

DPT-mediated Synthesis of 2-Aminoimidazolidin-4-ones from Thioureas Tethered to Amides

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Experimental Section

1. General Experimental for the Synthesis of Starting Materials

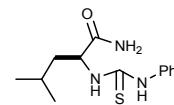
General Procedure for the Reaction of Isothiocyanates with Amino-amide Hydrochloride.

To a stirred solution of aminoamide hydrochloride (10.1 mmol) and triethylamine (30 mmol) in MeOH (30 mL) was added dropwise phenyl (or *n*-propyl) isothiocyanate (10 mmol) over few minutes at 0 °C. In case of free aminoamide, 1 equiv. of isothiocyanate was used in dry dichloromethane. After additional 0.5 h stirring, the reaction mixture was allowed to warm to room temperature. At the end of the reaction, the reaction mixture was concentrated *in vacuo* to afford crude product, which was purified by flash column chromatography using increasing polarity gradients of Hexane:EtOAc:CH₂Cl₂ to get the pure thiourea tethered to amide.

2. ¹H NMR Spectral data of Starting Materials

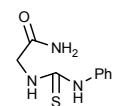
(S)-4-Methyl-2-(3-phenylthioureido)pentanamide (1a).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.92 (d, *J* = 6.0 Hz, 6 H), 1.50-1.72 (m, 3 H), 4.88 (m, 1 H), 7.05-7.15 (m, 2 H), 7.31 (m, 2 H), 7.52 (m, 2 H), 7.56 (br s, 1 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 9.68 (br s, 1 H).



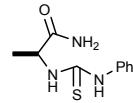
2-(3-Phenylthioureido)acetamide (1b).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.09 (d, *J* = 4.8 Hz, 2 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.18 (br s, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.48 (d, *J* = 7.5 Hz, 2 H), 7.54 (br s, 1 H), 7.73 (br t, *J* = 4.8 Hz, 1 H), 9.91 (br s, 1 H).



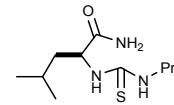
(S)-2-(3-Phenylthioureido)propanamide (1c).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.33 (d, *J* = 6.9 Hz, 3 H), 4.80 (m, 1 H), 7.05-7.53 (m, 5 H), 7.22 (br s, 1 H), 7.64 (br s, 1 H), 7.75 (br s, 1 H), 9.84 (br s, 1 H).



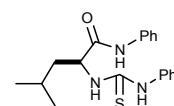
(S)-4-Methyl-2-(3-propylthioureido)pentanamide (1e).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.95-0.80 (m, 9 H), 1.67-1.35 (m, 5 H), 3.16 (m, 2 H), 4.79 (m, 1 H), 7.00 (br s, 1 H), 7.35 (br d, *J* = 7.2 Hz, 1 H), 7.42 (br s, 1 H), 7.54 (br s, 1 H).



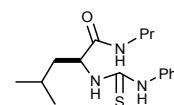
(S)-4-Methyl-2-(3-phenylthioureido)-N-phenylpentanamide (1f).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.93 (d, *J* = 6.0 Hz, 3 H), 0.94 (d, *J* = 6.0 Hz, 3 H), 1.53-1.80 (m, 3 H), 5.06 (m, 1 H), 7.05 (m, 1 H), 7.10 (m, 1 H), 7.31 (m, 4 H), 7.52 (m, 2 H), 7.61 (m, 2 H), 7.86 (br d, *J* = 8.1 Hz, 1 H), 9.71 (br s, 1 H), 10.19 (br s, 1 H)



(S)-4-Methyl-2-(3-phenylthioureido)-N-propylpentanamide (1g).

¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.84 (t, *J* = 7.5 Hz, 3 H), 0.90 (d, *J* = 6.3 Hz, 3 H), 0.91 (d, *J* = 6.3 Hz, 3 H), 1.42 (m, 2 H), 1.50-1.69 (m, 3 H), 3.03 (m, 2 H), 4.88 (m, 1 H), 7.09 (m, 1 H), 7.31 (m, 2 H), 7.51 (m, 2 H), 7.73 (br d, *J* = 5.7 Hz, 1 H), 8.12 (br t, *J* = 5.7 Hz, 1 H), 9.68 (br s, 1 H).



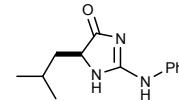
3. General Procedure for the Cyclization of Thioureas with DPT

A mixed solution of substituted thiourea (1.0 mmol), DPT (1.1 mmol) in dry solvent (6 mL) was stirred at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was diluted with water and ethyl acetate. The organic layer was washed with saturated NaHCO₃ solution and brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to give crude product, which was purified by flash column chromatography using 20-40% ethyl acetate in *n*-hexane as eluent to give pure product.

4. Analytical and Spectral data of the Products

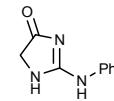
(S)-5-Isobutyl-2-(phenylimino)imidazolidin-4-one (2a).

White solid, mp: 99-100 °C; $[\alpha]^{25}_D -76.4^\circ$ (*c* 1.0, MeOH); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.90 (t, *J* = 7.8 Hz, 6 H), 1.80-1.65 (m, 3 H), 4.64 (m, 1 H), 6.88 (d, *J* = 8.1 Hz, 1 H), 6.94 (m, 1 H), 7.25 (m, 2 H), 7.42 (m, 2 H), 8.69 (br s, 1 H); ¹³C NMR (CDCl₃, 75.4 MHz) δ 21.9, 22.3, 25.0, 40.5, 41.5, 119.7, 121.1, 124.5, 129.4, 137.8, 155.2; IR (solid) 3310, 2944, 1633 (C=O), 1595, 1548, 1445, 1231 cm⁻¹; MS *m/e* (rel intensity) 232 (M⁺ + 1, 3), 231 (M⁺, 4), 188 (29), 175 (100), 146 (16). HRMS (EI) *m/z*: [M]⁺ calculated for C₁₃H₁₇N₃O, 231.1372. found: 231.1359.



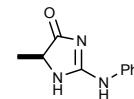
2-(Phenylimino)imidazolidin-4-one (2b).

Needle-type white solid, mp: 160-162 °C (*n*-hexane/*iso*-PrOH); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.12 (d, *J* = 6.0 Hz, 2 H), 6.69 (br t, *J* = 6.0 Hz, 1 H), 6.94 (m, 1 H), 7.25 (m, 2 H), 7.41 (m, 2 H), 8.92 (br s, 1 H); ¹³C NMR (DMSO-*d*₆, 75.4 MHz) δ 28.3, 118.1, 118.5, 121.7, 128.7, 139.7, 154.7; IR (solid) 3330, 3304, 1640 (C=O), 1597, 1560, 1442, 1312, 1231, 1134 cm⁻¹; MS *m/e* (rel intensity) 176 (M⁺ + 1, 6), 175 (M⁺, 38), 174 (100), 131 (20), 119 (87), 91 (22), 77 (17). HRMS (EI) *m/z*: [M]⁺ calculated for C₉H₉N₃O, 175.0746. found: 175.0761



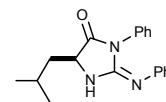
(S)-5-Methyl-2-(phenylimino)imidazolidin-4-one (2c).

White solid, mp: 158-160 °C; $[\alpha]^{25}_D -110.6^\circ$ (*c* 1.0, MeOH); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.47 (d, *J* = 7.2 Hz, 3 H), 4.68 (m, 1 H), 6.88 (d, *J* = 7.5 Hz, 1 H), 6.94 (m, 1 H), 7.33 (m, 2 H), 7.47 (m, 2 H), 8.68 (br s, 1 H); ¹³C NMR (DMSO-*d*₆, 75.4 MHz) δ 18.5, 36.6, 118.1, 120.9, 121.8, 128.7, 139.6, 154.1; IR (solid) 3310, 1633 (C=O), 1595, 1548, 1445, 1231 cm⁻¹; MS *m/e* (rel intensity) 190 (M⁺ + 1, 6), 189 (M⁺, 46), 188 (100), 145 (32), 119 (91), 93 (27), 77 (14). HRMS (EI) *m/z*: [M]⁺ calculated for C₁₀H₁₁N₃O, 189.0902. found: 189.0907.



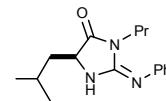
(S)-5-Isobutyl-2-(phenylimino)-3-phenylimidazolidin-4-one (3f).

White solid, mp: 104-106 °C; $[\alpha]^{25}_D +38.7^\circ$ (*c* 1.0, MeOH); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.91 (d, *J* = 6.6 Hz, 6 H), 1.50-1.70 (m, 2 H), 1.87 (m, 1 H), 4.19 (m, 1 H), 6.88 (m, 2 H), 6.95 (m, 1 H), 7.25 (m, 2 H), 7.31-7.58 (m, 5H + NH); ¹³C NMR (CDCl₃, 75.4 MHz) δ 22.0, 23.3, 25.1, 56.2, 122.4, 123.3, 127.4, 12.4, 129.2, 129.5, 132.4, 147.8, 149.8, 173.4; IR (solid) 3313, 2959, 2928, 2870, 1659 (C=O), 1589, 1498, 1412, 1323, 1185, 1167, 1129, 1094, 1070 cm⁻¹; MS *m/e* (rel intensity) 308 (M⁺ + 1, 22), 307 (M⁺, 91), 264 (77), 251 (44), 194 (55), 131 (30), 119 (100), 92 (39), 77 (81). HRMS (EI) *m/z*: [M]⁺ calculated for C₁₉H₂₁N₃O, 307.1685. found: 307.1691.



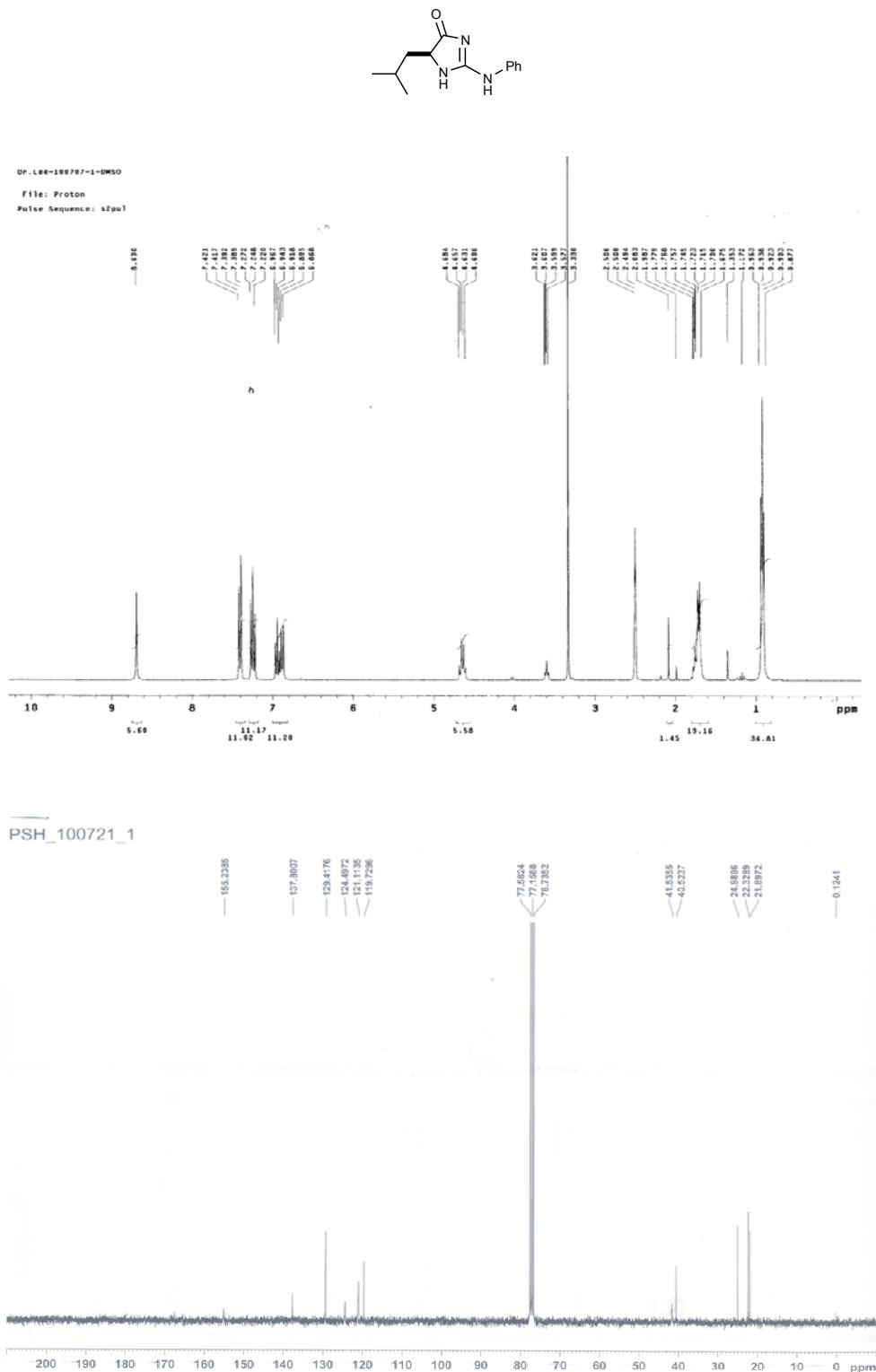
(S)-5-Isobutyl-2-(phenylimino)-3-propylimidazolidin-4-one (3g).

White solid, mp: 81-83 °C ; $[\alpha]^{25}_D +26.3^\circ$ (*c* 1.0, MeOH); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.80-0.92 (m, 9 H), 1.35-1.68 (m, 4 H), 1.78 (m, 1 H), 3.48 (t, *J* = 7.2 Hz, 2 H), 3.97 (m, 1 H), 6.90 (m, 2 H), 6.96 (m, 1 H), 7.24-7.29 (m, 2 H + NH); ¹³C NMR (CDCl₃, 75.4 MHz) δ 11.4, 21.2, 21.9, 23.3, 25.1, 40.9, 41.6, 56.1, 122.5, 123.2, 129.6, 148.0, 149.8, 174.3; IR (solid) 3332, 3278, 2959, 2933, 2872, 1666 (C=O), 1591, 1490, 1450, 1371, 1317, 1212, 1114, 1097, 1019 cm⁻¹; MS *m/e* (rel intensity) 274 (M⁺ + 1, 15), 273 (M⁺, 55), 244 (14), 230 (18), 188 (100), 175 (71), 156 (80), 145 (73), 119 (31), 86 (30), 77 (39). HRMS (EI) *m/z*: [M]⁺ calculated for C₁₆H₂₃N₃O, 273.1841. found: 273.1849.

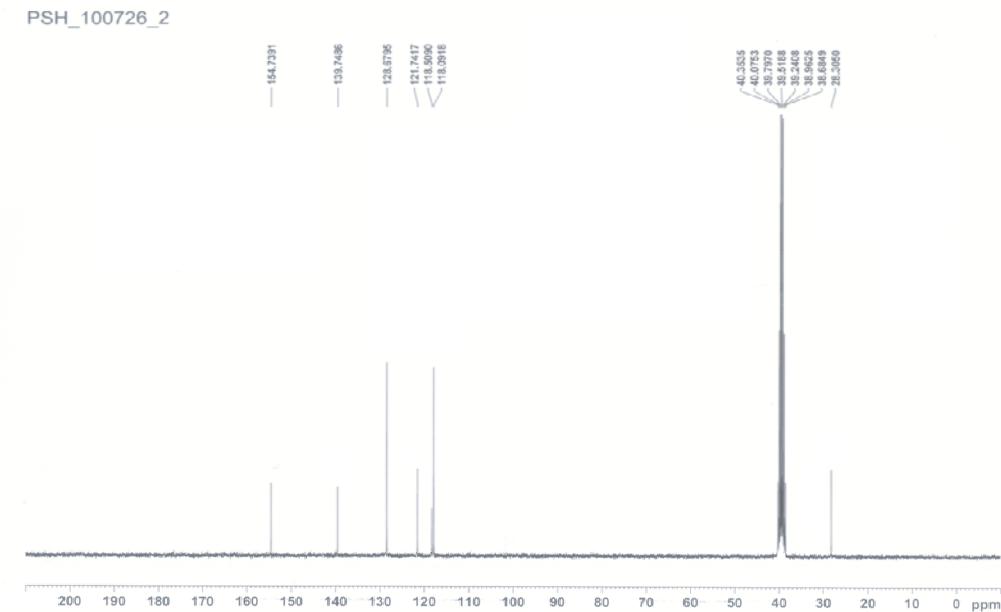
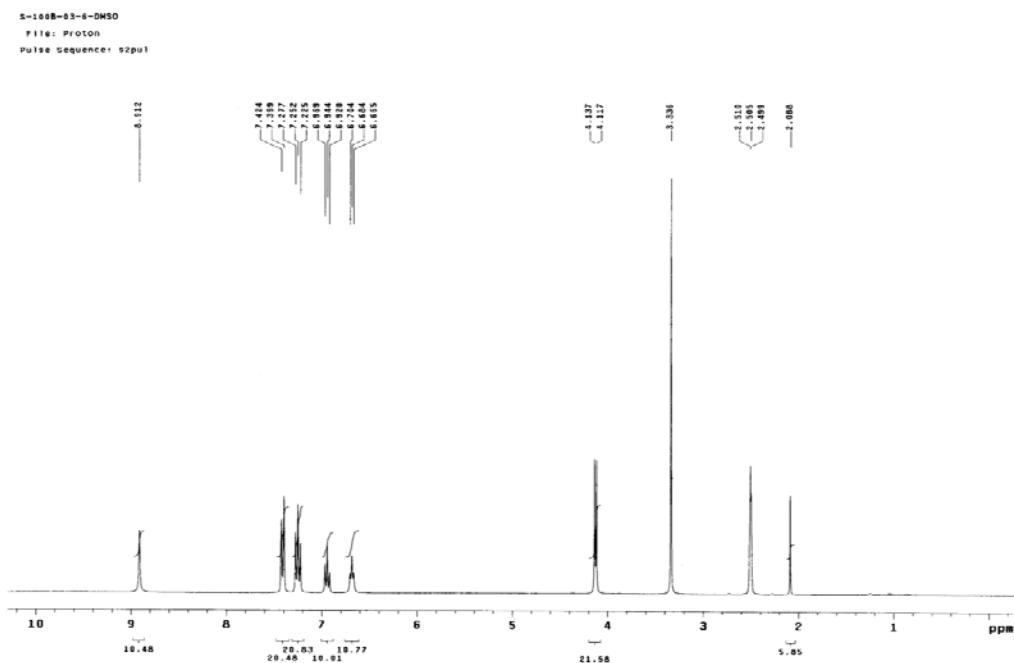
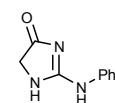


5. ^1H NMR and ^{13}C NMR Spectra of the Products

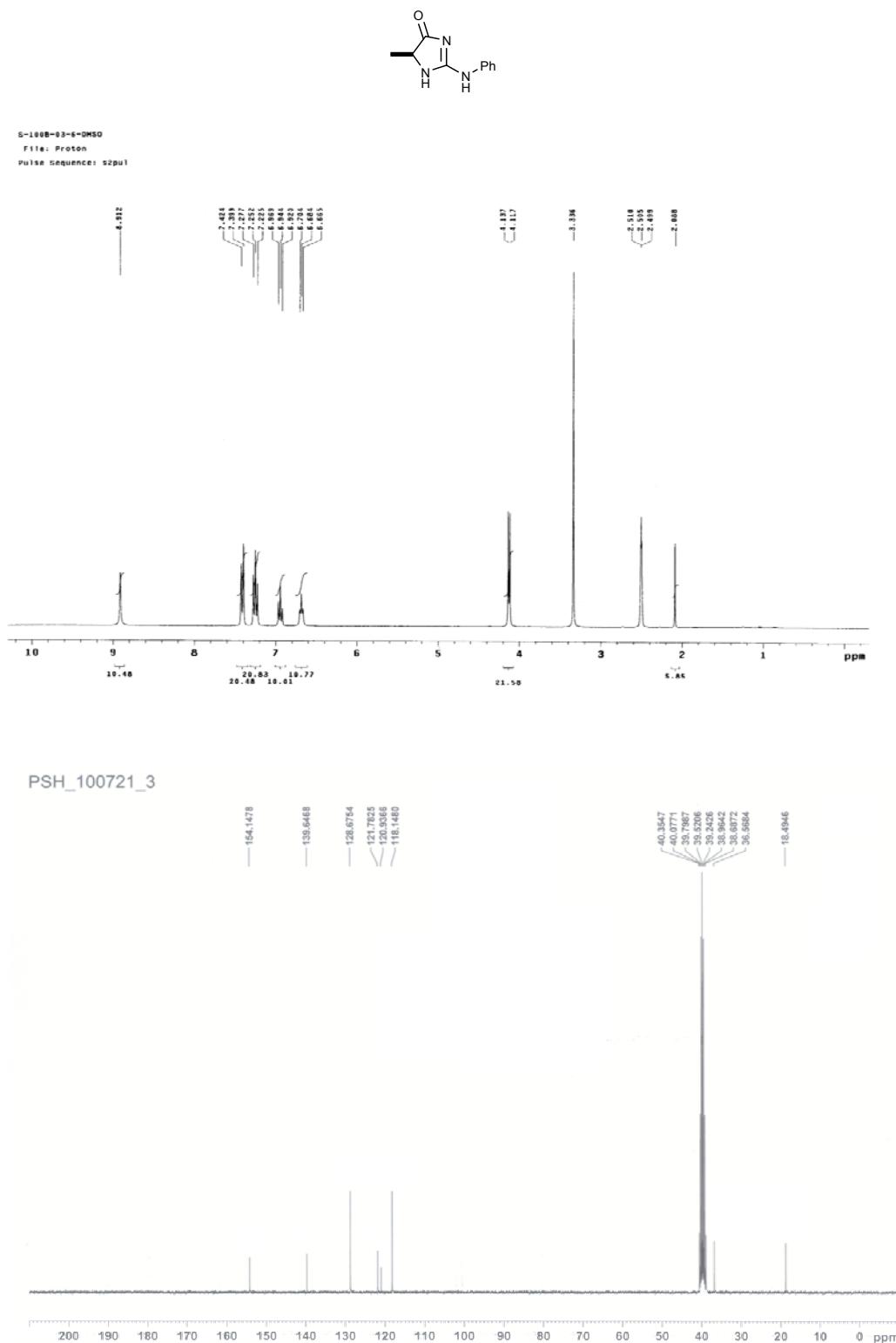
^1H NMR and ^{13}C NMR of **2a**



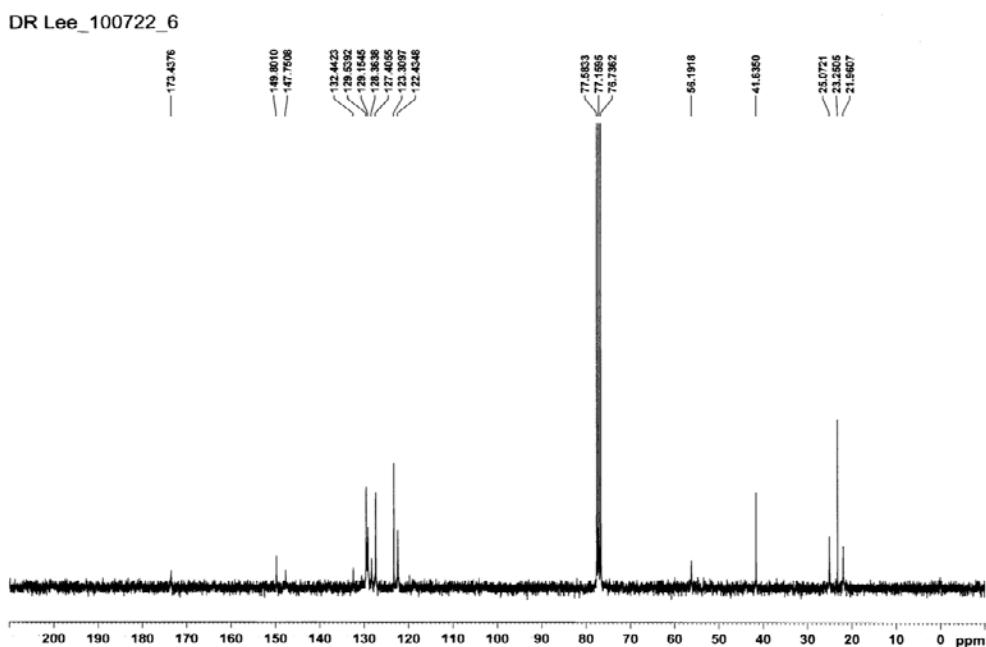
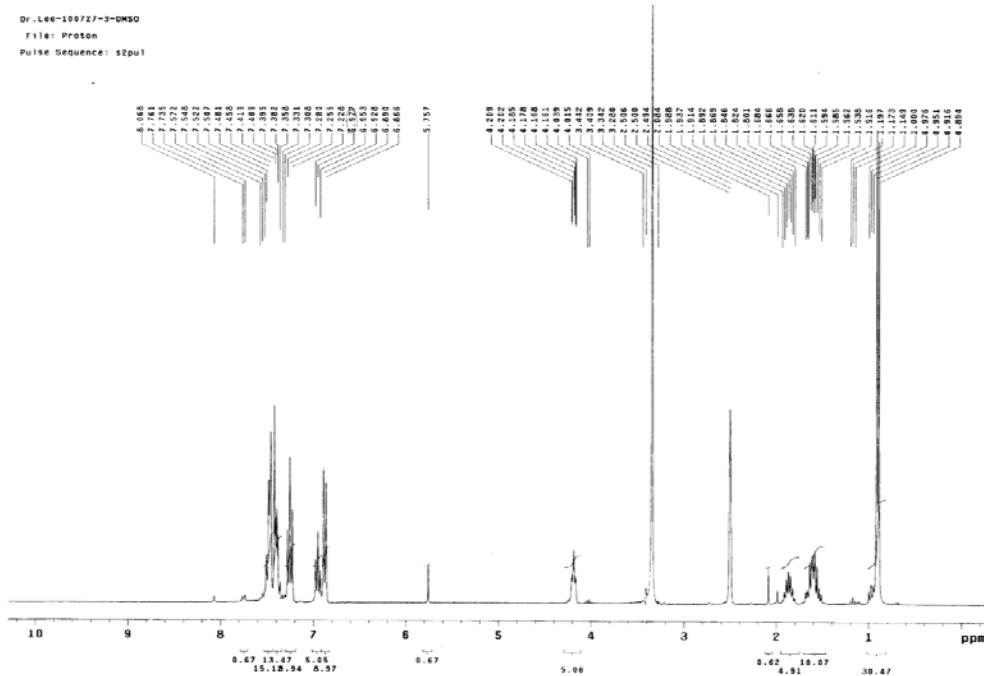
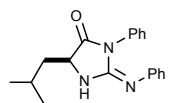
¹H NMR and ¹³C NMR of **2b**



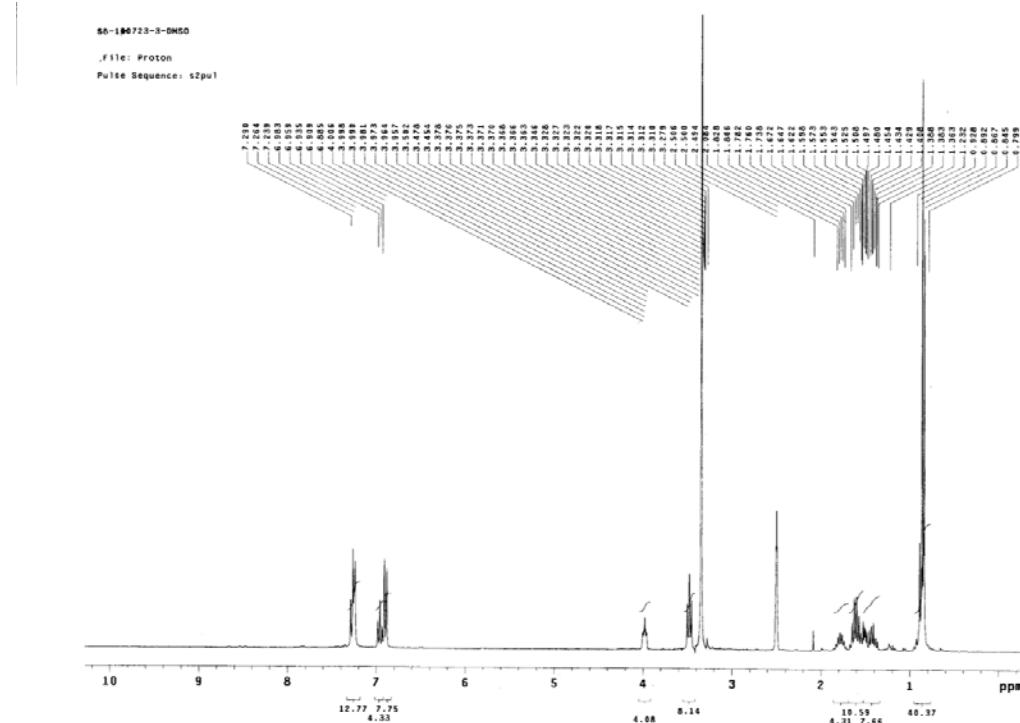
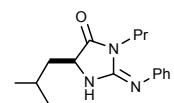
¹H NMR and ¹³C NMR of **2c**



^1H NMR and ^{13}C NMR of **3f**



¹H NMR and ¹³C NMR of **3g**



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