Electronic Supplementary Information

Biomimetic folding of small organic molecules driven by multiple non-covalent interactions†

Tangxin Xiao,[‡*a] Lixiang Xu,[‡a] Jie Wang,[a] Zheng-Yi Li,[a] Xiao-Qiang Sun,[*a] Leyong Wang,[*a,b]

[a]*Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology, School of Petrochemical Engineering, Changzhou University, Changzhou, 213164, China. E-mail: xiaotangxin@cczu.edu.cn, xqsun@cczu.edu.cn*

[b]*School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210023, China. E-mail: lywang@nju.edu.cn*

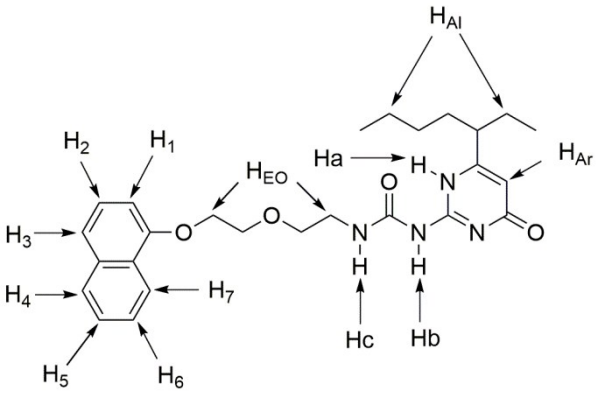
‡These authors contributed equally to this work.

Table of contents

1. Materials and methods

All reactions were carried out under normal pressure unless noted. The commercially available reagents and solvents were either employed as purchased or dried according to procedures described in the literature. All yields were given as isolated yields. **N1**[S1], **L1**[S2] and **L2**[S3] were prepared according to literature procedure. NMR spectra were recorded on a Bruker AVANCE III 300 MHz or a Bruker AVANCE III 400 MHz spectrometer with internal standard tetramethylsilane (TMS) and solvent signals as internal references, where $CDCl_3$ was dried using neutral aluminum oxide. COSY experiments were performed on a Bruker AVANCE III 300 MHz spectrometer. NOESY experiments were performed on a Bruker AVANCE III 400 MHz spectrometer. DOSY experiments were performed on a Bruker AVANCE III 600 MHz spectrometer. Low-resolution electrospray ionization mass spectra (LR-ESI-MS) were obtained on LCMS2020. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on an Agilent Technologies 6540 UHD Accurate-Mass. Scanning electron microscopy (SEM) images were recorded on a JSM-6360LA. Single crystal X-ray data was measured on a Bruker SMART APEX II CCD diffractometer (Mo Kα radiation, λ = 0.71073 Å). Structure solutions and refinements were carried out using the SHELXTL-PC software package.[S4] Data collection and structure refinement details can be found in the CIF files.

2. ^{1}H -^{1}H COSY of M1



Scheme S1 Structure of **M1**

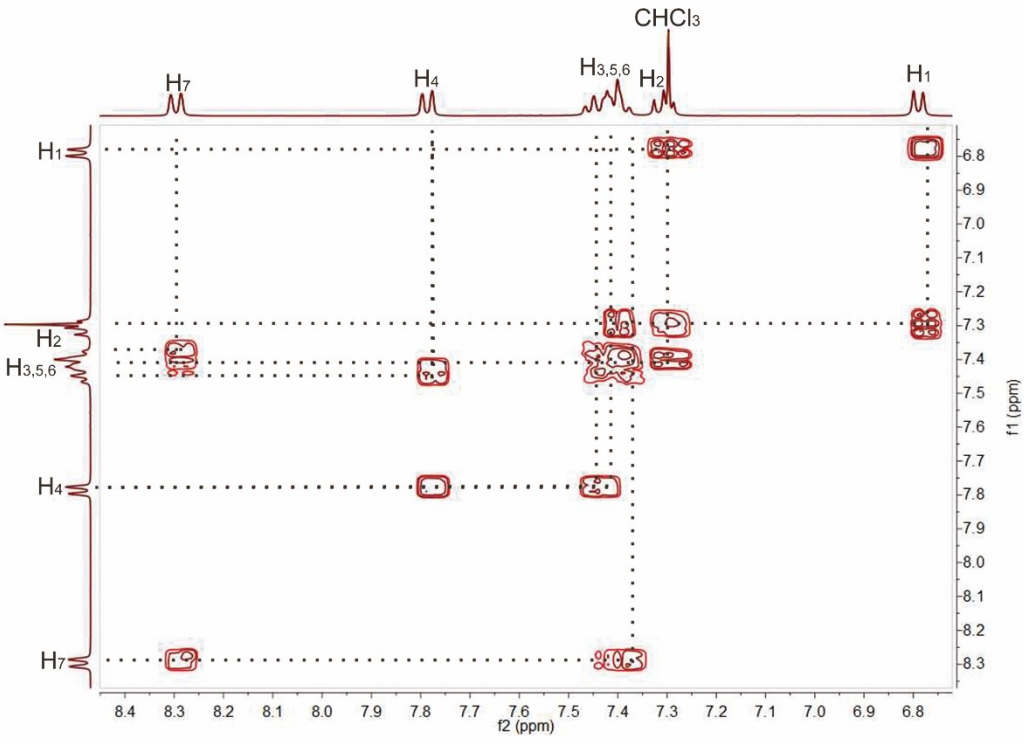


Figure. S1 ^{1}H-^{1}H COSY (300 MHz, $CDCl_3$, 298 K, 128 mM) of **M1**. Dashed line serves to guide the eye.

3. NOESY of M1

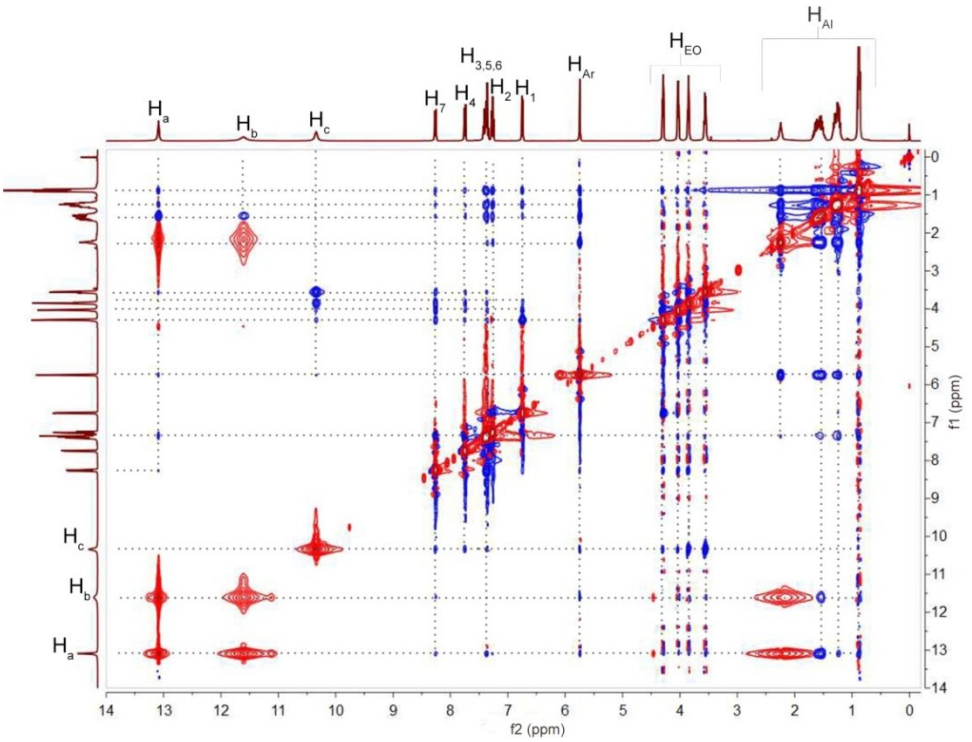


Figure. S2 NOESY NMR spectrum (400 MHz, $CDCl_3$, 298 K, 128 mM) of **M1**. Dashed line serves to guide the eye.

4. DOSY of M1

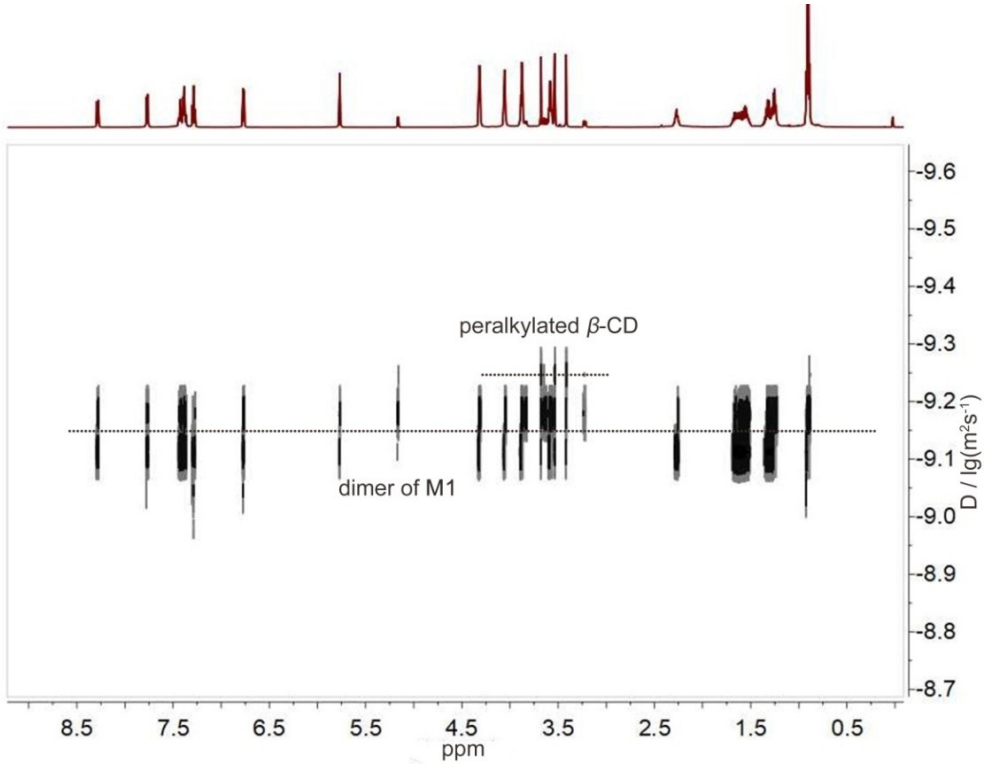


Figure. S3 DOSY spectra (600 MHz, $CDCl_3$, 298 K) of **M1** in 128 mM with the addition of peralkylated *β*-CD as internal standard.

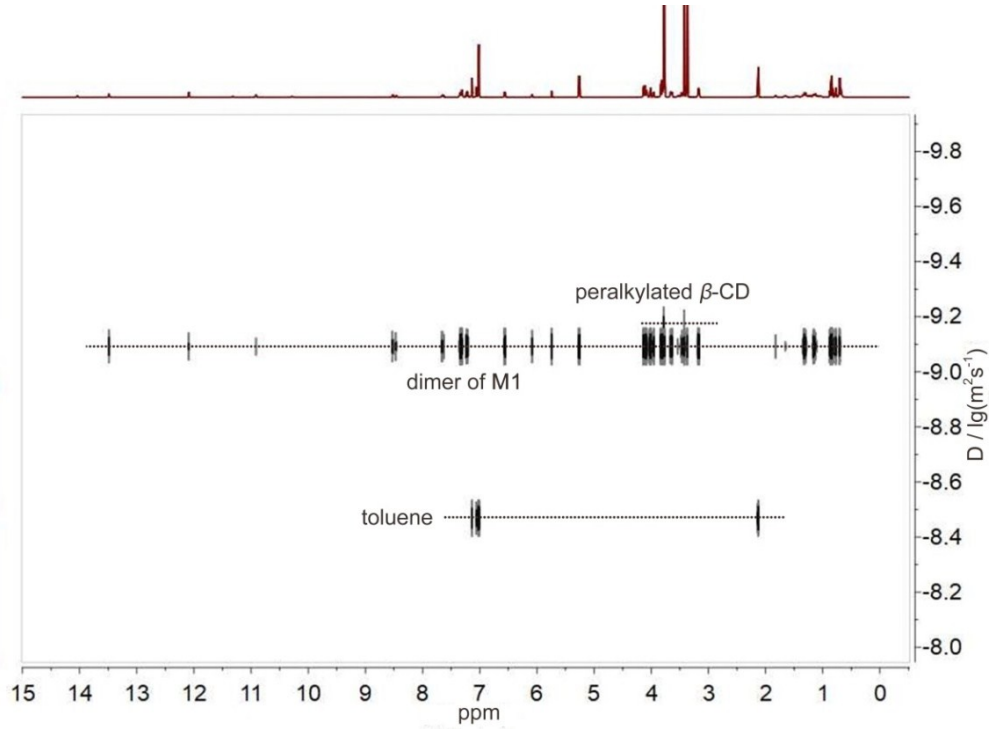


Figure. S4 DOSY spectra (600 MHz, toluene-d_8, 298 K) of **M1** in 16 mM with the addition of peralkylated *β*-CD as internal standard.

5. Concentration-dependent 1H NMR spectra of M1

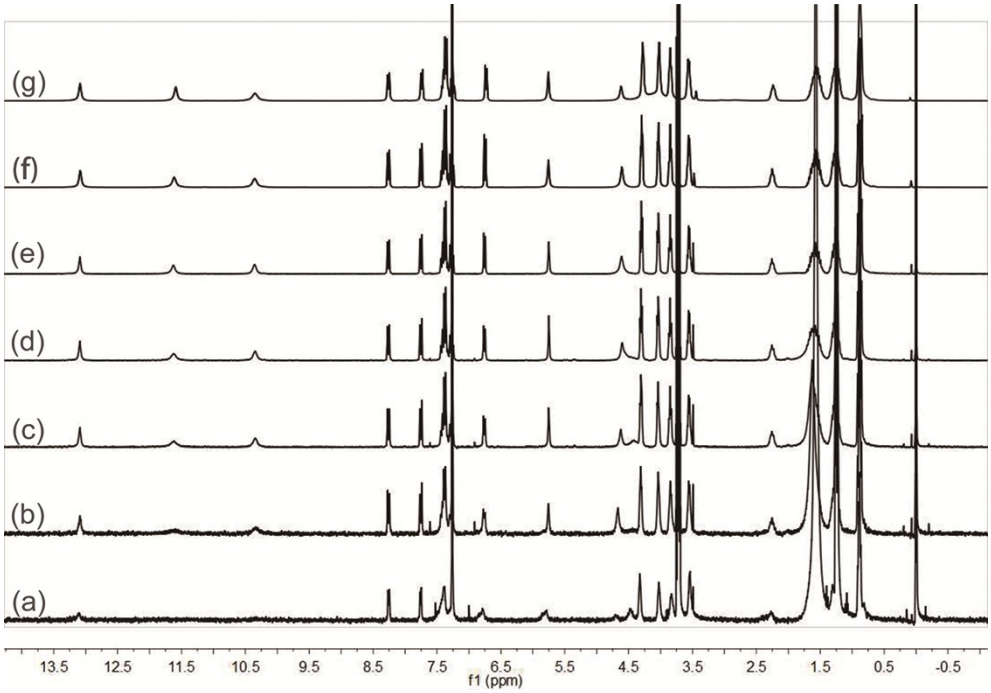


Figure. S5 ^{1}H NMR spectra (300 MHz, $CDCl_3$, 298 K) of **M1** at different monomer concerntration: (a) 2, (b) 4, (c) 8, (d) 16, (e) 32, (f) 128, and (g) 500 mM.

6. Crystallographic Data for M2

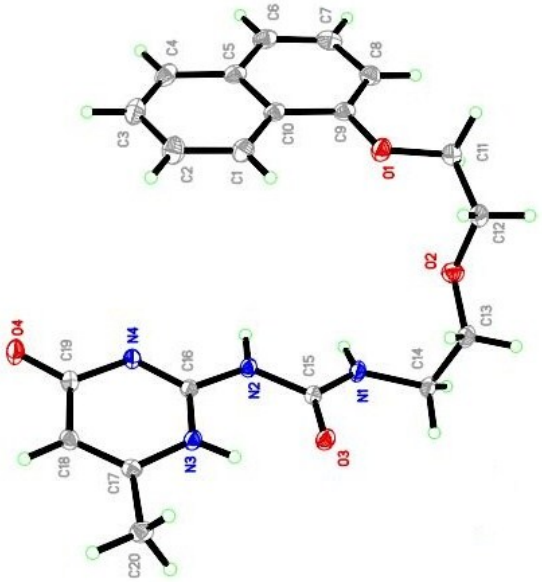
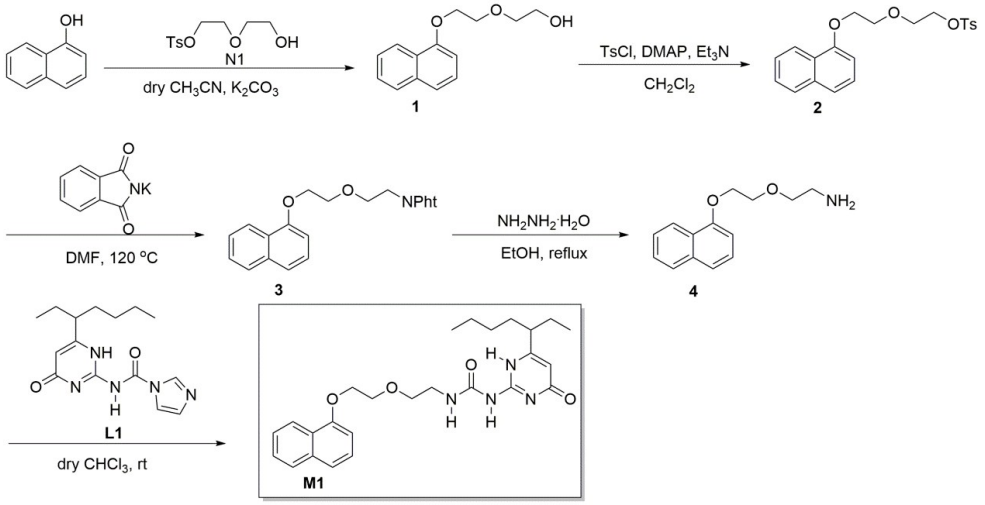


Figure. S6 ORTEP drawing of **M2**

Table S1 Crystal data and structure refinement parameter for **M2**

CCDC number	1847847
Empirical formula	$C_{20}H_{22}N_4O_4$
Formula weight	382.42
Temperature	153(2)
Wavelength	1.5406 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
a	7.3086(4) Å
b	11.3812(8) Å
c	14.9481(9) Å
α	68.663(2) Å
β	88.391(2) Å
γ	88.415(13) Å
Volume	1157.51(13) $Å^3$
Z	2
Density (calculated)	1.4396
Absorption coefficient	0.432
F(000)	520
Crystal size	0.26 × 0.22 × 0.19 mm^3
Theta range for data collection	2.79 to 27.59°
Index ranges	-8<=h<=7, -12<=k<=13, -17<=l<=17
Reflections collected	4009
Independent reflections	8141 [R(int) = 0.0211]
Completeness to theta = 25.010°	100.0 %
Absorption correction	multi-scan
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.028
Final *R* indices [$I > 2\text{sigma}(I)$]	$R_1 = 0.0510$, $wR_2 = 0.1237$
R indices (all data)	$R_1 = 0.0571$, $wR_2 = 0.1293$
Largest diff. peak and hole	0.710 and -0.670 $e \cdot Å^{-3}$

7. Synthetic procedures and characterization of M1 and M2



Scheme S2 Synthesis of the **M1**

7.1 Synthesis of compound 1:

1-naphthalenol (1.20 g, 7.5 mmol) was added to a degassed mixture of **N1** (2.34 g, 9.0 mmol), K_2CO_3 (4.14 g, 30.0 mmol), and a catalytic amount of LiBr in dry MeCN (70 mL). The reaction mixture was heated under reflux for 24 h and filtered after cooling. The residue was dissolved in water (200 mL) and extracted with ethyl acetate (100 mL × 2). The organic layer was combined with the previously obtained filtrate, which was washed carefully with H_2O (100 mL × 4) and brine (100 mL × 3) and dried over $MgSO_4$. After the solvent was removed, the crude product was purified by silica-gel column chromatography (eluent: hexane/ethyl acetate = 10:1, v/v) to afford the target compound **1** as a light brown oil (1.37 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.34-8.22 (m, 1H, naphthalene-*H*), 7.84-7.75 (m, 1H, naphthalene-*H*), 7.52-7.42 (m, 3H, naphthalene-*H*), 7.40-7.32 (m, 1H, naphthalene-*H*), 6.83 (d, *J* = 7.5 Hz, 1H, naphthalene-*H*), 4.35-4.30 (m, 2H, C*H*$_2$O), 4.04-3.99 (m, 2H, C*H*$_2$O), 3.81-3.73 (m, 4H, C*H*$_2$O). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.5, 134.5, 127.5, 126.5, 125.8, 125.7, 125.3, 122.0, 120.6, 105.0, 72.6, 69.8, 67.9, 61.9. ESI-MS: *m/z* calcd for $[M + Na + CH_3CN]^+$ = 296.11, found = 296.00; HR-ESI-MS ($C_{14}H_{16}O_3$): *m/z* calcd for $[M + H]^+$ = 233.1172, found = 233.1171 (100.0%).

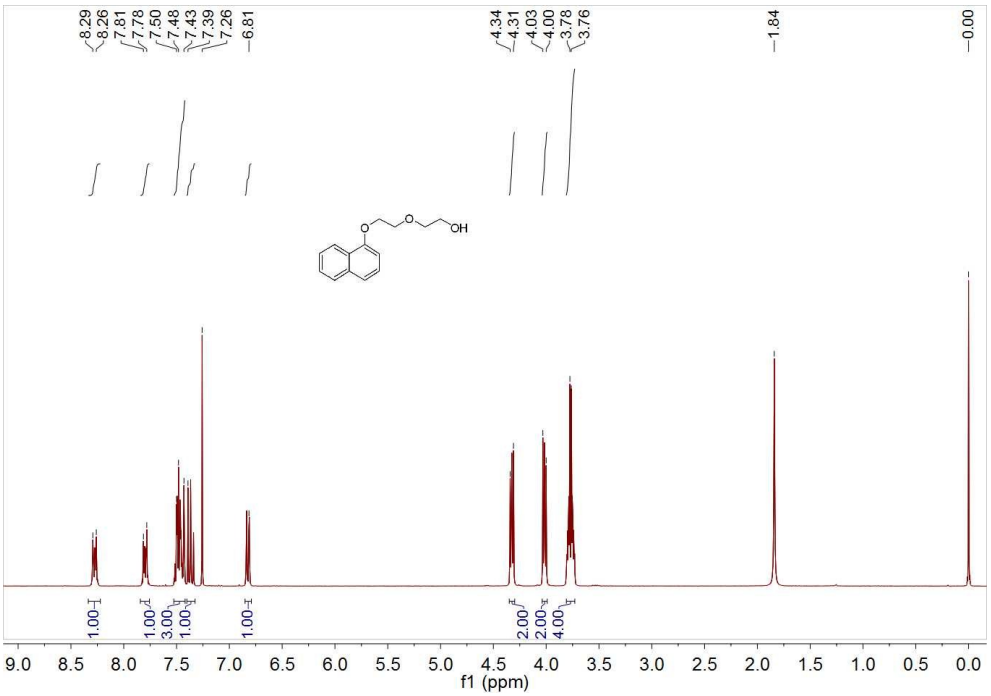


Figure. S7 ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **1**

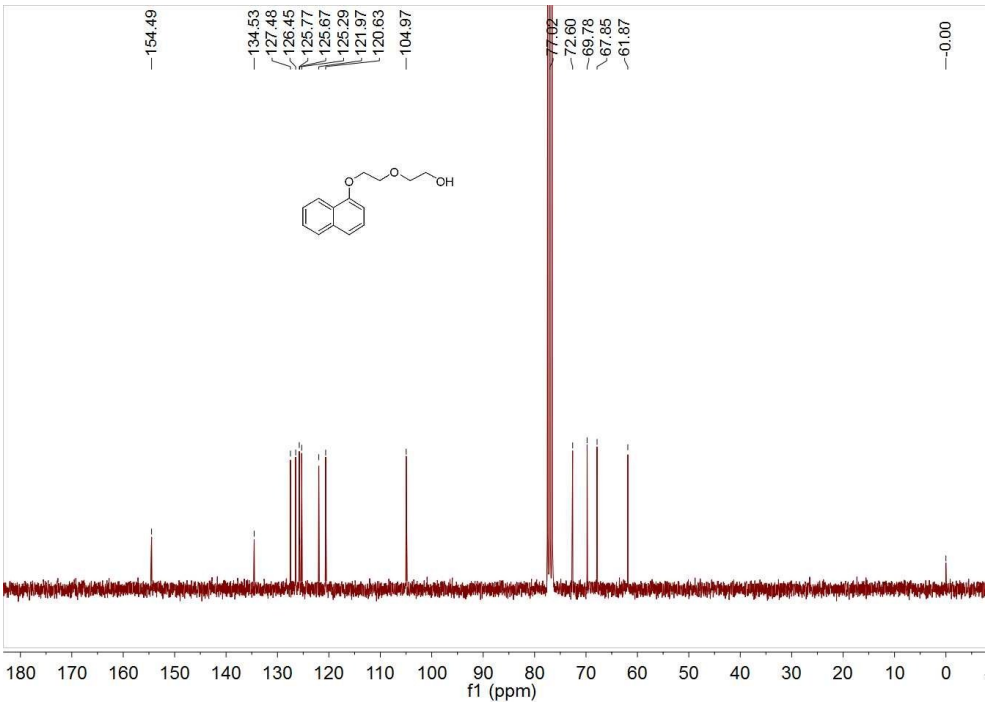


Figure. S8 ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **1**

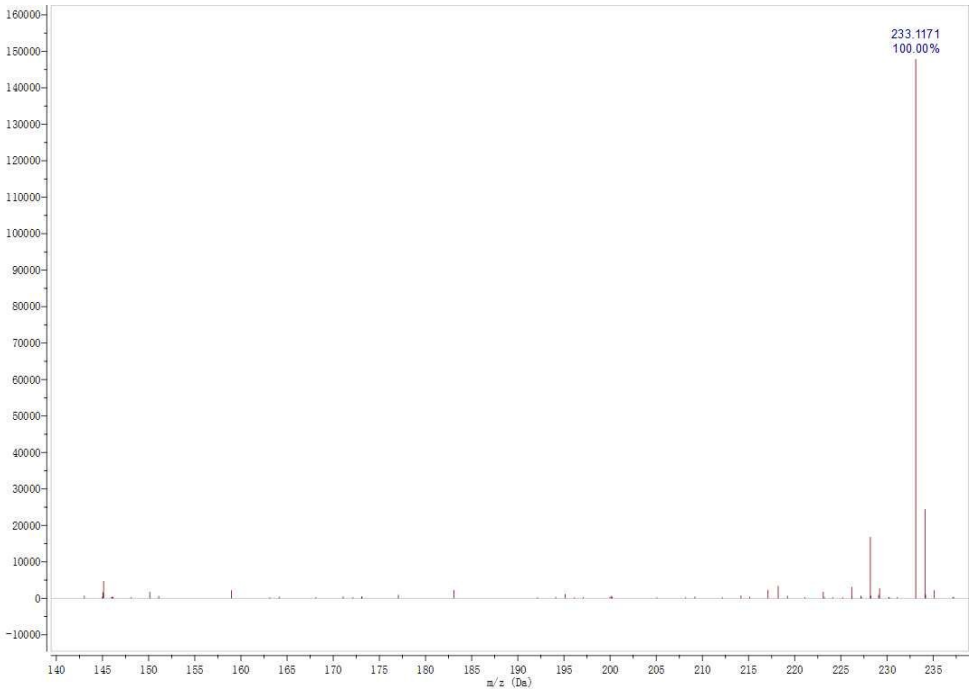


Figure. S9 HR-ESI-MS of **1**

7.2 Synthesis of compound 2:

Tosyl chloride (1.24 g, 6.5 mmol), Et_3N (0.90 g, 8.9 mmol) and a catalytic amount of dimethylaminopyridine (72 mg, 0.6 mmol) were added to a solution of **1** (1.37 g, 5.9 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The mixture was slowly raised to room temperature. After stirring for 10 hours, the reaction solution was washed with 1 M HCl (150 mL × 2), saturated Na_2CO_3 (200 mL × 3), brine (200 mL × 3), and dried over $MgSO_4$. After the solvent was removed with an evaporator under reduced pressure, the resulting residue was subjected to silica-gel column chromatography (eluent: hexane/ethyl acetate = 10:1, v/v) to afford the target compound **2** as a yellowish oil (1.59 g, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.27-8.17 (m, 1H, naphthalene-*H*), 7.84-7.73 (m, 3H, naphthalene-*H* and Ts-*H*), 7.52-7.41 (m, 3H, naphthalene-*H* and Ts-*H*), 7.40-7.32 (m, 1H, naphthalene-*H*), 7.24 (m, 2H, Ts-*H*), 6.78 (d, *J* = 7.5 Hz, 1H, naphthalene-*H*), 4.25-4.19 (m, 4H, OCH_2), 3.95-3.90 (m, 2H, OCH_2), 3.86-3.81 (m, 2H, OCH_2), 2.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.4, 144.8, 134.5, 133.0, 129.8, 128.0, 127.4, 126.4, 125.8, 125.6, 125.3, 122.0, 120.6, 104.9, 70.0, 69.3, 69.0, 67.8, 21.6. ESI-MS: *m/z* calcd for $[M + Na + CH_3CN]^+$ =

450.12, found = 450.00; HR-ESI-MS ($C_{21}H_{22}O_5S$): *m/z* calcd for $[M + NH_4]^+$ = 404.1526, found = 404.1527 (100.0%).

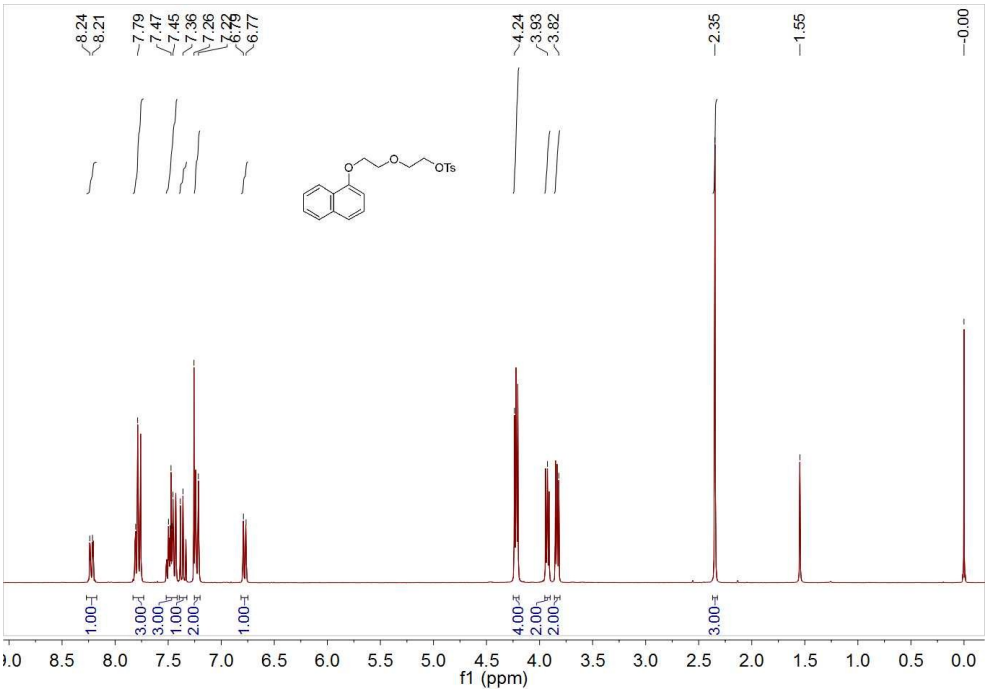


Figure. S10 ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **2**

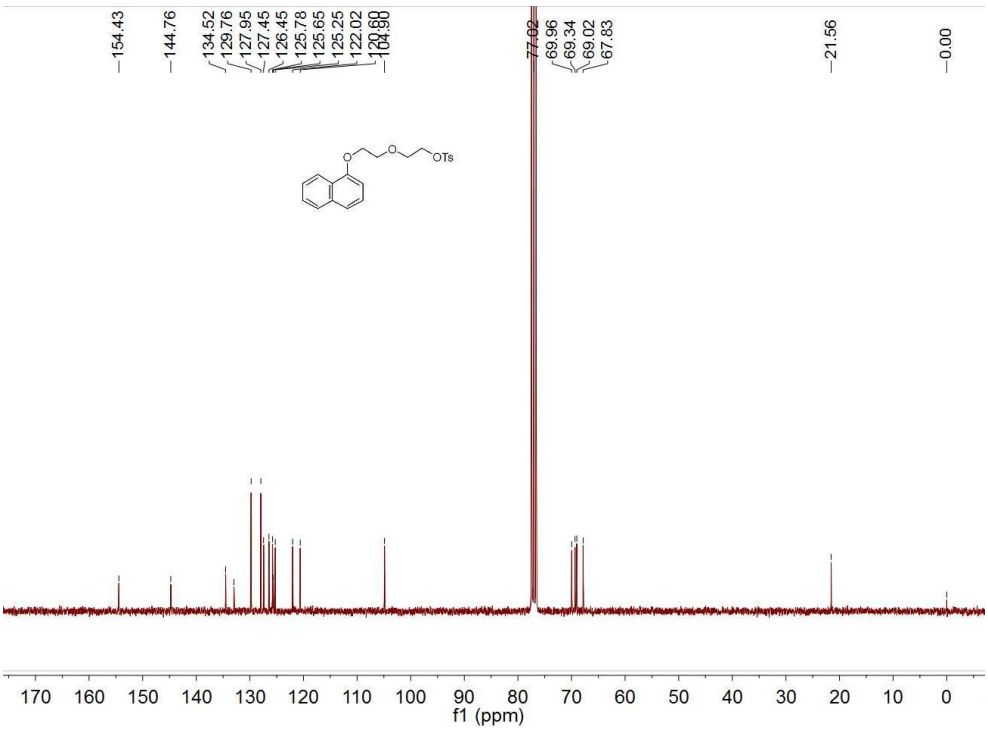


Figure. S11 ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **2**

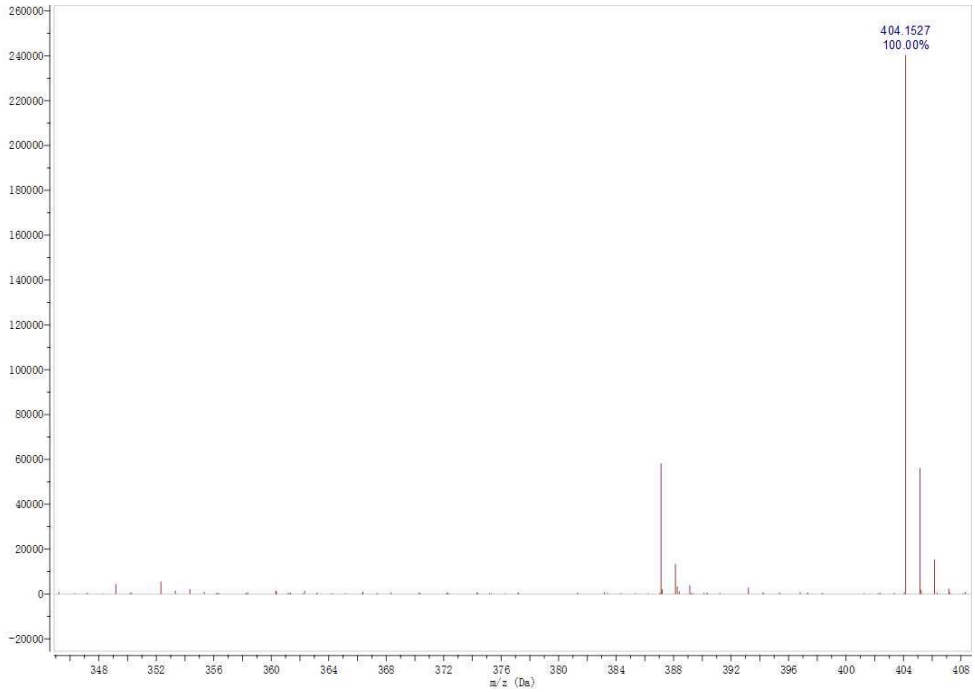


Figure. S12 HR-ESI-MS of **2**

7.3 Synthesis of compound 3:

To a solution of compound **2** (1.58 g, 4.1 mmol) in DMF (30 mL) was added potassium phthalimide (1.15 g, 6.2 mmol) at room temperature under N_2 atmosphere. The reaction mixture was heated at 120 °C for 12 h and then poured into water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (150 mL × 3) and the combined extracts were washed with brine (50 mL × 3), and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was chromatographed over silica gel (eluent: hexane/ethyl acetate = 10:1, v/v) to afford compound **3** as a white solid (1.12 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.23-8.13 (m, 1H, naphthalene-*H*), 7.79-7.71 (m, 3H, naphthalene-*H* and phthlimide-*H*), 7.65-7.59 (m, 2H, phthlimide-*H*), 7.48-7.36 (m, 3H, naphthalene-*H*), 7.33-7.27 (m, 1H, naphthalene-*H*), 6.75 (d, *J* = 6.6 Hz, 1H, naphthalene-*H*), 4.27-4.22 (m, 2H, OCH_2), 3.01-3.88 (m, 6H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.3, 154.5, 134.4, 133.8, 132.0, 127.3, 126.3, 125.7, 125.6, 125.1, 123.2, 122.1, 120.4, 104.8, 69.3, 68.2, 67.8, 37.4. ESI-MS: *m/z* calcd for $[M + Na + CH_3CN]^+$ = 425.13, found = 425.00; HR-ESI-MS ($C_{22}H_{19}NO_4$): *m/z* calcd for $[M + H]^+$ = 362.1387, found = 362.1389 (100.0%). m.p.: 110-112 °C.

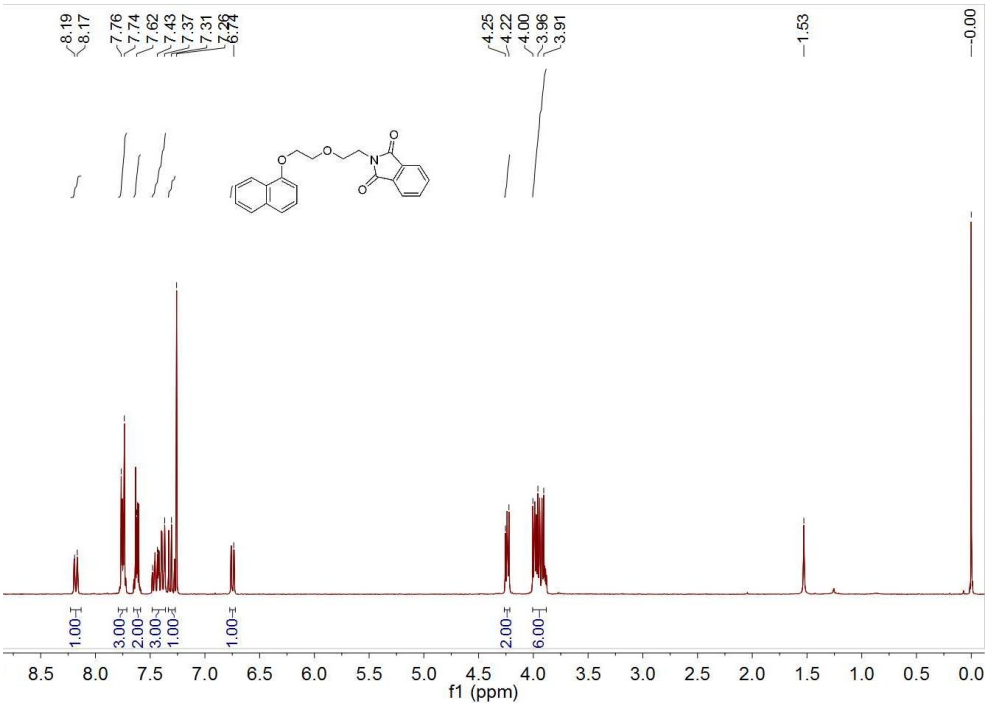


Figure. S13 ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **3**

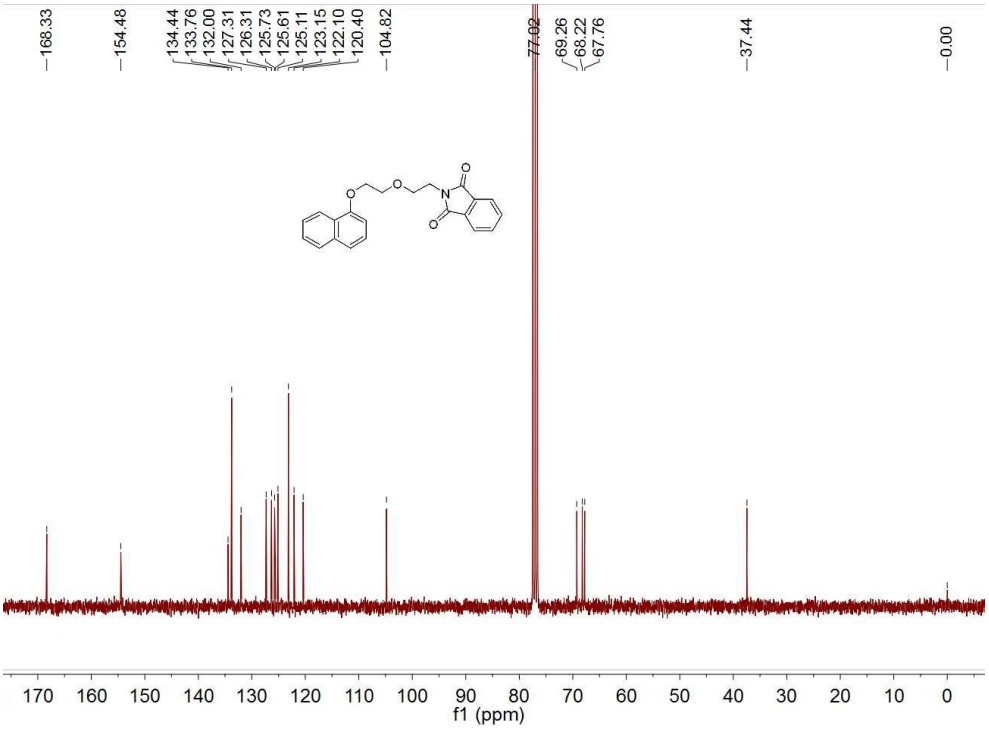


Figure. S14 ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **3**

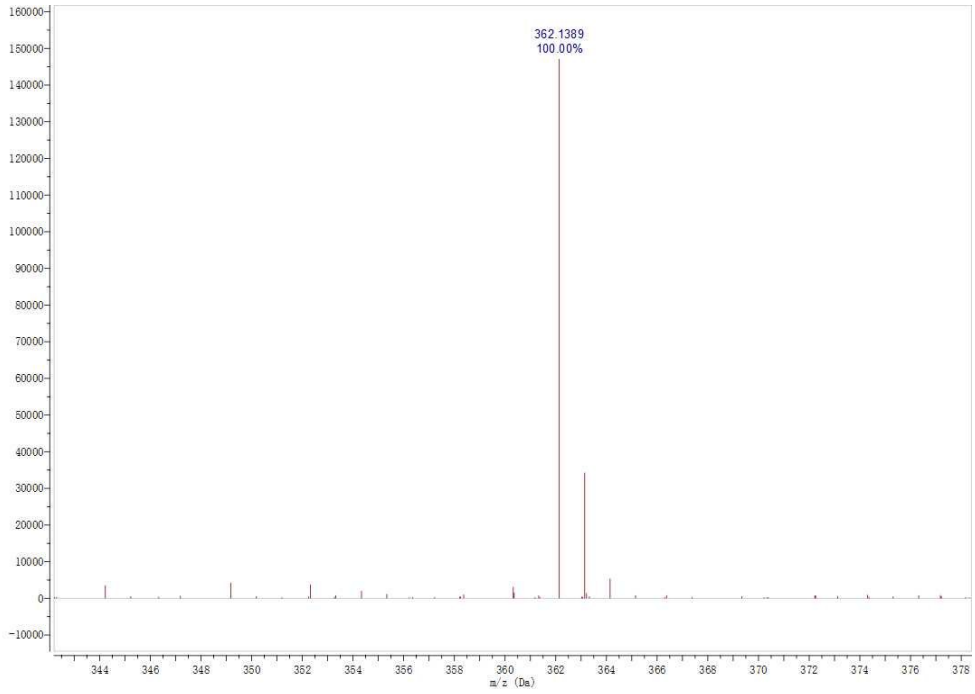


Figure. S15 HR-ESI-MS of **3**

7.4 Synthesis of compound 4:

To a solution of **3** (0.92 g, 2.6 mmol) in EtOH (30 mL) was added dropwise hydrazine monohydrate (0.52 g, 10.3 mmol) and the mixture was then refluxed for 24 hours under N_2 atmosphere. The solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with H_2O (150 mL × 3), brine (150 mL × 3), and dried over anhydrous $MgSO_4$. After the solvent was removed with an evaporator under reduced pressure, the resulting residue was subjected to column chromatography over alumina (eluent: 1% MeOH in CH_2Cl_2 → 5% MeOH in CH_2Cl_2) to give the desired compound **4** as a yellow oil (0.51 g, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.46-8.06 (m, 1H, naphthalene-*H*), 7.85-7.71 (m, 1H naphthalene-*H*), 7.53-7.40 (m, 3H, naphthalene-*H*), 7.39-7.29 (m, 1H, naphthalene-*H*), 6.82 (d, *J* = 7.5 Hz, 1H, naphthalene-*H*), 4.34-4.27 (m, 2H, OCH_2), 4.00-3.94 (m, 2H, OCH_2), 3.66 (t, *J* = 5.1 Hz, 2H, OCH_2), 2.93 (s, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.5, 134.5, 127.4, 126.4, 125.8, 125.7, 125.2, 122.0, 120.5, 104.9, 73.10, 69.59, 67.86, 41.69. ESI-MS: *m/z* calcd for $[M + H]^+$ = 232.13, found = 232.05; HR-ESI-MS ($C_{14}H_{17}NO_2$): *m/z* calcd for $[M + H]^+$ = 232.1332, found = 232.1329 (100.0%).

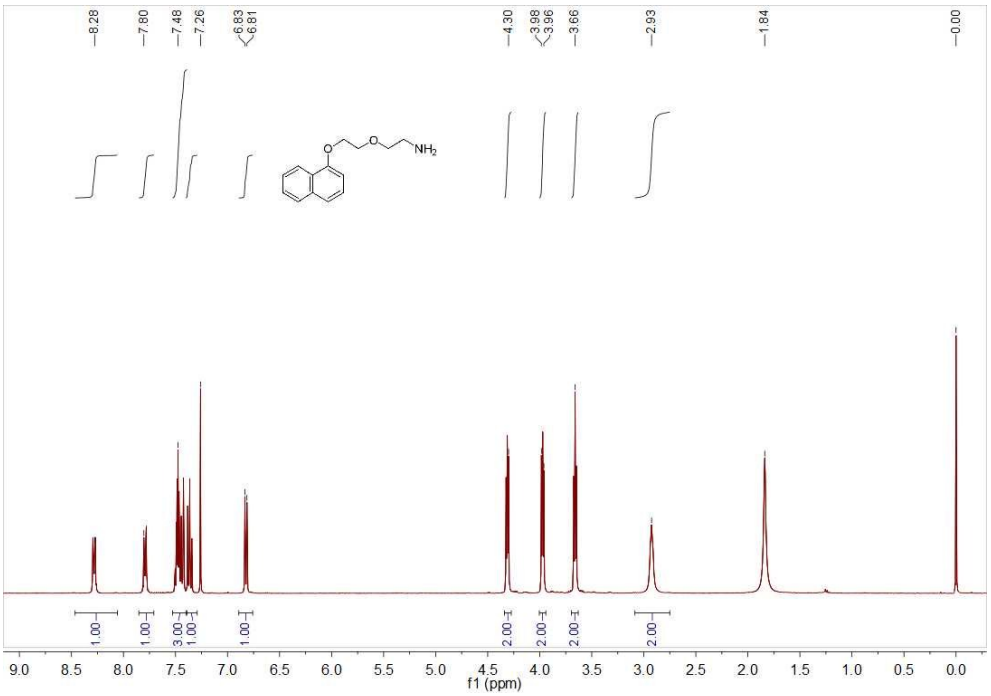


Figure. S16 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of **4**

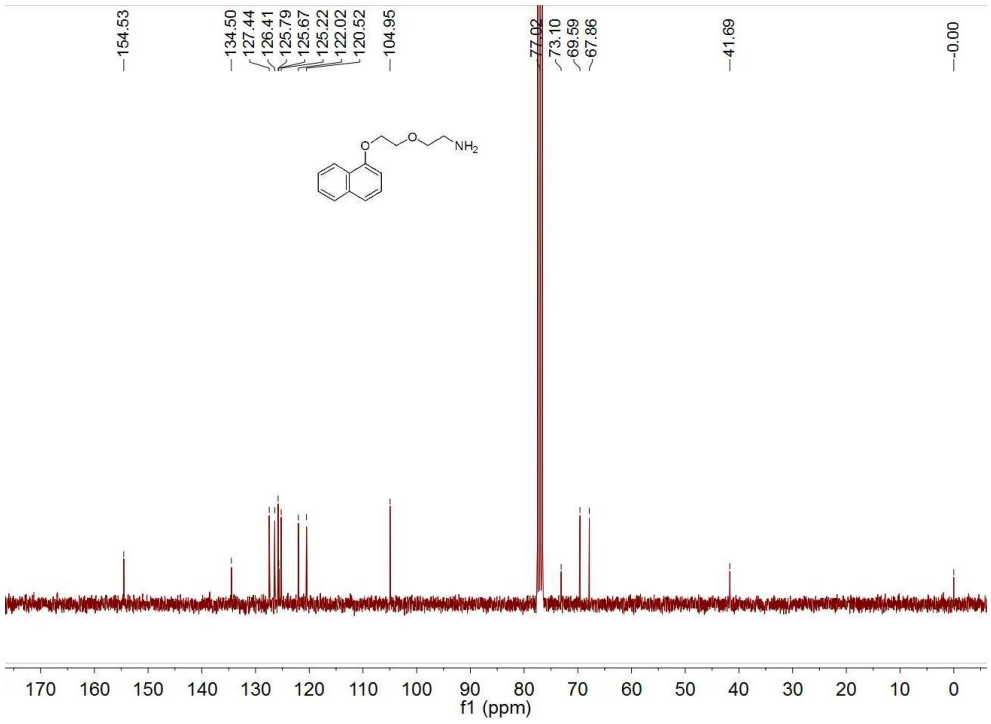


Figure. S17 ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **4**

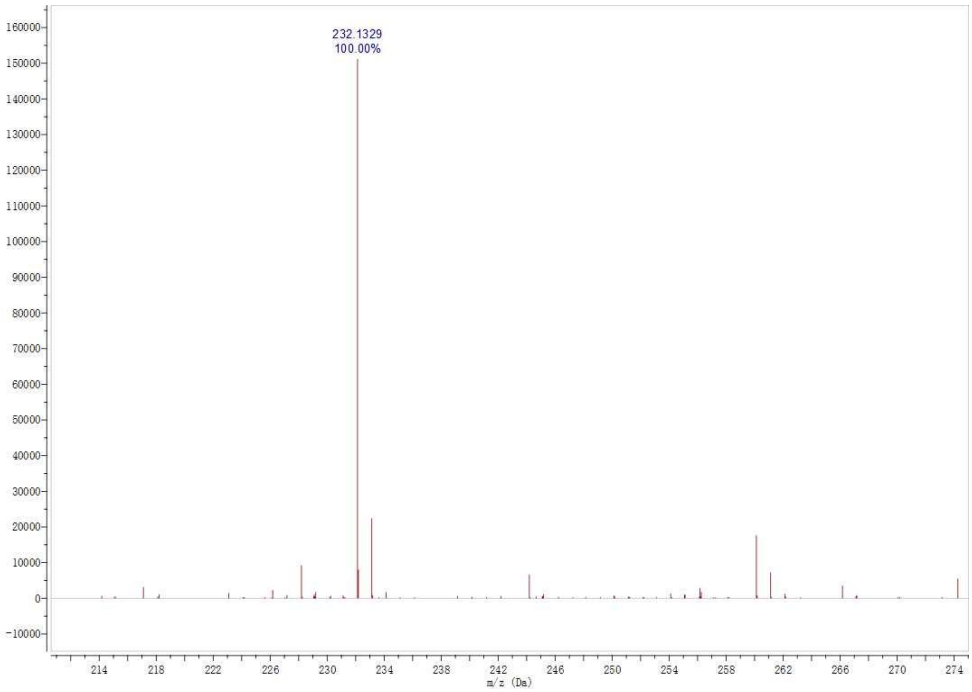


Figure. S18 HR-ESI-MS of **4**

7.5 Synthesis of compound M1:

Imidazolide **L1** (1.01 g, 3.7 mmol) and **4** (0.52 g, 2.2 mmol) were dissolved in 60 mL of dry $CHCl_3$ and this solution was stirred for 12 h under nitrogen at room temperature. To the reaction mixture 30 mL of $CHCl_3$ was added and the mixture was washed with 1 M HCl (50 mL × 2), saturated $NaHCO_3$ (100 mL × 2), brine (100 mL × 2), and dried over anhydrous $MgSO_4$. After the solvent was removed, the resulting residue was subjected to column chromatography over silica gel (eluent: $CHCl_3$) to afford compound **M1** as a light yellow oil (0.90 g, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 13.09 (s, 1H, N*H*), 11.64 (br s, 1H, N*H*), 10.35 (s, 1H, N*H*), 8.26 (d, *J* = 8.2 Hz, 1H, naphthalene-*H*), 7.75 (d, *J* = 7.8 Hz, 1H, naphthalene-*H*), 7.45-7.25 (m, 4H, naphthalene-*H*), 6.75 (d, *J* = 7.6 Hz, 1H, naphthalene-*H*), 5.74 (s, 1H, alkylidene-*H*), 4.33-4.26 (m, 2H, OCH_2), 4.08-3.99 (m, 2H, OCH_2), 3.90-3.79 (m, 2H, OCH_2), 3.60-3.49 (m, 2H, OCH_2), 2.31-2.20 (m, 1H, C*H*(CH_2)$_2$), 1.68-1.48 (m, 4H, CH_2), 1.34-1.18 (m, 4H, CH_2), 0.93-0.82 (m, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 173.0, 157.0, 155.3, 154.7, 154.5, 134.5, 127.4, 126.3, 125.7, 125.0, 122.1, 120.3, 106.1, 104.6, 70.0, 69.5, 67.8, 65.0, 45.2, 39.8, 32.8, 29.3, 26.5, 22.5, 13.9, 11.6. ESI-MS: *m/z* calcd for $[M + CF_3COO]^-$ = 579.26, found = 579.10; HR-ESI-MS ($C_{26}H_{34}N_4O_4$): *m/z*

calcd for $[M + H]^+$ = 467.2653, found = 467.2654 (45.47%); *m/z* calcd for $[2M + H]^+$ = 933.5233, found = 933.5224 (100.0%).

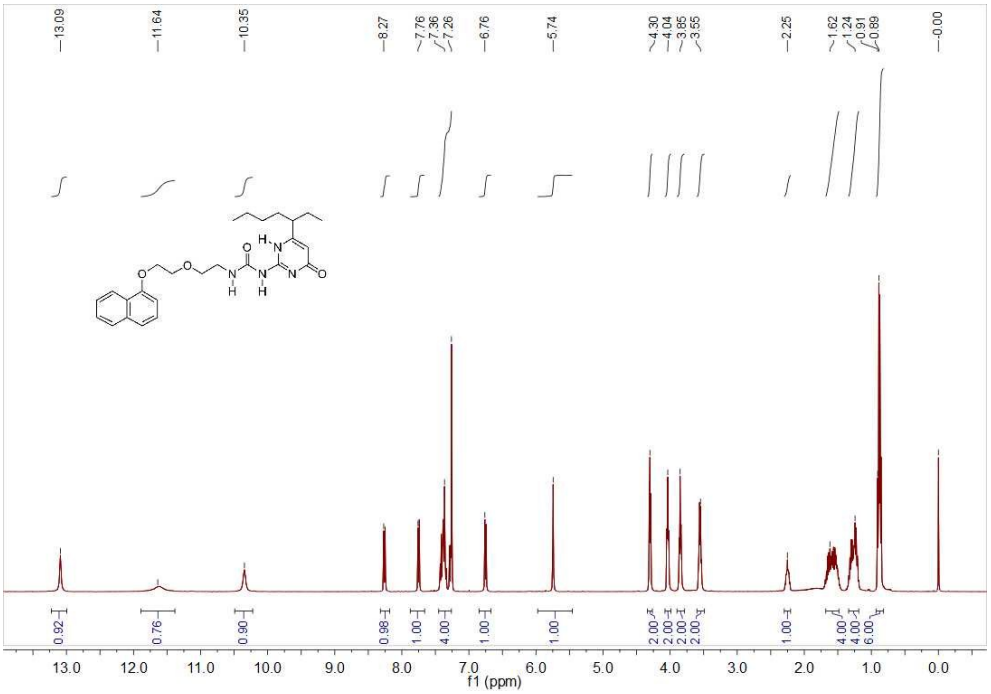


Figure. S19 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of **M1**

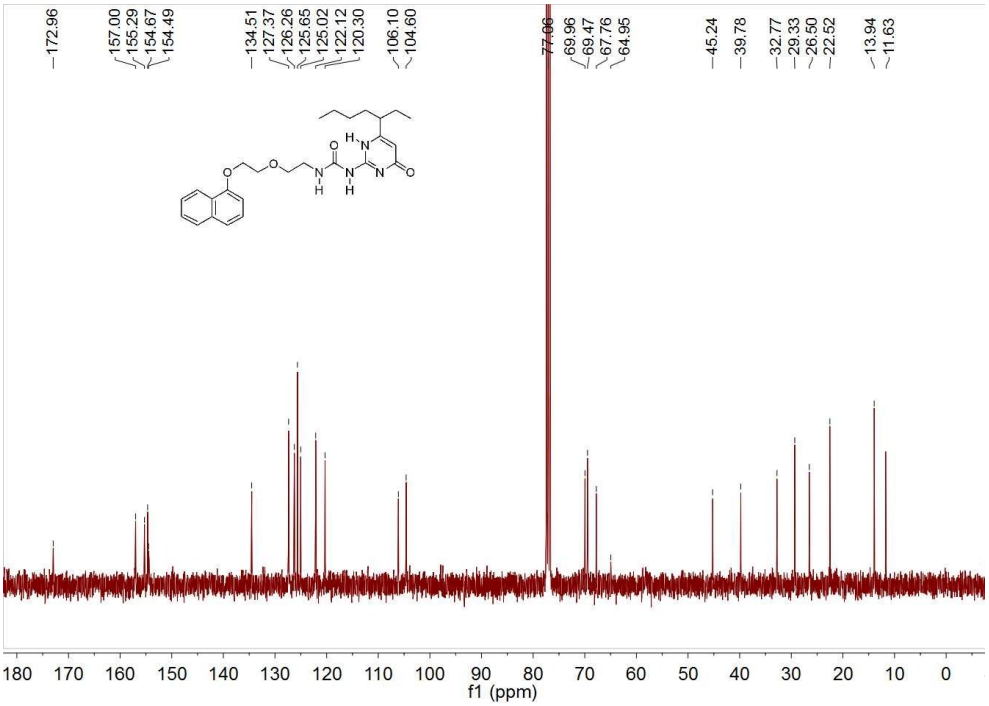


Figure. S20 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of **M1**

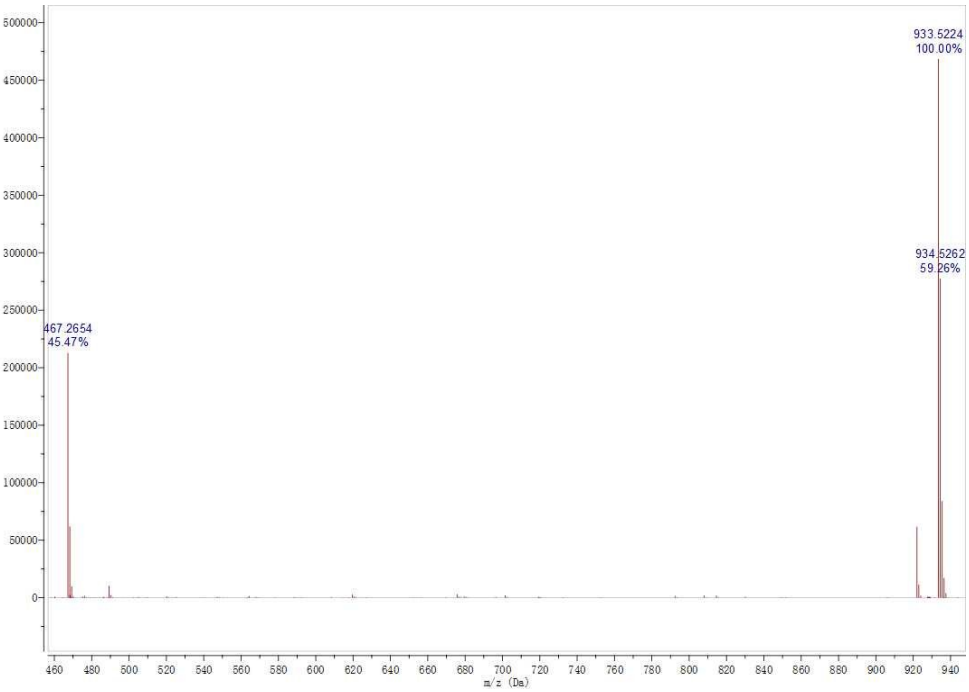
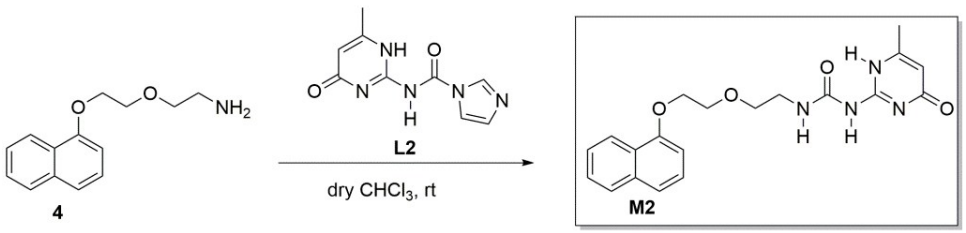


Figure. S21 HR-ESI-MS of **M1**



Scheme S3 Synthesis of the **M2**

7.6 Synthesis of compound M2:

Imidazolide **L2** (0.92 g, 4.2 mmol) and **4** (0.27 g, 1.2 mmol) were dissolved in 30 mL of dry $CHCl_3$ and this solution was stirred for 12 h under nitrogen at room temperature. To the reaction mixture 20 mL of $CHCl_3$ was added and the organic layer was washed with 1 M HCl (35 mL), saturated $NaHCO_3$ (50 mL × 3), brine (20 mL × 3), and dried over anhydrous $MgSO_4$. After the solvent was removed, the resulting residue was subjected to column chromatography over silica gel (eluent: $CHCl_3$) to afford compound **M2** as a white solid (0.20 g, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 12.86 (s, 1H, N*H*), 11.40 (s, 1H, N*H*), 10.30 (s, 1H, N*H*), 8.23 (d, *J* = 8.2 Hz, 1H, naphthalene-*H*), 7.72 (d, *J* = 7.7 Hz, 1H, naphthalene-*H*), 7.44-7.25 (m, 4H, naphthalene-*H*), 6.72 (d, *J* = 7.5 Hz, 1H, naphthalene-*H*), 5.66 (s, 1H, alkylidene-*H*), 4.31-4.25 (m, 2H, OCH_2), 4.06-

4.01 (m, 2H, OCH_2), 3.88-3.81 (m, 2H, OCH_2), 3.59-3.50 (m, 2H, OCH_2), 2.11 (s, 3H, CH_3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 171.7, 155.7, 153.6, 153.0, 146.8, 133.4, 126.3, 125.2, 124.6, 124.5, 123.9, 121.0, 119.1, 105.4, 103.4, 68.9, 68.5, 66.6, 38.8, 17.8. ESI-MS: *m/z* calcd for [M + CF_3COO]$^-$ = 495.16, found = 495.05; HR-ESI-MS ($C_{20}H_{22}N_4O_4$): *m/z* calcd for [M + H]$^+$ = 383.1714, found = 383.1716 (47.93%); *m/z* calcd for [2M + H]$^+$ = 765.3355, found = 765.3350 (100.0%). m.p.: 144-147 °C.

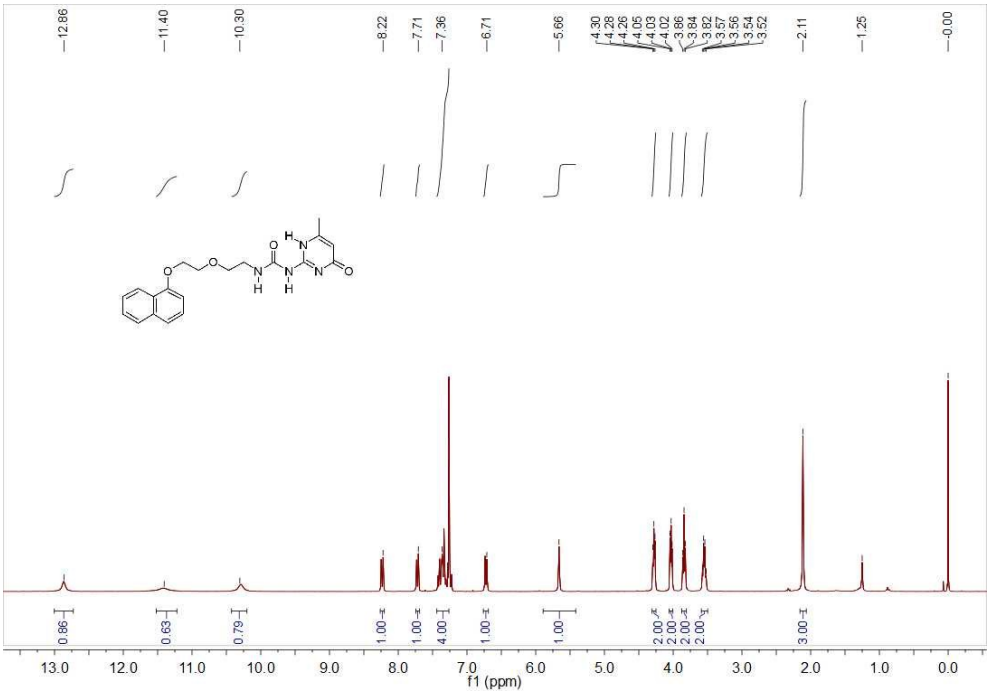


Figure. S22 ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **M2**

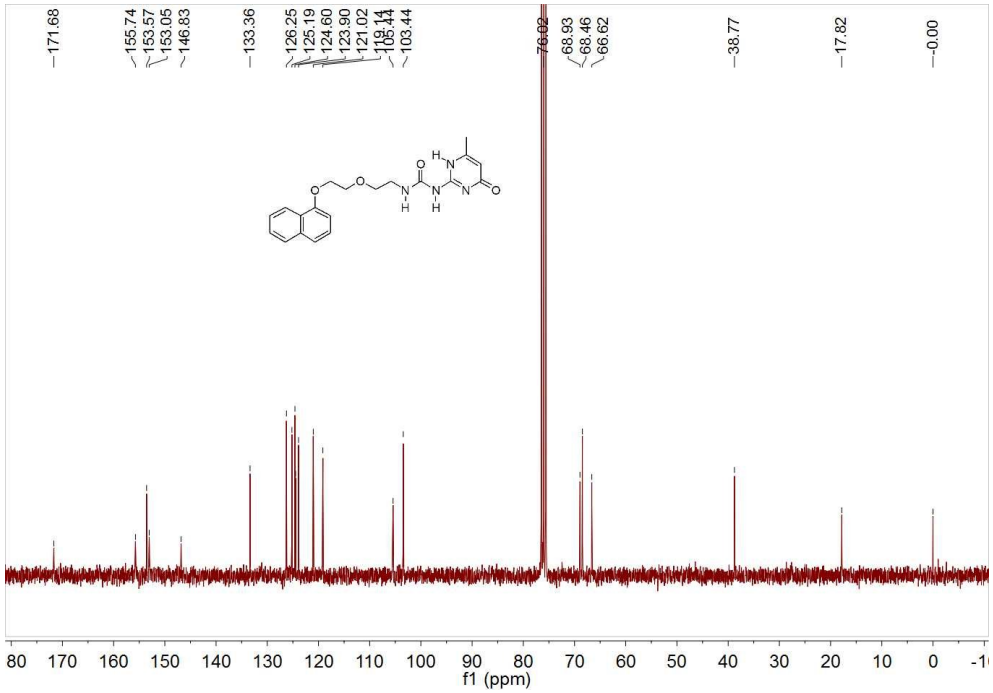


Figure. S23 ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of **M2**

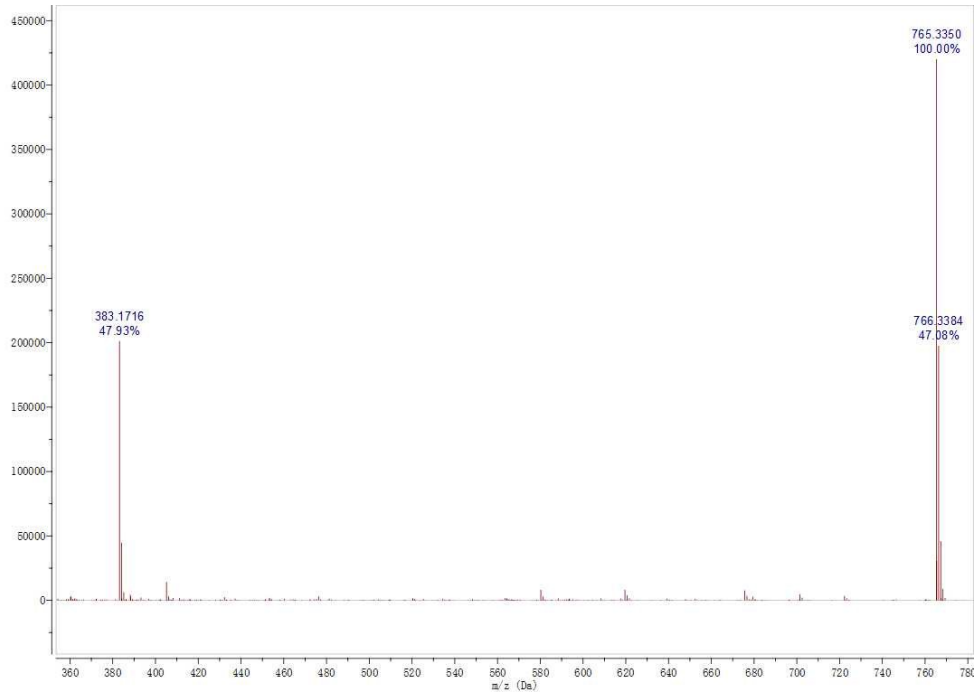


Figure. S24 HR-ESI-MS of **M2**

8. Reference

S1. Sato, R.; Kozuka, J.; Ueda, M.; Mishima, R.; Kumagai, Y.; Yoshimura, A.; Minoshima, M.; Mizukami, S.; Kikuchi, K., *J. Am. Chem. Soc.*, 2017, **139,** 17397-17404.

S2. Ma, Y.-Z.; Xiao, H.; Yang, X.-F.; Niu, L.-Y.; Wu, L.-Z.; Tung, C.-H.; Chen, Y.-Z.; Yang, Q.-Z., *J. Phys. Chem. C.*, 2016, **120,** 16507-16515.

S3. Rodrigues, M. V. N.; Barbosa, A. F.; da Silva, J. F.; dos Santos, D. A.; Vanzolini, K. L.; de Moraes, M. C.; Corrêa, A. G.; Cass, Q. B., *Bioorg. Med. Chem.*, 2016, **24,** 226-231.

S4. Sheldrick, G. M. *SHELXL-97*: Crystal Structure Refinement, University of Göttingen: Göttingen, Germany, 1997.