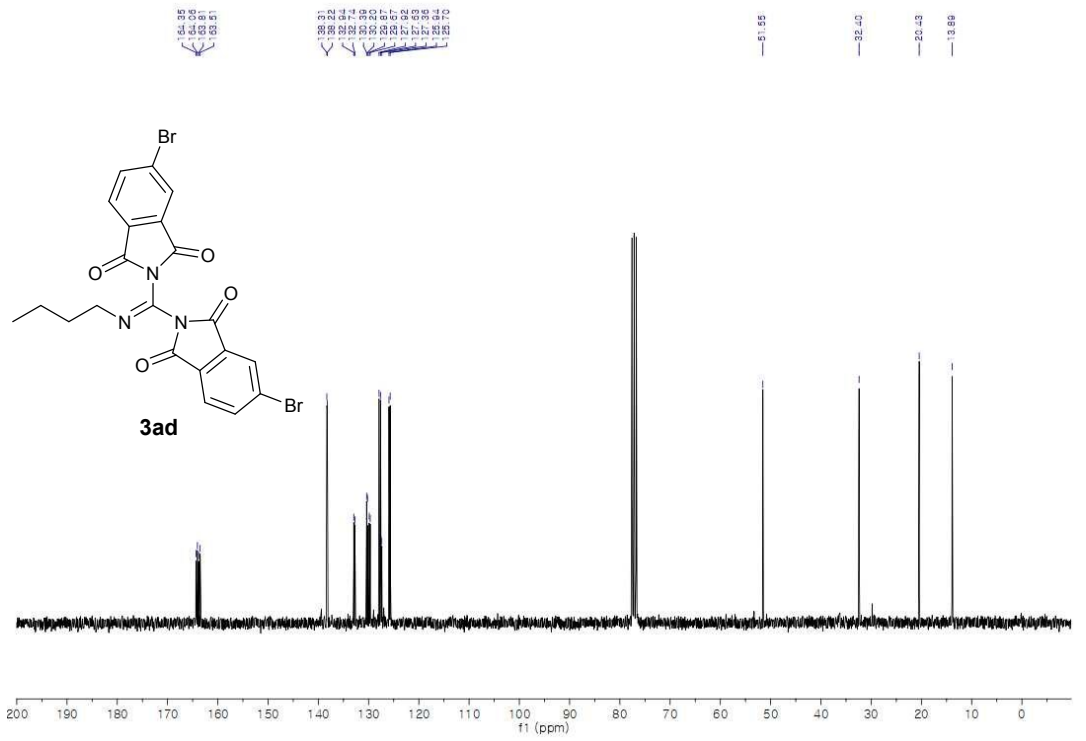
^{13}C NMR (125 MHz, $CDCl_3$)



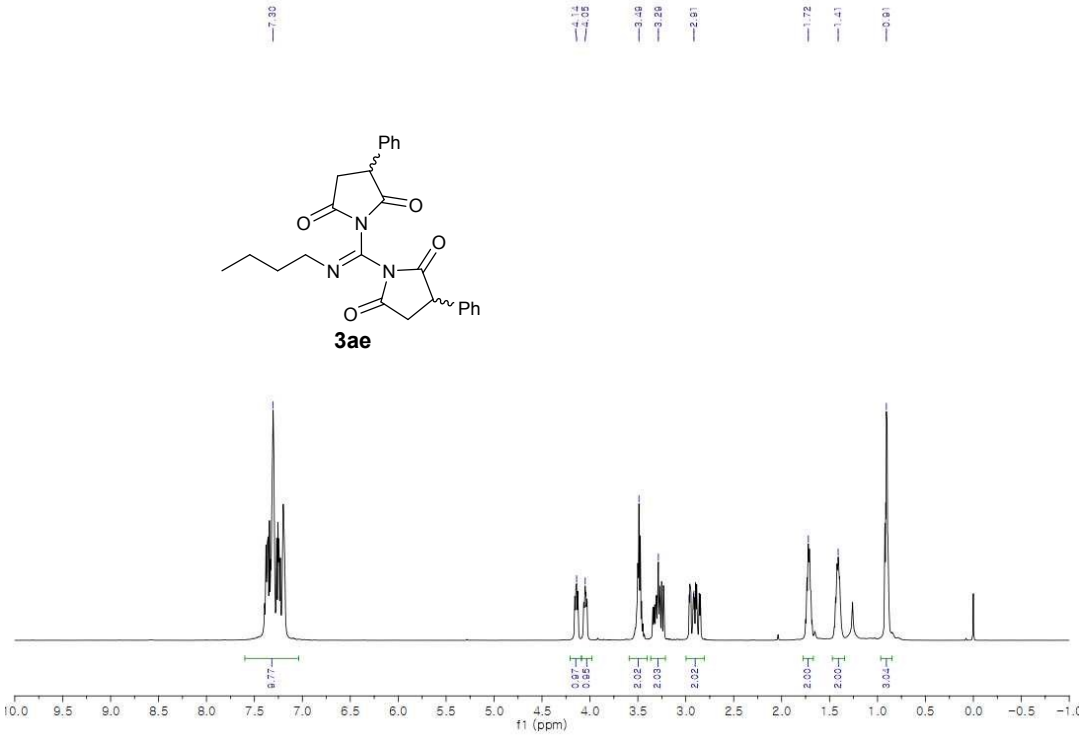
^{1}H NMR (300 MHz, $CDCl_3$)



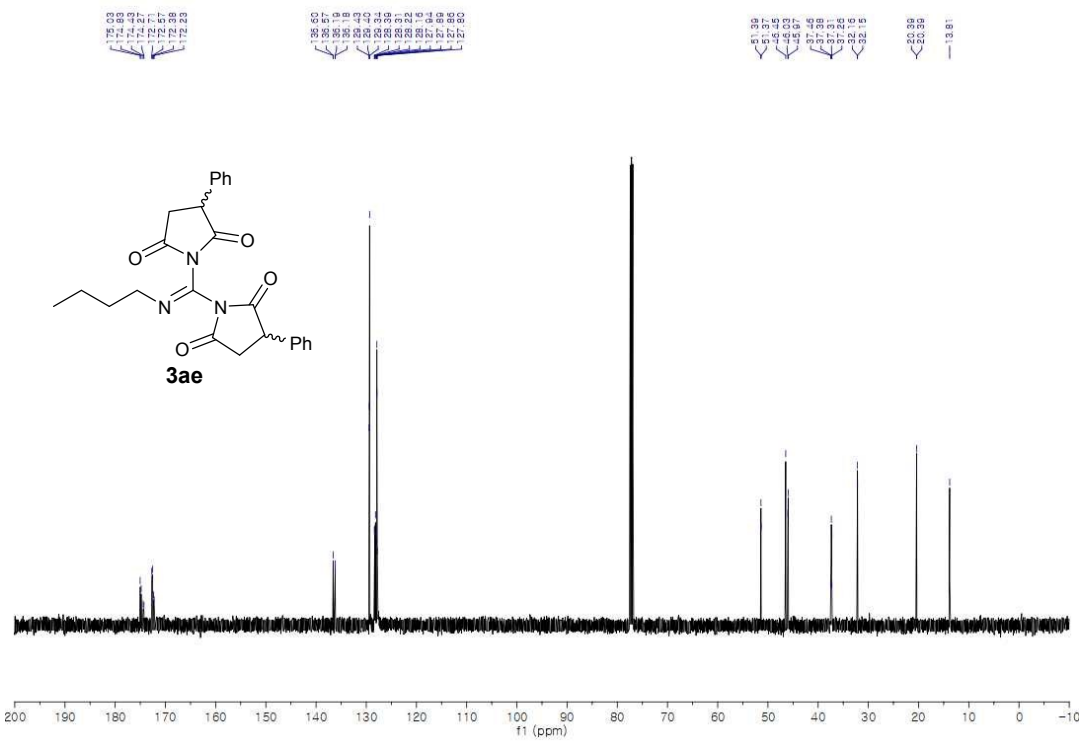
^{13}C NMR (75 MHz, $CDCl_3$)



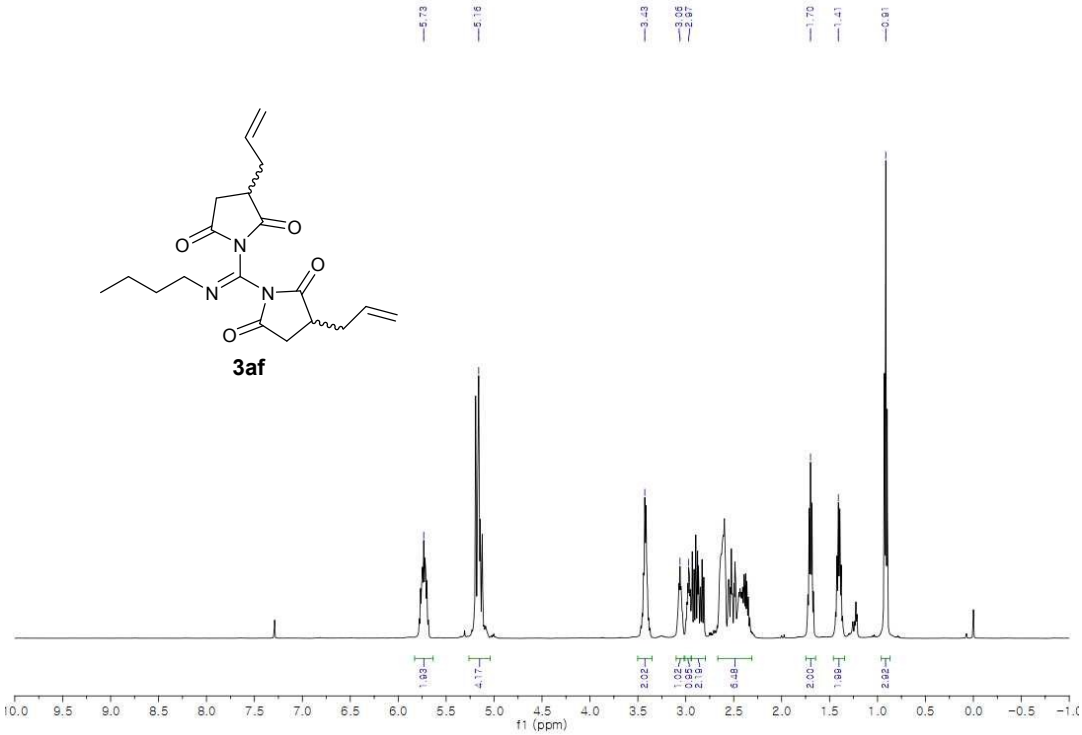
^{1}H NMR (500 MHz, $CDCl_3$)



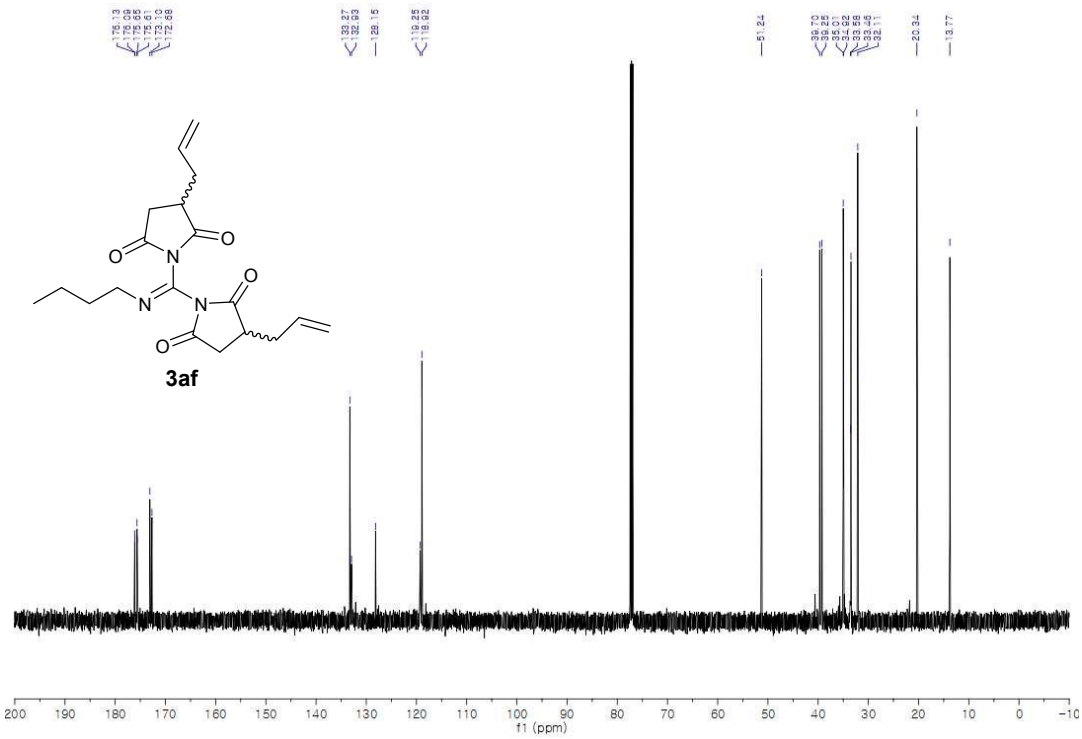
^{13}C NMR (125 MHz, $CDCl_3$)



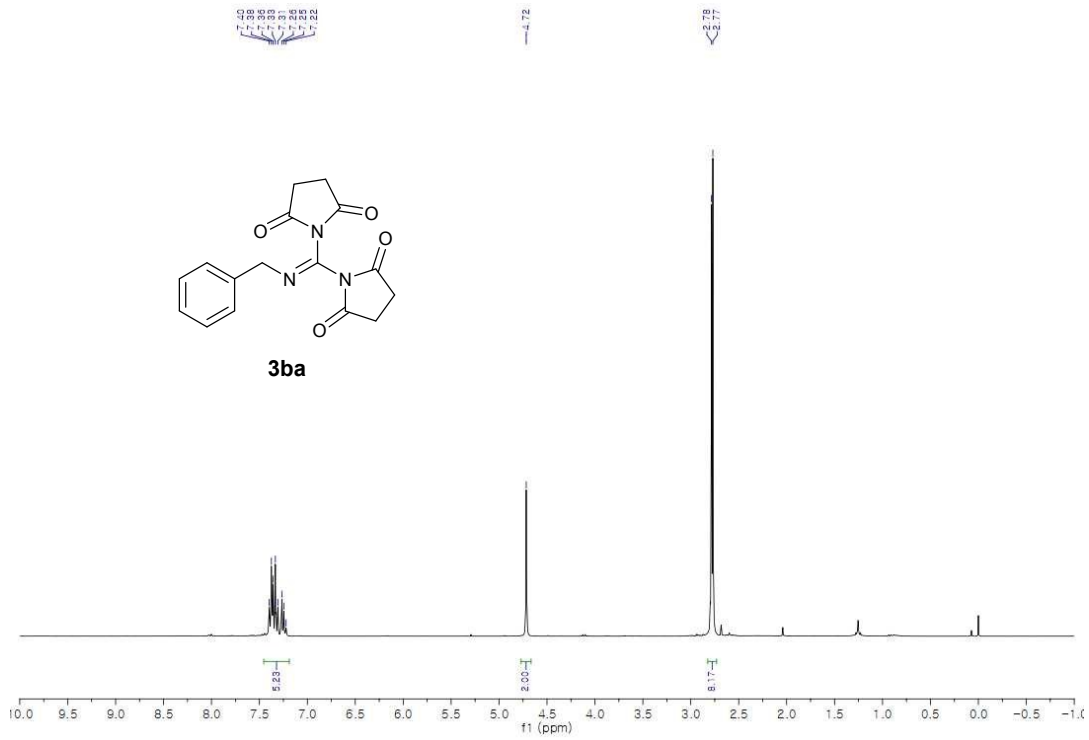
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

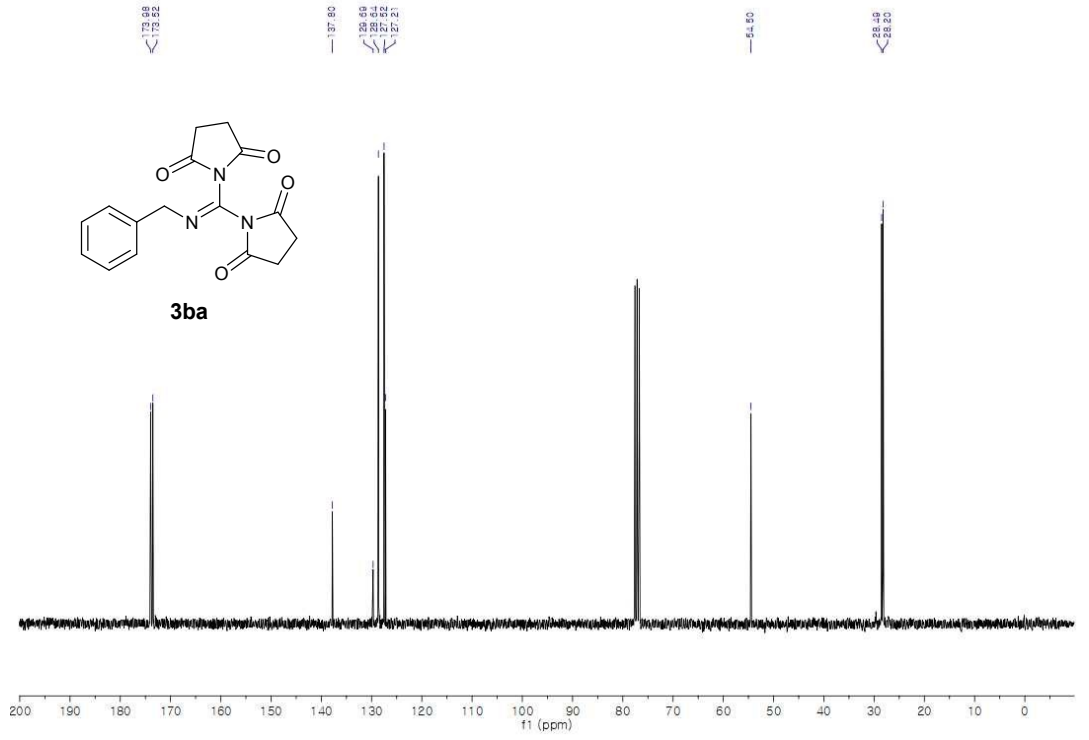


^{1}H NMR (300 MHz, $CDCl_3$)



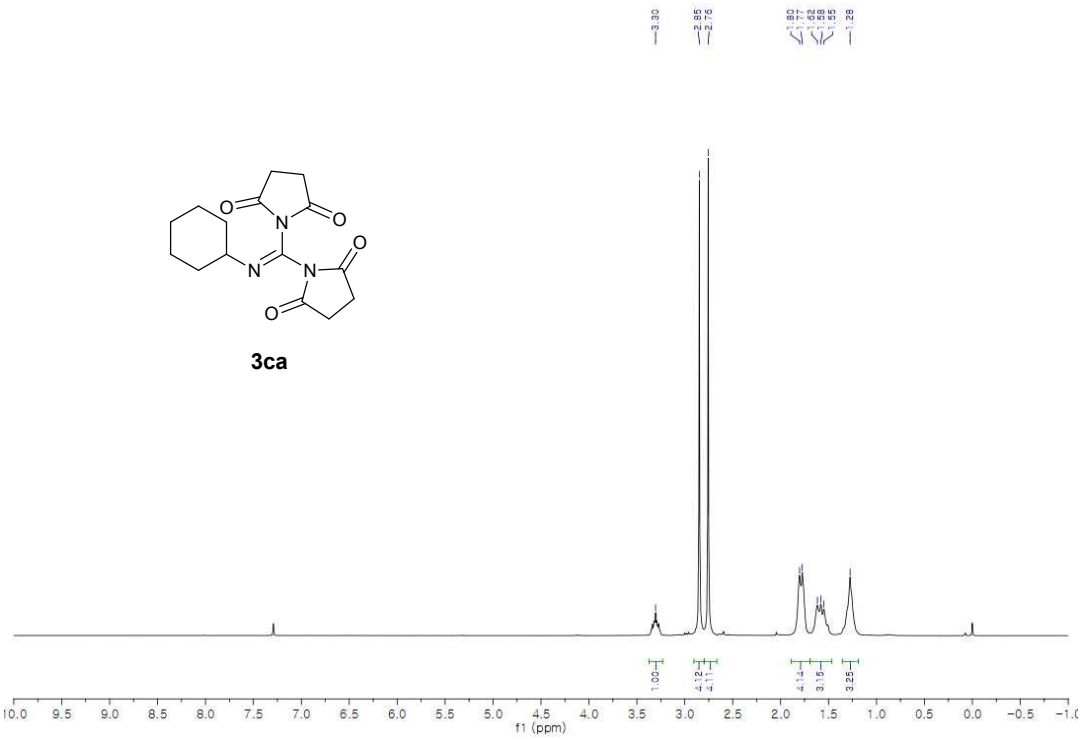
3ba

^{13}C NMR (75 MHz, $CDCl_3$)



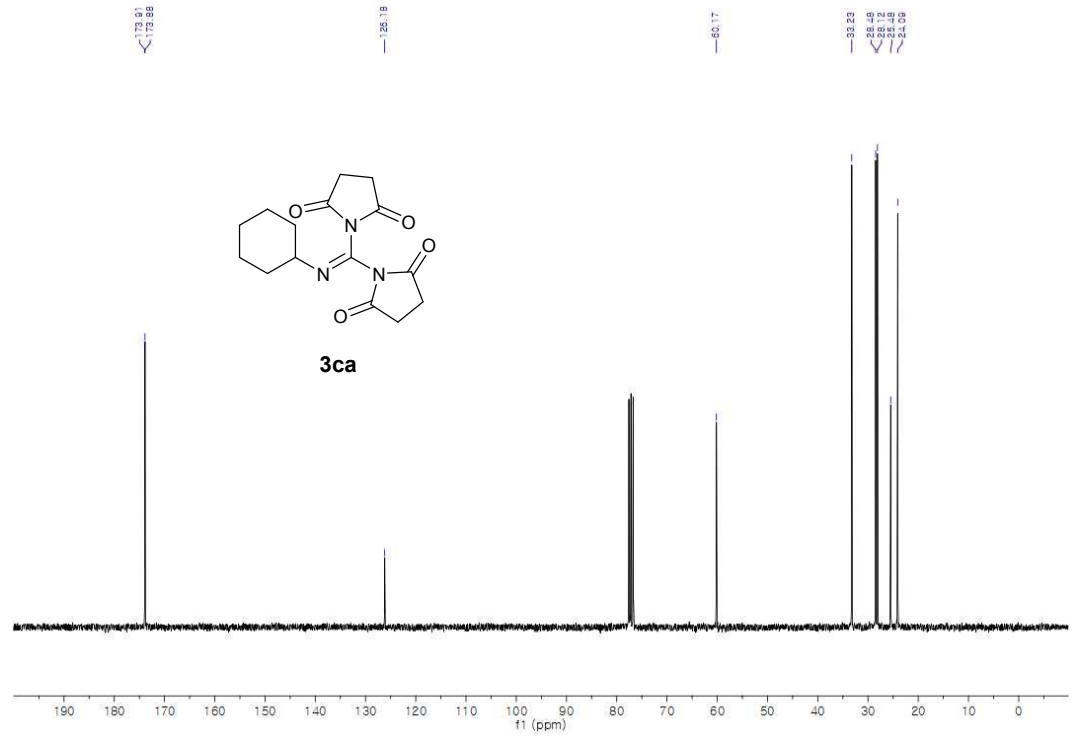
3ba

^{1}H NMR (300 MHz, $CDCl_3$)



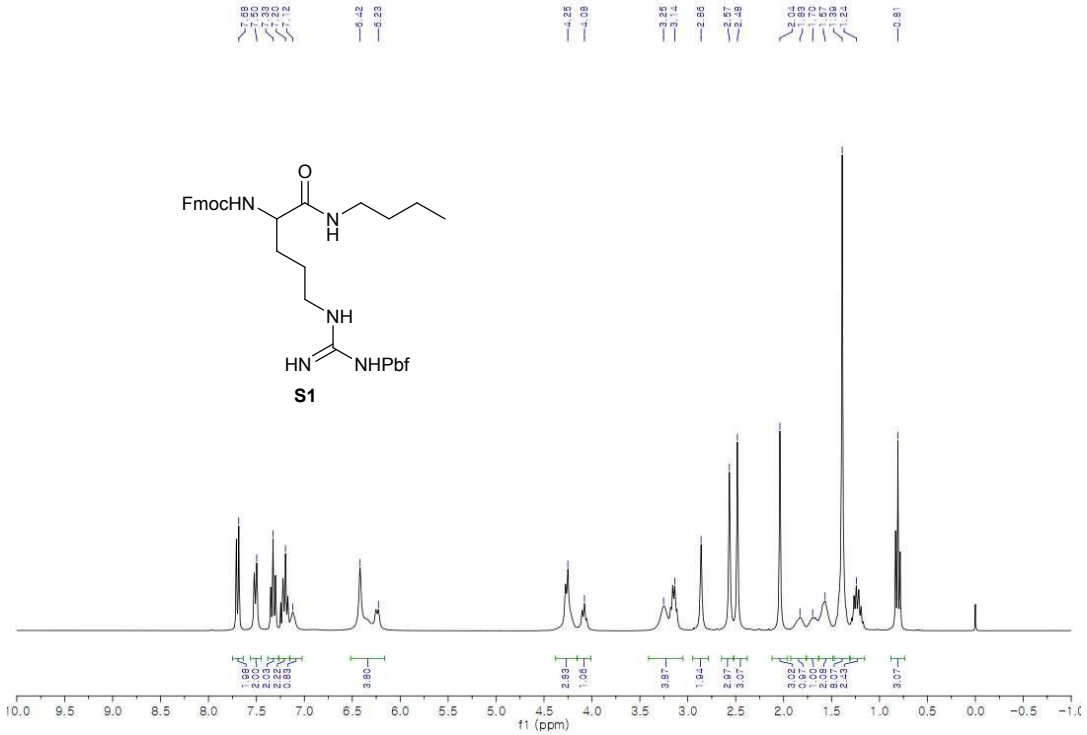
3ca

^{13}C NMR (75 MHz, $CDCl_3$)

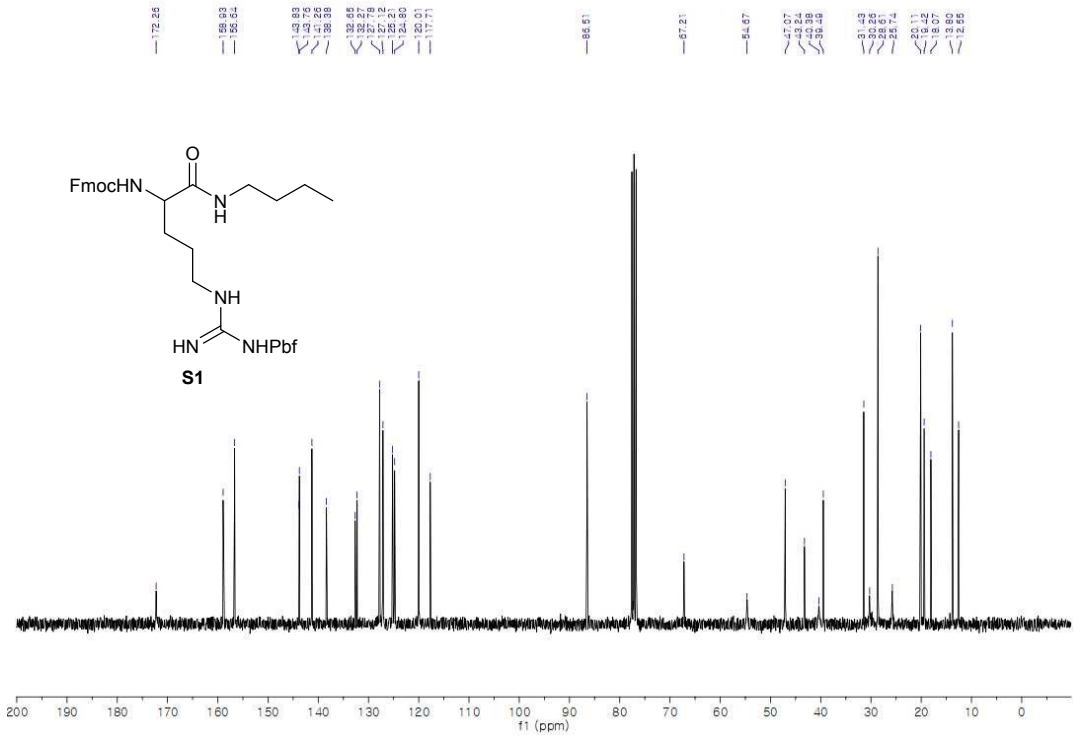


3ca

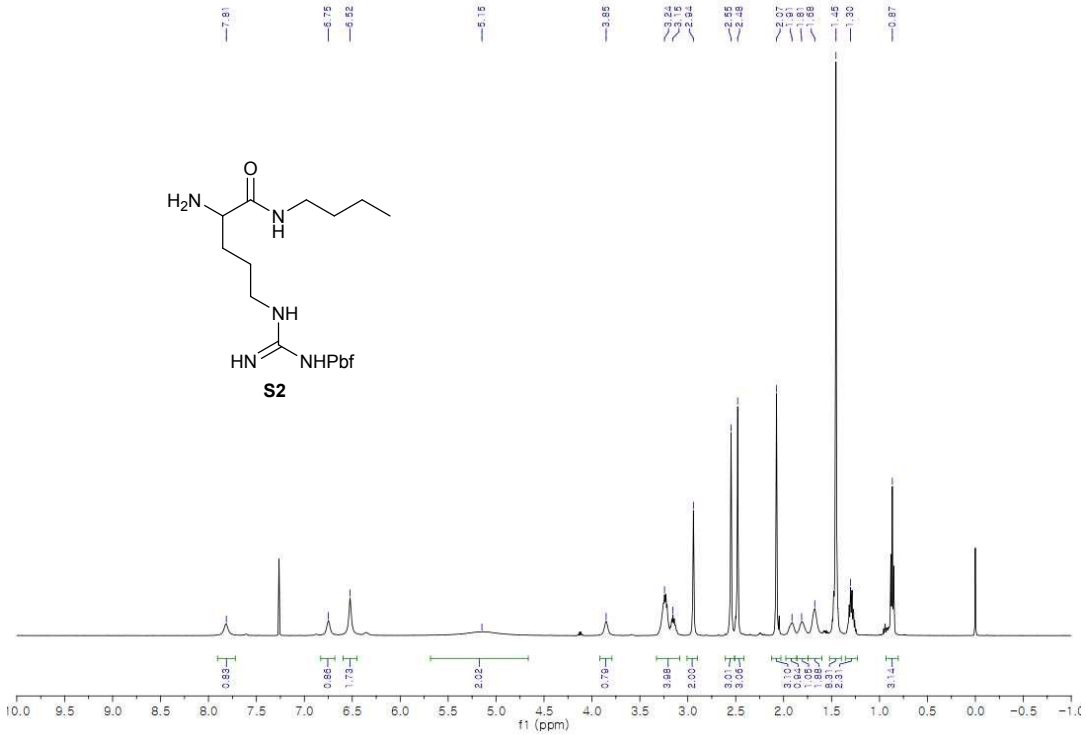
^{1}H NMR (300 MHz, $CDCl_3$)



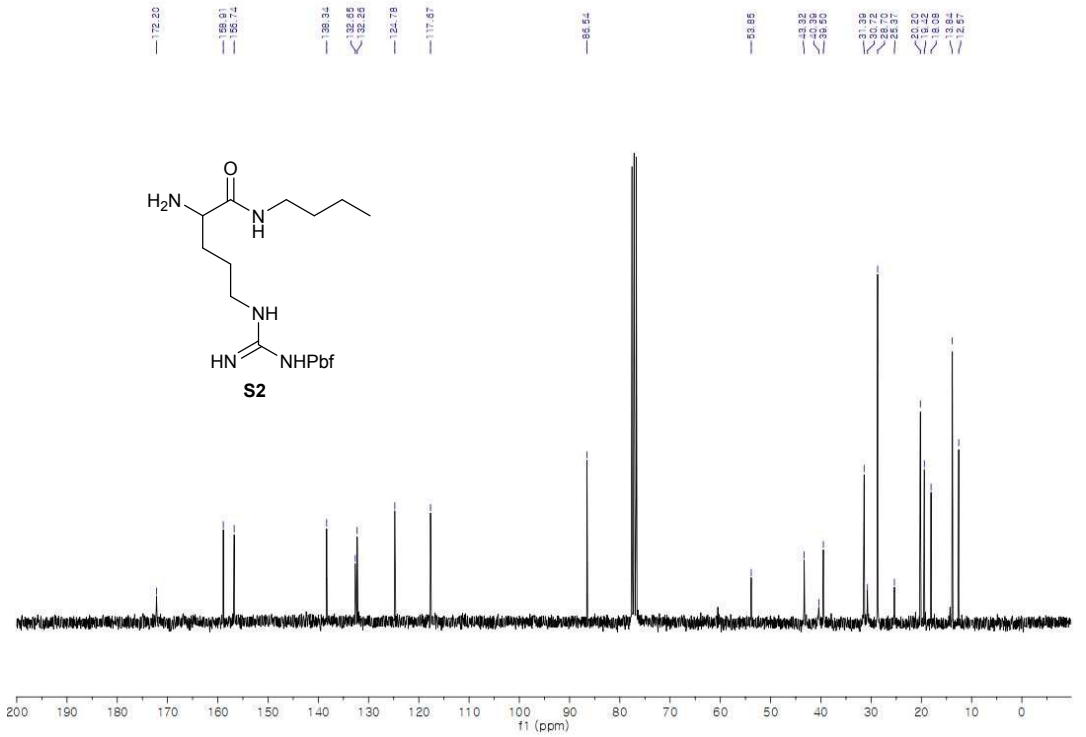
^{13}C NMR (75 MHz, $CDCl_3$)



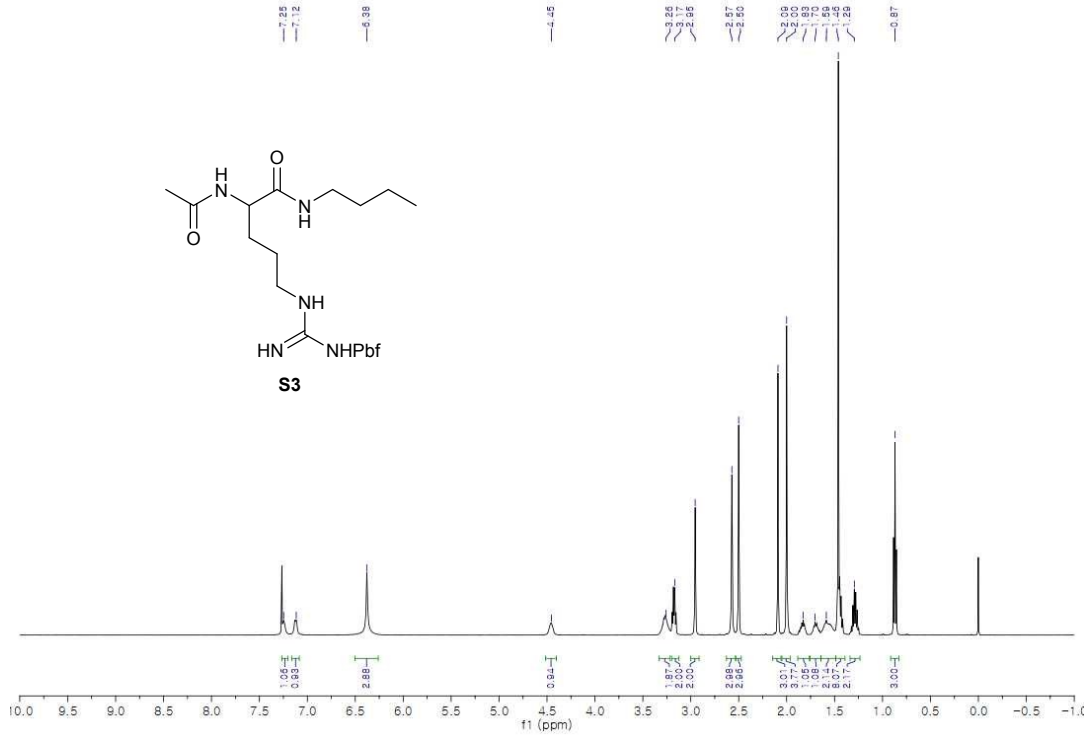
^{1}H NMR (500 MHz, $CDCl_3$)



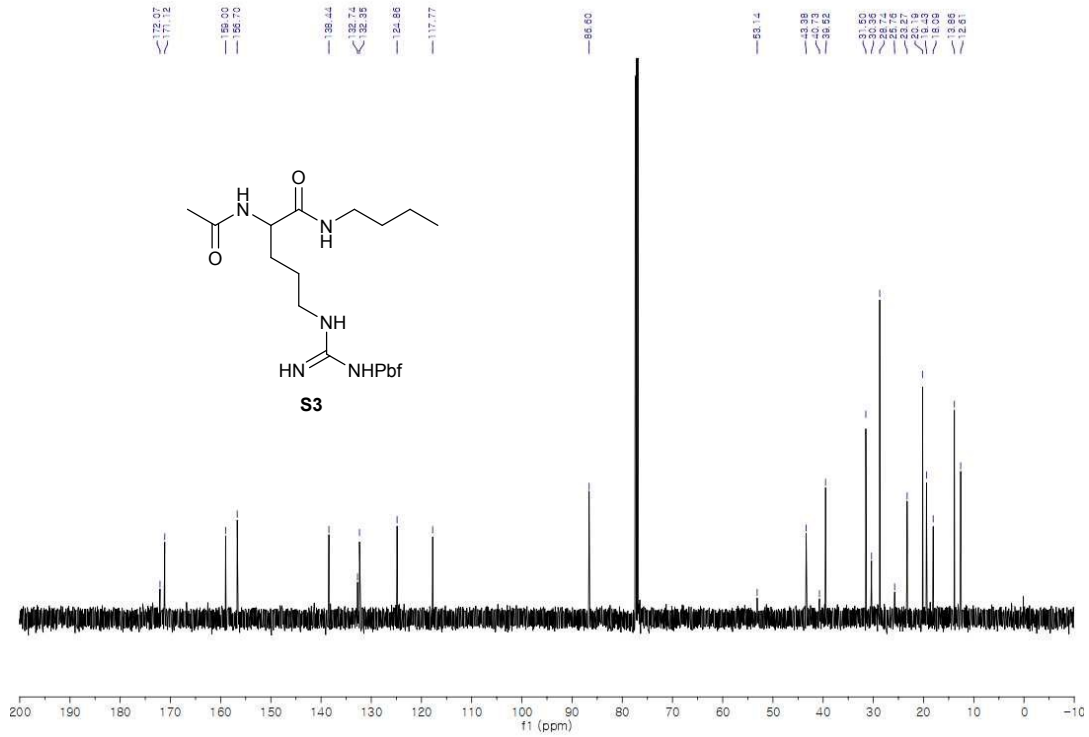
^{13}C NMR (75 MHz, $CDCl_3$)



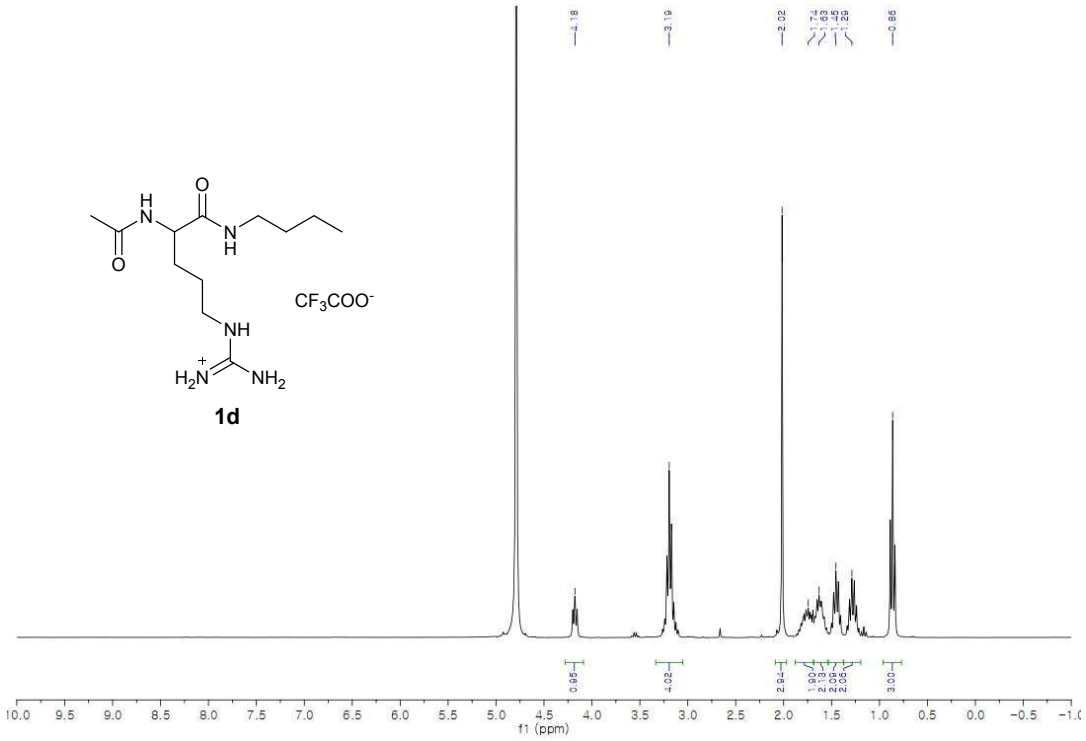
^{1}H NMR (500 MHz, $CDCl_3$)



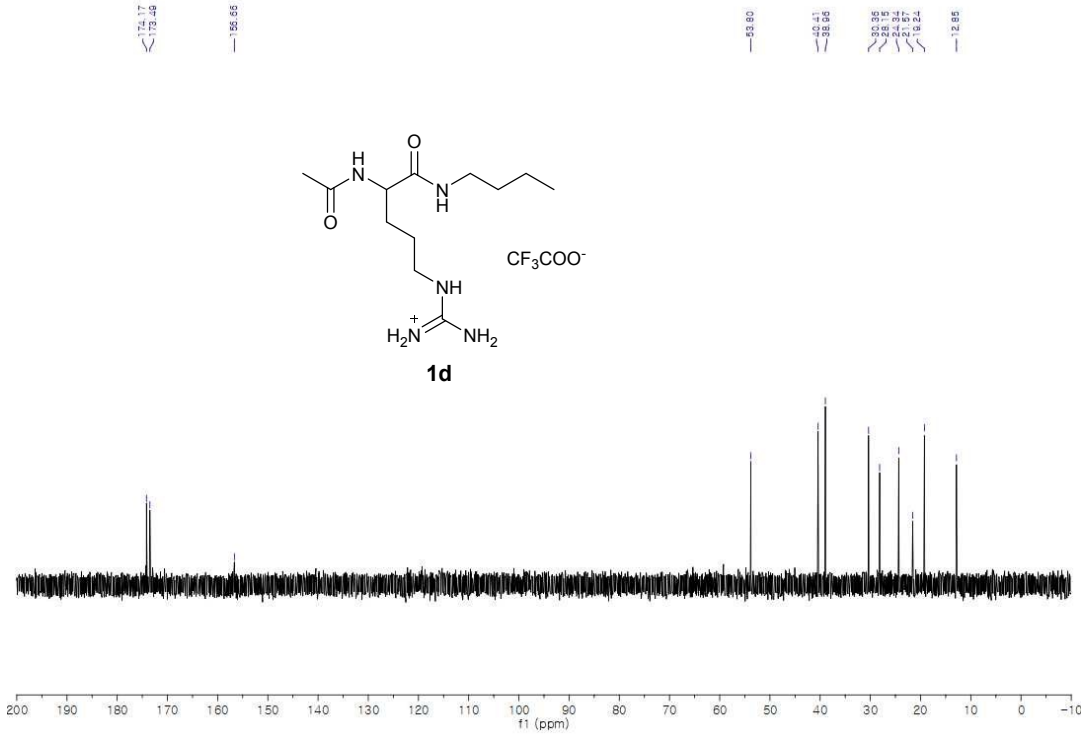
^{13}C NMR (125 MHz, $CDCl_3$)



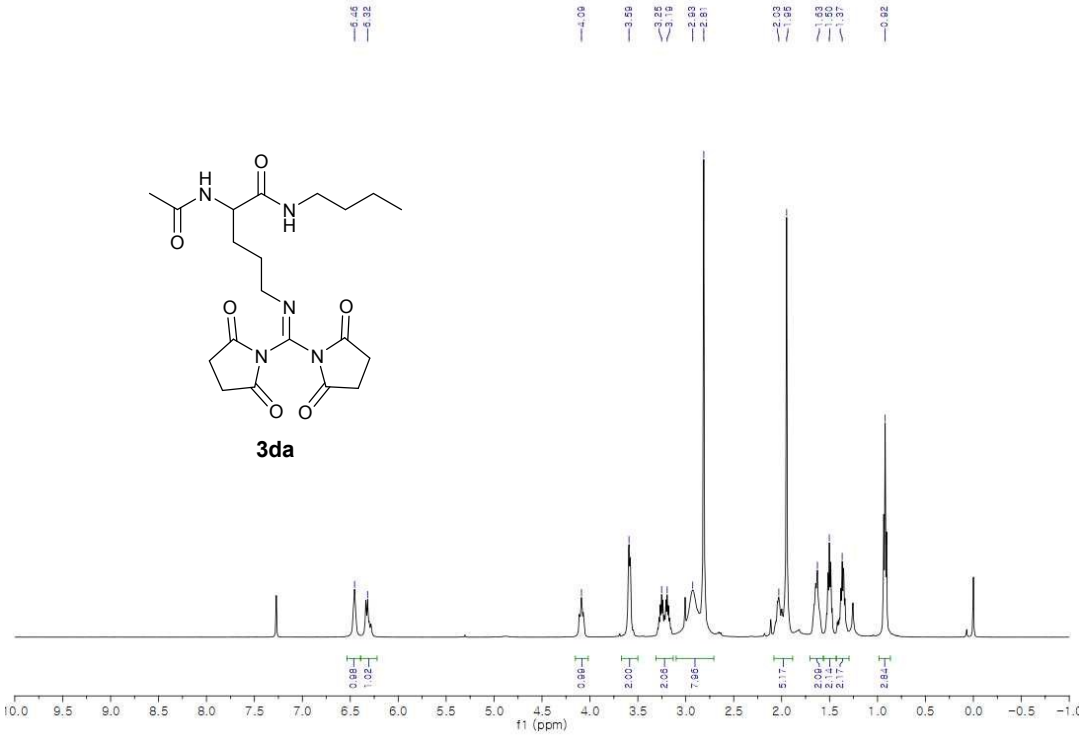
^{1}H NMR (300 MHz, D_2O)



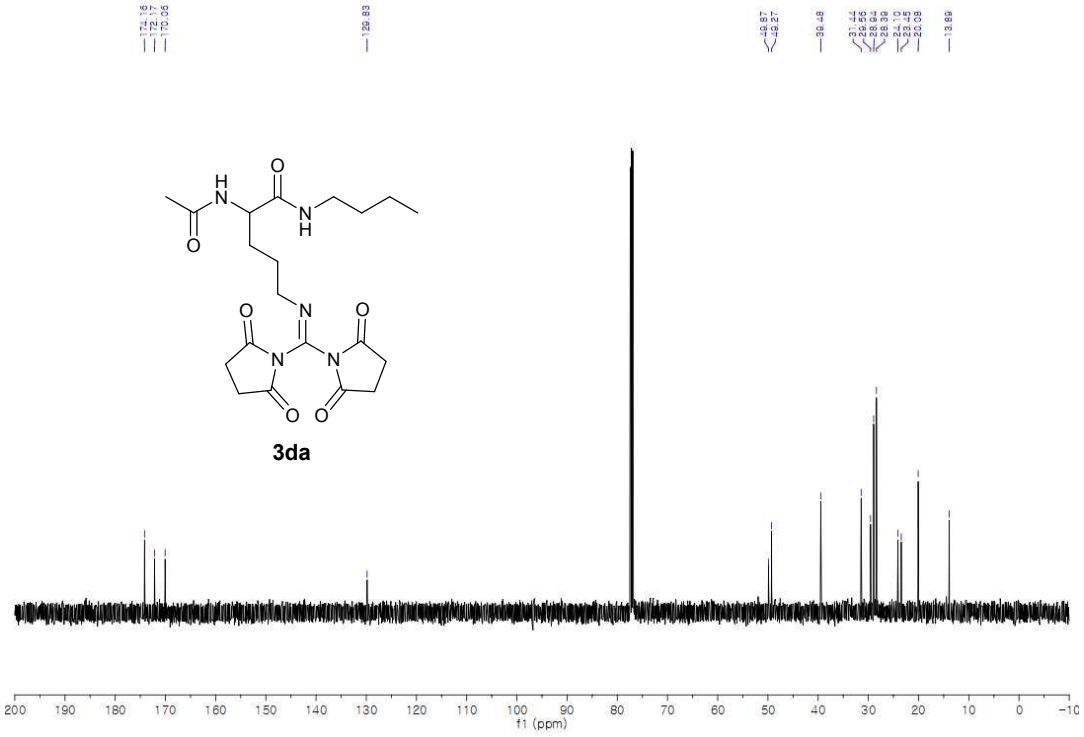
^{13}C NMR (125 MHz, D_2O)



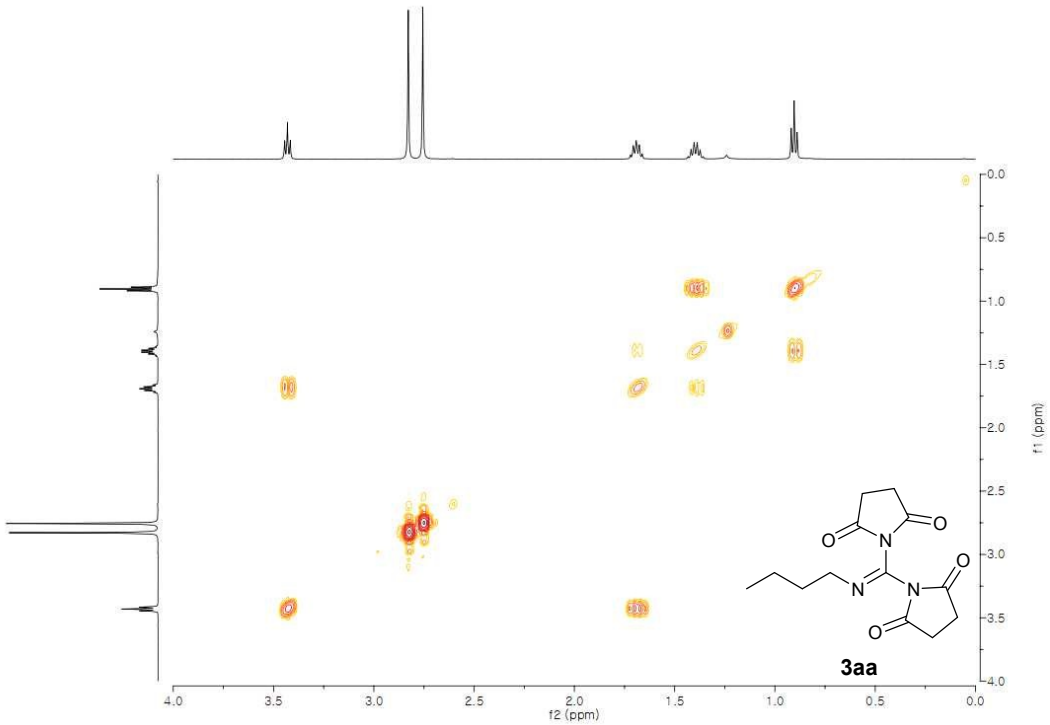
^{1}H NMR (500 MHz, $CDCl_3$)



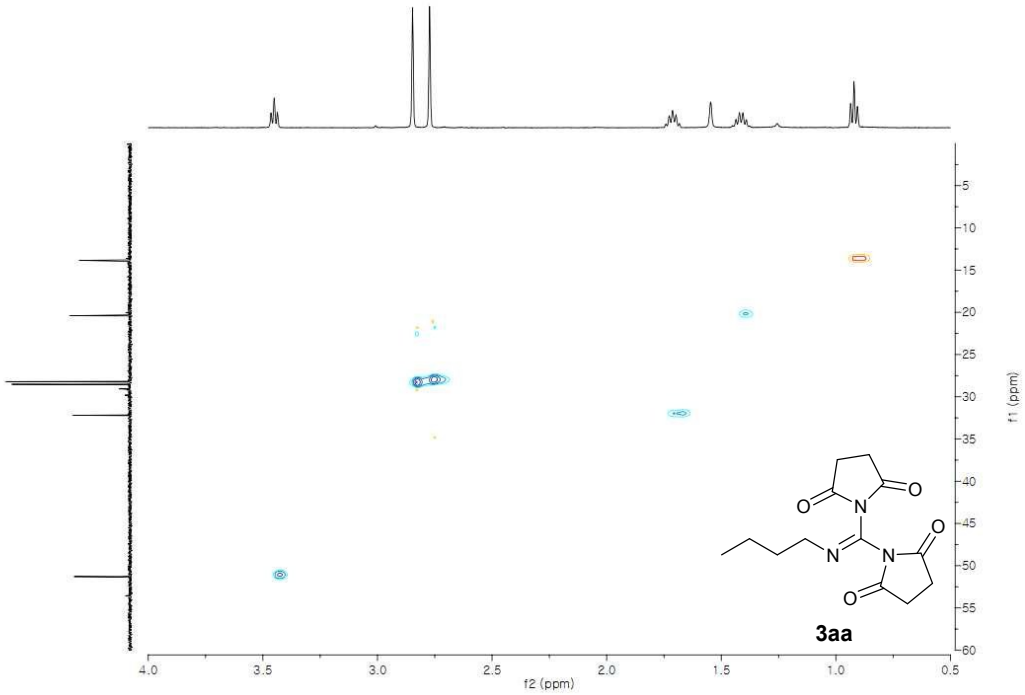
^{13}C NMR (125 MHz, $CDCl_3$)



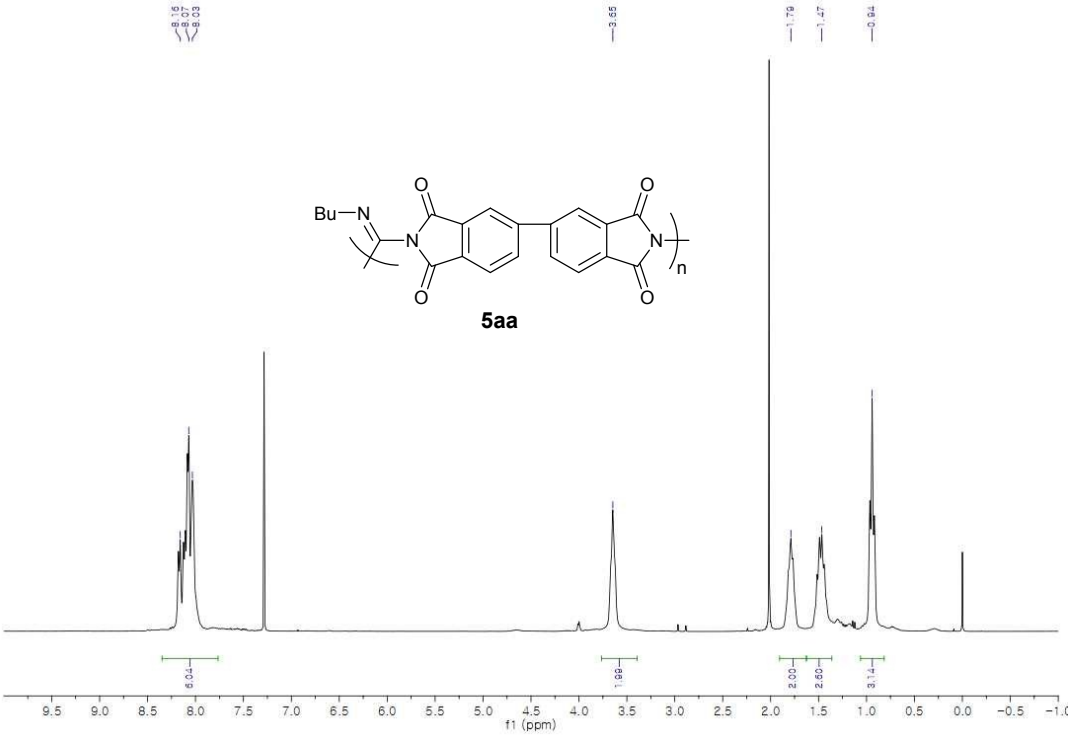
gCOSY (500 MHz, $CDCl_3$)



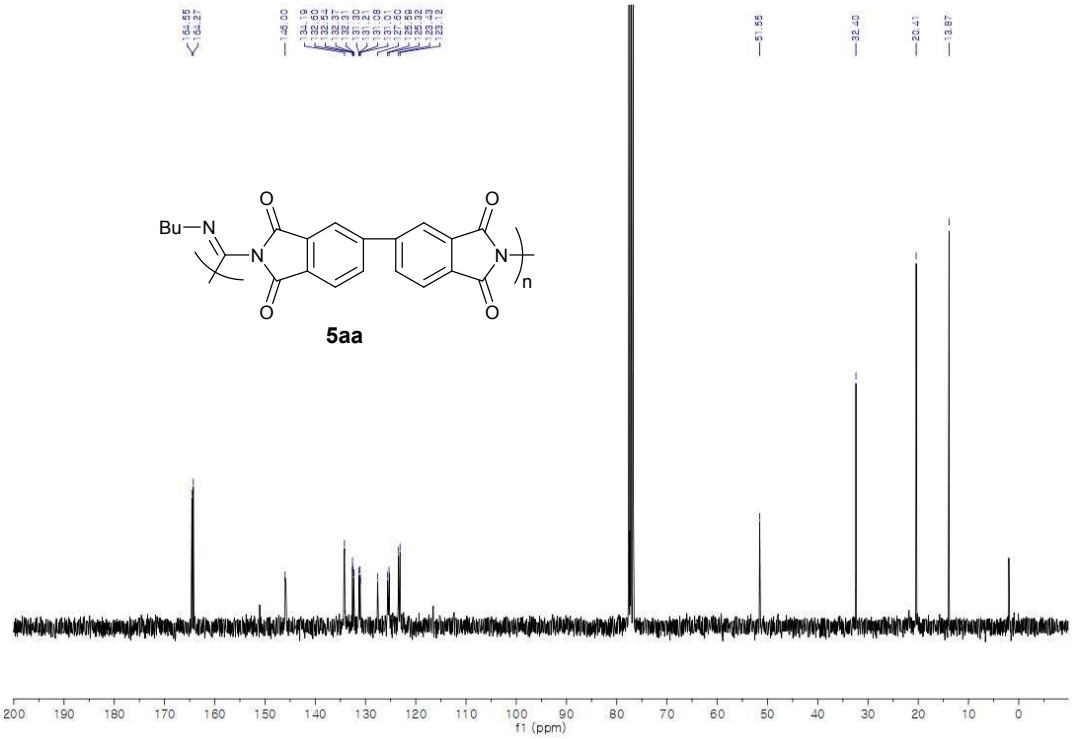
HSQC (500 MHz, $CDCl_3$)



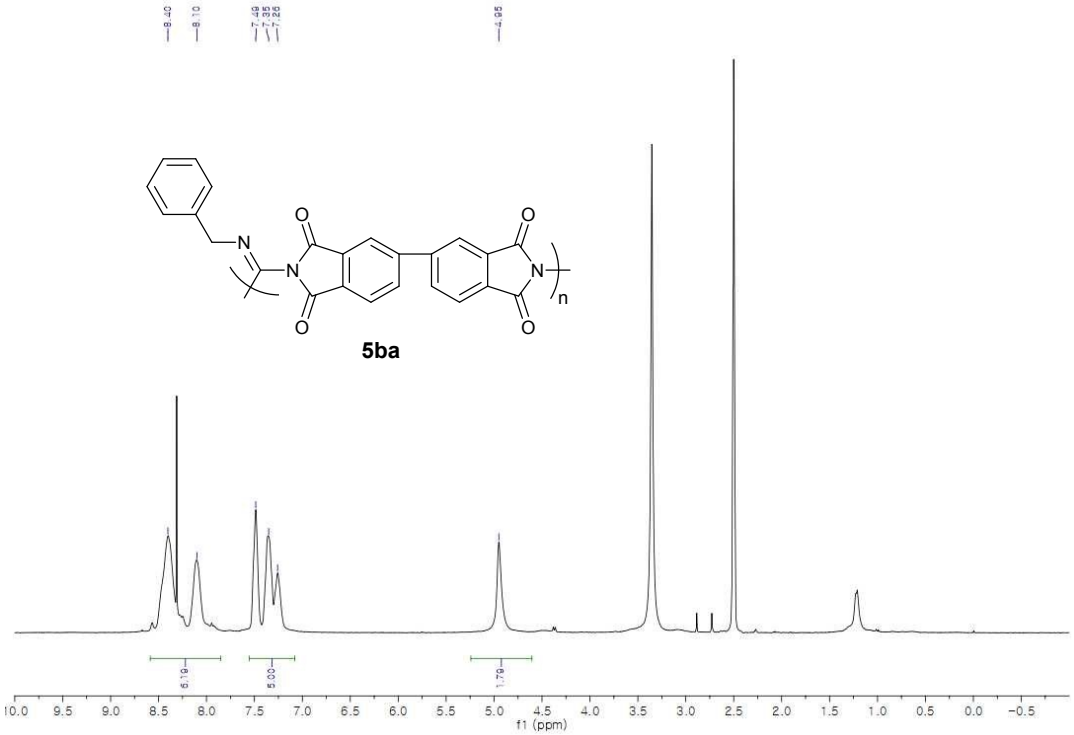
^{1}H NMR (300 MHz, $CDCl_3$)



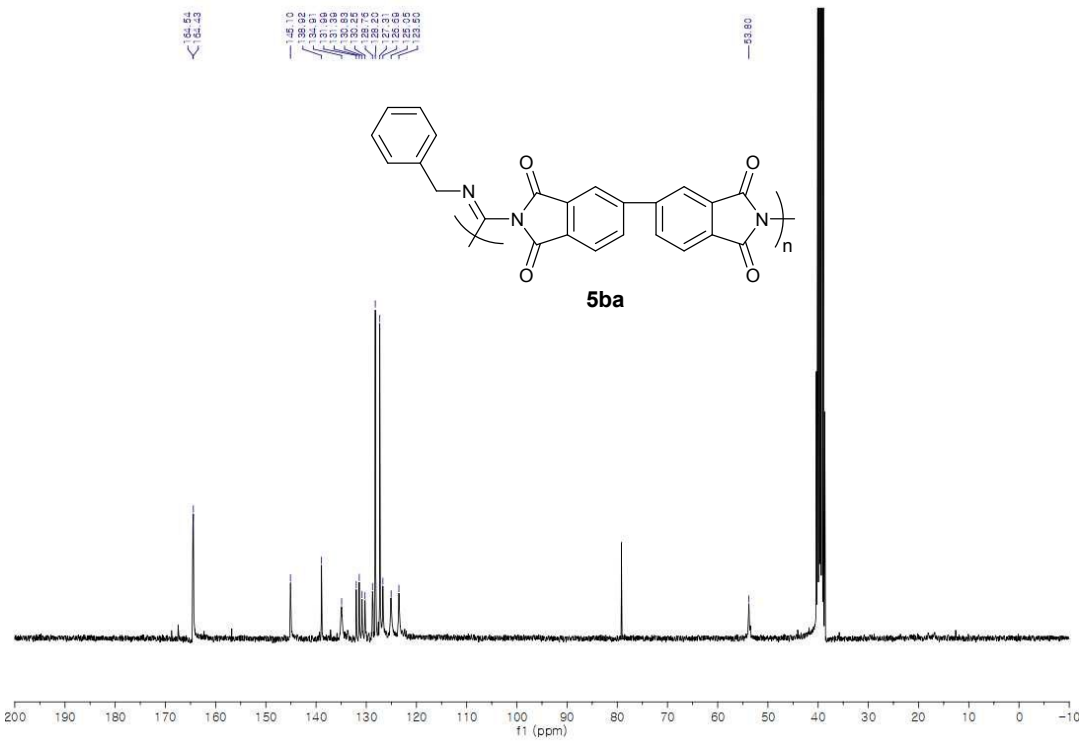
^{13}C NMR (75 MHz, $CDCl_3$)



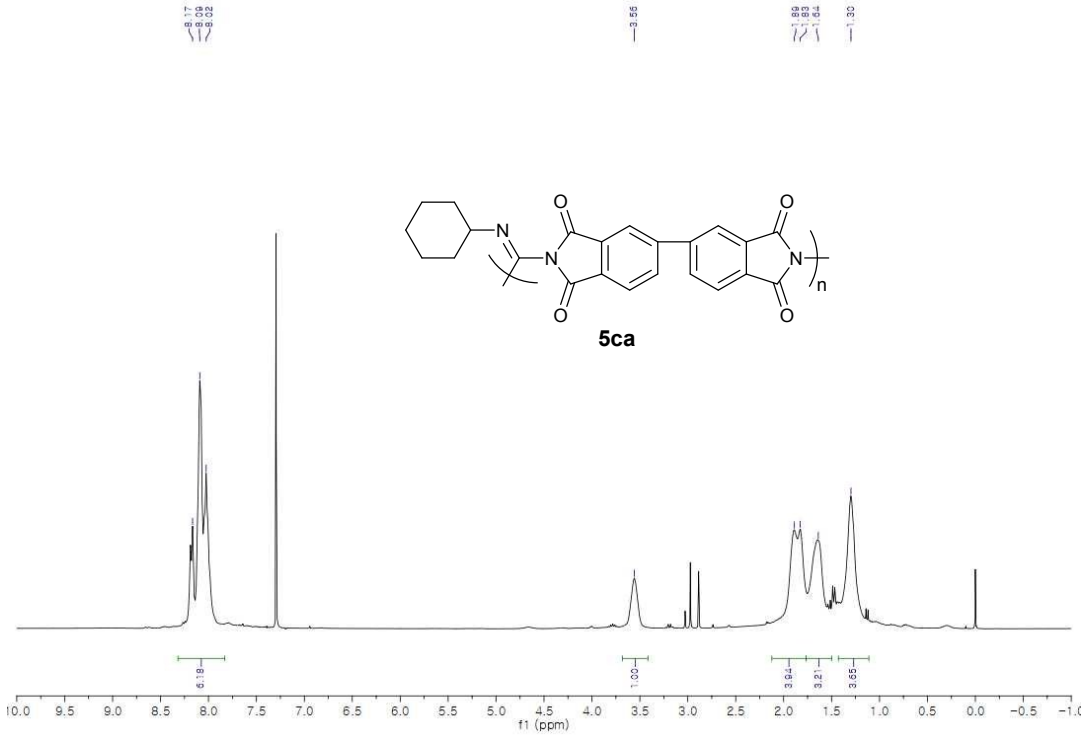
^{1}H NMR (300 MHz, DMSO-d_6)



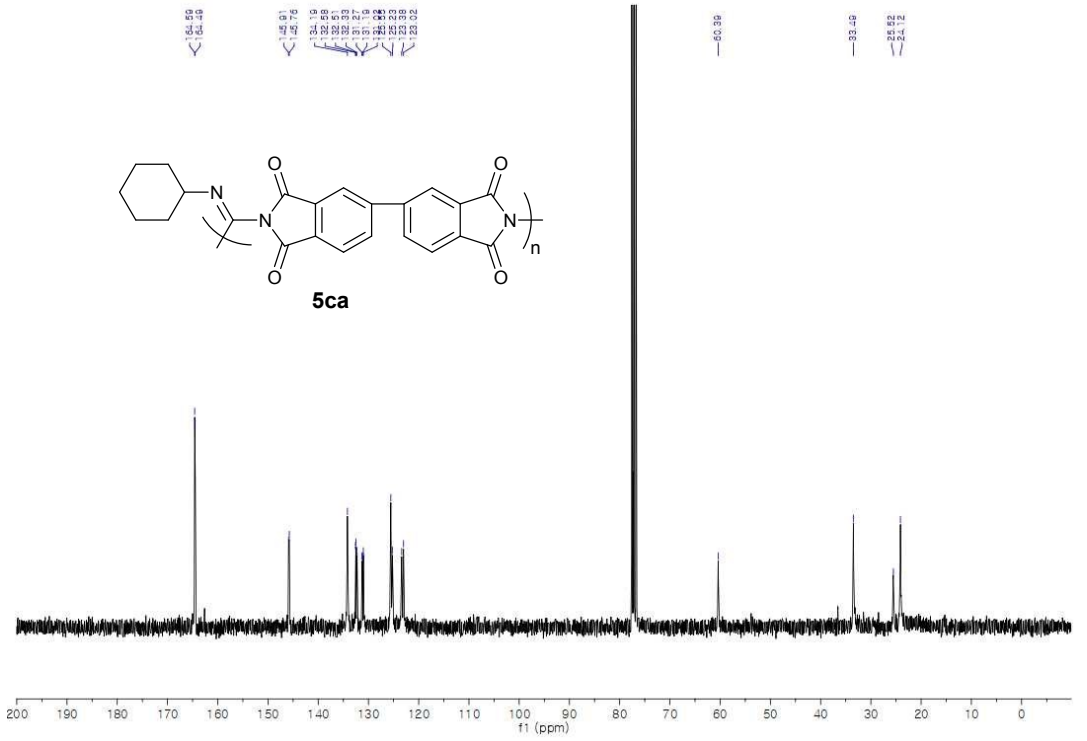
^{13}C NMR (75 MHz, DMSO-d_6)



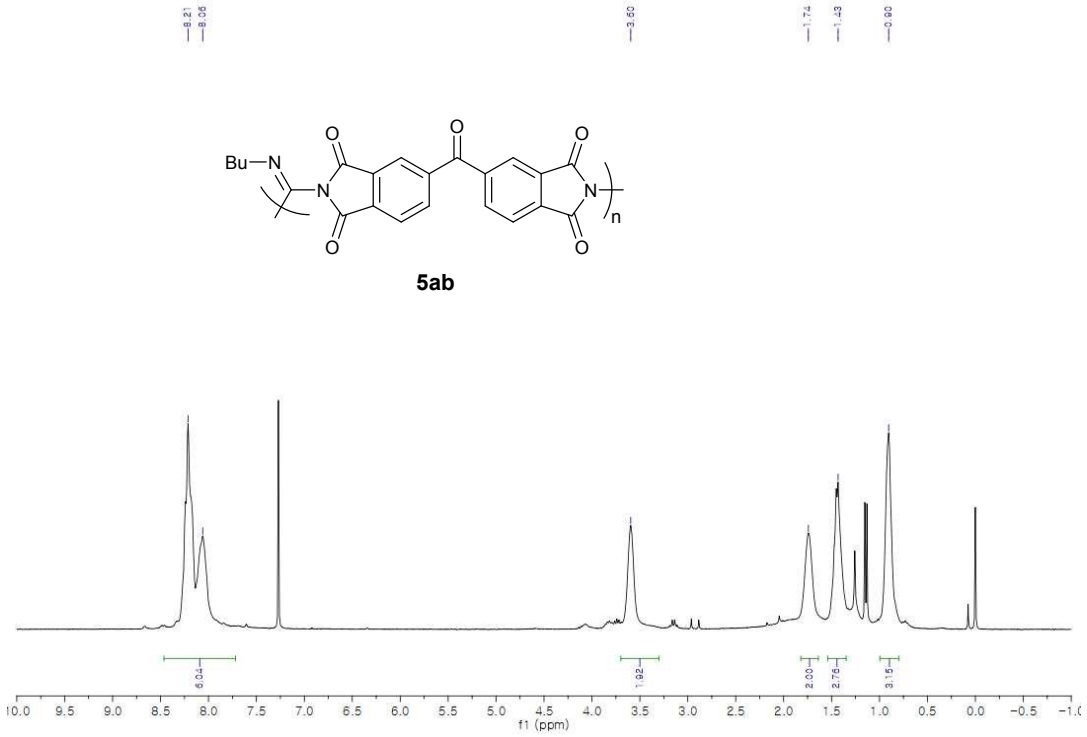
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

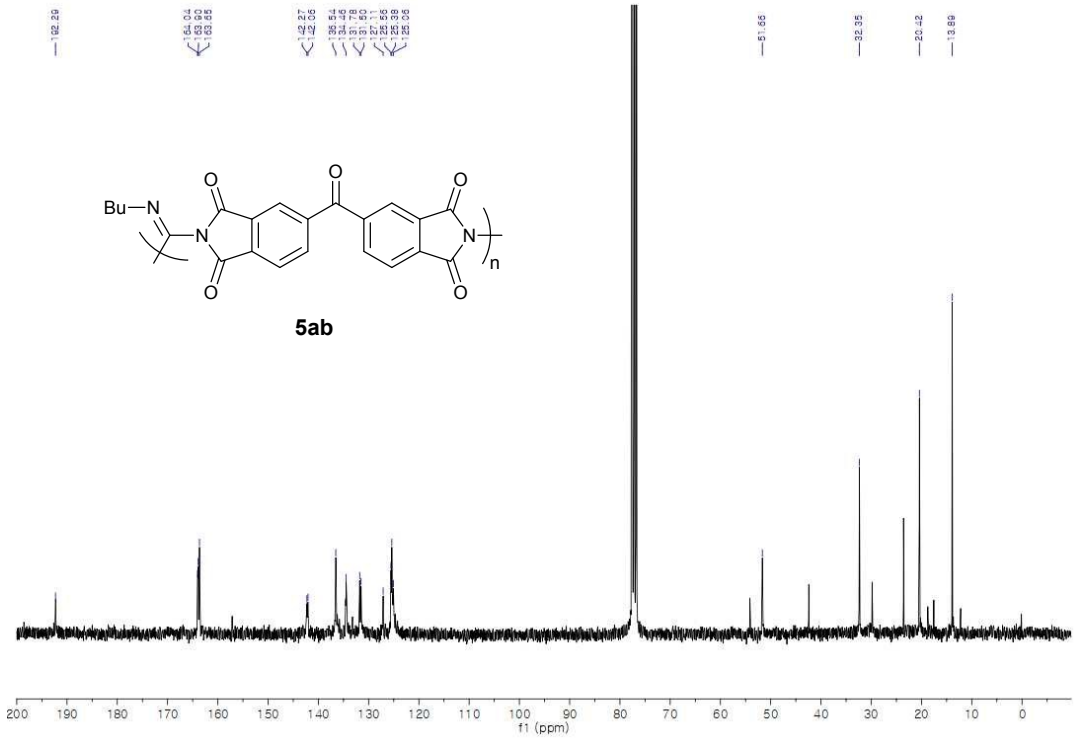


^{1}H NMR (300 MHz, $CDCl_3$)



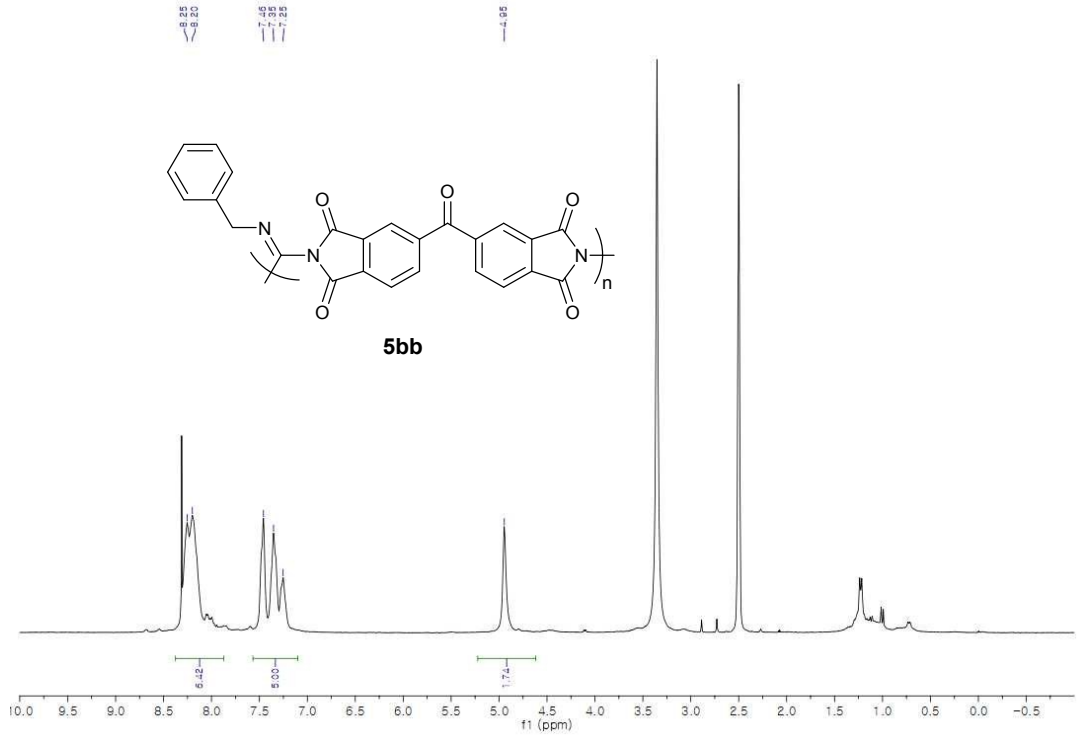
5ab

^{13}C NMR (75 MHz, $CDCl_3$)



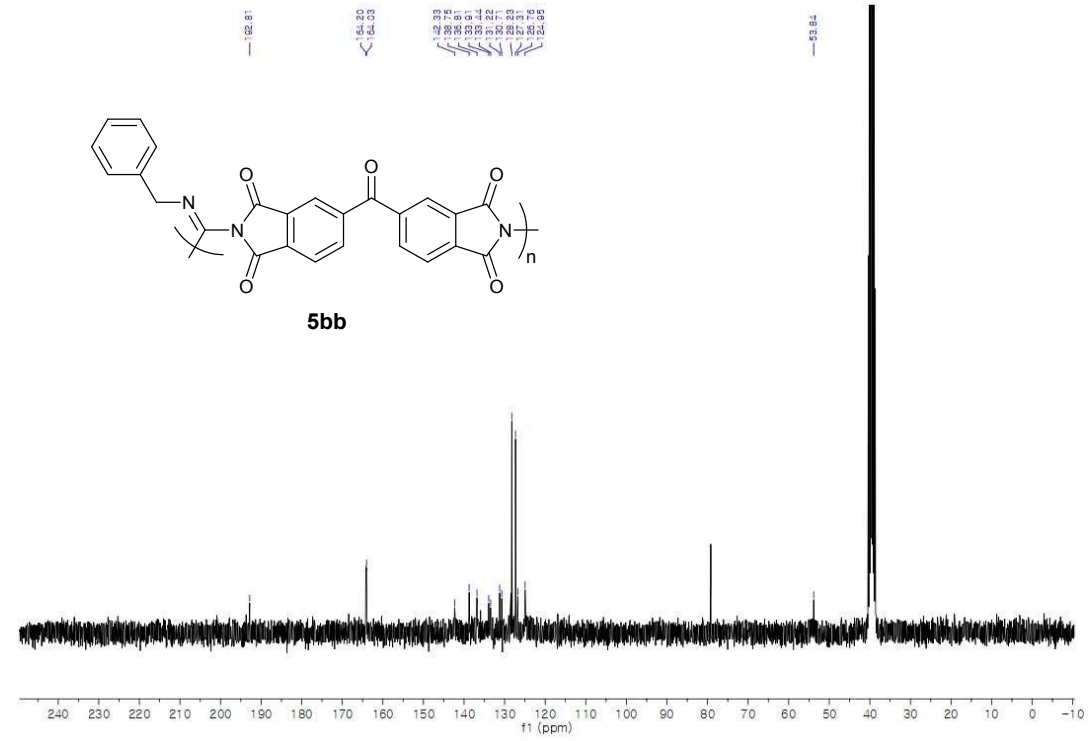
5ab

^{1}H NMR (300 MHz, DMSO-d_6)



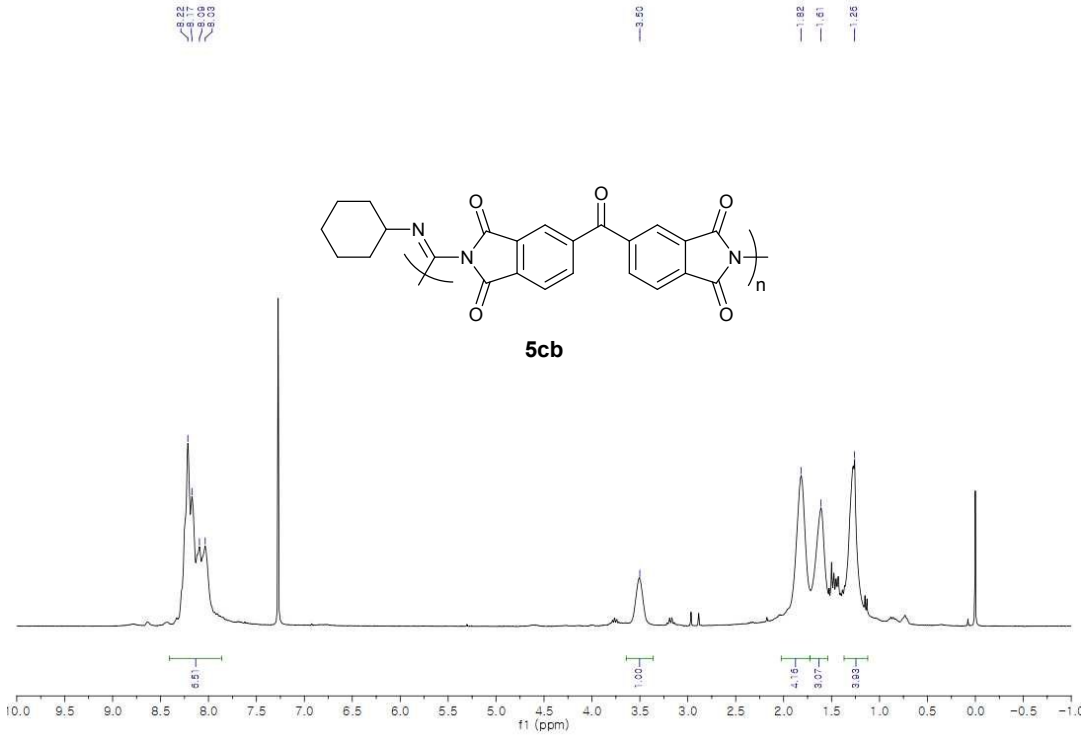
5bb

^{13}C NMR (75 MHz, DMSO-d_6)

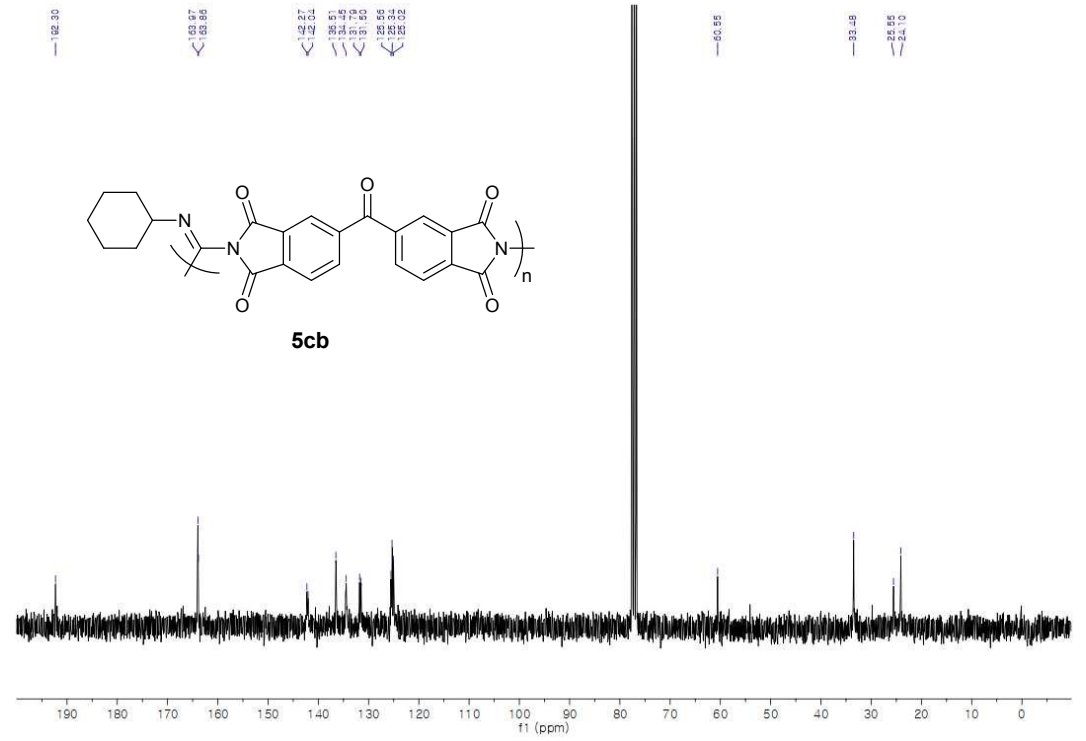


5bb

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



4. FTIR Spectra of Poly(GCDI) 5aa

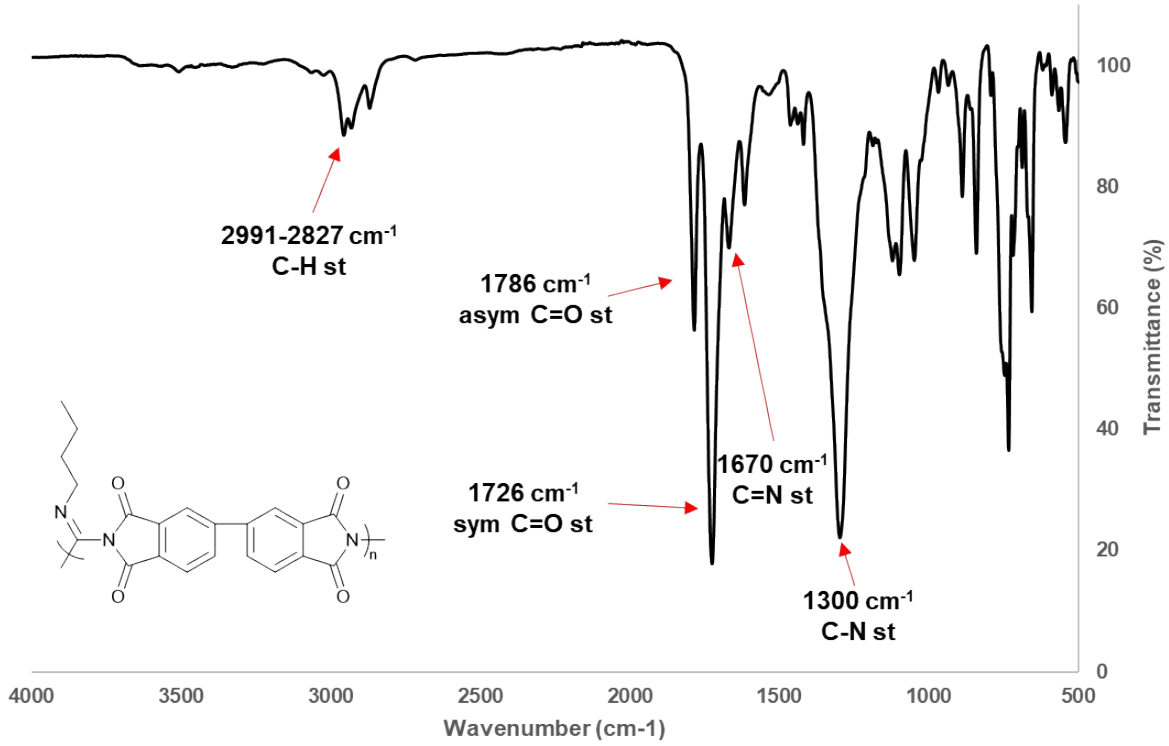


Figure S1. ATR-FTIR spectra of poly(GCDI) **5aa**. Representative peaks are indicated.

5. A Proposed Mechanism for the Formation of the GCDI Structure

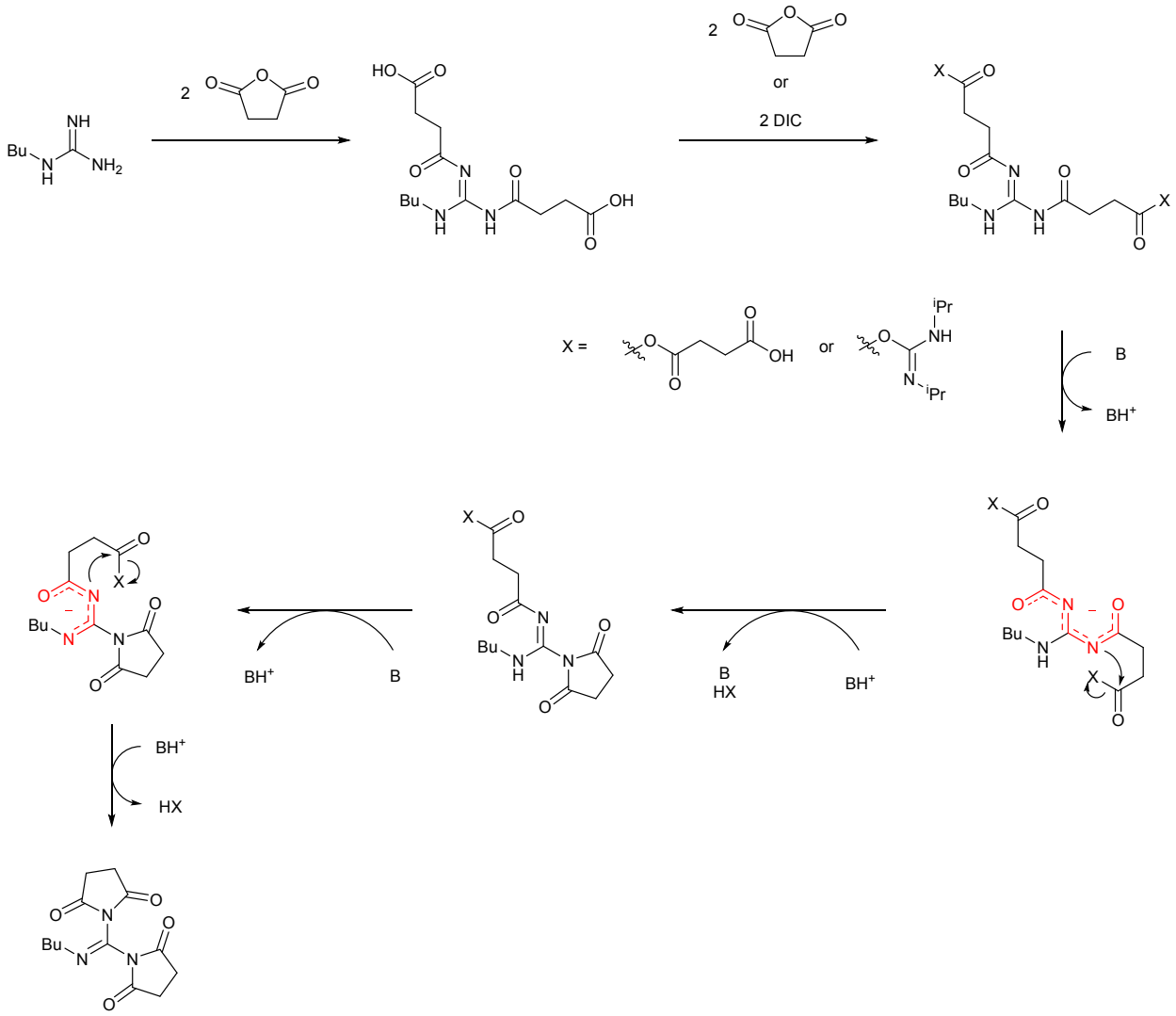


Figure S2. A proposed mechanism for the formation of the GCDI structure. B indicates base, *i.e.* DIPEA or K_2CO_3. Resonance-stabilized intermediates are indicated in red.

A. Mechanistic Studies for the GCDI Formation by ESI/MS Experiments

To a solution of butylguanidine hydrochloride (15.2 mg; 0.100 mmol; 1.00 equiv.) and succinic anhydride (20.0 mg; 0.200 mmol; 2.00 equiv.) in DMF (1.00 ml), DIPEA (0.0850 ml; 0.500 mmol; 5.00 equiv.) was added. The reaction mixture was stirred for 24 h at an ambient temperature. An aliquot was taken and diluted with H_2O/ACN (v/v 1:1). The sample was analyzed by ESI/MS-(+) to detect possible reaction intermediates.

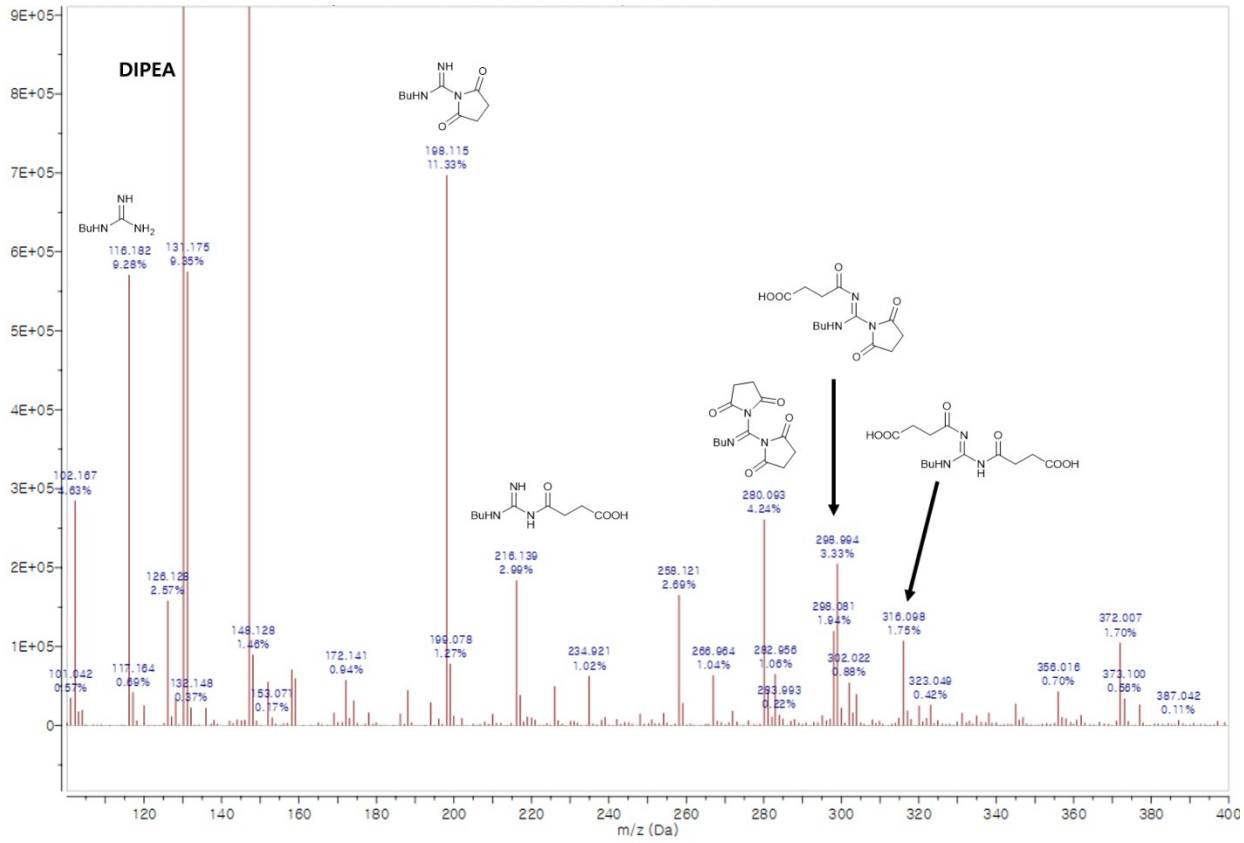


Figure S3. ESI/MS-(+) spectrum for the reaction of butylguanidine hydrochloride with succinic anhydride.

B. Reaction of Butylguanidine with Methyl-4-chloro-4-oxobutyrate

To a solution of butylguanidine hydrochloride (303 mg; 2.00 mmol; 1.00 equiv.) in DMF (10.0 ml), TEA (0.986 ml; 7.00 mmol; 3.50 equiv.) and methyl-4-chloro-4-oxobutyrate (0.544 ml; 4.20 mmol; 2.10 equiv.) were added. The reaction mixture was stirred at an ambient temperature for overnight and concentrated under reduced pressure. The crude mixture was diluted with 50 ml of ethyl acetate and 50 ml of aqueous HCl (0.01 M). The organic layer was further washed with 50 ml of brine twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexane/ethyl acetate) was conducted to afford the guanidine amic-acid ester product (yellowish oil, 81.9 mg, 24%). No GCDI was detected.

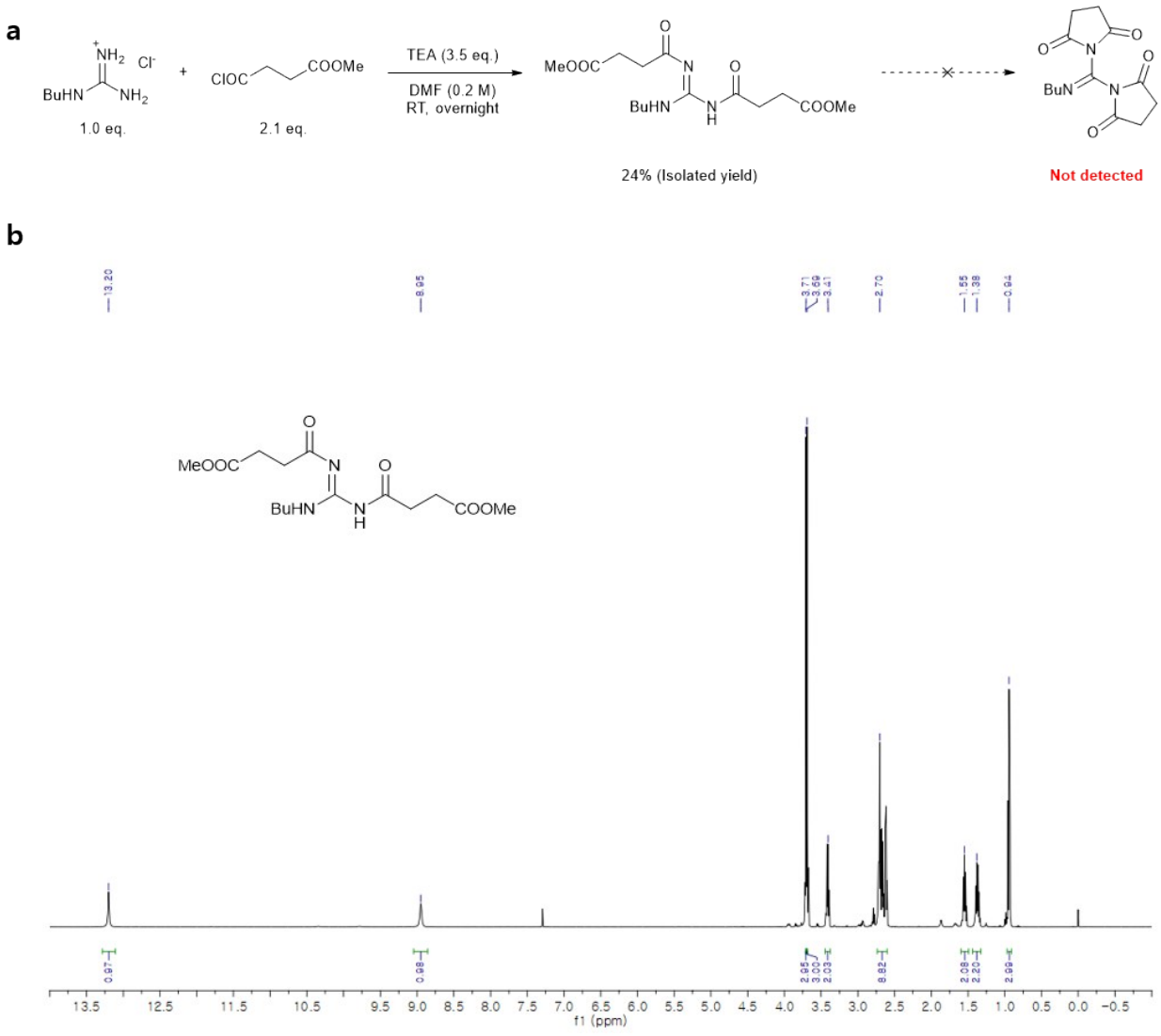


Figure S4. Reaction of butylguanidine hydrochloride with methyl-4-chloro-4-oxobutyrate. (a) Reaction scheme and (b) ^{1}H-NMR spectrum of the guanidine amic-acid ester product. The NMR spectrum was recorded on Varian NMR System 500 MHz ($CDCl_3$).

6. Degradation Studies of Compounds 3aa, 3ab and 3ac

Degradation of each compound was measured by ^{1}H-NMR spectroscopy. Each compound was dissolved in deuterated solvents ($CDCl_3$, DMSO-d_6, D_2O, CD_3OD, and 250 mM pD 3.1, 5.5, 7.5, and 9.6 deuterated phosphate buffer) at the concentration of about 5 mg/ml. The solution was incubated at 37 °C and at several time points, ^{1}H-NMR spectra were recorded on Bruker Avance DPX-300 (300 MHz) or Varian NMR System 500 MHz (500 MHz) spectrometer.

A. Degradation of **3aa** in $CDCl_3$, DMSO-d_6, and D_2O

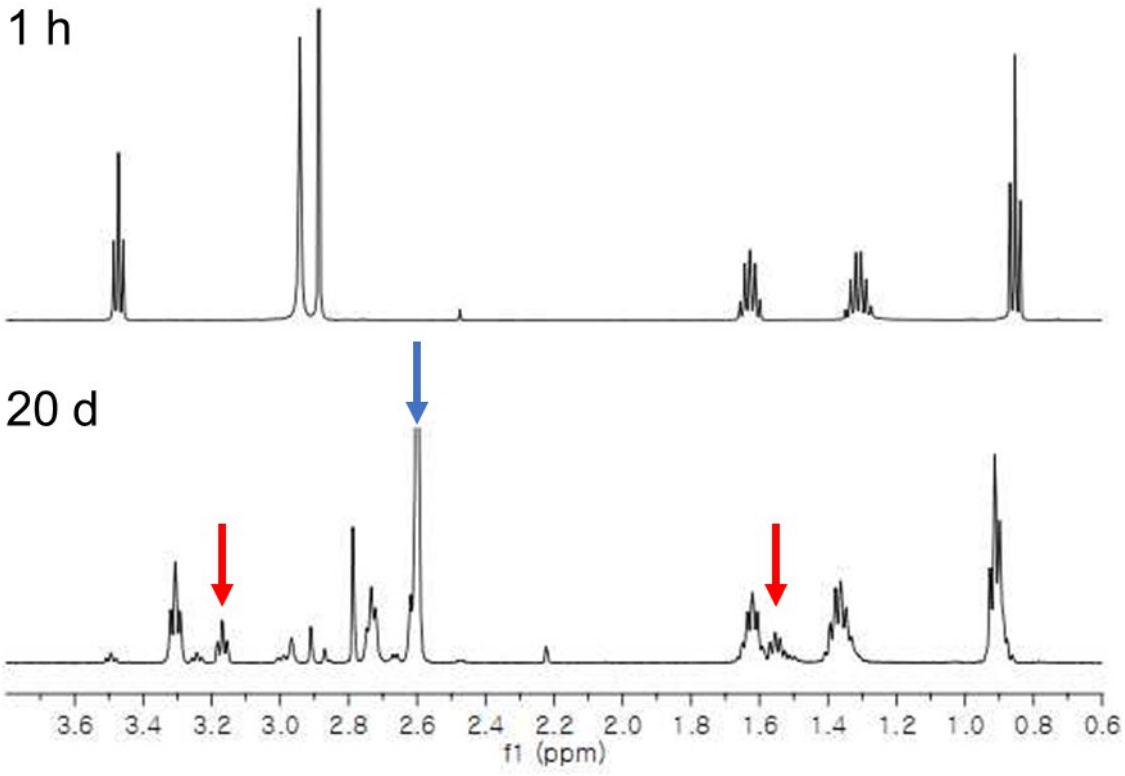


Figure S5. 3aa was incubated in D_2O (5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Varian NMR System 500 MHz. After incubation for 20 days, release of butylguanidine (red arrow) and succinic acid (blue arrow) was observed.

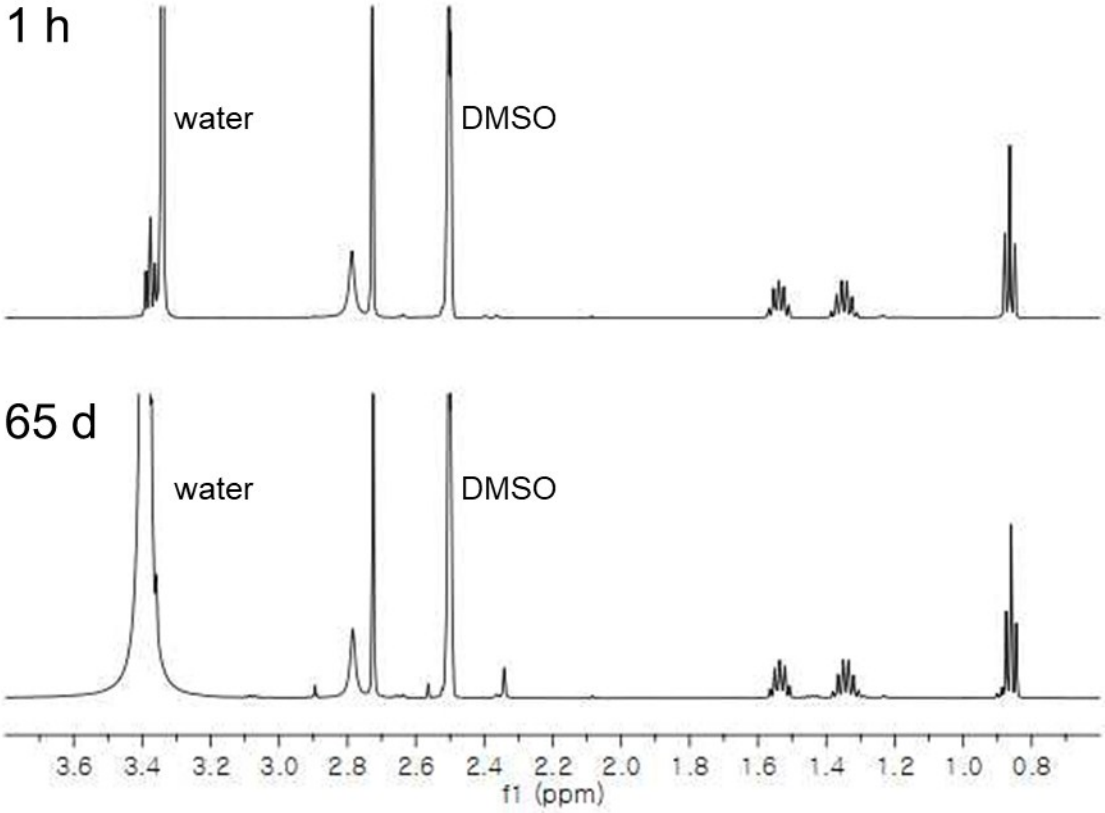


Figure S6. 3aa was incubated in DMSO-d_6 (5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Varian NMR System 500 MHz. No significant change was observed for 65 days.

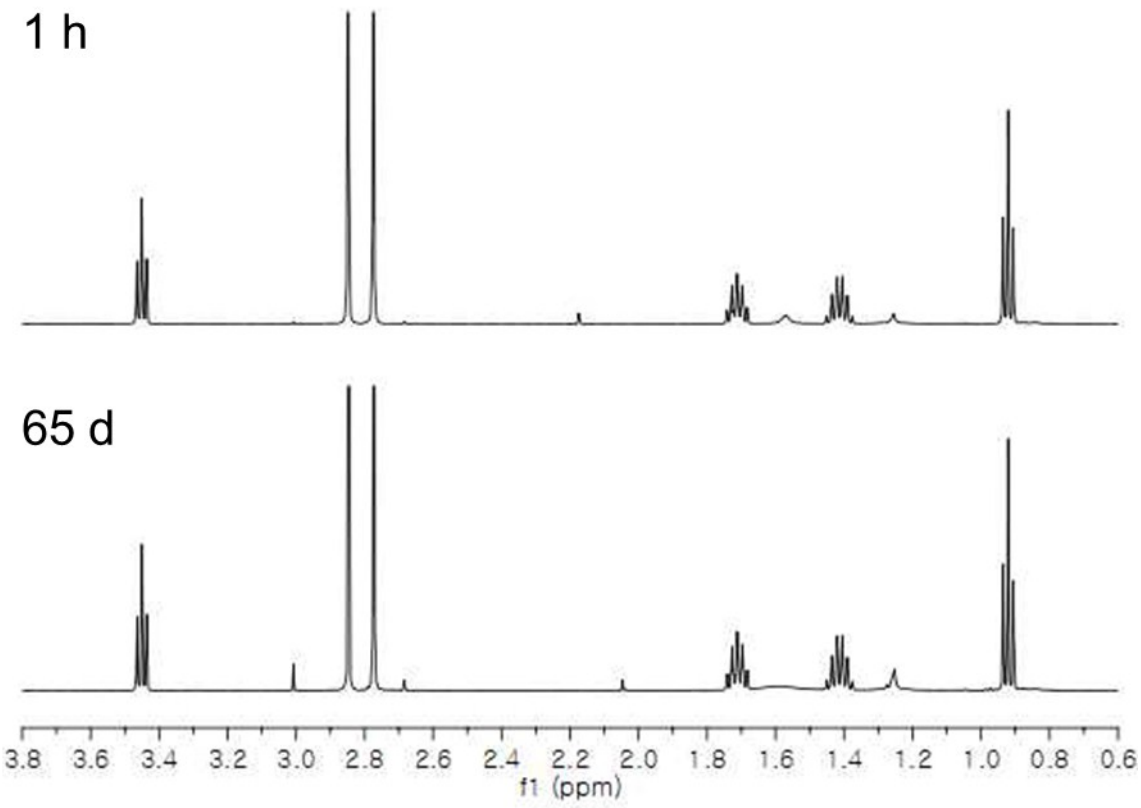


Figure S7. 3aa was incubated in $CDCl_3$ (5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Varian NMR System 500 MHz. No significant change was observed for 65 days.

B. Degradation of **3aa** under Various pH Conditions

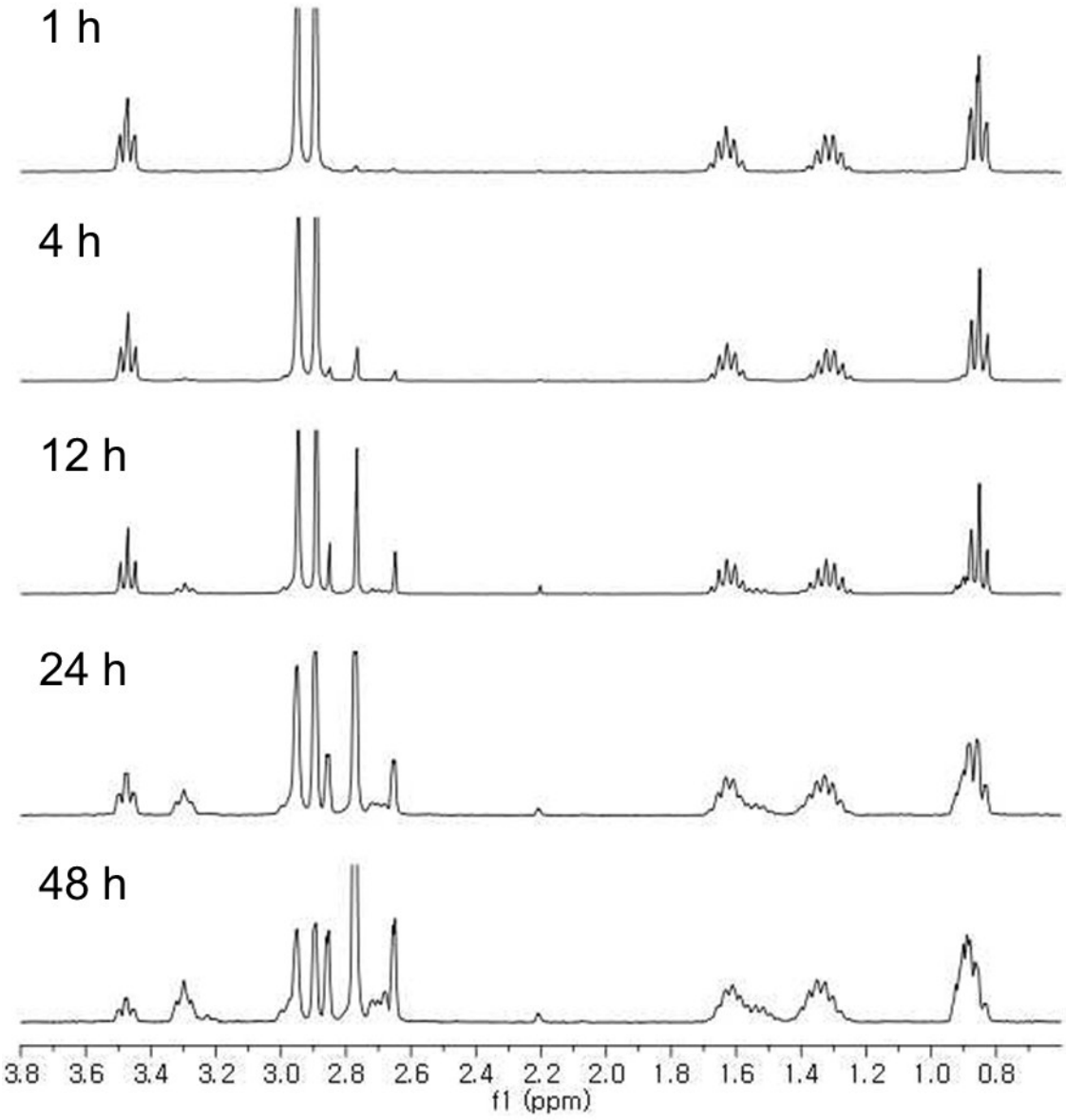


Figure S8. 3aa was incubated in 250 mM deuterated phosphate buffer (pD 3.1, 5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Bruker Avance DPX-300.

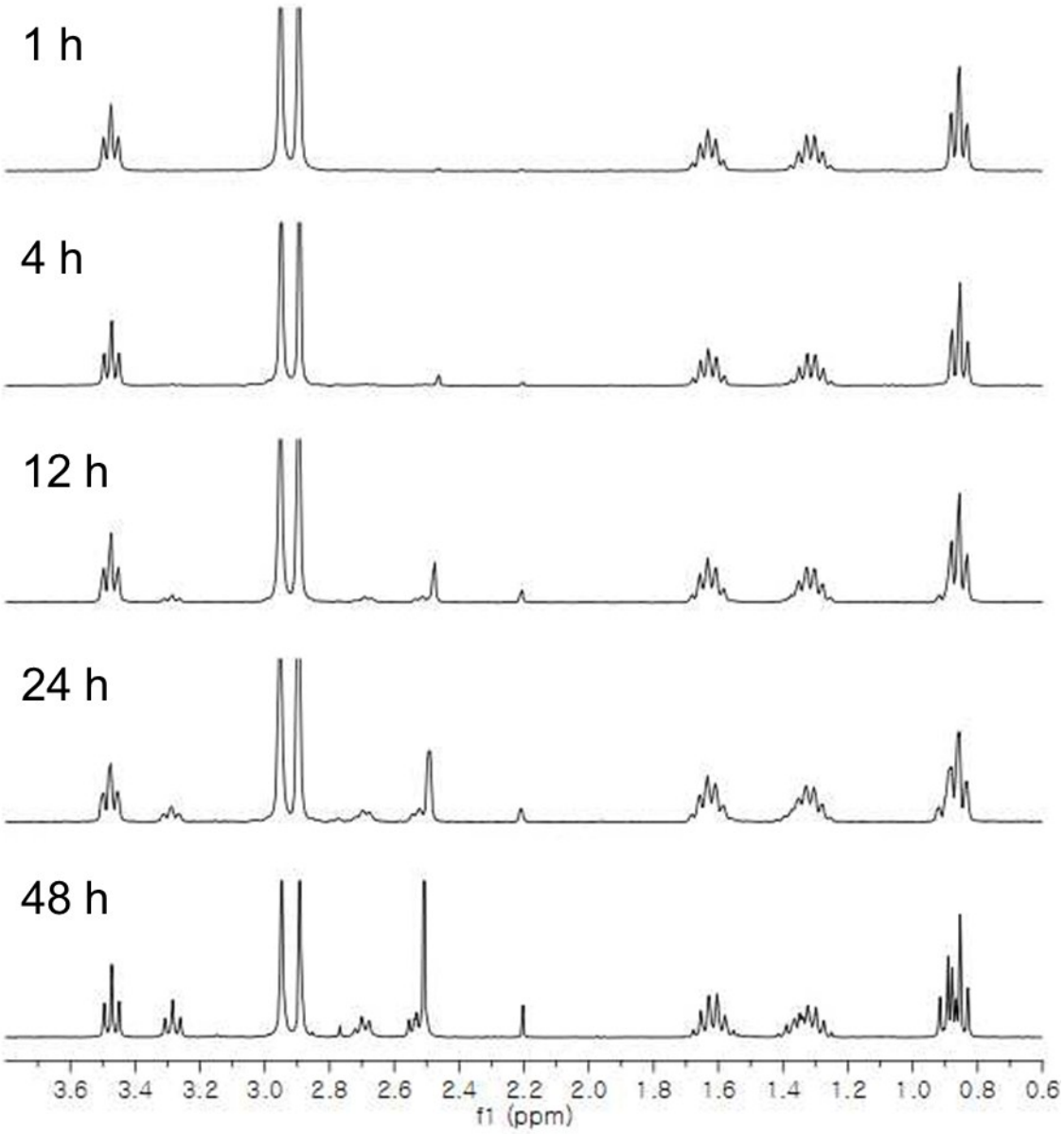


Figure S9. 3aa was incubated in 250 mM deuterated phosphate buffer (pD 5.5, 5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Bruker Avance DPX-300.

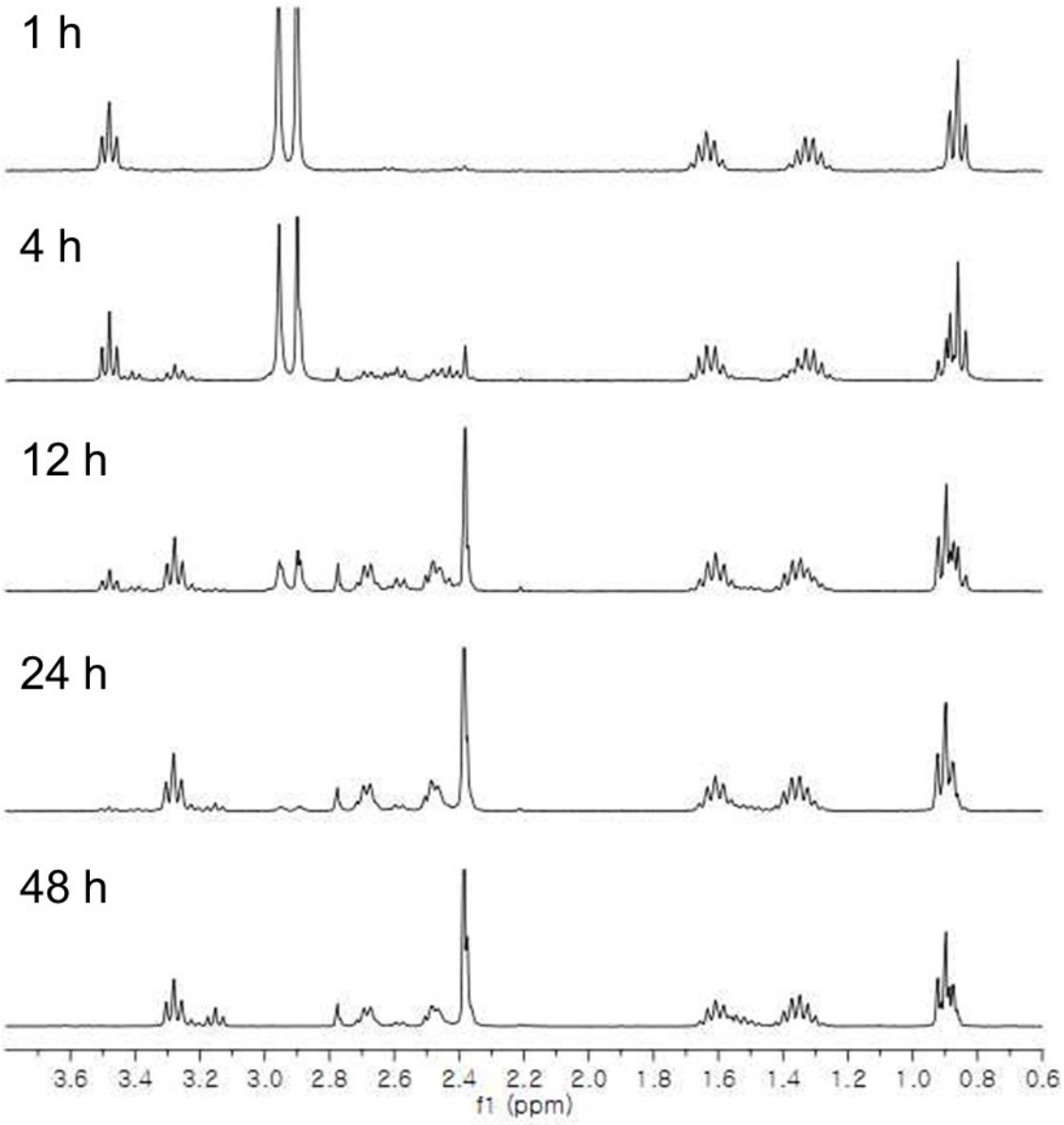


Figure S10. 3aa was incubated in 250 mM deuterated phosphate buffer (pD 7.5, 5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Bruker Avance DPX-300.

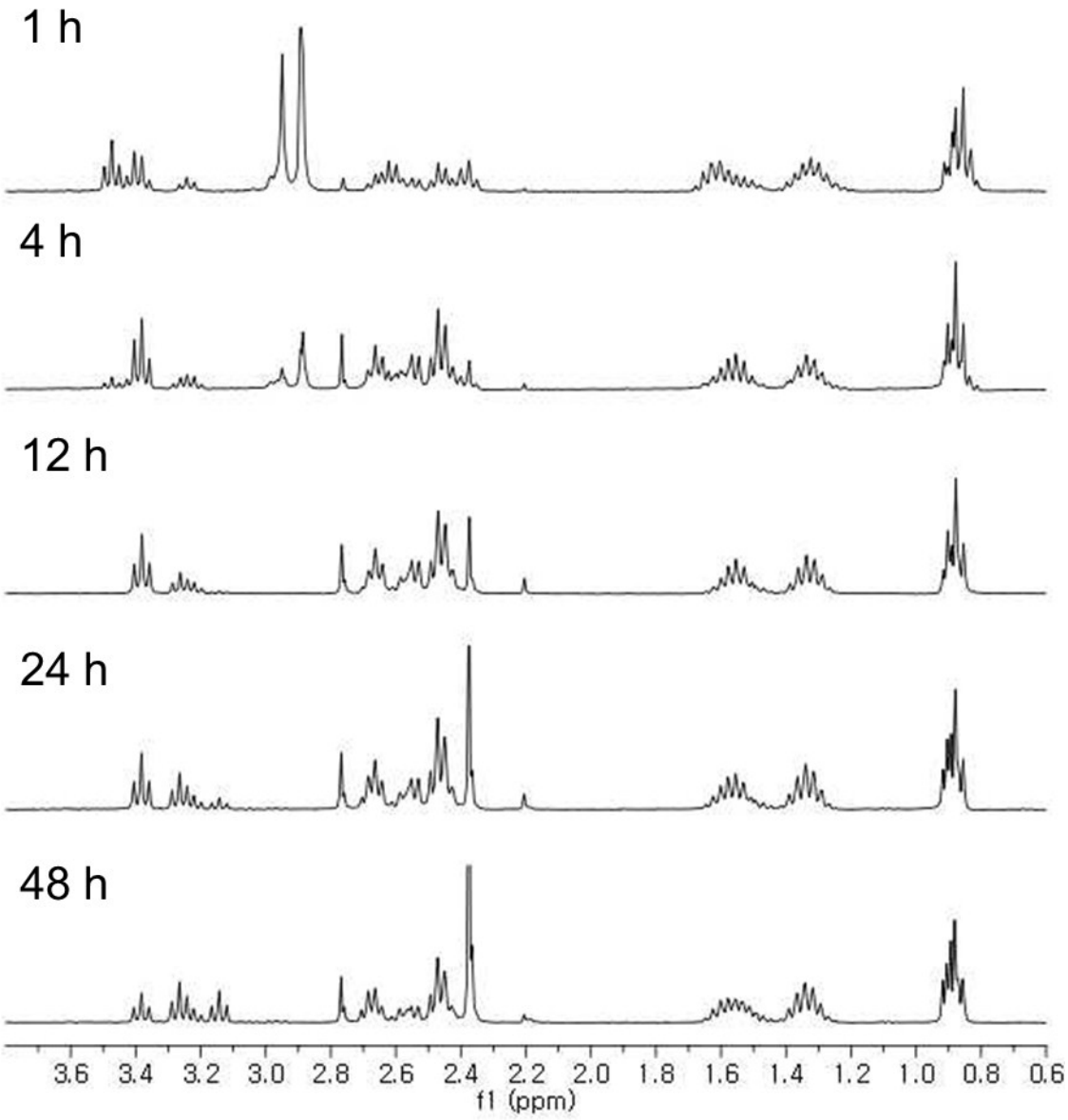


Figure S11. 3aa was incubated in 250 mM deuterated phosphate buffer (pD 9.6, 5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Bruker Avance DPX-300.

C. Degradation of **3ab** and **3ac** in CD_3OD

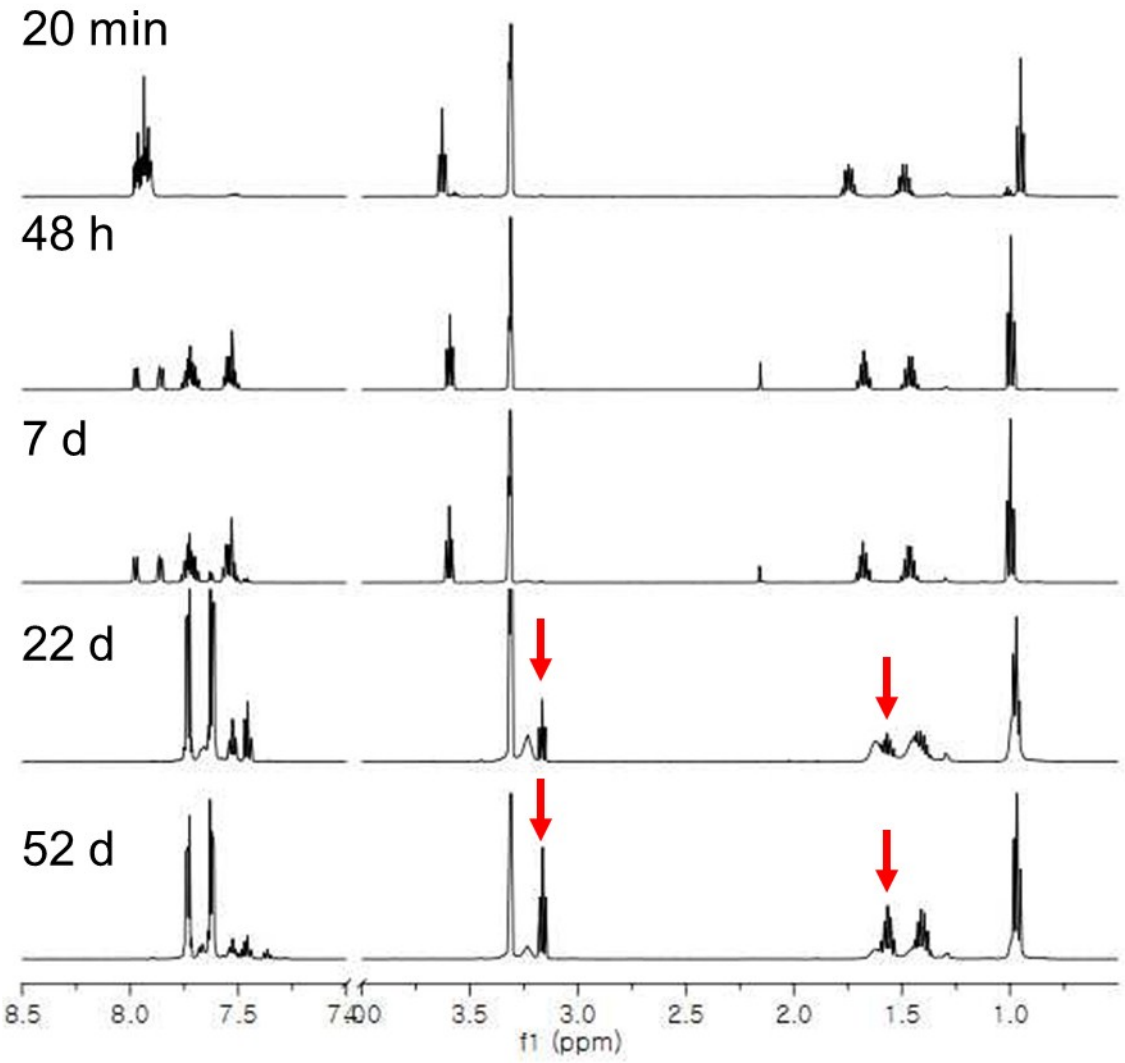


Figure S12. 3ab was incubated in CD_3OD (5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Varian NMR System 500 MHz. **3ab** was decomposed to the corresponding guanidine-amic acid within 48 h. The resulting guanidine-amic acid was stable in CD_3OD for several days. The release of butylguanidine (red arrow) was observed after further incubation.

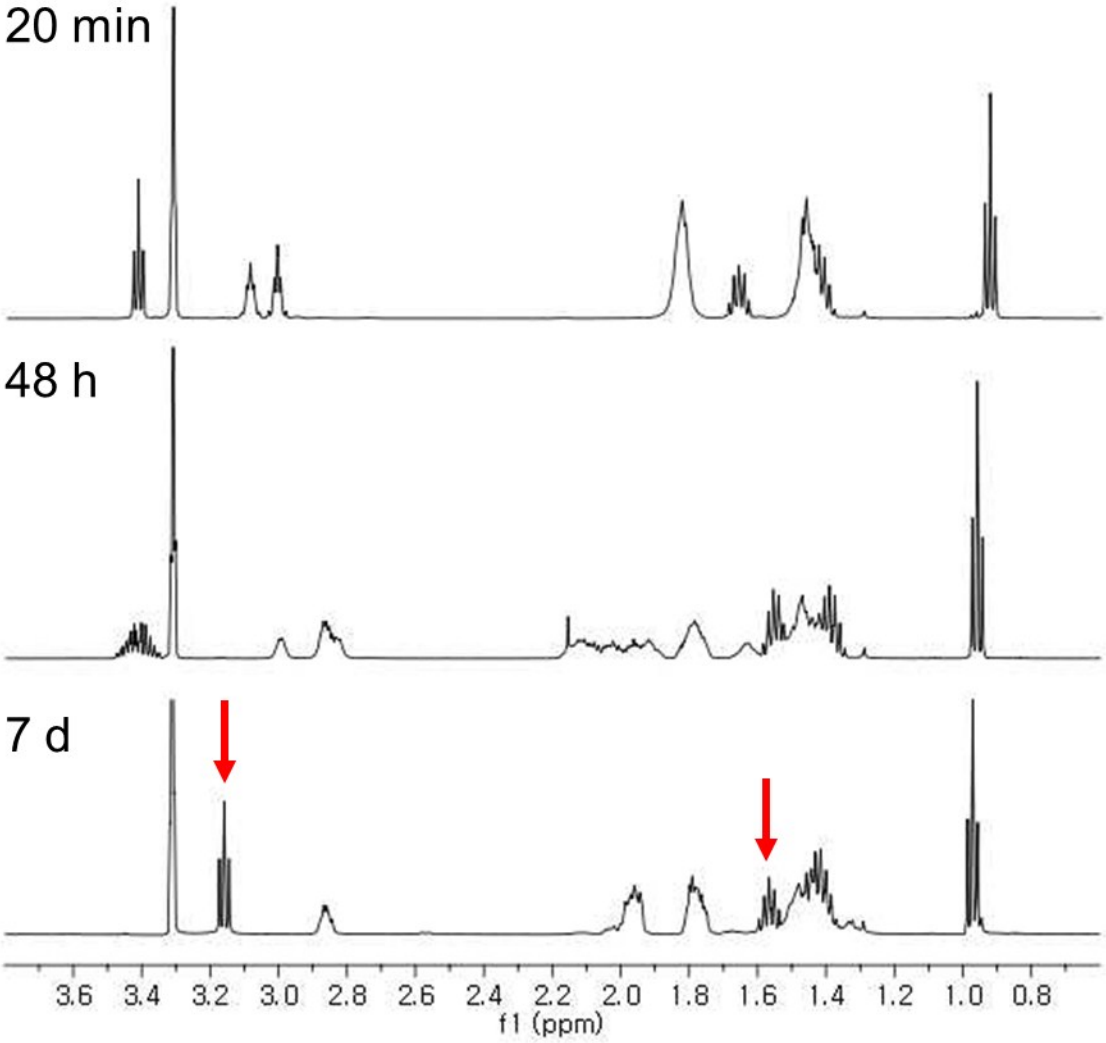


Figure S13. 3ac was incubated in CD_3OD (5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Varian NMR System 500 MHz. Similar to **3ab**, **3ac** seems to be decomposed to yield corresponding guanidine-amic acid within 48 h. After incubation for 7 days, **3ac** completely degraded into butylguanidine (red arrow).

D. Degradation of *N*-methylsuccinimide in CD_3OD

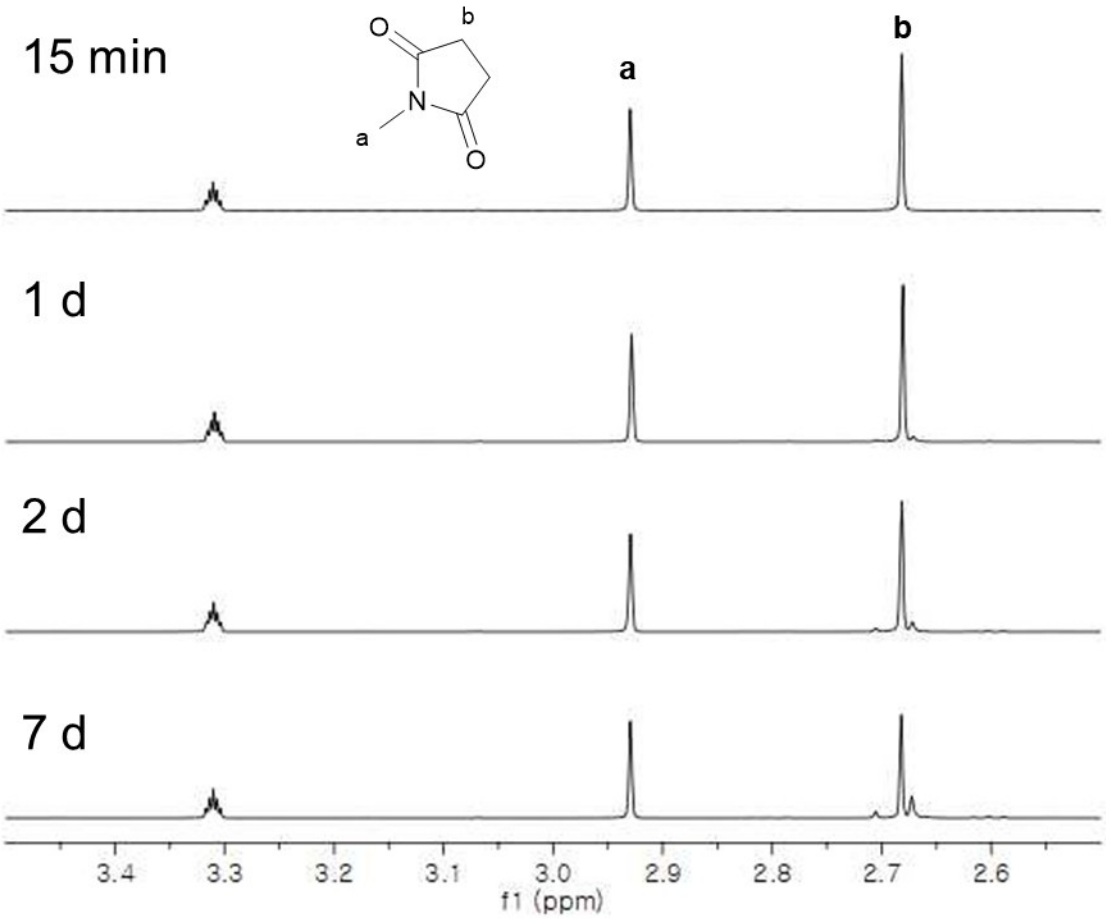


Figure S14. *N*-methylsuccinimide was incubated in CD_3OD (5 mg/ml, 37 °C) and ^{1}H-NMR spectra were recorded on Varian NMR System 500 MHz. After incubation for 2 days, only 11% of the compound was decomposed. After 7-day incubation, 31% was decomposed. The decomposed ratio was calculated from the ratio of integration values of peak a and b.

E. Degradation of **3ab** in Presence of Benzylamine and Benzylmercaptan

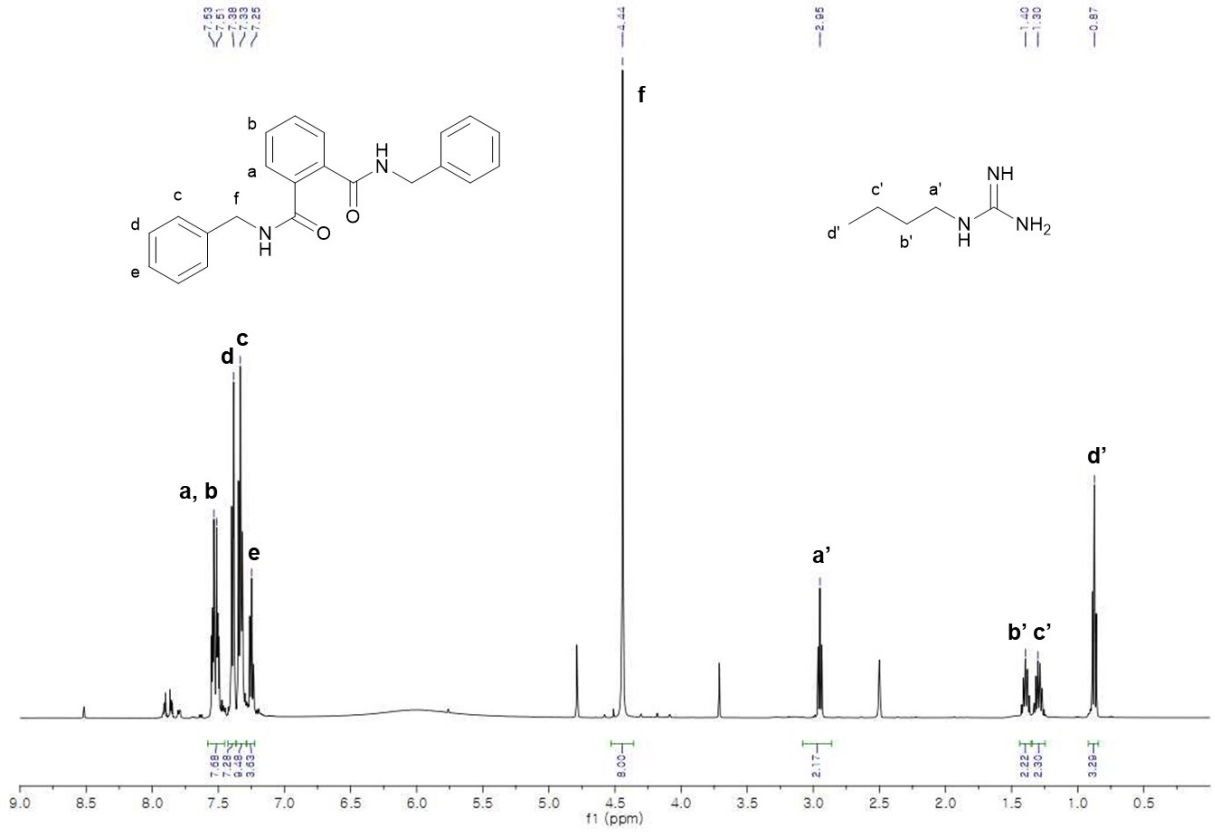


Figure S15. 3ab was incubated in DMSO-d_6 (0.1 M) in presence of 4 equiv. of benzylamine at ambient temperature for 2 h, then ^{1}H-NMR spectrum was recorded on Varian NMR System 500 MHz. **3ab** was almost completely decomposed into butylguanidine and *N*,*N'*-dibenzylphthalamide.

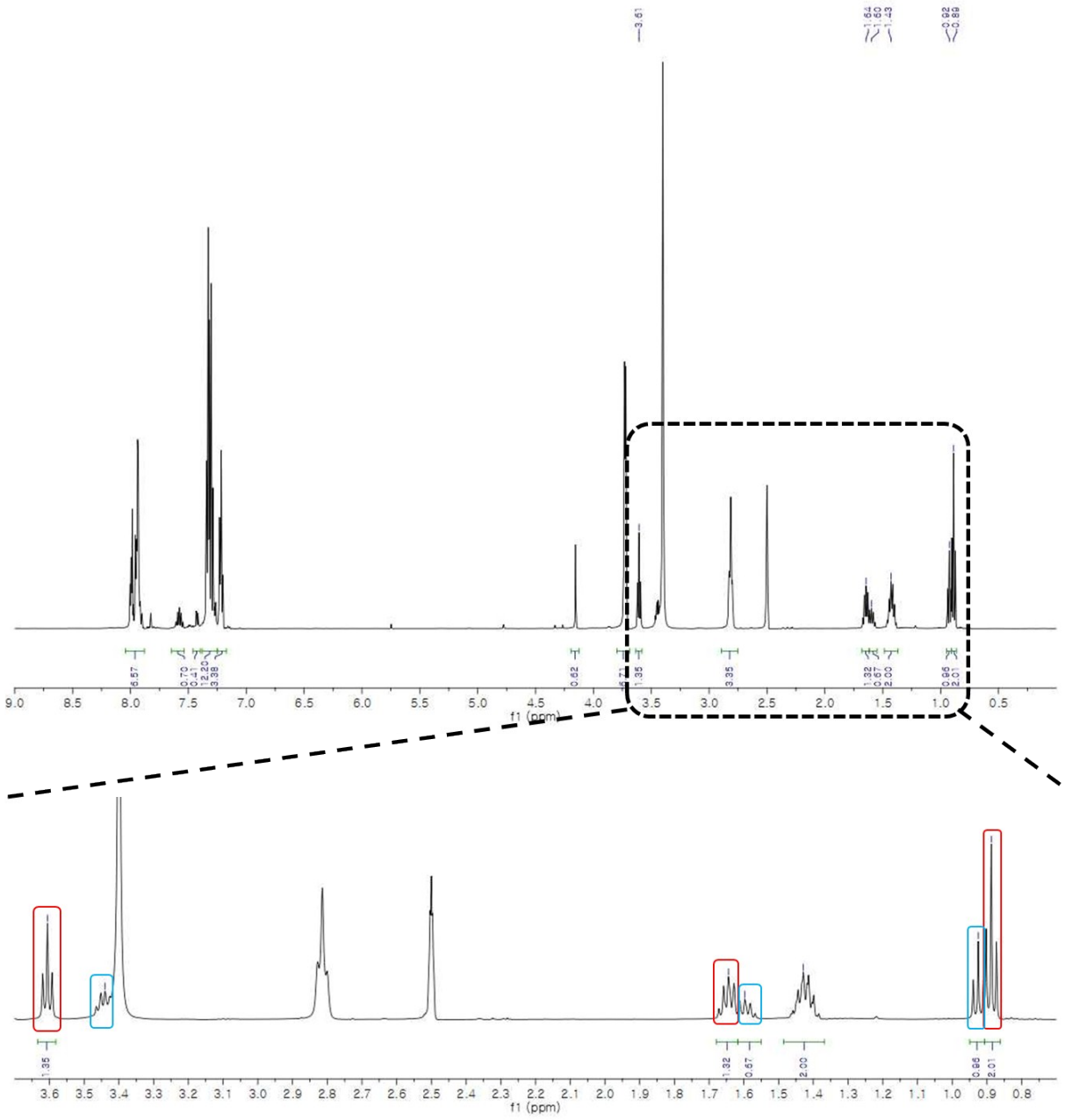


Figure S16. 3ab was incubated in DMSO-d_6 (0.1 M) in presence of 4 equiv. of benzylmercaptan at ambient temperature for 2 h, then ^{1}H-NMR spectrum was recorded on Varian NMR System 500 MHz. 33% of **3ab** was decomposed, but release of butylguanidine was not observed. The decomposed ratio was calculated from the integration values of peaks from **3ab** (indicated in red) and newly observed peaks (indicated in blue).

F. Proposed Mechanism for GCDI Degradation in Aqueous Conditions

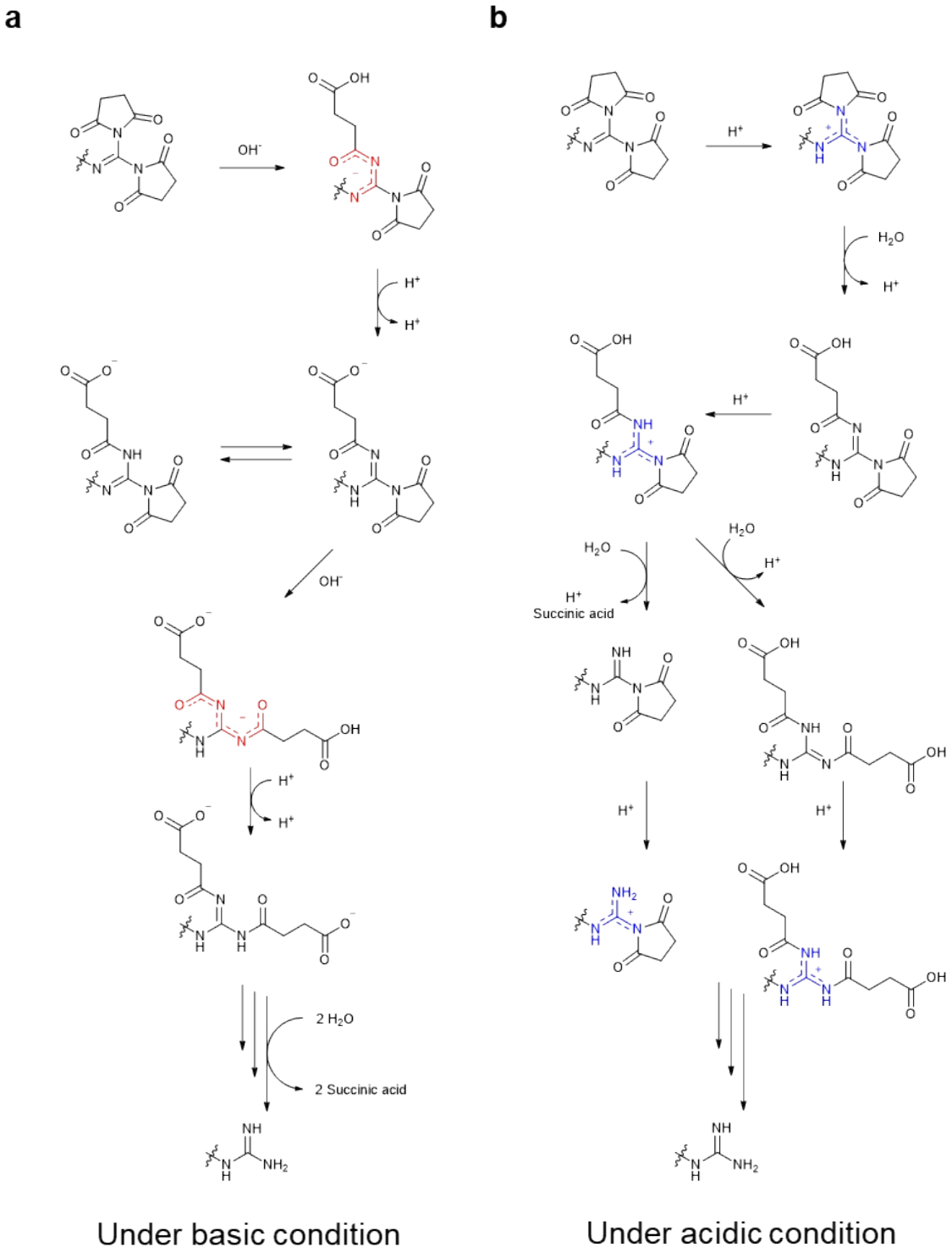


Figure S17. Proposed mechanisms for GCDI degradation under aqueous conditions. (a) basic and (b) acidic conditions. Resonance-stabilized intermediates are indicated in red and blue, respectively.

- Mechanistic Studies for the GCDI Degradation by ESI/MS Experiments

The model GCDI **3aa** was dissolved in 100 mM pH 2.9 ammonium formate buffer or 100 mM pH 7.4 ammonium bicarbonate buffer at the concentration of about 5 mg/ml. The solution was incubated at 37 °C for the indicated time. An aliquot was taken and diluted with H_2O/ACN (v/v 1:1). The sample was analyzed by ESI/MS-(+) to detect possible reaction intermediates.

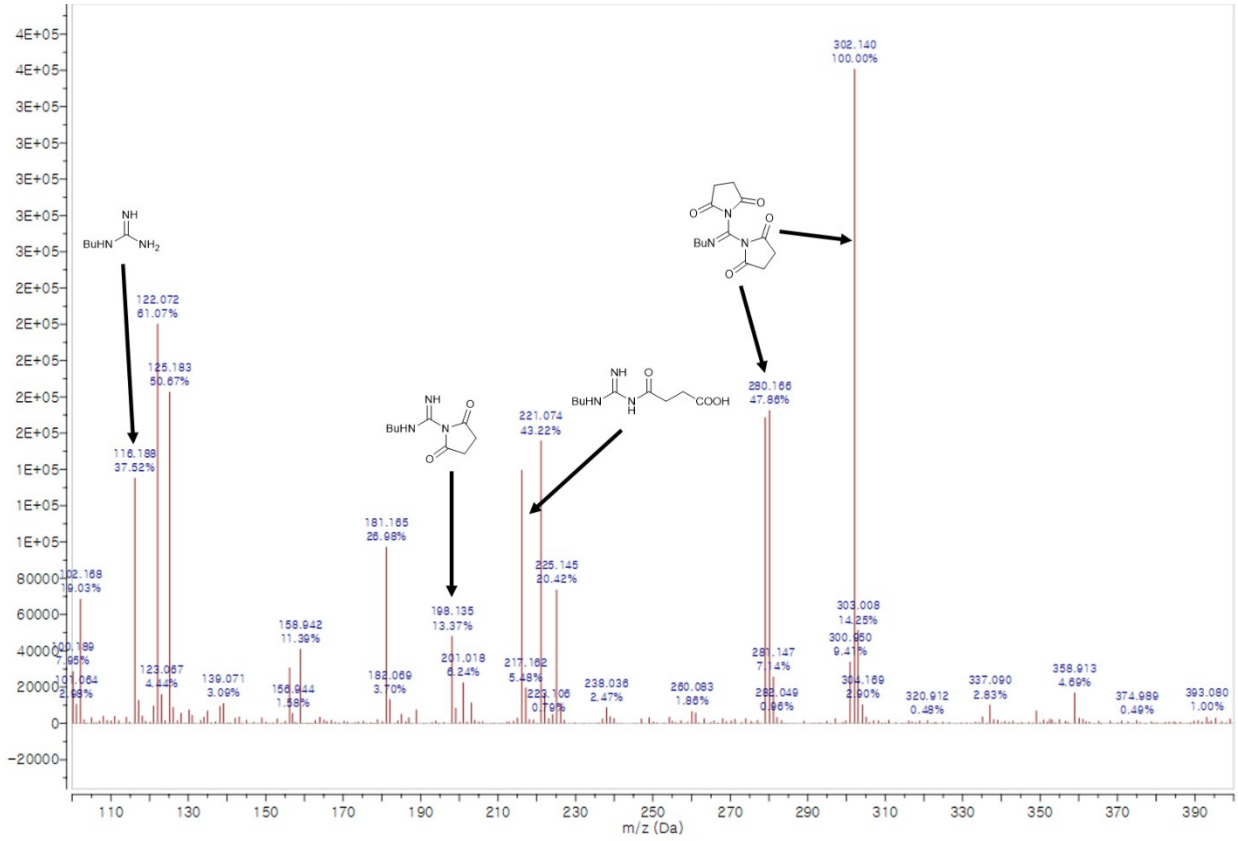


Figure S18. ESI/MS-(+) spectrum for the degradation of **3aa** at pH 2.9. The spectrum was recorded after 48 h incubation.

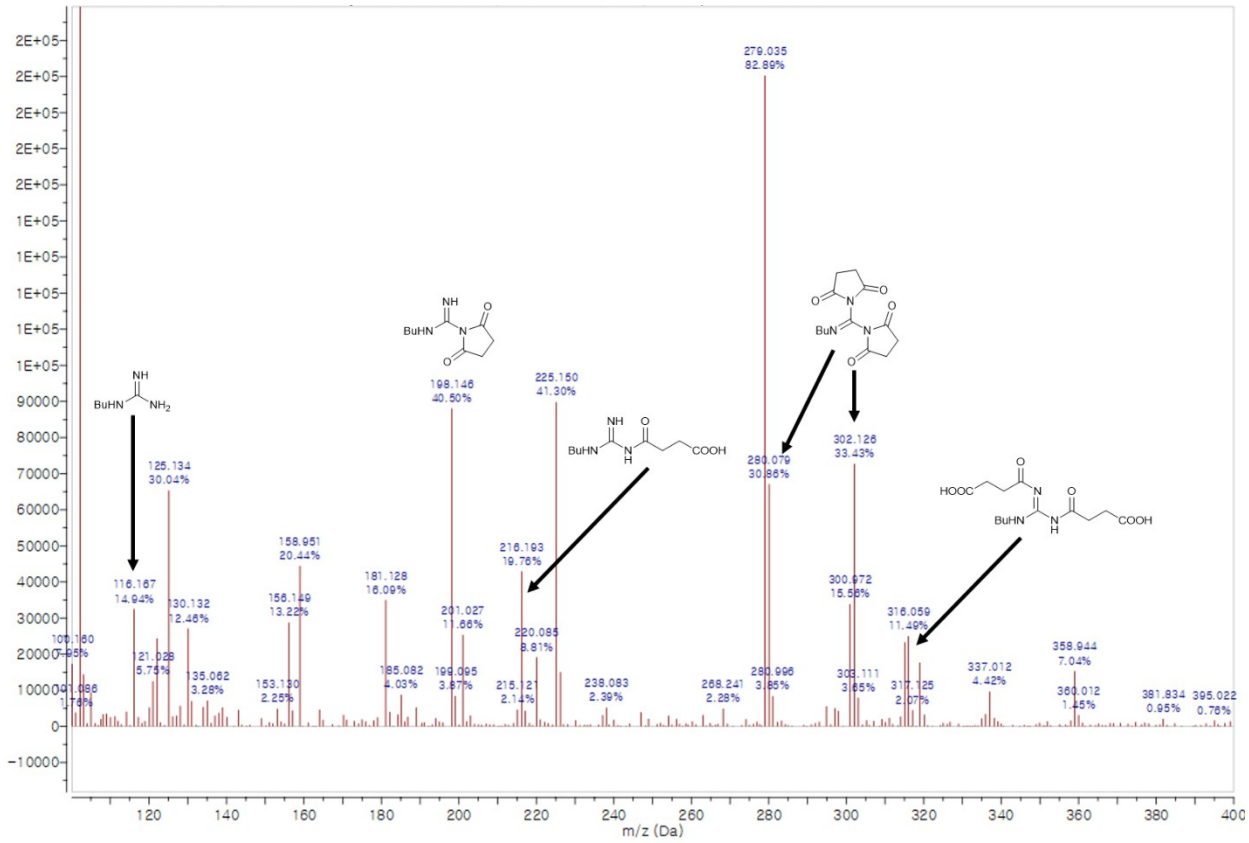


Figure S19. ESI/MS-(+) spectrum for the degradation of **3aa** at pH 7.4. The spectrum was recorded after 1.5 h incubation.

7. Degradation Studies of Poly(GCDI) 5aa

Degradation of poly(GCDI) **5aa** was traced by GPC. 10 mg of **5aa** (Initial M_n = 1,700 and M_w = 3,000) was dissolved in 2 ml of chloroform, chloroform/methanol/triethylamine (v/v/v = 1/0.95/0.05), or chloroform/methanol/acetic acid (v/v/v = 1/0.95/0.05). The reaction mixture was smoothly shaken at 37 °C. At each time point, 200 µl of the reaction mixture was taken and the solvent was removed *in vacuo*. The residual was redissolved in 200 µl of chloroform, filtered through a 0.20 µm PTFE filter and injected into the GPC. Gel permeation chromatography (GPC) was performed on Young Lin YL9100 GPC System equipped with Shodex K-803 column. Chloroform was used as the mobile phase at a flow rate of 0.7 ml/min. The column was maintained at 50 °C.

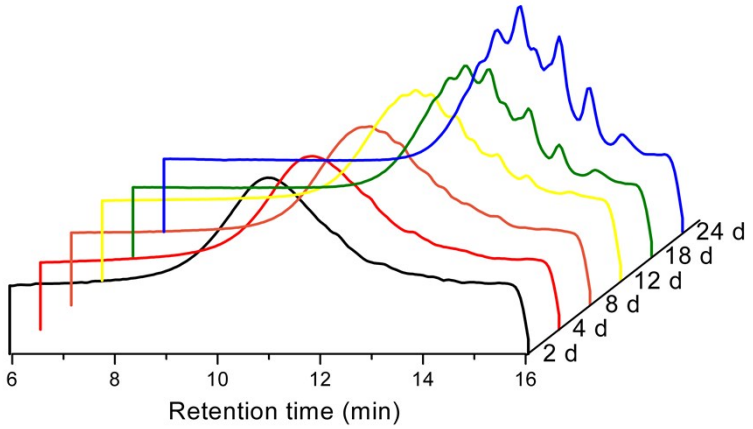


Figure S20. 5aa was incubated in chloroform/methanol/acetic acid (v/v/v = 1/0.95/0.05) at 37 °C. After 2, 4, 8, 12, 18 and 24 d incubation, GPC traces were recorded.

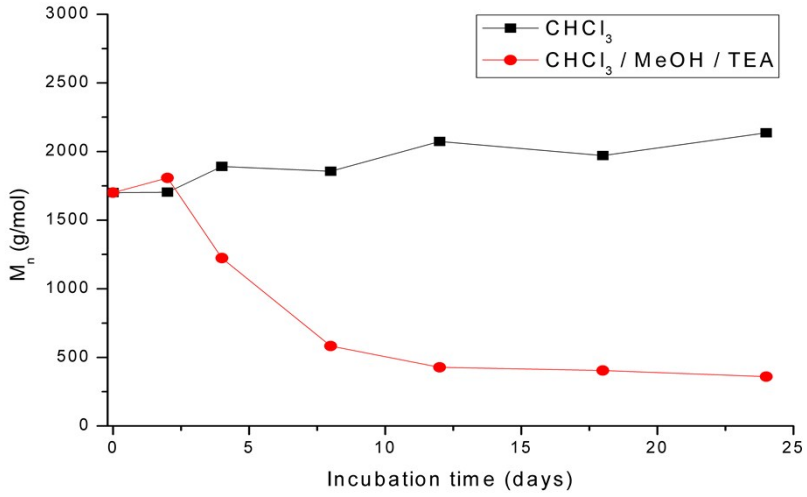


Figure S21. Decrease in the number-average molecular weight of **5aa** in GPC chromatogram (Fig. 2) during incubation.

8. Single Crystal X-Ray Diffraction (SC-XRD)

- Crystallization of compound **3aa**

33.3 mg of **3aa** was dissolved in 0.5 ml of DCM. 2 ml of hexane was added and turbidity was observed. The mixture was vortexed and filtered. The resulting filtrate was incubated at ambient temperature. After 4 h-incubation, crystal formation was observed and the vessel was sealed.

- X-ray Crystallographic Analysis

All data were collected on a Bruker SMART APEX II ULTRA diffractometer equipped with multilayer monochromated Mo Kα radiation (λ = 0.710 73 Å) generated by a rotating anode. The cell parameters for the compounds were obtained from a least-squares refinement of the spot (from 36 collected frames). Data collection, data reduction, and multi-scan absorption correction were carried out using the software package APEX2[1]. All of the calculations for the structure determination were carried out using the SHELXTL package[2].

CCDC 1845126 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Table S4. Crystal Structure and Structure Refinement for compound **3aa**

Empirical formula	$C_{13}\ H_{17}\ N_3\ O_4$	
Formula weight	279.29	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.69440(10) Å	α= 90°.
	b = 8.73060(10) Å	β= 94.1674(8)°.
	c = 16.4787(2) Å	γ = 90°.
Volume	1391.04(3) $Å^3$	
Z	4	
Density (calculated)	1.334 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	592	
Crystal size	0.309 x 0.215 x 0.140 mm^3	
Theta range for data collection	2.365 to 28.297°.	
Index ranges	-12<=h<=11, -10<=k<=11, -21<=l<=21	
Reflections collected	13751	
Independent reflections	3451 [R(int) = 0.1023]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.7011	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3451 / 0 / 181	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.1386	
R indices (all data)	R1 = 0.0650, wR2 = 0.1472	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.240 and -0.362 $e.Å^{-3}$	

9. DFT Analysis

The density functional theory (DFT) calculations at unrestricted B3LYP/6-31G(d,p) level was carried out using the quantum chemical package Gaussian 09W[3]. The geometry of **3aa** was fully optimized in the gas phase and the empirical-dispersion correction was used during optimization.

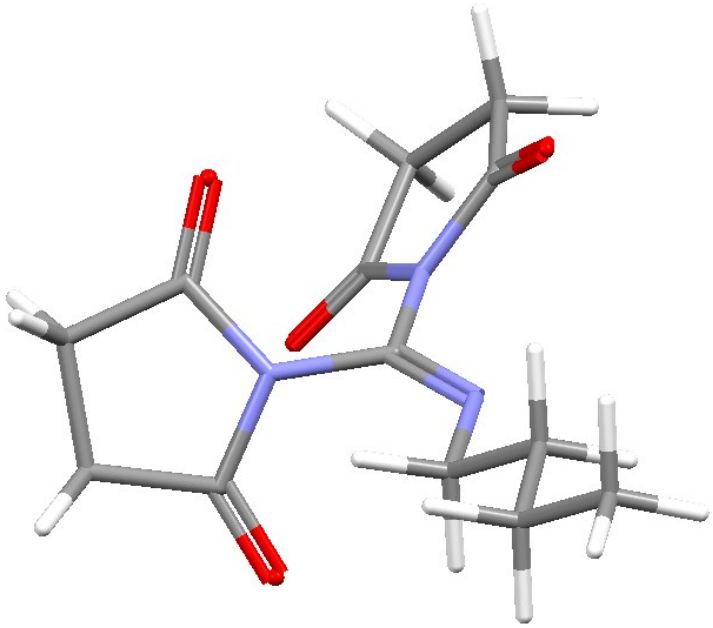


Figure S22. DFT-optimized molecular structure of **3aa**

Table S5. The optimized atomic coordinates of **3aa** in gas phase at uB3LYP with the 6-31G(d,p) basis set.

Atom	X	Y	Z
C	4.741723	-0.01996	-0.04429
H	4.620233	0.770139	-0.79821
H	4.983087	0.493056	0.896801
C	3.420776	-0.77897	0.116532
H	3.525681	-1.56648	0.872454
H	3.161016	-1.28552	-0.82155
C	2.265745	0.14095	0.520557
H	2.477311	0.621402	1.482939
H	2.150316	0.951668	-0.21478

C	5.903188	-0.93427	-0.44405
H	5.69824	-1.43679	-1.396
H	6.836382	-0.37279	-0.55566
H	6.068317	-1.71204	0.309921
C	-0.06939	-0.21148	0.310397
N	1.051541	-0.63855	0.685364
C	-0.17797	2.24981	0.620111
C	-1.48719	2.827376	-1.34961
C	-0.90457	3.404739	-0.05362
H	-1.01298	3.226056	-2.25158
H	-2.56436	2.973254	-1.45665
H	-0.20708	4.232644	-0.20144
H	-1.67726	3.74592	0.641022
C	-2.47443	-0.64898	0.765238
C	-2.60546	-2.92952	-0.06985
C	-3.44863	-1.78922	0.512852
H	-2.95215	-3.28466	-1.04273
H	-2.54112	-3.79927	0.59072
H	-4.21119	-1.42317	-0.18057
H	-3.95321	-2.03695	1.45004
N	-1.20293	-1.06609	0.346383
N	-0.37723	1.097628	-0.17539
C	-1.20184	-2.36031	-0.23983
C	-1.2106	1.332841	-1.28637
O	-0.25857	-2.88406	-0.77196
O	-2.73091	0.442895	1.228253
O	-1.61175	0.475121	-2.03989
O	0.450089	2.272862	1.65013

10. References

(1) *APEX2*, version 2009.1; Data collection and Processing software; Bruker AXS Inc.: Madison, WI, 2008.

(2) *SHELXTL-PC*, version 6.14; Program for solution and refinement of crystal structure; Bruker AXS Inc.: Madison, WI, 2001.

(3) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A., Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.