Discovery and Structural Modification of 1-phenyl-3-(1-phenyl)-urea derivatives as Inhibitors of complement

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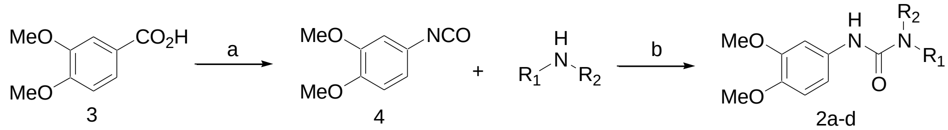
Supporting Information

General Methods:

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Benzene were distilled from sodium, DMF was distilled in a vacuum. All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction vessels were oven-dried. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates, visualized under UV and charred using phosphomolybdic acid solution followed by heating. Products were purified by flash column chromatography (FCC) on 230–400 mesh silica gel. Petroleum ether refers to the fraction with boiling range 60–90℃. ^{1}H (300 MHz) NMR spectra were recorded on a Varian Mercury-Vx 300 M Fourier transform spectrometer. The chemical shifts were reported in δ (ppm) using the δ7.26 signal of $CDCl_3$ (^{1}H NMR) as internal standards. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a spectrometer operating at 75 MHz. Low-resolution mass data were obtained on an Agilent 6110 Single Quadrupole LC/MS System.

Experimental Procedures

Scheme 1. Synthesis of compounds **2a–d**



Reagents and conditions: (a) DPPA, Et_3N, benzene, then reflux. (b) DCM, 45-80% (two steps)

4-Isocyanato-1, 2-dimethoxy-benzene (**4**) To a solution of 3, 4-dimethoxy-benzoic acid **3** (210mg, 1.2 mmol) in 5 mL of anhydrous benzene was added (0.25ml, 1.7mmol) of triethylamine and DPPA (0.3 ml, 1.44 mmol). After 3 h at room temperature, the reaction mixture was heated under reflux for 2 h until the nitrogen gas evolution had ceased. The reaction mixture was then washed with a saturated NH_4Cl solution and water, dried over $MgSO_4$, and concentrated. The residue was not purified.

General procedure for preparation of compounds **1** and **2a-d**.
To a crude aryl isocyanate in 5ml CH_2Cl_2 added variety amines (1.5mmol), the mixture was stirring 10 minutes. The solvent was removed under reduced pressure. The obtained residue was titrated with petroleum ether. The precipitate was collected by filtration, washed with petroleum ether and dried in vacuum to yield 1(254mg, 71% for two steps).
1: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (d, J=6.9Hz, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 4.88 – 4.98(m, 1H), 5.62 (d, J = 7.5 Hz, 1H), 6.56 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.67 (d, J = 8.4Hz, 1H), 6.99 (d, J = 2.1Hz, 1H), 7.07 (s,1H), 7.19 – 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.22, 49.74, 55.83, 56.33, 105.41, 111.86, 112.34, 125.98, 127.26, 128.77, 132.85, 144.56, 145.16, 149.26, 156.36ppm; LC–MS: m/z: 301$[M+H]^+$, 323 $[M+Na]^+$;

Among the following list compound, some compounds were pure enough and some were need purified by flash chromatography on silica gel (PE: EtOAc = 2:1).
2a: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.68 (s, 3H), 3.71 (s, 3H), 4.32 (d, J=5.7, 2H), 6.55 – 6.60 (m, 1H), 6.82 (s, 2H), 7.18 (s, 1H), 7.35 – 7.39 (m, 3H), 7.43 – 7.48 (m, 2H), 7.61 – 7.65 (m, 4H), 8.41 (s, 1H).

2b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.68 (s, 3H), 3.70 (s, 3H), 4.75 (d, J=5.4, 2H), 6.53 – 6.55 (m, 1H), 6.81 (s, 2H), 7.17 (s, 1H), 7.47 – 7.49 (m, 2H), 7.56 – 7.59 (m, 2H), 7.85 (t, 1), 7.79 (d, 1H), 8.13 (d, 1H), 8.36 (s, 1H).

2c: ^{1}H NMR ($CDCl_3$, 300 MHz):δ 1.37 (d, J=6.9Hz, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 4.93 – 4.98 (m, 1H), 5.62 (d, J = 7.5 Hz, 1H), 6.56 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.67 (d, J = 8.4Hz, 1H), 6.99 (d, J = 2.1Hz, 1H), 7.07 (s, 1H), 7.25 – 7.26 (m, 5H).

2d: ^{1}H NMR ($CDCl_3$, 300 MHz):δ 3.02 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 4.59 (s, 2H), 6.24(s, 1H), 6.66 (dd, J1= 8.4Hz, J2 = 2.1Hz, 1H), 6.74 (d, J = 8.4Hz, 1H), 7.22 (d, J = 2.1Hz, 1H), 7.33 – 7.36 (m, 5H).

With the similar method for syntheses of compounds 5a-e.
5a: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (d, J = 6.6Hz, 3H), 4.88 – 4.92 (m, 1H), 5.59 (d, J = 7.2 Hz, 1H), 6.98 – 7.03 (m, 2H), 7.27 – 7.28 (m, 5H), 7.28 – 7.30 (m, 3H).

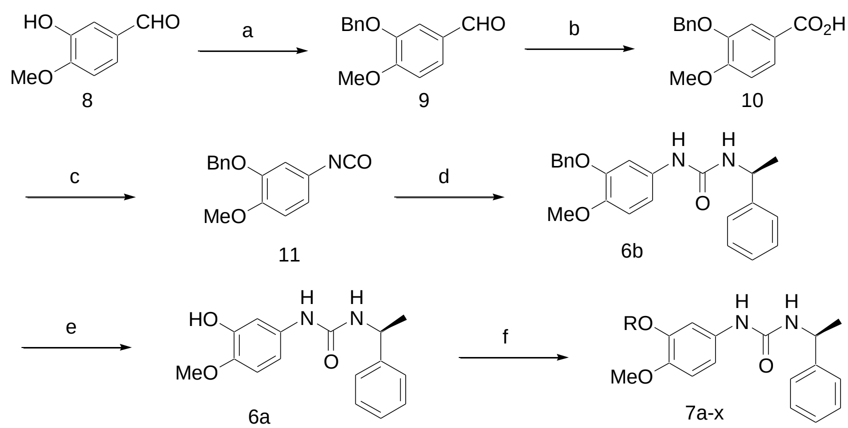
5b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (d, J = 6.6Hz, 3H), 4.98 (s, 1H), 6.31 (s, 1H), 7.18 – 7.20 (m, 4H), 7.30 – 7.33 (m, 5H).

5c: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (d, J = 6.6Hz, 3H), 3.78 (s, 3H), 4.95 (s, 1H), 4.95 – 5.00 (m, 1H), 6.02(s, 1H), 6.84 (d, J = 8.7Hz, 2H), 7.13 (d, J = 8.7Hz, 2H), 7.27 – 7.28 (m, 5H).

5d: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (d, J = 6.6Hz, 3H), 3.78 (s, 3H), 4.90 (s, 1H), 4.97 – 5.01 (m, 1H), 5.78 (s, 1H), 6.75 – 6.77 (m, 1H), 7.19 – 7.21 (m, 3H), 7.27 – 7.30 (m, 5H).

5e: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (d, J = 6.6Hz, 3H), 4.88 – 4.93 (m, 1H), 5.98 (s, 1H), 7.27 – 7.28 (m, 5H), 7.93(dd, 2H), 8.10 (d, 1H), 8.16 (d, 1H).

Scheme 2. Synthesis of compounds 7a–x



Reagents and conditions: (a) benzyl bromide, K_2CO_3, acetone, 98%. (b) 30%H_2O_2, NaH_2PO_4, $NaClO_2$, acetonitrile, H_2O, 72%. (c)DPPA, Et_3N, benzene, then reflux. (d) (s)-α-Phenylethylamine, DCM, 48% (two steps). (e) Hydrogen, 5% palladium on activated carbon, DMF, 85%. (f) alkyl bromide, K_2CO_3, 18-crown-6, DMF, 80-95%.

3-Benzyloxy-4-methoxy-benzaldehyde (9) To solution of isovanillin **8** (3.04g, 20mmol) in 50 mL of acetone was added excess of anhydrous K_2CO_3 (11g, 80mmol) and benzyl bromide (3.42g, 20mmol). The mixture refluxed 12 h, then the solution was concentrated under reduced pressure, and the residue was diluted with 50 mL of EtOAc and 5 mL of H_2O. The aqueous phase was extracted with EtOAc. The combined organic phases were then washed with water and brine, dried over Na_2SO4, filtered and concentrated under reduced pressure to yield the product **9** (4.7g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H), 5.18 (s, *2*H), 6.99 (d, J = 8.7Hz, 1H), 7.32 – 7.40 (m, 2H), 7.45 – 7.47 (m, 5H), 9.82 (s, 1H).

3-Benzyloxy-4-methoxy-benzoic acid (10) 30% H_2O_2 (159mg, 4.69mmol) was added to a solution of 3-Benzyloxy-4-methoxy-benzaldehyde **9** (1.08g, 4.46mmol) and NaH_2PO_4 (0.16g, 0.134mmol) in acetonitrile (25 mL) and H_2O (5mL) at room temperature. Then the solution was cooled to 0°C, added with a solution of $NaClO_2$ (0.562g, 6.24mmol) in 8 mL H_2O, the progress was not exceeded 10°C. After additional the solution was stirring overnight. The reaction mixture was then added 10% $Na_2S_2O_3$ solution and extracted with EtOAc, wash with water. The organic phase was washed with 10%$NaHCO_3$ solution, then the aqueous phase was acid with 1N HCl, and extracted with EtOAc, the organic phase was wash with water, brine and dried over Na_2SO_4, filtered, and concentrated in vacuo to give the acid **10** (0.78g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H), 5.22 (s, *2*H), 6.99 (d, J = 9Hz, 1H), 7.33 – 7.45 (m, 2H), 7.45 – 7.47 (m, 5H).

Compound 11 was prepared according to the procedure for compound **4** except using acid 10.

1-(3-Benzyloxy-4-methoxy-phenyl)-3-(1-phenyl-ethyl)-urea (6b) To a crude isocyanate **11** in 5ml CH_2Cl_2 added (s)-α-Phenylethylamine, the mixture was stirring 10 minutes. The solvent was removed under reduced pressure. The obtained residue was titrated with petroleum ether. The precipitate was collected by filtration, washed with petroleum ether and dried in vacuum to yield **6b** (537mg, 48% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (d, J=7.2 Hz, 3H), 3.85 (s, 3H), 4.82 (d, J = 7.5 Hz, 1H), 4.93 – 4.98 (m, 1H), 5.08 (s, *2*H), 5.99 (s, 1H), 6.69 – 6.72 (m, 1H), 6.81 (d, J = 6Hz, 1H), 6.8 (d, J = 2Hz, 1H), 7.24 – 7.42 (m, 10H).

1-(3-Hydroxy-4-methoxy-phenyl)-3-(1-phenyl-ethyl)-urea (6a) Compound 6b (389mg, 1.03mmol) and 5%Pd/C (40mg) in 10ml DMF was hydrogenation (H_2 1 atm) for 24 h and the residue was filtered, diluted with 30 mL of EtOAc and 5 mL of H_2O. The aqueous phase was extracted with EtOAc. The combined organic phases were then washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield white solid 6a (250mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40(d, J = 6.9 Hz, 3H), 3.82(s, 3H), 4.91 – 4.96 (m, 1H), 5.28 (d, J = 7.5 Hz, 1H), 5.86 (s, 1H), 6.70 – 6.77(m, 3H), 7.24 – 7.30(m, 5H)

General Procedure for preparation of compounds 6c-e, 7a-x.
A mixture of compound 6a (20mg, 0.07mmol), appropriate alkyl bromide (0.1mL), K_2CO_3 (80mg, 0.57 mmol) and catalytic18-crown-6 in dry DMF (2 mL) was stirring for 12 h. The residue was diluted with 20 mL of EtOAc and 5 mL of H_2O. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine, dried over Na_2SO4, filtered and concentrated under reduced pressure to yield the desired products.

6c: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.37 (t, 3H), 1.39 (d, J = 6.6 Hz, 3H), 3.80 (s, 3H), 3.97 – 4.02 (m,2H), 4.96 – 4.99 (m, 1H), 5.30 (d, J = 7.8Hz, 1H), 6.60 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.63 (s, 1H), 6.73 (d, J = 8.4Hz, 1H), 6.97 (d, J = 1.8Hz, 1H), 7.24 - 7.31(m, 5H).

6d: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.43 (d, J = 6.6 Hz, 3H), 3.82 (s, 3H), 4.52 (d, J = 5.7Hz, 2H), 4.94 – 5.00 (m, 1H), 5.18 (d, J = 7.2Hz, 1H), 5.23 (d, J = 10.5Hz, 1H), 5.35(d, J = 15.3Hz, 1H), 5.95 – 6.06 (m, 1H), 6.44(s, 1H), 6.65 (dd, J1 = 8.4Hz, J2 = 1.8Hz, 1H), 6.76 (d, J = 8.4Hz, 1H), 6.94 (d, J = 1.8Hz, 1H), 7.24 – 7.31 (m, 5H).

6e: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.26 (t, 3H), 1.34 (d, J = 6.6 Hz, 3H), 3.83 (s, 3H), 4.18 – 4.26 (m, 2H), 4.66 (s, 2H), 4.95 – 4.99 (m, 1H), 5.01 (d, J = 5.4Hz, 1H), 6.26 (s, 1H), 6.78 (d, 2H), 6.86 (s, 1H), 7.28 – 7.31 (m, 5H).

7a: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.94 (t, 3H), 1.35 (d, J = 5.4 Hz, 3H), 1.72 – 1.79 (m,2H), 3.76 (s, 3H), 3.82 (t, 2H), 4.90 – 4.95 (m, 1H), 5.72 (d, J = 7.8Hz, 1H), 6.56 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.67(d, J = 8.4Hz, 1H), 7.05(d, J = 1.8Hz, 1H), 7.24-7.31(m, 5H).

7b : ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.93 (t, 3H), 1.39 (d, J = 5.4 Hz, 3H), 1.45 – 1.48 (m, 2H), 1.75 – 1.83 (m, 2H), 3.79 (s, 3H), 3.92 (t, 2H), 4.90 – 4.95 (m, 1H), 5.41 (d, J = 7.8Hz, 1H), 6.59 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.72 (d, J = 8.4Hz, 1H), 6.81 (s, 1H), 6.98 (d, J = 1.8Hz, 1H), 7.24-7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.09, 19.41, 23.19, 31.41, 49.78, 56.56, 68.78, 107.06, 112.52, 112.65, 126.04, 127.27, 128.78, 132.73, 144.49, 145.70, 149.07, 156.226 ppm; LC–MS: m/z : 343$[M+H]^+$, 365 $[M+Na]^+$.

7c: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.39 (t, 3H), 1.40(d, J = 5.4 Hz, 3H), 1.43 – 1.45 (m, 2H), 1.70 – 1.79 (m, 2H), 3.79 (s, 3H), 3.91 (t, 2H), 4.89 - 4.94 (m, 1H), 5.41(d, J = 7.8 Hz, 1H), 6.59 (dd, J1 = 8.4Hz, J2 = 1.8Hz, 1H), 6.72 (d, J = 8.4Hz, 1H), 6.81(s, 1H), 6.98 (d, J = 1.8Hz, 1H), 7.27 – 7.28 (m, 5H).

7d: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.86 (t, 3H), 1.26 – 1.30 (m, 6H), 1.35 (d, J = 7.2Hz, 3H), 1.72 – 1.77 (m, 2H), 3.77 (s, 3H), 3.86 (t, 2H), 4.89 – 4.94 (m, 1H), 5.65 (d, 1H), 6.56 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.69 (d, J = 8.4Hz, 1H), 7.02 (d, J = 2.1Hz, 1H), 7.11 (s, 1H), 7.26 – 7.28 (m, 5H)

7e: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (t, 3H), 1.25 – 1.28 (m, 8H), 1.41 (d, J = 7.2Hz, 3H), 1.72 – 1.77 (m, 2H), 3.80 (s, 3H), 3.92 (t, 2H), 4.93 – 4.96 (m, 1H), 5.01 (d, 1H), 6.62 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.75 (d, J = 8.4Hz, 1H), 6.94 (d, J = 2.1Hz, 1H), 7.27 – 7.28 (m,5H).

7f: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (t, 3H), 1.26 – 1.35 (m, 10H), 1.39 (d, J = 7.2Hz, 3H), 1.76 – 1.91 (m, 2H), 3.79 (s, 3H), 3.90 (t, 2H), 4.92 – 4.94 (m, 1H), 5.46 (d, 1H), 6.57 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.72 (d, J = 8.4Hz, 1H), 6.85 (s, 1H), 6.95 (d, J = 2.1Hz, 1H), 7.28 – 7.34 (m, 5H)

7g: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (t, 3H), 1.25 – 1.28 (m, 14H), 1.40 (d, J = 7.2Hz, 3H), 1. 75 – 1.80 (m, 2H), 3.81 (s, 3H), 3.92 (t, 2H), 4.94 – 4.96 (m, 1H), 5.23 (d, 1H), 6.31 (s, 1H), 6.62 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.73 (d, J = 8.4Hz, 1H), 6.95 (d,J = 2.1Hz, 1H), 7.27 – 7.28 (m,5H).

7h：^{1}H NMR ($CDCl_3$，300 MHz): δ 0.87 (t, 3H), 1.25 – 1.30 (m, 18H), 1.42 (d, J = 7.2Hz, 3H), 1.79 – 1.81 (m, 2H), 3.82 (s, 3H), 3.93 (t, 2H), 4.97 – 5.00 (m, 1H), 5.17 (d, 1H), 6.43 (s, 1H), 6.60 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.74 (d, J = 8.4Hz, 1H), 6.94 (d, J = 2.1Hz, 1H), 7.29 – 7.30 (m,5H).

7i:^{1}H NMR ($CDCl_3$，300 MHz): δ 1.28 (d, J = 6.6 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H), 1.40 (d, J = 6.6 Hz, 3H), 3.82 (s, 3H), 4.41 – 4.45 (m, 1H), 4.91 – 4.98 (m, 1H), 5.32 (d, 1H), 6.63 (dd, J1 = 8.7 Hz, J2 = 2.1Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 2.1 Hz, 1H), 7.27 – 7.28 (m, 5H).

7j: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.96 (d, J = 6.6 Hz, 6H), 1.38 (d, J = 6.9 Hz, 3H), 2.07 – 2.11 (m, 1H), 3.66 (d, J = 6.6Hz, 2H), 3.79 (s, 3H), 4.92 – 4.97 (m, 1H), 5.42 – 5.43 (m, 1H), 6.56 (dd, J1 = 8.7 Hz, J2 = 2.1Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 7.28 – 7.31 (m, 5H).

7k: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.92 (d, J = 6Hz, 6H), 1.40 (d, J = 6.6Hz, 3H), 1.67 – 1.80 (m, 3H), 3.80 (s, 3H), 3.94 (t, 2H), 4.93 – 4.98 (m, 1H), 5.32 (d, 1H), 6.60 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.66 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.1Hz, 1H), 7.25 – 7.30 (m, 5H).

7l: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.90 (d, J = 6.6 Hz, 6H), 1.26 – 1.34 (m, 2H), 1.47 (d, J = 7.2 Hz, 3H), 1.58 – 1.61 (m, 1H), 1.80 – 1.86 (m, 2H), 3.84 (s, 3H), 3.91 (t, 2H), 4.96 – 4.98 (m, 1H), 5.23(m, 1H), 6.59 (dd, J1 = 8.7 Hz, J2 = 2.4 Hz, 1H), 6.73(d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 7.26-7.36(m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.75, 23.20, 27.29, 28.04, 35.16, 49.77, 56.55, 69.41, 107.09, 112.48, 112.71, 126.04, 127.27, 128.79, 132.72, 144.49, 145.70, 149.07, 156.23; LC–MS: m/z : 371$[M+H]^+$,393 $[M+Na]^+$.

7m ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.39 (d, J = 6.6Hz, 3H), 3.79 (s, 3H), 4.64 (s, 2H), 4.92 – 4.96 (m, 1H), 5.50 (d, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.96 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 7.05(d, J = 2.1Hz, 1H), 7.27 – 7.28 (m, 5H).

7n: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.43 (d, J = 6.6Hz, 3H), 1.64 – 1.72 (m, 2H), 3.81 (s, 3H), 3.95 (t, 2H), 4.93 – 4.97 (m, 1H), 5.11 – 5.17 (m, 2H), 5.82 – 5.95 (m, 1H), 6.45 (m, 1H), 6.63 (m, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.94 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 7.26 – 7.33 (m, 5H).

7o: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.37 (d, J = 6.6Hz, 3H), 1.83 – 1.87 (m, 2H), 2.15 – 2.17 (m, 2H), 3.78 (s, 3H), 3.89 (t, 2H), 4.93 – 4.98 (m, 3H), 5.46 (s, 1H), 5.78 – 5.85 (m, 1H), 6.62 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.71 (d, J = 8.4Hz, 1H), 6.99 (d,J = 2.1Hz, 1H), 7.23 – 7.26 (m, 5H).

7p: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.38 (d, J = 6.6 Hz, 3H), 1.76 (s, 3H), 3.80 (s, 3H), 4.39 (s, 2H), 4.95 (s, 1H), 4.97 – 4.99 (m, 1H), 5.02 (s, 1H), 5.42 (d, 1H), 6.62 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 6.98 (d, J = 2.1Hz, 1H), 7.28 – 7.30 (m, 5H).

7q: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.45 (d, J = 6.6 Hz, 3H), 3.42 (s, 3H), 3.75 – 3.78 (m, 2H), 3.82 (s, 3H), 4.10 – 4.12 (m, 2H), 4.88 (d, 1H), 4.93 – 4.98 (m, 1H), 6.10 (s, 1H), 6.71 (dd, J1 = 2.1Hz, J2=8.4Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 2.1Hz,1H), 7.30 – 7.32 (m, 5H).

7r: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.39 (d, J = 6.6 Hz, 3H), 2.63 – 2.67 (m, 1H), 2.80 – 2.83 (m, 1H), 3.29 – 3.32 (m, 1H), 3.79 (s, 3H), 3.83 – 3.90 (m, 1H), 4.18 (dt, 1H), 4.91 – 4.96 (m, 1H), 5.40 (d, J = 7.2Hz, 1H), 6.70 (m, 2H), 7.01(m, 1H), 7.27 – 7.28 (m, 5H).

7s: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.43 (d, J = 6.6Hz, 3H), 1.79 (s, 2H), 3.83 (s, 3H), 4.64 (s, 2H), 4.97 – 5.01 (m, 1H), 5.13 (d, 1H), 6.41 (s, 1H), 6.77 (s, 2H), 6.97 (s, 1H), 7.27 – 7.31 (m, 5H).

7t: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.08 (t, 3H), 1.44 (d, J = 6.6Hz, 3H), 2.14 – 2.21 (m, 2H), 3.83 (s, 3H), 4.66 (s, 2H), 4.95 – 5.05 (m, 2H), 6.23 (s, 1H), 6.78 (s, 2H), 6.97 (s, 1H), 7.31 – 7.34 (m, 5H).

7u: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.40 (d, J = 6.6Hz, 3H), 1.82 – 1.85 (m, 4H), 1.98 – 2.01 (m, 2H), 2.20

– 2.24 (m, 1H), 2.86 (d, 3H), 2.99 – 3.04 (m, 2H), 3.68 (d, 2H), 3.74 (s, 3H), 4.91 – 4.96 (m, 2H), 5.88 (d, 1H), 6.67 (d, J = 7.8Hz, 1H), 6.74 (d, J=7.8Hz, 1H), 6.99 (s, 1H),7.31 – 7.33 (m, 5H).

7v: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.43 (d, J = 6.6Hz, 3H), 1.45 – 1.47 (m, 2H), 1.68 – 1.70 (m, 4H), 2.67 – 2.69 (m, 2H), 2.85 (t, 2H), 3.26 – 3.30 (m, 2H), 3.73 (s, 3H), 3.98 (t, 2H), 4.92 – 4.96 (m, 1H), 6.20 (d, 1H), 6.66 (d, J = 8.7Hz, 1H), 6.86 (d, J = 2.1Hz, 1H), 6.99 (dd, J1 = 8.7Hz，J2 = 2.1Hz, 1H), 7.27 - 7.35 (m, 5H).

7w: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.42 (d, J = 6.6Hz, 3H), 1.81 – 1.83 (m, 4H), 2.74 – 2.76 (m, 4H), 2.93 (t, 2H), 3.72 (s, 3H), 3.95 (t, 2H), 4.91 – 4.95 (m, 1H), 6.13 (s, 1H), 6.65 (d, J1 = 8.7Hz, 1H), 6.86 (s, 1H), 6.89 (d, J = 8.7Hz, 1H), 7.02 (s, 1H), 7.26 – 7.32(m, 5H).

7x: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.99 (m, 2H), 1.22 – 1.27 (m, 5H), 1.44 (d, J = 6.6Hz, 3H）, 1.71 – 1.75 (m, 2H), 1.85 – 1.88 (m, 2H), 3.72 (d, J = 6.2 Hz, 2H), 3.82 (s, 3H), 4.98 – 5.00 (m, 2H), 6.21 (s, 1H), 6.64 (dd, J1 = 8.7Hz，J2 = 2.1Hz, 1H), 6.77 (d, J = 8.7Hz, 1H), 6.90 (d, J = 2.1Hz, 1H), 7.30 – 7.32 (m, 5H).

Compound 6f-k was prepared according to the procedure for compound **6c** except using vanillin replaced isovanillin.
6f: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.38 (d, J = 6.6Hz, 3H), 3.77 (s, 3H), 4.88 – 4.90 (m, 1H), 5.55 (d, 1H), 6.47 (dd, J1 = 8.7Hz，J2 = 2.1Hz, 1H), 6.71 (d, J = 8.7Hz, 1H), 7.04 (d, J = 2.1Hz, 1H), 7.26 – 7.29 (m, 5H).

6g: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.45 (d, J = 6.6Hz, 3H), 3.82 (s, 3H), 4.96 – 4.99 (m, 2H), 5.09 (s, 2H), 6.20 (s, 1H), 6.55 (dd, J1 = 8.7Hz，J2 = 2.1Hz, 1H), 6.77 (d, J = 8.7Hz, 1H), 6.97 (d, J = 2.1Hz, 1H), 7.24 – 7.30 (m, 5H), 7.37 – 7.42 (m, 5H).

6h : ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.41 (t, 3H),1.42 (d, J = 6.6 Hz, 3H), 3.81 (s, 3H), 4.01 – 4.08 (m,2H), 4.97 – 5.01 (m, 1H), 6.01 (d, J = 7.8Hz, 1H), 6.62 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.79 (d, J = 8.4Hz, 1H), 6.93 (d, J = 1.8Hz, 1H), 7.31 – 7.35 (m, 5H).

6i: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.46 (d, J = 6.6Hz, 3H), 3.81 (s, 3H), 4.55 (d, J = 5.7Hz, 2H), 4.96 – 5.01 (m, 1H), 5.26 (d,J = 10.5Hz, 1H), 5.38 (d, J=16.8Hz, 1H), 6.02 – 6.14 (m, 1H), 6.61 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.78 (d, J = 8.4Hz, 1H), 6.94 (d, J = 1.8Hz, 1H), 7.31 – 7.33 (m, 5H).

6j: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.27 (t, 3H), 1.35 (d, J = 6.6 Hz, 3H), 3.85 (s, 3H), 4.25 – 4.28 (m, 2H), 4.68 (s, 2H), 4.98 – 5.01 (m, 1H), 5.42 (d, J = 5.4Hz, 1H), 6.64 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.81 (d, J = 8.4Hz, 1H), 7.01 (d, J = 1.8Hz, 1H), 7.28 – 7.30 (m, 5H).

6k: ^{1}H NMR ($CDCl_3$，300 MHz): δ 1.44(s, 9H), 1.47 (d, J = 6.6Hz, 3H), 3.46 – 3.51 (m, 2H), 3.84 (s, 3H), 4.030 – 4.03 (m, 2H), 4.96 (d, 1H), 4.98 – 5.01 (m, 1H), 6.58 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.78 (d, J = 8.4Hz, 1H), 7.02 (d, J = 1.8Hz, 1H), 7.32 – 7.34 (m, 5H).

Compound 12a-f was prepared according to the procedure for compound **6b** except using substituted pentyloxyl-aryl aldehyde replaced isovanillin. Some compounds were purified by flash chromatography on silica gel (PE : EtOAc = 2:1).
12a: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.89 (t, 3H), 1.38 – 1.40 (m, 2H), 1.43 (d, J = 6.6Hz, 3H), 1.68 – 1.72 (m, 2H), 3.89 (t, 2H), 4.87 – 4.92 (m, 1H), 5.30 (d, 1H), 6.56 – 6.57 (m, 1H), 6.58 (s, 1H), 6.68 – 6.70 (m, 1H), 6.96 (s, 1H), 7.12 (t, 1H), 7.30 – 7.34 (m, 5H).

12b: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (t, 3H), 1.37 – 1.39 (m, 2H), 1.43 (d, J = 6.6Hz, 3H), 1.67 – 1.74 (m, 2H), 3.70 (s, 1H), 3.85 (t, 2H), 4.92 – 4.94 (m, 1H), 5.36 (d, 1H), 6.15 – 6.16 (m, 1H), 6.43 (dd, 2H), 6.64 (s, 1H), 7.29 – 7.30 (m, 5H).

12c: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.92 (t, 3H), 1.35 – 1.38 (m, 4H), 1.52 (d, J = 6.6Hz, 3H), 1.58 – 1.69

(m, 2H), 3.72 (s, 1H), 3.87 (t, 2H), 4.87 (d, 1H), 4.93 – 4.95 (m, 1H), 6.44 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.72(d, J = 8.4Hz, 1H), 6.80 (s, 1H), 7.28 – 7.35 (m, 5H), 7.80 (d, J = 1.8Hz, 1H).

12d: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (t, 3H), 1.39 – 1.43 (m, 2H), 1.44 (d, J = 6.6Hz, 3H), 1.69 – 1.73 (m, 2H), 3.90 (t, 2H), 4.96 – 5.00 (m, 1H), 5.20 (d, 1H), 6.65 – 6.67 (m, 1H), 6.82 (m, 2H), 7.15 (m, 1H), 7.28 – 7.30 (m, 5H).

12e: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.92 (t, 3H), 1.25 – 1.33 (m, 4H), 1.48 (d, J = 6.6Hz, 3H), 1.70 – 1.73 (m, 2H), 3.76 (s, 1H), 3.89 (t, 2H), 4.88 (d, 1H), 4.94 – 4.96 (m, 1H), 6.42 – 6.44 (m, 2H), 7.28 (m, 5H), 7.73 (d, J = 9.3Hz, 1H).

12f：^{1}H NMR ($CDCl_3$，300 MHz): δ 0.94 (t, 3H), 1.36 – 1.44 (m, 4H), 1.43 (d, J = 6.6Hz, 3H), 1.86 – 1.87 (m, 2H), 3.79 (s, 1H), 4.01 (t, 2H), 5.02 – 5.04 (m, 1H), 5.32 (d, 1H), 5.70 (s, 1H), 6.33 (s, 1H), 7.30 – 7.32 (m, 5H).

Compound 13a-f was prepared according to the procedure for compound **11** except using 1-bromo-pentane replaced benzyl bromide, then the isocyanate was treated with various amine afforded desired compound. Some compounds were purified by flash chromatography on silica gel (PE: EtOAc = 2:1).
13a:^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, 3H), 1.23 (d, J=6.6Hz, 3H), 1.41 – 1.48 (m, 2H), 1.72 – 1.80 (m, 2H), 2.89 – 2.91 (m, 1H), 3.17 – 3.21 (m, 1H), 3.45 – 3.52 (m, 1H), 3.76 (s, 1H), 3.88 (t, 2H), 4.90 – 4.92 (m, 1H), 6.52 (dd, J1 = 8.4Hz, J2 = 1.8Hz, 1H), 6.54 (s, 1H), 6.68 (d, J = 8.4Hz, 1H), 6.88 (d, J = 1.8Hz, 1H), 7.13 – 7.17 (m, 3H), 7.26 – 7.28 (m, 2H).

13b: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.93 (t, 3H), 1.18 (d, J = 6.6Hz, 3H), 1.45 – 1.50 (m, 2H), 1.80 – 1.86 (m, 4H), 2.99 – 3.02 (m, 1H), 3.25 – 3.29 (m, 2H), 3.78 (s, 1H), 3.89 (t, 2H), 4.76 4.78 (m, 1H), 6.26 (s, 1H), 6.65 (dd, J1 = 8.4Hz, J2 = 1.8Hz, 1H), 6.78 (d, J = 8.4Hz, 1H), 6.93 (d, J = 1.8Hz, 1H), 7.15 – 7.18 (m, 3H), 7.26 – 7.28 (m, 2H).

13c: ^{1}H NMR ($CDCl_3$，300 MHz):δ 0.93 (t, 3H), 1.37 -1.46 (m, 4H), 1.65 (m, 4H), 1.79 (m, 2H), 2.00 (m, 1H), 2.40 (m, 1H), 2.99 (m, 1H), 3.80 (s, 1H), 3.97 (t, 2H), 5.47 (m, 1H), 6.67 (dd, J1 = 8.4Hz, J2 = 1.8Hz, 1H), 6.73 (d, J = 8.4Hz, 1H), 7.17 (d, J = 1.8Hz, 1H), 7.28 (m, 5H).

13d: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.92 (t, 3H), 1.37 -1.46 (m, 2H), 1.68 – 1.77 (m, 2H), 2.38 – 2.43 (m, 1H), 2.64 – 2.74 (m, 1H), 2.76 – 2.79 (m, 1H), 3.76 (s, 1H), 3.89 (t, 2H), 5.21 – 5.26 (m, 1H), 6.63 (d, 1H), 6.57 (dd, J1 = 8.4Hz, J2 = 1.8Hz , 1H), 6.60 (d, J = 8.4Hz, 1H), 6.99 (d, J =1.8Hz, 1H), 7.10 – 7.13 (m, 1H), 7.20 – 7.24 (m, 2H), 7.28 (m, 2H).

13e: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.96 (t, 3H), 1.42 – 1.46 (m, 2H), 1.75 – 1.82 (m, 2H), 1.88 – 1.92 (m, 4H), 2.40 – 2.45 (m, 1H), 3.23 – 3.26 (m, 1H), 3.77 (s, 3H), 3.95 (t, 2H), 4.89 – 4.95 (m, 1H), 5.91 (s, 1H), 6.31 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.69 (d, J = 8.4Hz, 1H), 7.12 (d, J = 2.1Hz, 1H), 7.33 – 7.35 (m, 5H).

13f: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (t, 3H), 0.96 (t, 3H), 1.43 – 1.51 (m, 2H), 1.72 – 1.83 (m, 4H), 3.84 (s, 3H), 3.94 (t, 2H), 4.74 – 4.78 (m, 1H), 4.85 (d, 1H), 5.98 (s, 1H), 6.66 (dd, J1 = 8.7Hz, J2 = 2.1Hz, 1H), 6.77 (d, J = 8.7Hz, 1H), 6.89 (d, J = 2.1Hz, 1H), 7.28 – 7.33 (m, 5H).

Compound 14a, 14d-e, 14g-h and 15a-m was prepared according to the procedure for compound **11** except using 1-bromo-4-methyl-pentane replaced benzyl bromide. Then the isocyanate was treated with various amine afforded desired compounds. Some compounds were purified by flash chromatography on silica gel (PE: EtOAc = 2:1).
14a: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.90 (d, J = 6.6 Hz, 6H), 1.26 – 1.32 (m, 2H), 1.52 (d, J = 6.6Hz, 3H), 1.52 – 1.62 (m, 1H), 1.80 – 1.86 (m, 2H), 2.71 (s, 3H), 3.81 (s, 3H), 3.99 (t, 2H), 5.72 – 5.74 (m, 1H), 6.38 (s, 1H), 6.72 (dd, J1 = 5.4Hz, J2 = 2.1Hz, 1H)，6.74 (d, J = 5.4Hz, 1H)，7.25 (d, J = 2.1Hz, 1H), 7.26-7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.78, 22.78, 27.35, 28.05, 29.28, 35.21, 52.32, 56.61,

69.44, 106.98, 112.09, 112.26, 127.28,127.49, 128.77, 133.17, 141.49, 145.58, 148.099, 156.16; LC–MS: m/z : 385$[M+H]^+$, 407$[M+Na]^+$

14d: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.89 (d, J = 6.6Hz, 6H), 1.23 – 1.38 (m, 2H), 1.55 (d, J=7.2Hz, 3H), 1.58 – 1.62 (m, 1H), 1.77 – 1.87 (m, 2H), 3.32 – 3.37 (m, 4H), 3.79 (s, 3H), 3.95 (t, 2H), 5.63 – 5.65 (m, 1H), 6.68 – 6.72 (m, 2H), 7.15 (s, 1H), 7.29 – 7.38 (m, 5H), 8.16 (d, 1H).

14e: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.91 (d, J = 6.6Hz, 6H), 1.24 – 1.33 (m, 2H), 1.45 – 1.55 (m, 1H), 1.60 (d,J = 7.2Hz, 3H), 1.75 – 1.83 (m, 2H), 3.30 – 3.35 (m, 4H), 3.80 (s, 3H), 3.95 (t, 2H), 5.52 – 5.54 (m, 1H), 6.59 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.71 (d, J = 8.4Hz, 1H), 7.08 (d, J = 2.1Hz, 1H), 7.29 – 7.34 (m, 5H).

14g: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.88 (d, J = 6.6 Hz, 6H), 1.28 – 1.32 (m, 2H), 1.45 – 1.52 (m, 3H), 1.58 (d, J = 7.2 Hz, 3H), 1.79 – 1.81 (m, 2H), 3.33 – 3.35 (m, 2H), 3.58 – 3.61 (m, 2H), 3.78 (s, 3H), 3.94 (t, 2H), 5.55 (m, 1H), 6.68 (m, 2H), 7.30 – 7.33 (m, 6H).

14h: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.92(d, J = 6.6 Hz, 6H), 1.25 – 1.30 (m, 4H), 1.59 – 1.62 (m, 1H), 1.53 (d, J = 7.2 Hz, 3H), 1.83 – 1.86 (m, 4H), 3.34 – 3.37 (m, 2H), 3.81 (s, 3H), 3.99 (t, 2H), 5.78 – 5.80 (m, 1H), 6.73 – 6.78 (m, 2H), 7.30 – 7.39 (m, 6H).

15a: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.90 (d, J = 6.6 Hz, 6H), 1.29 – 1.35 (m, 2H), 1.43 (d, J = 7.2 Hz, 3H), 1.61 – 1.64 (m, 1H), 1.81 – 1.88 (m, 2H), 3.85 (s, 3H), 3.95 (t, 2H), 4.83 (d, 1H), 4.96 – 5.00 (m, 1H), 6.07 (s, 1H), 6.68 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.80 (d, J = 8.4Hz, 1H), 6.89 (d, J = 2.1Hz, 1H), 7.18 (m, 1H), 7.22 (d, 2H), 7.33 (d, 1H).

15b: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.91 (d, J = 6.6 Hz, 6H), 1.32 – 1.35 (m, 2H), 1.45 (d, J = 7.2 Hz, 3H), 1.61 – 1.65 (m, 1H), 1.86 (m, 2H), 3.88 (s, 3H), 3.95 (t, 2H), 4.98 – 5.01 (m, 1H), 5.01 (d, 1H), 6.68 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.81 (d, J = 8.4Hz, 1H), 6.90 (d, J = 2.1Hz, 1H), 7.18 (d, 2H), 7.35 (d, 2H).

15c: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.89 (d, J = 6.6 Hz, 6H), 1.25 – 1.34 (m, 2H), 1.49 (d, J = 7.2 Hz, 3H), 1.62 – 1.64 (m, 1H), 1.80 – 1.85 (m, 2H), 3.84 (s, 3H), 3.97 (t, 2H), 5.29 (d, 1H), 5.39 – 5.43 (m, 1H), 6.28 (s, 1H), 6.71 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.80 (d, J = 8.4Hz, 1H), 6.90 (d, J = 2.1Hz, 1H), 7.38 – 7.42 (m, 1H), 7.52 – 7.56 (m, 2H), 7.86 (d, J = 8.4Hz, 1H).

15d: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.90 (d, J = 6.6 Hz, 6H), 1.26 – 1.34 (m, 2H), 1.50 (d, J = 7.2 Hz, 3H), 1.62 – 1.66 (m, 1H), 1.84 (m, 2H), 3.85 (s, 3H), 3.97 (t, 2H), 5.31 (d, 1H), 5.44 – 5.48 (m, 1H), 6.73 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.85 (d, J = 8.4Hz, 1H), 6.98 (d, J = 2.1Hz, 1H), 7.54 (d, 2H), 7.95 (d, 2H).

15e: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.86 (d, J = 6.6 Hz, 6H), 1.24 – 1.27 (m, 2H), 1.34 (d, J = 7.2 Hz, 3H), 1.59 – 1.63 (m, 1H), 1.82 – 1.87 (m, 2H), 3.76 (s, 3H), 3.84 (t, 2H), 4.81-4.83 (m, 1H), 5.32 (d, 1H), 6.63 – 6.73 (m, 3H), 6.94 – 7.01 (m, 3H), 7.27 (m, 1H).

15f: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.87 (d, J = 6.6 Hz, 6H）, 1.22 -1.27 (m, 2H), 1.45 (d, J = 7.2 Hz, 3H), 1.59 – 1.62 (m, 1H), 1.76 – 1.79 (m, 2H), 3.78 (s, 3H), 3.86 (t, 2H), 4.82 – 4.87 (m, 1H), 5.17 – 5.19 (m, 1H), 6.57 – 6.59 (m, 2H), 6.69 – 6.75 (m, 2H), 6.91 – 6.99 (m, 1H), 7.19 – 7.24 (m, 2H).

15g: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.90 (d, J = 6.6Hz, 6H), 1.23 – 1.30 (m, 2H), 1.43 (d, J = 6.6Hz, 3H), 1.58 – 1.62 (m, 1H), 1.82 – 1.87 (m, 2H), 3.84 (s, 3H), 3.92 (t, 2H), 4.86 (d, 1H), 4.93 – 4.96 (m, 1H), 6.10 (s, 1H), 6.65 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.79 (d, J = 8.4Hz, 1H), 6.89 (d, J = 2.1Hz, 1H), 6.99 – 7.03 (m, 2H), 7.28 – 7.29 (m, 2H).

15h: ^{1}H NMR ($CDCl_3$，300 MHz): δ 0.87 (d, J = 6.6Hz, 6H), 1.24 – 1.29 (m, 2H), 1.34 (d, J = 6.6Hz, 3H), 1.56 – 1.62 (m, 1H), 1.75 – 1.83 (m, 2H), 3.80 (s, 3H), 3.89 (t, 2H), 4.97 – 5.01 (m, 1H), 5.45 (d, 1H), 6.58 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.73 (d, J = 8.4Hz, 1H), 6.89 (s, 1H), 6.99 (d, J = 2.1Hz, 1H), 7.33 (d, J =

8.4Hz, 2H), 7.51 (d, J = 8.4Hz, 2H).

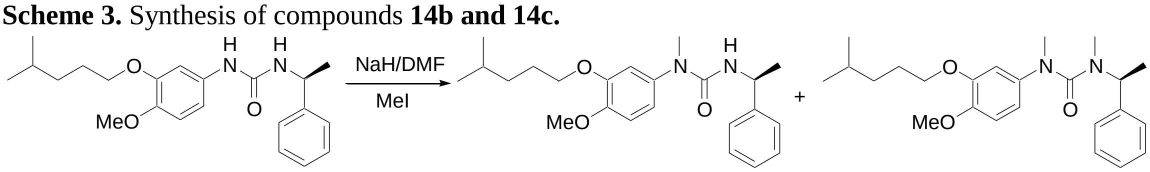
15i: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, J = 6.6Hz, 6H), 1.24 – 1.29 (m, 2H), 1.36 (d, J = 6.6Hz, 3H), 1.55 – 1.60 (m, 1H), 1.74 – 1.82 (m, 2H), 3.82 (s, 3H), 3.92 (t, 2H), 4.95 – 4.99 (m, 1H), 5.25 (d, 1H), 6.62 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.76 (d, J = 8.4Hz, 1H), 6.98 (d, J = 2.1Hz, 1H), 7.34 (d, J = 7.2Hz, 2H), 7.54 (d, J = 7.2Hz, 2H).

15j: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (d, J = 6.6 Hz, 6H), 1.24 – 1.30 (m, 2H), 1.37 (d, J = 7.2 Hz, 3H), 1.51 – 1.58 (m, 1H), 1.78 – 1.81 (m, 2H), 3.78 (s, 3H), 3.88 (s, 3H), 3.88 (t, 2H), 4.97 – 5.02 (m, 1H), 5.35 (d, 1H), 6.59 (m, 1H), 6.74 (m, 2H), 6.98 (s, 1H), 7.28 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 7.8 Hz, 2H).

15k: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, J = 6.6 Hz, 6H), 1.24 – 1.30 (m, 2H), 1.38 (d, J = 7.2 Hz, 3H), 1.52 – 1.58 (m, 1H), 1.78 – 1.81 (m, 2H), 3.80 (s, 3H), 3.90 (t, 2H), 4.89 (d, 1H), 4.96 – 4.99 (m, 1H), 6.61 (m, 1H), 6.76 (m, 2H), 6.98 (d, 1H), 7.33 (d, J = 7.8Hz, 2H), 8.01 (d, J = 7.8Hz, 2H).

15l: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, 3H), 1.43 (d, J = 6.6Hz, 3H), 1.42 – 1.47 (m, 2H), 1.74 – 1.81 (m, 2H), 2.31 (s, 3H), 3.82 (s, 3H), 3.94 (t, 2H), 4.93 – 4.99 (m, 1H), 5.02 (d, 1H), 6.26 (s, 1H), 6.61 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.76 (d, J = 8.4Hz, 1H), 6.92 (d, J = 2.1Hz, 1H), 7.12(d, J = 7.8Hz,2H), 7.18(d, J = 7.8Hz, 2H).

Scheme 3. Synthesis of compounds **14b and 14c.**



7l 14b 14c

To a solution of 1-[4-methoxy-3-(4-methyl-pentyloxy)-phenyl]-3-(1-phenyl-ethyl)-urea **7l** (111mg, 0.3 mmol) in 3 mL of anhydrous DMF at 0 °C was added 60% sodium hydride (24mg, 0.6mmol). After the mixture was stirred for 20 min, iodomethane (85mg, 0.6mmol) was added. The reaction mixture was then stirred at room temperature for 0.5 h and was diluted with 20 mL of ethyl acetate and 20 mL of H_2O, and the aqueous phase was extracted with 20 mL of ethyl acetate. The combined organic phases were then processed in the usual way and chromatographed (PE:EtOAc = 8:1) to yield **14b** (15mg, 13%) and **14c** (80mg, 67%).

14b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, J = 6.6Hz, 6H), 1.30 – 1.33 (m, 2H), 1.37 (d, J = 6.6Hz, 3H), 1.58 – 1.62 (m, 1H), 1.85 – 1.88 (m, 2H), 3.12 (s, 3H), 3.88 (s, 3H), 3.94 (t, 2H), 4.57 (m, 1H), 4.96 – 4.99 (m, 1H), 6.72 (d, J = 2.1Hz, 1H), 6.78 (dd, J1 = 8.4Hz, J2 = 2.1Hz, 1H), 6.87 (d, J = 8.4Hz, 1H), 7.26 – 7.30 (m, 5H).

14c: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (d, J = 6.6 Hz, 6H), 1.32 – 1.35 (m, 2H), 1.37 (d, J = 6.6Hz, 3H), 1.62 – 1.65 (m, 1H), 1.85 – 1.89 (m, 2H), 2.19 (s, 3H), 3.19 (s, 3H), 3.81 (s, 3H), 3.90 (t, 2H), 5.55 – 5.58 (m,1H), 6.62 (s, 1H), 6.65 (d, J = 8.4Hz, 1H), 6.78 (d, J = 8.4Hz, 1H), 7.26 – 7.30 (m, 5H).

Compound 14f was prepared according to the procedure for compound **14b** except using 3-bromo-propan-1-ol replaced iodomethane.

14f: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (d, J = 6.6 Hz, 6H), 1.29 – 1.36 (m, 2H), 1.35 (d, J = 6.6Hz, 3H), 1.57 – 1.66 (m, 3H), 1.85 – 1.87 (m, 2H), 3.61 – 3.69 (m, 2H), 3.77 – 3.79 (m, 2H), 3.89 (s, 3H), 3.89 – 3.94 (m, 2H), 4.53 (d, 1H), 4.97 – 5.02 (m, 1H), 6.65 (d, J = 2.1Hz, 1H), 6.75 (dd, J1 = 2.1Hz, J2 = 8.4Hz, 1H), 6.88 (d, J = 8.4Hz, 1H), 7.26 – 7.30 (m, 5H).

Haemolytic assay

Sheep erythrocytes were washed in GVB^{++} buffer (5×VBS stock buffer, 0.1% gelatine, 1mM $MgCl_2$, 0.15mM $CaCl_2$) and then incubated with rabbit anti-sheep erythrocyte antibodies (1:3000) to prepare sensitized erythrocytes (EAs). Normal human serum (NHS) was used as the complement source. EAs (25μl) were incubated with $DGVB^{++}$ buffer (100μl) and 1:40 diluted NHS (25μl) containing various dilutions of tested compounds (2μl in DMSO) at 37℃ for 1h. Water and DMSO were used as 100% lysis control and vehicle control for the assay, respectively. The reaction mixture was centrifuged and the supernatant was removed to a new plate. Optical density was measured at 405nm and the percent inhibition was calculated. Optical density was measured at 405nm and the percent hemolysis was calculated by the formula: hemolysis% = ODsample / ODvehicle control × 100%. The activity of compound was expressed as IC_{50}, the concentration that reduces hemolysis by 50%.

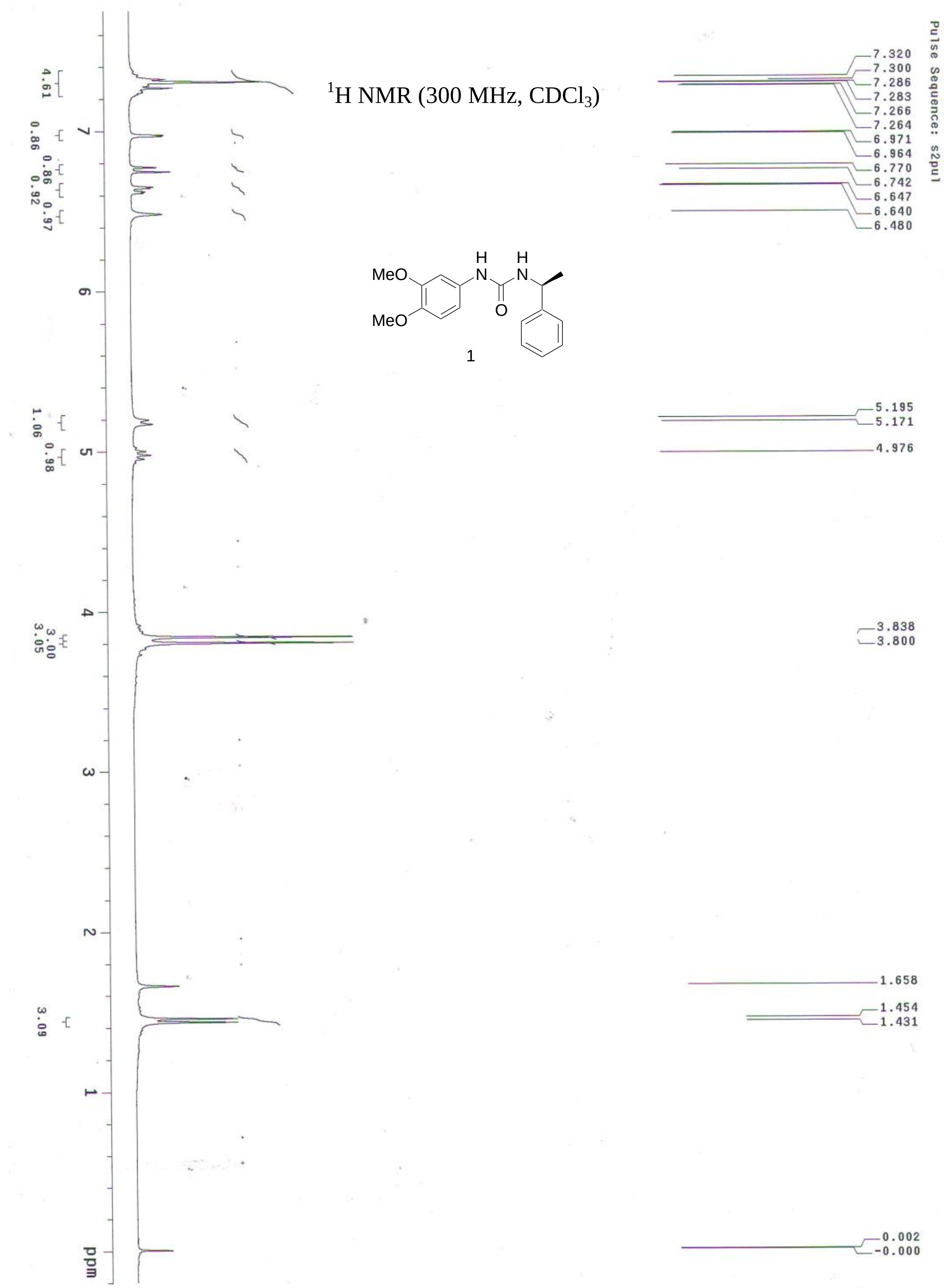
Quantitative assays to determine the activities of the three pathways of complement (ELISA assay)
The procedure was performed according to a previously published ptotocol**(1,2)**. Microtiter plates were coated overnight at 4℃ with purified human IgM (10μg/ml, Beijing Biosythesis Biotechnology Co., LTD), mannan (5μg/ml, sigma) or zymosan (20μg/ml, sigma) diluted in 75mM sodium carbonate buffer (pH 9.6) for classical, lectin and alternative pathway, respectively. After washing in phosphate-buffered saline (PBS)/0.05% Tween-20, the wells were blocked with 10% bovine serum in PBS at room temperature for 1h. 1:40 diluted NHS in GVB^{++} buffer (classical or lectin pathway) or Mg-EGTA buffer (alternative buffer, 5×VBS stock buffer, 0.1% gelatine, 7mM $MgCl_2$, 25mg/ml D-glucose, 10mM EGTA) were added to the plates and incubated for 1h for the deposition of C3d, C4c or C9 at 37℃. The reaction was stopped by washing 4 times with PBS/0.05% Tween-20. Subsequently, rabbit polyclonal antibodies against C3d (DAKO), C4c (DAKO) or mouse monoclonal antibody against C9 (abcam) diluted 1:1000 in blocking solution were added and the plates were incubated at room temperature for 1h. After washing 4 times with PBS/0.05% Tween-20, HRP-labeled secondary antibody against rabbit (1:2000, DAKO) or mouse (1:500, Beijing Biosythesis Biotechnology Co., LTD) were added and incubated at room temperature for 1h. Finally, wells were washed 4 times with PBS/0.05% Tween-20, and 0.1mg/ml TMB in substrate buffer (0.1M citric acid, 0.2M disodium hydrogen phosphate, pH5.4) containing 0.3% H_2O_2 were added. The reaction was stopped after 30min by adding 1N H_2SO_4 and the absorbance measured at 450nm.

(1) Skliris, A.; Happonen, K. E.; Terpos, E.; Labropoulou, V.; Børset, M.; Heinegård, D.; Blom, A. M.; Theocharis, A. D. Serglycin inhibits the classical and lectin pathways of complement via its glycosaminoglycan chains: implications for multiple myeloma. *Eur. J. Immunol.* **2011**, 41, 437–449.

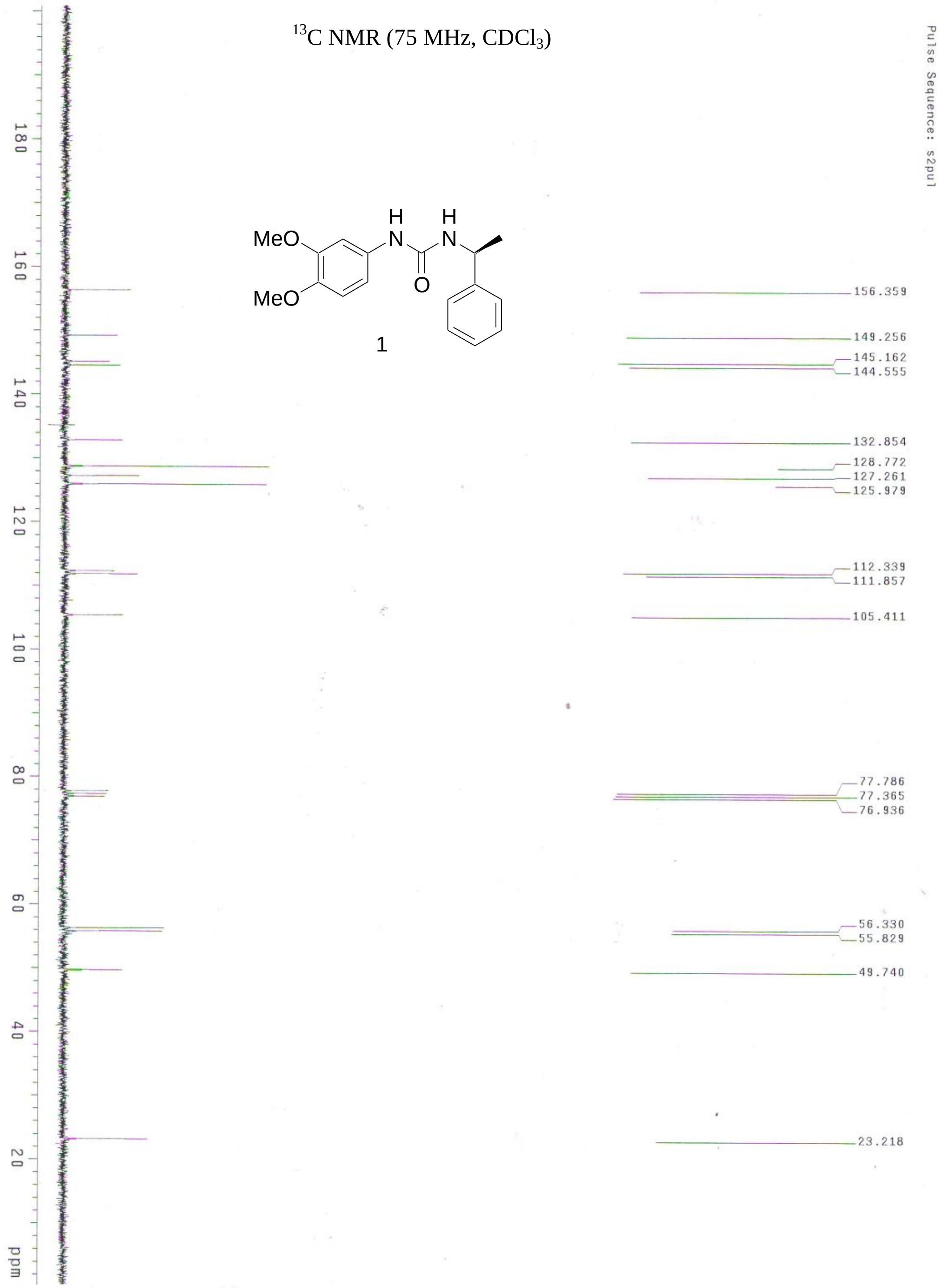
(2) Seelen, M. A.; Roos, A.; Wieslander, J.; Mollnes, T. E.; Sjöholm, A. G.; Wurzner, R.; Loos, M.; Tedesco, F.; Sim, R. B.; Garred, P.; Alexopoulos, E.; Turner, M. W.; Daha, M. R. Functional analysis of the classical, alternative and MBL pathways of the complement system: standardization and validation of a simple ELISA. *J. Immunol. Methods* **2005**, 296(1–2), 187–198.

[1]H NMR (300 MHz, $CDCl_3$)

1



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



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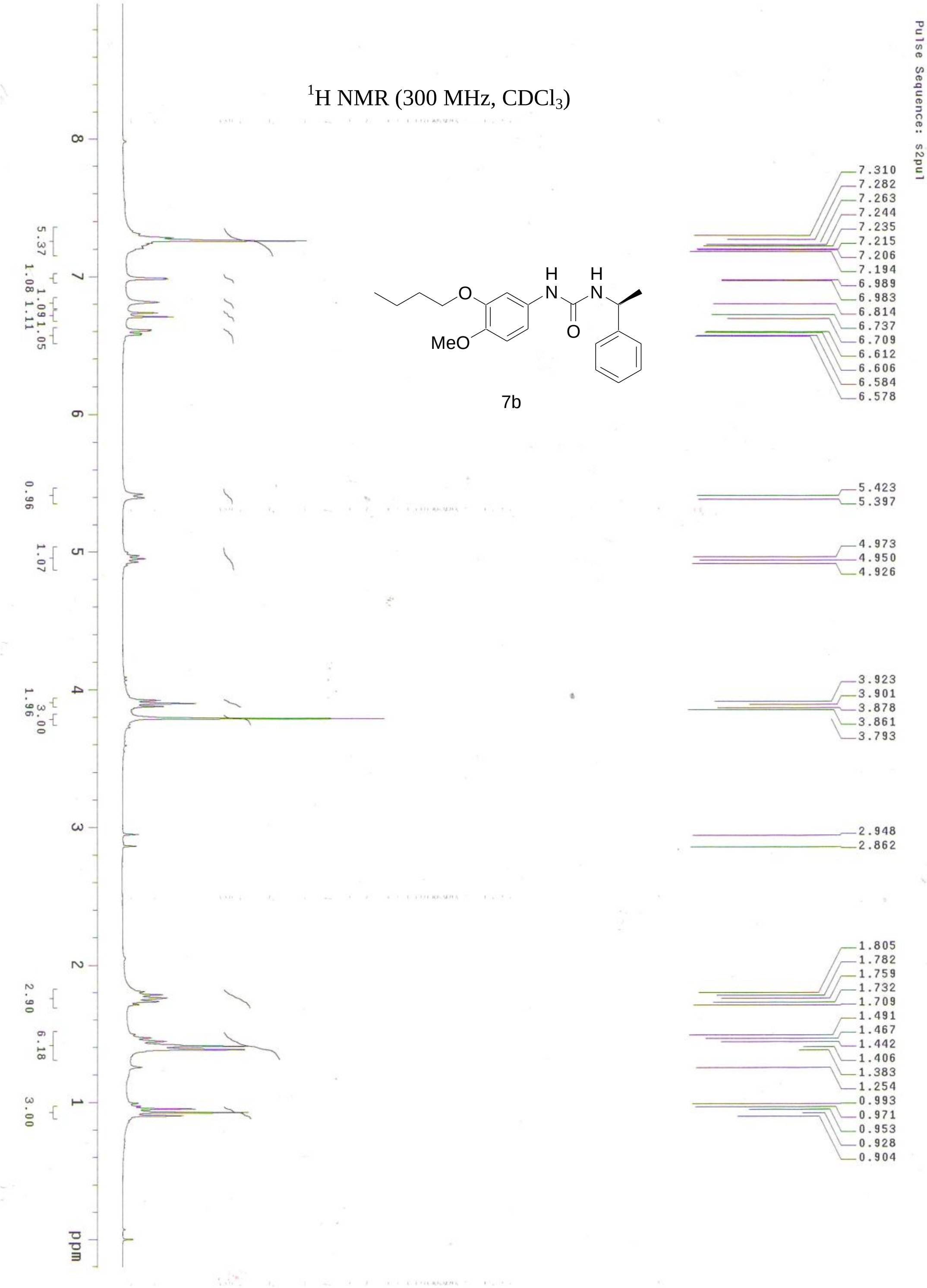
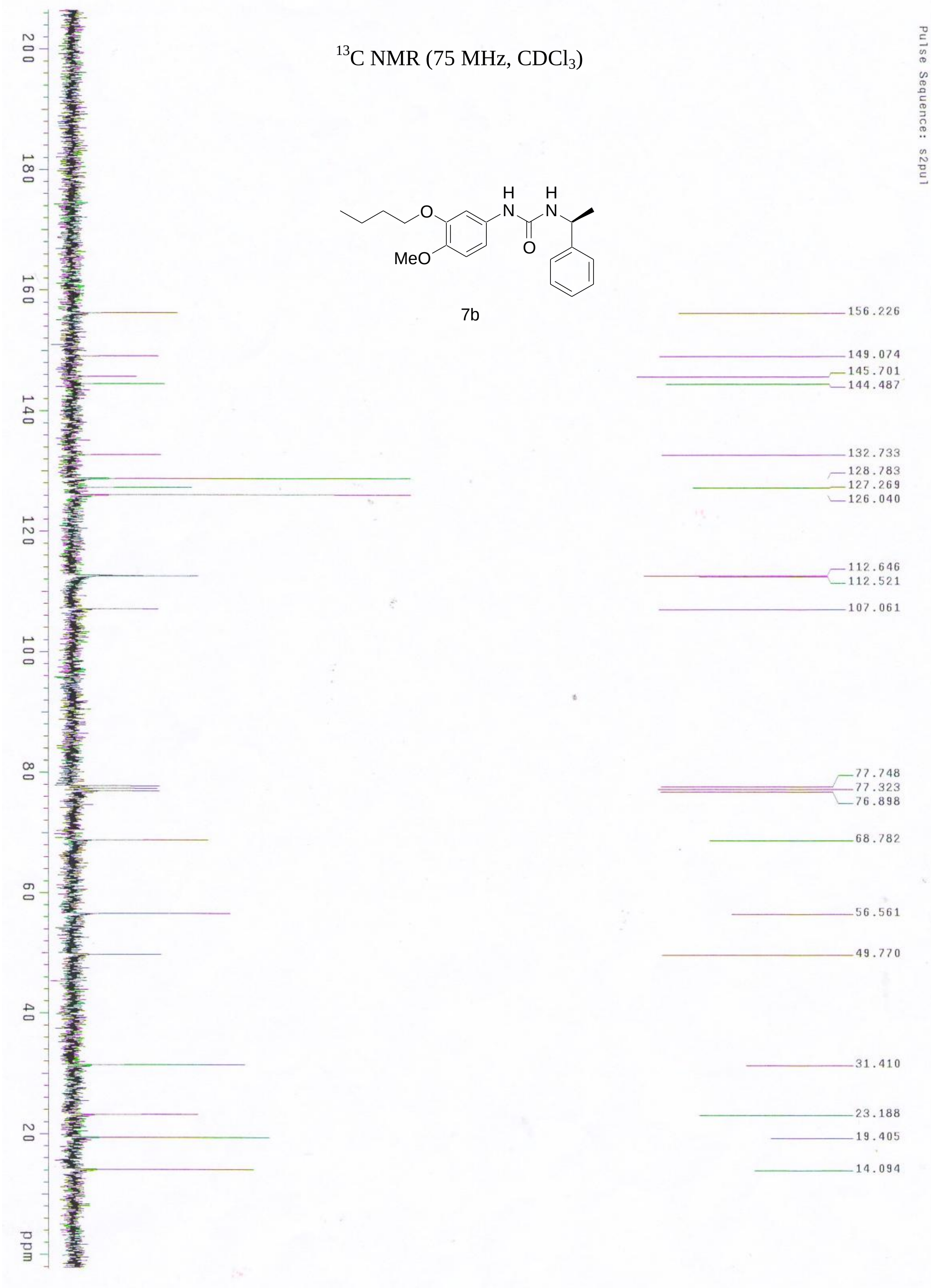


7b

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

7b



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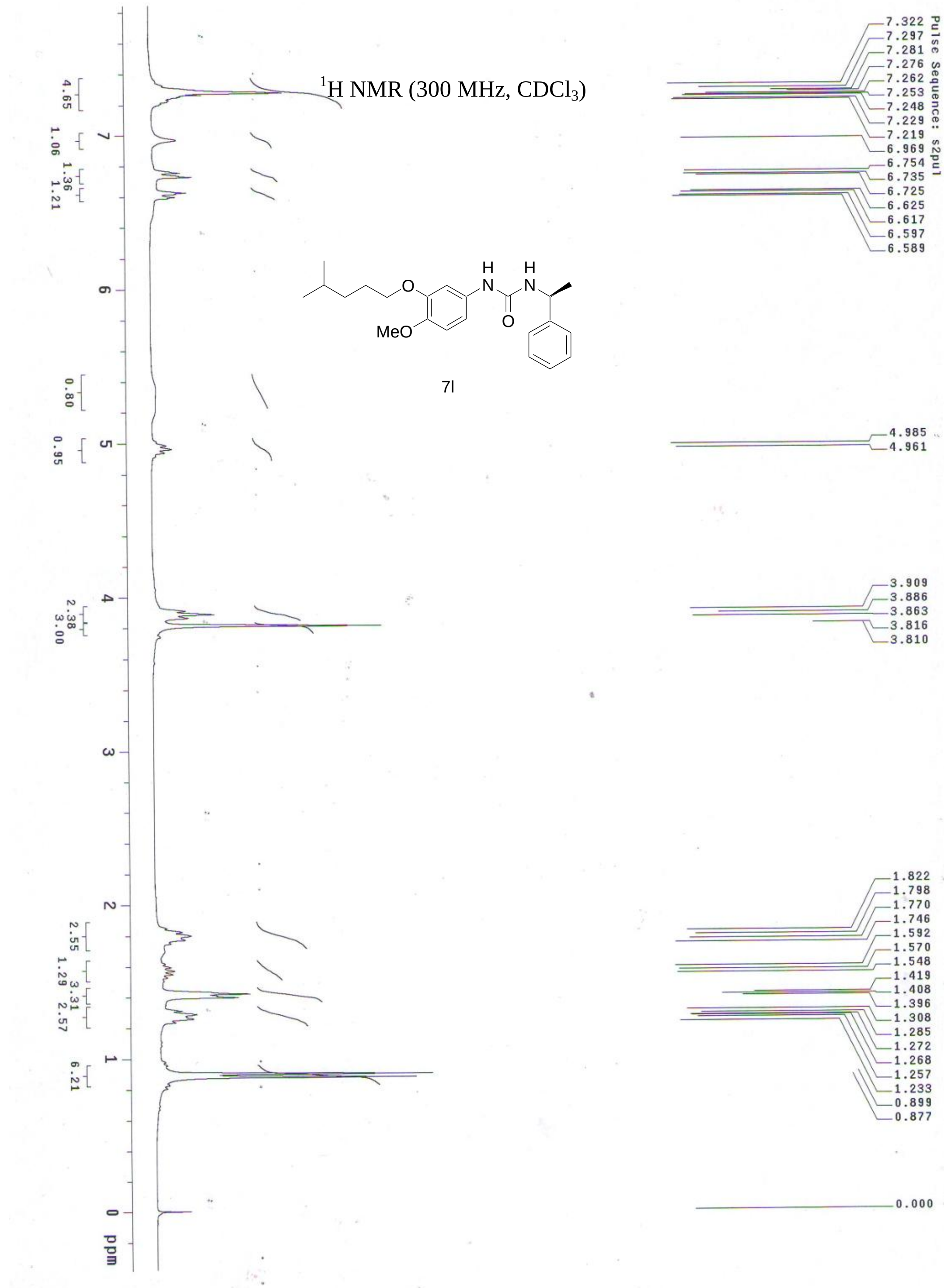
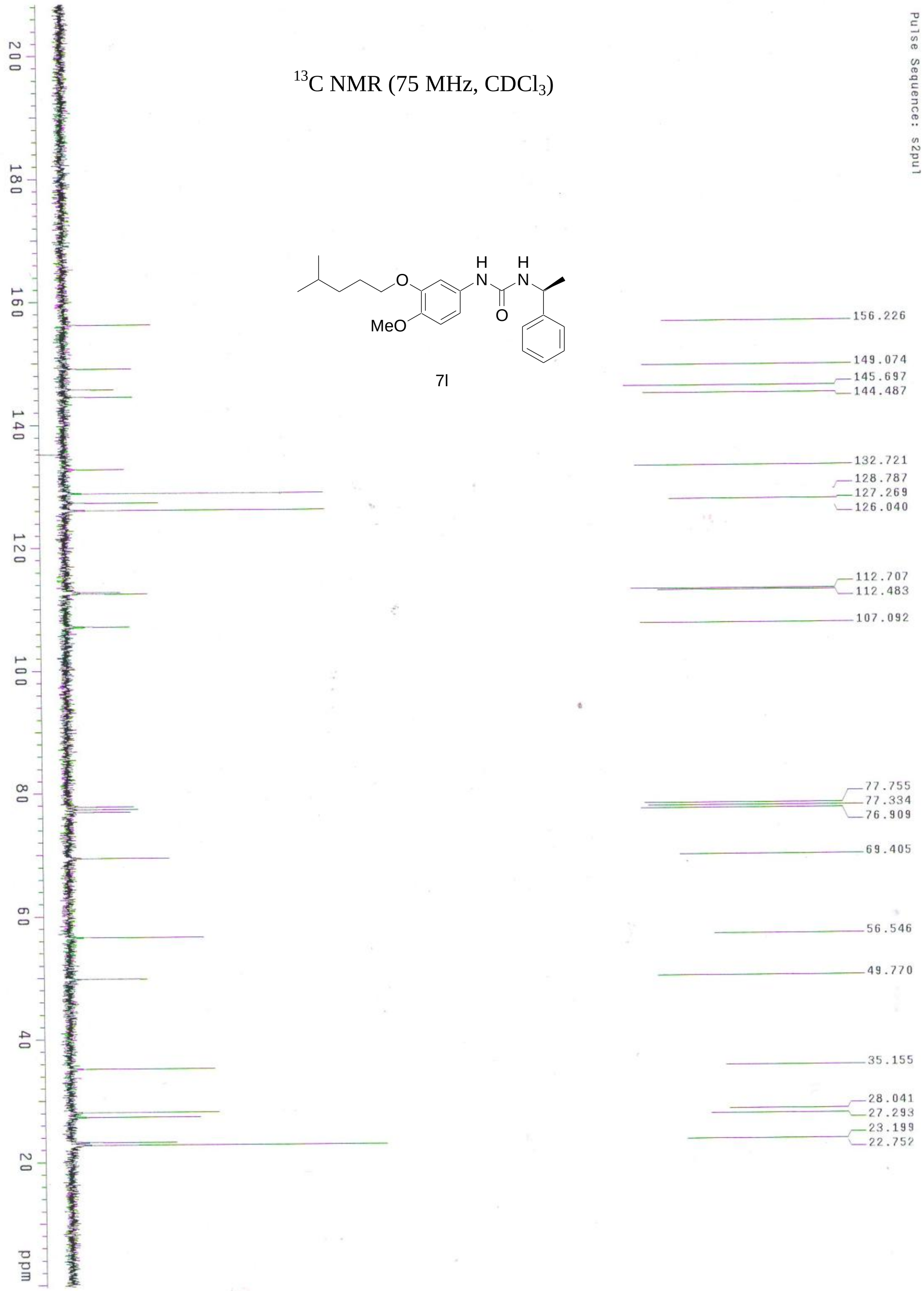
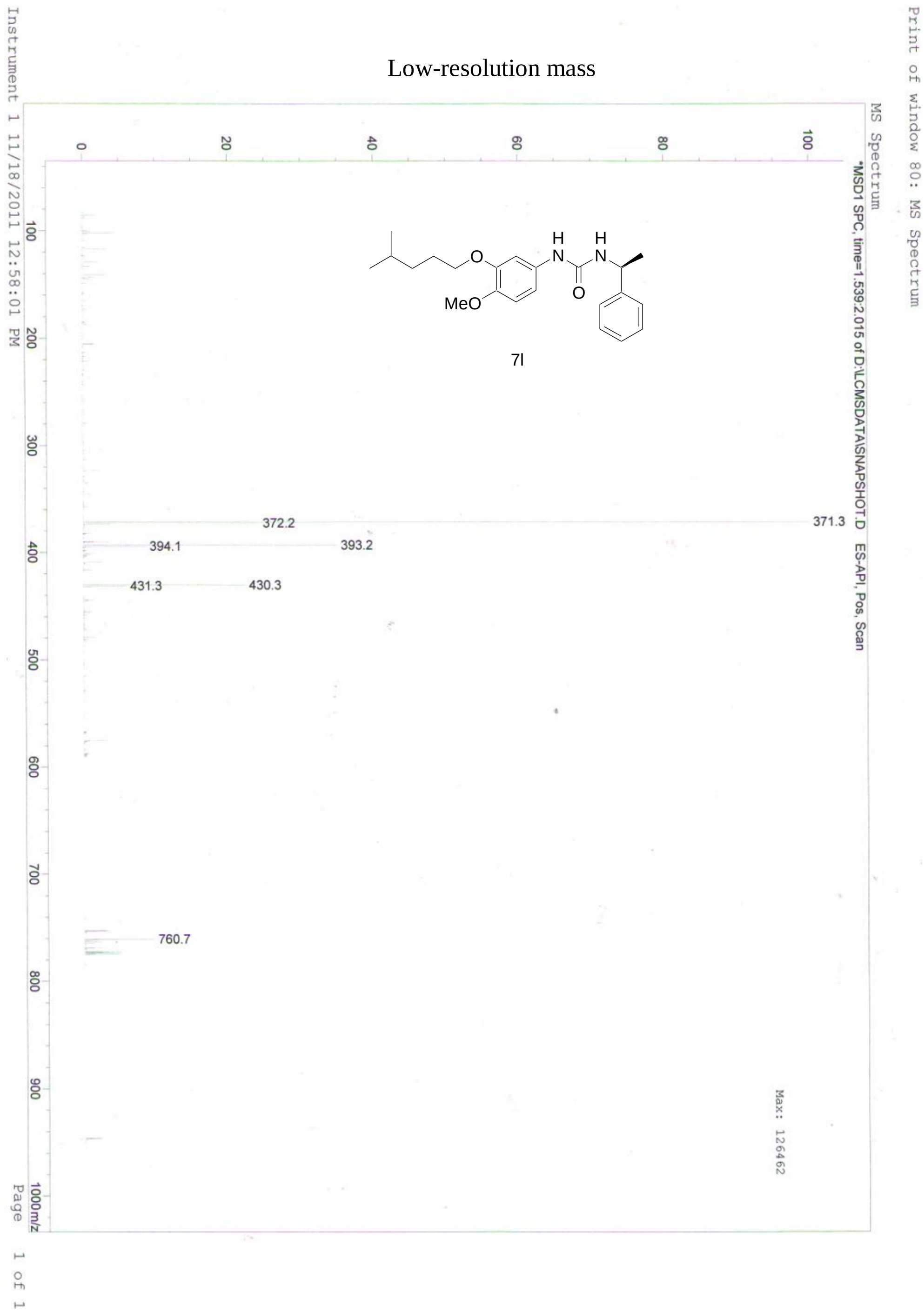


7l

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



Low-resolution mass



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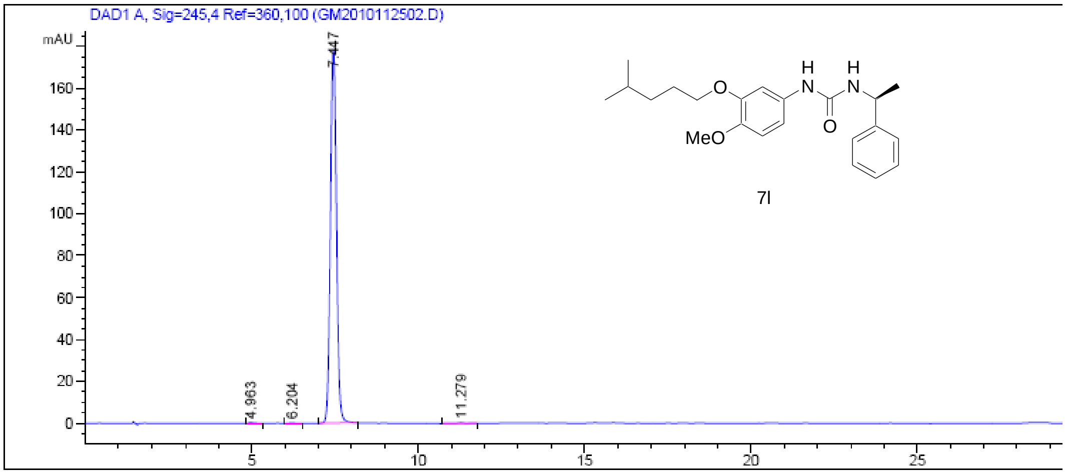

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面积百分比报告
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稀释因子 : 1.0000
内标使用乘积因子和稀释因子

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3	7.447	BB	0.1955	2255.80322	178.39891	99.3029
4	11.279	VB	0.3011	6.95686	3.10886e-1	0.3062

总量 : 2271.63875 179.37234

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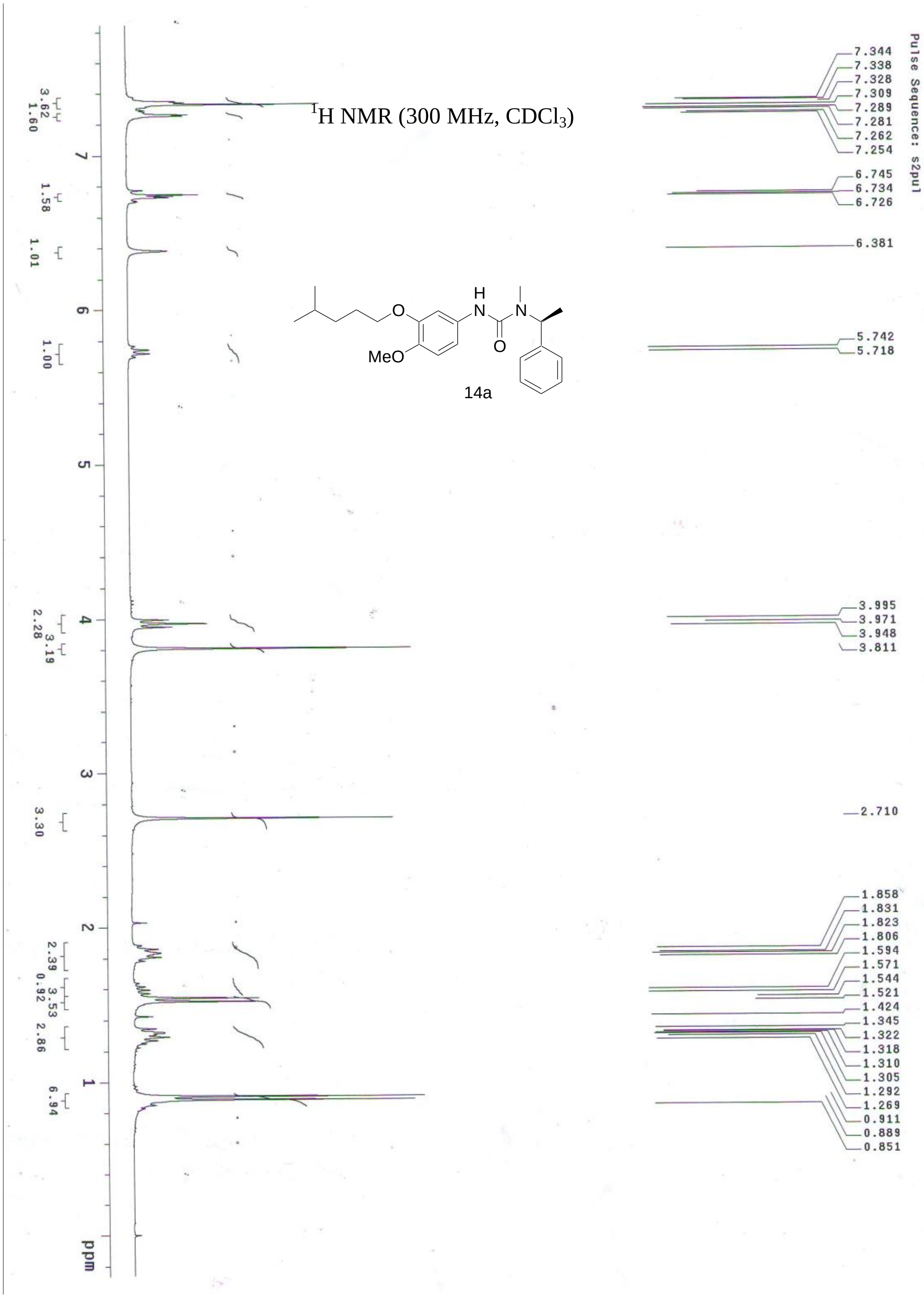
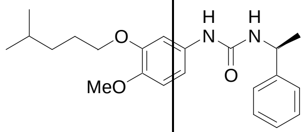
*** 报告结束 ***

仪器 1 2011-12-25 1:08:59 下午 页 1/1



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

14a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H
N
N
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O
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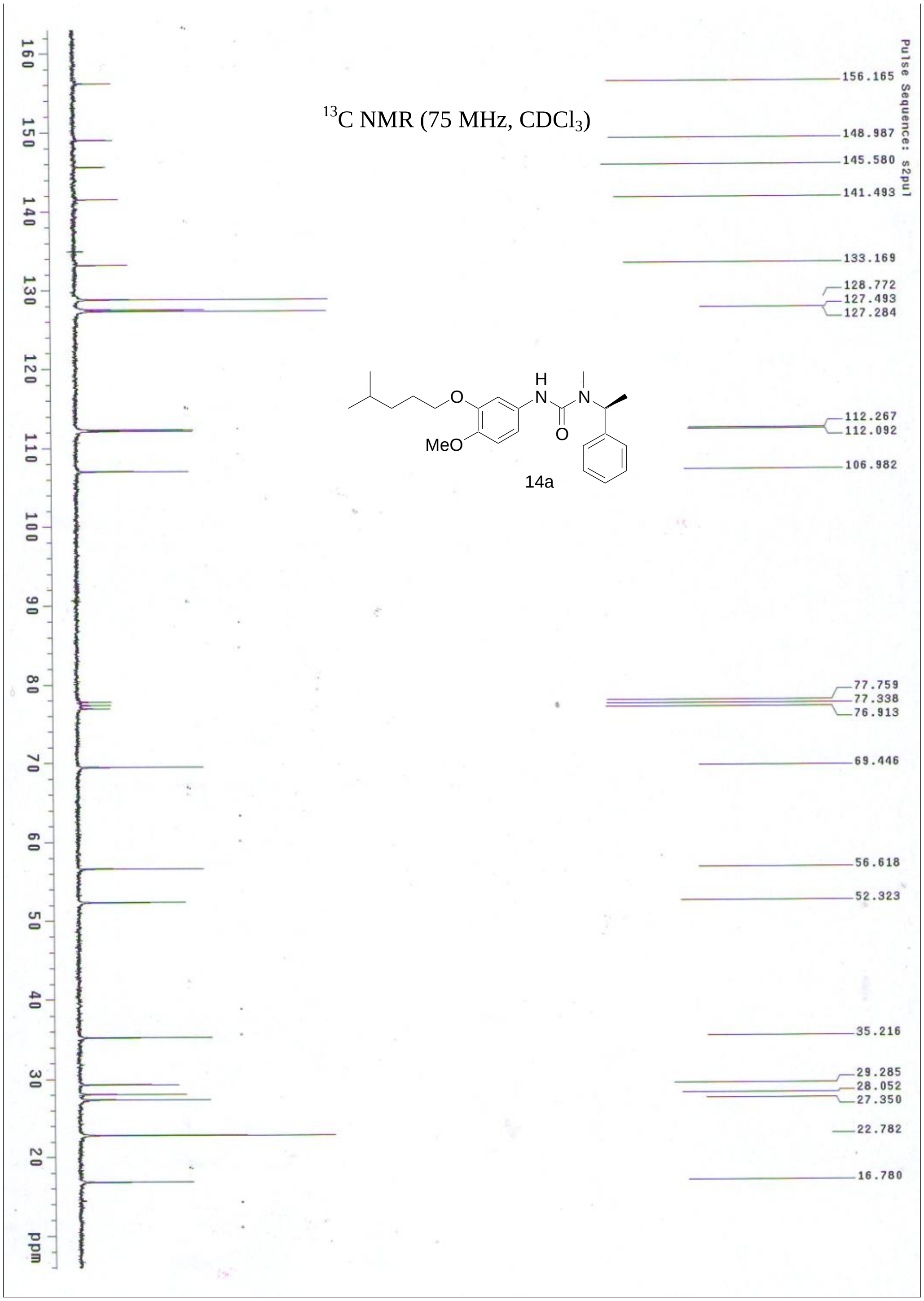
7l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