

# Improved Synthesis of Isogranulatimide, a G2 Checkpoint Inhibitor. Syntheses of Didemnimide C, Isodidemnimide A, Neodidemnimide A, 17-Methylgranulatimide and Isogranulatimides A, B, and C

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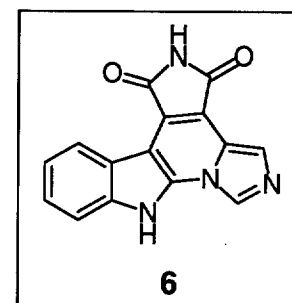
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## SUPPORTING INFORMATION

### Experimental

**General.** Flash chromatography<sup>1</sup> was carried out with 230-400 mesh silica gel (E. Merck). THF and Et<sub>2</sub>O were distilled from sodium/benzophenone, CH<sub>2</sub>Cl<sub>2</sub> and benzene were distilled from CaH<sub>2</sub> and MeOH was distilled from Mg with cat. I<sub>2</sub>. Commercial EtOH (reagent grade), MeCN (HPLC grade) and nitrobenzene (reagent grade) were used without further purification. DMSO and DMF were dried sequentially over molecular sieves. Molecular sieves were dried under vacuum with heating for 5 h prior to use. All reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame dried unless otherwise specified. <sup>1</sup>H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet), number of protons, coupling constant. All melting points are uncorrected.

**Isogranulatimide (6). Method A:** A stirred solution of didemnimide A (**8**) (27.6 mg, 0.099 mmol) in DMSO (5.0 mL) was heated to 140 °C for 2 h open to the atmosphere. The reaction mixture was then cooled to rt, diluted with EtOAc (30 mL) and treated with NaOH (10% aqueous solution, 5 mL). The organic layer was removed and washed with brine (3 X 10 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (20 g of silica gel, 10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 6.0 mg of didemnimide A (**8**) and 14.0 mg (51%, 65 % based on recovered starting material) of **6** as a

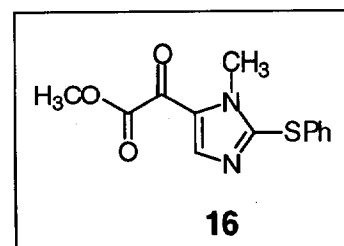


1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

purple solid. **Method B:** A stirred suspension of didemnimide A (**8**) (31.3 mg, 0.113 mmol) and Pd black (12.0 mg, 0.113 mmol) in nitrobenzene (4.0 mL) was heated to reflux for 20 h. The reaction mixture was cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and placed on a short plug of silica gel (5 g). The nitrobenzene was eluted using CH<sub>2</sub>Cl<sub>2</sub> and the crude product was eluted with 5:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH and concentrated. Flash chromatography (25 g of silica gel, 10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 23.3 mg (75%) of **6** as a purple solid that exhibited IR (KBr) 2732, 1758, 1719, 1586, 1568, 1368, 1234, 1109, 744 cm<sup>-1</sup>; <sup>1</sup>H NMR<sup>2</sup> (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.49 (bs, 1 H), 11.12 (bs, 1 H), 8.91 (s, 1 H), 8.54 (d, 1 H, *J* = 7.6 Hz), 7.88 (s, 1 H), 7.70 (d, 1 H, *J* = 8.0 Hz), 7.45 (dd, 1 H, *J* = 8, 8 Hz), 7.37 (dd, 1 H, *J* = 8, 8 Hz); <sup>13</sup>C NMR<sup>2</sup> (100 MHz, DMSO-*d*<sub>6</sub>) δ 169.9, 169.0, 135.6, 134.9, 126.9, 126.0, 124.7, 123.1, 122.3, 121.8, 121.3, 121.0, 113.9, 112.3, 97.6; HREIMS calcd for C<sub>15</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub> 276.0647, found 276.0644.

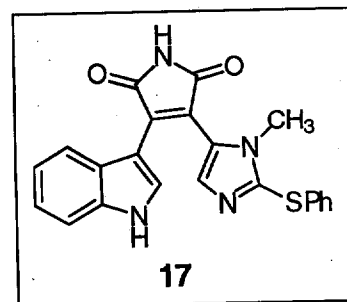
**Methyl 2-(1-methyl-1*H*-2-phenylthioimidazol-5-**

**yl)glyoxylate (**16**).** To a cold (-78 °C), stirred solution of diisopropylamine (175 μL, 1.25 mmol) in Et<sub>2</sub>O (2.0 mL) and DME (2.0 mL) was added a solution of *n*-BuLi (1.60 M in hexanes, 740 μL, 1.18 mmol) and the mixture was stirred for 0.5 h. A solution of 1-methyl-2-phenylthioimidazole (**15**) (140 mg, 0.737 mmol) in Et<sub>2</sub>O (3.0 mL) was added and the resulting solution was stirred at -78 °C for 0.25 h and at 0 °C for an additional 1 h. Dimethyl oxalate (520 mg, 4.40 mmol) was added in one portion and the mixture was allowed to warm to rt and stir for an additional 3h. The reaction mixture was then treated with saturated aqueous NH<sub>4</sub>Cl (5 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (35 g of silica gel, 70:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 84.5 mg (41%) of **16** as a beige solid that exhibited mp 98-99 °C; IR (KBr) 1736, 1651, 1437, 1277, 1216, 1013 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.22 (s, 1 H), 7.42-7.44 (m, 2 H), 7.34-7.37 (m, 3 H), 3.93 (s, 3 H), 3.92 (s, 3 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.9, 162.2, 151.8, 144.7, 132.4, 130.2, 129.9, 129.8, 129.1, 53.3, 34.3; HREIMS calcd for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S 276.0569, found 276.0564.

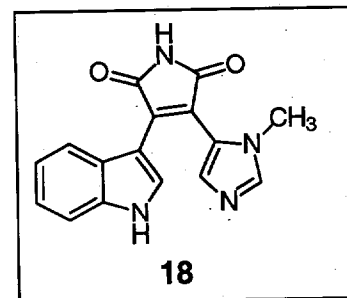


2. The <sup>1</sup>H and <sup>13</sup>C NMR signals for **6** shift depending on the concentration. The <sup>1</sup>H NMR spectrum was acquired at a concentration of 1 mg/mL and the <sup>13</sup>C NMR spectrum was acquired at a concentration of 5 mg/mL.

**16-Phenylthiodidemnimide C (17).** To a stirred solution of *t*-BuOK (28 mg, 0.25 mmol) in DMF (1.0 mL) at rt was added sequentially 4Å molecular sieves (~ 50 mg) and a solution of **16** (28 mg, 0.10 mmol) and indole-3-acetamide (22 mg, 0.13 mmol) in DMF (1.5 mL). The reaction mixture was heated to 40 °C and stirred for 48 h. The dark purple solution was treated with hydrochloric acid (1 N, 1.0 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine (4 X 10 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (20 g of silica gel, 30:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 35 mg (88%) of **17** as a red solid that exhibited mp >240 °C (decomp.); IR (KBr) 2500-3600, 1760, 1713, 1631, 1581, 1441, 1339, 744 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.06 (bs, 1 H), 11.19 (bs, 1 H), 8.09 (d, 1 H, *J* = 2.1 Hz), 7.46 (d, 1 H, *J* = 8.0 Hz), 7.14-7.31 (m, 6 H), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.81 (dd, 1 H, *J* = 8, 8 Hz), 6.47 (d, 1 H, *J* = 8.1 Hz), 3.07 (s, 3 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 171.6, 171.4, 138.6, 136.4, 134.6, 133.7, 132.7, 131.8, 129.4, 127.4, 126.7, 126.6, 124.5, 122.5, 120.8, 119.5, 117.9, 112.4, 104.8, 32.4; HREIMS calcd for C<sub>22</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>S 400.0994, found 400.0985.



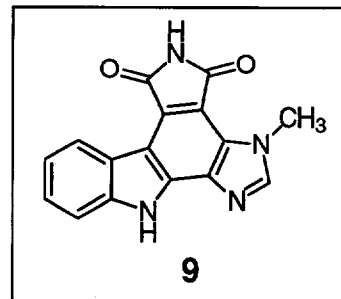
**Didemnimide C (18).** To a refluxing solution of **17** (46.7 mg, 0.117 mmol) in EtOH (10.0 mL) was added Raney Ni (W-2, 50% slurry in water, ~120 mg) and the resulting suspension was refluxed for 1 h. The reaction mixture was then cooled to rt and filtered through Celite. The Celite was washed with DMF (6 mL) and MeOH-TFA (100:1, 30 mL), and the combined organic washes were concentrated. The residue was taken up in EtOAc (40 mL) and the solution was washed with aqueous NaHCO<sub>3</sub> (4 X 10 mL), brine (3 X 20 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (25 g of silica gel, 10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 26.4 mg (77%) of **18** as an orange solid that exhibited spectral data that was in accordance with that reported for the natural product<sup>3</sup>: IR (KBr) 3163, 3041, 1766, 1702, 1538, 1345, 1236, 1221, 748 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.97 (bs, 1 H), 11.09 (bs, 1 H), 8.06 (d, 1 H, *J* = 2.6 Hz), 7.69 (bs, 1 H), 7.44 (d, 1 H, *J* = 8.1 Hz), 7.10 (dd, 1 H, *J* = 8, 8 Hz), 7.07



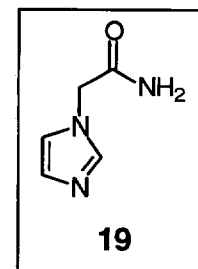
3. Vervoort, H. C.; Richards-Gross, S. E.; Fenical, W.; Lee, A. Y.; Clardy, J. *J. Org. Chem.* **1997**, *62*, 1486.

(bs, 1H), 6.78 (dd, 1 H,  $J = 8, 8$  Hz), 6.40 (d, 1 H,  $J = 8.1$  Hz), 3.17 (s, 3 H);  $^{13}\text{C}$  NMR<sup>4</sup> (100 MHz, DMSO- $d_6$ )  $\delta$  171.9, 171.7, 140.3, 136.4, 133.9, 132.0, 131.5, 124.7, 122.3, 122.3, 120.5, 119.7, 118.6, 112.2, 105.0, 32.0; HREIMS calcd for  $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$  292.0960, found 292.0957.

**17-Methylgranulatimide (9).** To a solution of **18** (20.5 mg, 0.070 mmol) in MeCN (30.0 mL) was added a catalytic amount of palladium-on-carbon (10% Pd), and the resulting mixture was sparged with argon for 0.5 h. The mixture was then irradiated (450-watt Hanovia medium pressure mercury vapour lamp, quartz reaction vessel) for 3.5 h. The reaction mixture was filtered through Celite and the Celite was washed with MeOH (30 mL) and DMF (40 mL). The MeOH washings were combined with the initial filtrate, while the DMF washings were collected separately. The MeCN-MeOH solution was concentrated and the resulting organic residue was triturated with MeOH (3 X 10 mL) to afford 2.4 mg of **9** as a yellow solid. The DMF washings were concentrated to provide 10.1 mg (total of 12.5 mg, 64%) of **9** as a yellow solid that exhibited mp  $>300$  °C; IR (KBr) 3257, 2951, 2726, 1734, 1703, 1650, 1505, 1479, 1461, 1393, 1326, 1225, 1068, 761, 744  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.58 (bs, 1 H), 11.04 (bs, 1 H), 8.94 (d, 1 H,  $J = 7.7$  Hz), 8.48 (s, 1 H), 7.60 (d, 1 H,  $J = 8.1$  Hz), 7.48 (dd, 1 H,  $J = 8, 8$  Hz), 7.30 (dd, 1 H,  $J = 8, 8$  Hz) 4.31 (s, 3 H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  170.7, 169.1, 147.1, 140.6, 135.6, 133.8, 128.5, 126.2, 124.0, 123.6, 121.3, 120.1, 113.0, 111.6, 109.8, 35.1; HREIMS calcd for  $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}_2$  290.0804, found 290.0800.



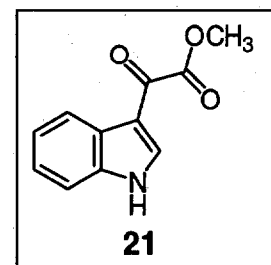
**Imidazol-1H-1-acetamide (19).** To a stirred suspension of NaH (60% dispersion in oil, 352 mg, 8.80 mmol) in DMF (5.0 mL) at 0 °C was added a solution of imidazole (536 mg, 8.00 mmol) in DMF (10.0 mL). The reaction mixture was warmed to rt and stirred for 0.5 h. The reaction mixture was then cooled to 0 °C and iodoacetamide (1.63 g, 8.81 mmol) was added in one portion. The resultant mixture was then warmed to rt and stirred for an additional 1.5 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and the NaI crystals which precipitated were removed by filtration. The



4. The  $^{13}\text{C}$  NMR signal reported herein at 118.6 was not reported for the natural product (see ref. 3). Instead, a signal at 134.1 was reported. A previous synthesis of didemnimide C (**18**) reported  $^{13}\text{C}$  NMR signals identical with those observed by us. See Terpin, A.; Winklhofer, C.; Schumann, S.; Steglich, W. *Tetrahedron* **1998**, *54*, 1745.

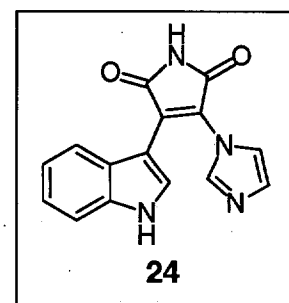
mother liquor was concentrated and the organic residue was placed on a basic alumina column (40 g). The column was eluted with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (6:1) and the eluate was concentrated. Flash chromatography (60 g of silica gel, 7:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude concentrate afforded 747 mg (75%) of **19** as a white solid that exhibited mp 185-186 °C (lit. 182-183 °C)<sup>5</sup>; IR (KBr) 3349, 3116, 1685, 1516, 1408, 1312, 1236, 1080, 750, 663 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.54 (s, 1 H), 7.51 (bs, 1 H), 7.20 (bs, 1 H), 7.06 (s, 1 H), 6.84 (s, 1 H), 4.61 (s, 2 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 168.5, 138.0, 127.5, 120.4, 48.4; HREIMS calcd for C<sub>5</sub>H<sub>7</sub>N<sub>3</sub>O 125.0589, found 125.0585.

**Methyl Indolyl-3-glyoxylate (21).** To a cold (0 °C) stirred solution of 3-indoleglyoxylic acid (**20**) (305 mg, 1.61 mmol) in MeOH (3.0 mL) and benzene (12.0 mL) was added (trimethylsilyl)diazomethane (2.0 M in hexanes, 1.60 mL, 3.20 mmol) and the reaction mixture was warmed to rt and stirred for 4 h. The solvent was removed in vacuo to provide a beige solid. Flash chromatography (40 g of silica gel, 25:1 then 10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH)



of the crude material afforded 327 mg (100%) of **21** as a beige solid that exhibited: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.40 (bs, 1 H), 8.44 (d, 1 H, *J* = 3.0 Hz), 8.15 (d, 1 H, *J* = 7.0 Hz), 7.54 (d, 1 H, *J* = 7.6 Hz), 7.24-7.31 (m, 2 H), 3.88 (s, 3 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 178.7, 163.9, 138.3, 136.7, 125.4, 123.8, 122.8, 121.1, 112.7, 112.4, 52.5; HREIMS calcd for C<sub>11</sub>H<sub>9</sub>NO<sub>3</sub> 203.0582, found 203.0587; Anal. Calcd. C, 65.01; H, 4.47; N, 6.90. Found: C, 65.16; H, 4.34; N, 6.77.

**Isodidemnimide A (24).** To a stirred solution of *t*-BuOK (140 mg, 1.25 mmol) in DMF (2.0 mL) at 0 °C was added a solution of **19** (31.1 mg, 0.249 mmol) and methyl indolyl-3-glyoxylate (**21**) (101 mg, 0.498 mmol) in DMF (3.0 mL). The reaction mixture was stirred for 12 h at rt and then heated to 45 °C for 3 h. The reaction mixture was then cooled and treated with saturated aqueous NH<sub>4</sub>Cl (5 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine (4 X 10 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (25 g of silica gel, 10:1 then 6:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 54.5 mg (79%) of **24** as a red solid that exhibited mp

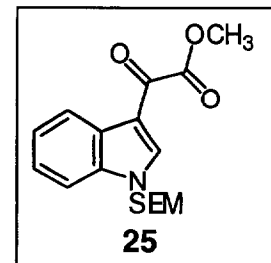


5. Sundberg, R. J.; Mente, D. C.; Yilmaz, I.; Gupta, G. *J. Heterocyclic Chem.* **1977**, *14*, 1279.

>300 °C; IR (KBr) 3121, 2729, 1767, 1719, 1651, 1495, 1340, 1239, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.04 (bs, 1 H), 11.28 (bs, 1 H), 8.03 (d, 1 H,  $J = 3.1$  Hz), 7.78 (s, 1 H), 7.45 (d, 1 H,  $J = 8.2$  Hz), 7.29 (s, 1 H), 7.11 (dd, 1 H,  $J = 8, 8$  Hz), 7.04 (s, 1 H), 6.80 (dd, 1 H,  $J = 8, 8$  Hz), 6.21 (d, 1 H,  $J = 7.6$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  170.4, 168.4, 137.8, 136.4, 131.6, 128.8, 125.8, 124.3, 124.1, 122.5, 120.6, 120.1, 119.6, 112.3, 102.3; HREIMS calcd for  $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}_2$  278.0804, found 278.0798.

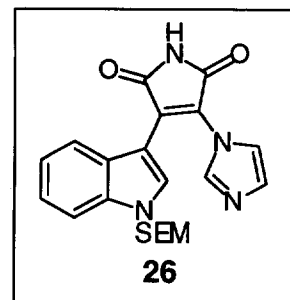
**Methyl [*N*-(2-trimethylsilylethoxy)methyl]indole-3-**

**glyoxylate (25).** To a cold (0 °C) stirred suspension of NaH (60% dispersion in mineral oil, 123 mg, 3.08 mmol) in THF (5.0 mL) was added a solution of **21** (500 mg, 2.46 mmol) in THF (20.0 mL) and the reaction mixture was stirred for 10 minutes at 0 °C and 50 minutes at rt. The yellow solution was then cooled to 0 °C, SEM-Cl (610  $\mu\text{L}$ , 3.44 mmol) was added and the reaction mixture was warmed to rt. After 1.5 h, the reaction mixture was treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL) and EtOAc (30 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 25 mL). The combined organic extracts were washed with brine (20 mL), dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography (50 g of silica gel, 3:2 petroleum ether-diethyl ether) of the crude material afforded 667 mg (82 %) of **25** as a colourless solid that exhibited mp 96-97 °C; IR (KBr) 3122, 1733, 1637, 1519, 1398, 1198, 1086, 752  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.41-8.44 (m, 2 H), 7.52-7.54 (m, 1 H), 7.33-7.38 (m, 2 H), 5.52 (s, 2 H), 3.94 (s, 3 H), 3.51 (t, 2 H,  $J = 8.1$  Hz), 0.89 (t, 2 H,  $J = 8.1$  Hz), -0.07 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ; 177.3, 163.0, 139.3, 136.5, 127.2, 124.5, 123.9, 122.8, 113.6, 110.8, 76.7, 66.6, 52.7, 17.6, -1.5; HREIMS calcd for  $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{Si}$  333.1397, found 333.1395.



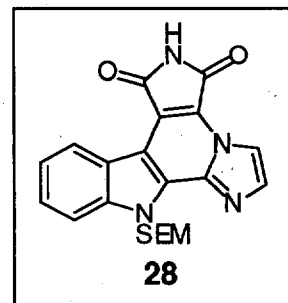
**1-[(2-trimethylsilylethoxy)methyl]isodidemnimide A**

**(26).** To a stirred suspension of **19** (12 mg, 0.096 mmol), **25** (40 mg, 0.12 mmol) and 4Å molecular sieves (~ 100 mg) in DMF (3.0 mL) at 0 °C was added a solution of *t*-BuOK (27 mg, 0.24 mmol) in DMF (2.0 mL) and the reaction mixture was stirred for 12 h at rt. The reaction mixture was then treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine (4 X 10 mL), dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography (25 g of silica gel, 30:1  $\text{CH}_2\text{Cl}_2$ -MeOH) of the crude

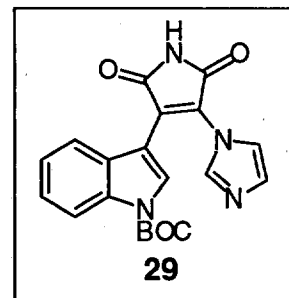


material afforded 5.0 mg (14%) of **27** as a yellow solid and 32.0 mg (82 %) of **26** as a yellow solid that exhibited mp 168 °C (decomp.); IR (KBr) 2953, 2719, 1769, 1723, 1656, 1519, 1337, 1235, 1083, 837, 741  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.95 (bs, 1 H), 7.99 (s, 1 H), 7.97 (bs, 1 H), 7.50 (d, 1 H,  $J = 8.1$  Hz), 7.24 (bs, 1 H), 7.24 (dd, 1 H,  $J = 8, 8$  Hz), 7.15 (bs, 1 H), 6.98 (dd, 1 H,  $J = 8, 8$  Hz), 6.37 (d, 1 H,  $J = 8.1$  Hz), 5.53 (s, 2 H), 3.55 (t, 2 H,  $J = 8.1$  Hz), 0.90 (t, 2 H,  $J = 8.1$  Hz), -0.07 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.3, 167.0, 137.8, 136.7, 133.9, 129.4, 125.4, 124.7, 124.3, 123.9, 122.4, 120.7, 119.6, 111.0, 102.9, 76.3, 66.6, 17.7, -1.5; HREIMS calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_3\text{Si}$  408.1618, found 408.1620.

**1-[(2-trimethylsilyloxy)methyl]isogranulatimide A (28)**. To a stirred solution of **26** (60.0 mg, 0.147 mmol) in MeCN (20 mL) was added palladium-on-carbon (8 mg, 10 % Pd) and the resulting mixture was sparged with Ar for 0.5 h. The reaction mixture was irradiated (450-watt Hanovia medium pressure mercury vapour lamp, quartz reaction vessel) for 2 h. The solvent was then removed in vacuo to provide a yellow residue. Flash chromatography (25 g of silica gel, 40:1  $\text{CH}_2\text{Cl}_2$ -MeOH) of the crude material afforded trace amounts (less than 1 mg) of 1-(SEM)-isogranulatimide B and 30.8 mg (52%) of **28** as a yellow solid that exhibited IR (KBr) 3108, 2707, 1757, 1721, 1650, 1364, 1291, 1080, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.78 (d, 1 H,  $J = 8.0$  Hz), 8.49 (s, 1 H), 7.87 (s, 1 H), 7.72 (d, 1 H,  $J = 8.0$  Hz), 7.56 (dd, 1 H,  $J = 8, 8$  Hz), 7.52 (bs, 1 H), 7.43 (dd, 1 H,  $J = 8, 8$  Hz), 6.50 (s, 2 H), 3.63 (t, 2 H,  $J = 8.2$  Hz), 0.91 (t, 2 H,  $J = 8.2$  Hz), -0.16 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.6, 163.6, 140.3, 137.8, 135.2, 131.0, 127.1, 125.5, 124.3, 122.8, 121.6, 118.0, 112.8, 111.4, 110.6, 74.0, 66.1, 17.9, -1.5; HREIMS calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3\text{Si}$  406.1461, found 406.1456.

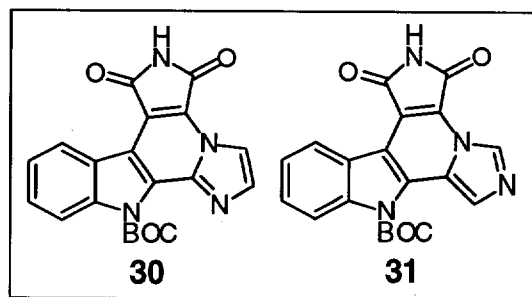


**1-tert-Butoxycarbonylisodidemnimide A (29)**. To a stirred suspension of NaH (60 % dispersion in mineral oil, 23 mg, 0.58 mmol) in DMF (2.0 mL) at 0 °C was added a solution of **24** (62 mg, 0.22 mmol) in DMF (2.0 mL) and the deep red reaction mixture was allowed to warm to rt over 1.5 h. A solution of di-tert-butyl dicarbonate (58 mg, 0.27 mmol) in DMF (2.0 mL) was added and the reaction mixture was stirred for a further 0.5 h at rt. The reaction mixture was treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and EtOAc (30 mL). The phases were separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (5 X 10 mL), dried



(MgSO<sub>4</sub>) and concentrated. Flash chromatography (40 g of silica gel, 30:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 84 mg (100 %) of **29** as a yellow solid that exhibited mp 133 °C; IR (KBr) 3400-2800, 1728, 1665, 1454, 1358, 1311, 1231, 1153, 1100, 736 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.52 (s, 1 H), 8.10 (d, 1 H, *J* = 8.4 Hz), 8.06 (s, 1 H), 7.85 (s, 1 H), 7.34 (dd, 1 H, *J* = 8, 8 Hz), 7.28 (s, 1 H), 7.03 (dd, 1 H, *J* = 8, 8 Hz), 7.00 (s, 1 H), 6.55 (d, 1 H, *J* = 8.0 Hz), 1.66 (s, 9 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.7, 166.6, 148.8, 137.7, 135.4, 130.3, 129.8, 128.7, 126.4, 125.6, 123.8, 121.2, 120.1, 119.1, 115.6, 106.6, 85.3, 28.1; HREIMS calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub> 378.1328, found 378.1329.

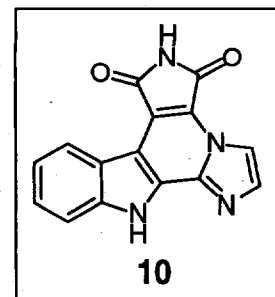
**1-*tert*-Butoxycarbonylisogranulatimide A (30) and 1-*tert*-Butoxycarbonyliso-**  
**granulatimide B (31).** A stirred solution of **29**  
(42.5 mg, 0.112 mmol) in MeCN (4.0 mL) was  
irradiated with a 275-watt light bulb for 1 h at  
rt. The solvent was removed in vacuo and the  
orange residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (6.0  
mL). MnO<sub>2</sub> (58 mg, 0.67 mmol) was added and



the stirred mixture was refluxed overnight. The mixture was cooled and filtered through a short plug of silica gel (elution with 5:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) and the filtrate was concentrated. Flash chromatography (30 g of silica gel, 25:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 20.2 mg (48 %) of **30** as a yellow solid that exhibited mp >300 °C; IR (KBr) 3226, 1776, 1724, 1649, 1380, 1310, 1287, 1157, 750, 729 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.46 (s, 1 H), 8.66 (d, 1 H, *J* = 8.1 Hz), 8.46 (d, 1 H, *J* = 1.1 Hz), 8.01 (d, 1 H, *J* = 8.4 Hz), 7.92 (d, 1 H, *J* = 1.1 Hz), 7.56 (dd, 1 H, *J* = 8, 8 Hz), 7.43 (dd, 1 H, *J* = 8, 8 Hz), 1.69 (s, 9 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 167.9, 164.8, 148.6, 138.4, 137.2, 135.3, 127.9, 127.7, 126.3, 123.8, 123.5, 121.8, 115.6, 113.4, 113.3, 112.6, 85.7, 27.3; HREIMS calcd for C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> 376.1172, found 376.1176. Also obtained was 7.8 mg (19 %) of **31** as a purple solid that exhibited<sup>6</sup> IR (KBr) 2980, 1729, 1654, 1526, 1370, 1299, 1150, 1130, 740 cm<sup>-1</sup>; HREIMS calcd for C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> 376.1172, found 376.1177.

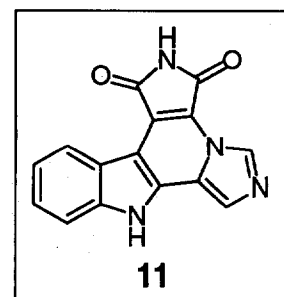
6. Compound **31** was insufficiently soluble in DMSO-*d*<sub>6</sub> or other standard NMR solvents for complete characterization.

**Isogranulatimide A (10). Method A:** To a stirred solution of **28** (16 mg, 0.040 mmol) in MeCN (5.0 mL) and H<sub>2</sub>O (0.2 mL) was added LiBF<sub>4</sub> (37 mg, 0.40 mmol) and the reaction mixture was heated to reflux overnight. The solvent was removed in vacuo and the yellow residue was dissolved in DMF (4 mL). The solution was diluted with EtOAc (30 mL), washed with brine (4 x 15 mL), dried (MgSO<sub>4</sub>) and concentrated. Trituration of the residue with Et<sub>2</sub>O gave 9.2 mg (84 %) of **10** as a yellow solid. **Method B:** A



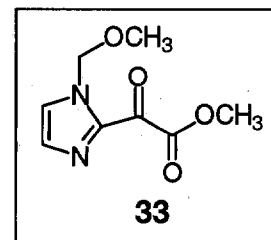
suspension of **30** (21 mg, 0.056 mmol) in nitrobenzene (1.5 mL) was heated to reflux for 1 h. The mixture was cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and placed on a short plug of silica gel. The nitrobenzene was eluted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL) followed by CH<sub>2</sub>Cl<sub>2</sub>-MeOH (10:1, 40 mL) and **10** was eluted with CH<sub>2</sub>Cl<sub>2</sub>-MeOH-TFA (200:40:1, 100 mL). The CH<sub>2</sub>Cl<sub>2</sub>-MeOH-TFA fraction was concentrated under reduced pressure to provide a yellow residue that was dissolved in EtOAc (50 mL). The solution was washed with water (2 X 25 mL), saturated aqueous NaHCO<sub>3</sub> (2 X 15 mL), brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated to provide 12 mg (78 %) of **10** as a yellow solid that exhibited mp > 300 °C; IR (KBr) 3184, 2931, 2692, 1756, 1718, 1656, 1365, 1309, 1134, 730 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.14 (bs, 1 H), 11.27 (bs, 1 H), 8.63 (d, 1 H, *J* = 8.1 Hz), 8.46 (s, 1 H), 7.90 (s, 1 H), 7.66 (d, 1 H, *J* = 8.0 Hz), 7.50 (dd, 1 H, *J* = 8, 8 Hz), 7.36 (dd, 1 H, *J* = 8, 8 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 168.5, 165.3, 139.6, 137.6, 134.0, 129.7, 126.5, 123.1, 121.9, 121.4, 120.9, 117.8, 112.8, 112.5, 109.7; HREIMS calcd for C<sub>15</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub> 276.0647, found 276.0638.

**Isogranulatimide B (11).** A suspension of **31** (14 mg, 0.037 mmol) in nitrobenzene (1.5 mL) was heated to reflux for 1 h. The reaction mixture was cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and filtered through a short plug of silica gel (10 g silica gel). The nitrobenzene was eluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL), while CH<sub>2</sub>Cl<sub>2</sub>-MeOH (5:1, 50 mL) was used to elute **11**. Removal of solvent provided 8.5 mg (83%) of **11** as a deep red solid that exhibited mp >300 °C; IR (KBr) 3400, 3180, 1761, 1719, 1651, 1556, 1519,



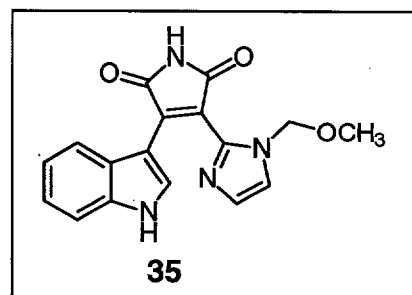
1504, 1365, 1313, 1249, 1011, 964, 740  $\text{cm}^{-1}$ ;  $^1\text{H NMR}^7$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.99 (s, 1 H), 11.23 (s, 1 H), 8.87 (bs, 1 H), 8.53 (d, 1 H,  $J = 7.9$  Hz), 7.94 (bs, 1 H), 7.66 (d, 1 H,  $J = 8.0$  Hz), 7.43 (dd, 1 H,  $J = 8, 8$  Hz), 7.34 (dd, 1 H,  $J = 8, 8$  Hz);  $^{13}\text{C NMR}^7$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  169.1, 165.9, 138.7, 132.0, 128.4, 125.0, 122.3, 122.4, 121.3, 121.2, 119.8, 119.6, 119.3, 112.0, 104.4; HREIMS calcd for  $\text{C}_{15}\text{H}_8\text{N}_4\text{O}_2$  276.0647, found 276.0649.

**Methyl (1-methoxymethyl-1*H*-imidazol-2-yl)glyoxylate (33).** To a cold ( $-48$  °C), stirred solution of 1-methoxymethyl-1*H*-imidazole (32) (335 mg, 2.99 mmol) in THF (15.0 mL) was added a solution of *n*-BuLi (1.50 M in hexanes, 2.30 mL, 3.45 mmol) and the resultant mixture was stirred for 1 h. The reaction mixture was then cooled to  $-78$  °C and added to a solution of dimethyl oxalate (1.17 g, 9.92 mmol) in THF (10.0 mL) at  $-78$  °C and the mixture was stirred at  $-78$



°C for an additional 20 min. The reaction mixture was treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and EtOAc (15 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine (10 mL), dried ( $\text{MgSO}_4$ ), and concentrated. Flash chromatography (50 g of silica gel, 50:1  $\text{CH}_2\text{Cl}_2$ -MeOH) of the crude material afforded 290 mg (49%) of **33** as an oil that exhibited IR (film) 2957, 1744, 1679, 1412, 1276, 1215, 1109, 1005  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (s, 1 H), 7.33 (s, 1 H), 5.71 (s, 2 H), 3.96 (s, 3 H), 3.33 (s, 3 H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.9, 164.3, 140.6, 132.9, 126.9, 78.8, 57.5, 53.4; HREIMS calcd for  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_4$  198.0641, found 198.0646.

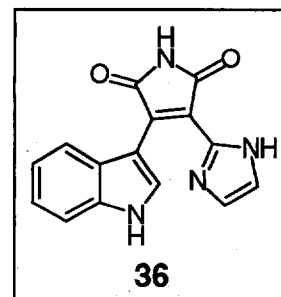
**14-methoxymethylneodidemnimide A (35).** To a stirred solution of **33** (142 mg, 0.717 mmol) and indole 3-acetamide (62.7 mg, 0.360 mmol) in DMF (5.0 mL) was added a solution of *t*-BuOK (101 mg, 0.902 mmol) in DMF (5.0 mL) at rt. The reaction mixture was stirred overnight at rt and then was heated to  $45$  °C and stirred for an additional 20 h. The reaction mixture was cooled to rt and treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and EtOAc (20 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine (4 X 10 mL), dried



7. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals for **11** shift depending on the concentration. The  $^1\text{H}$  NMR spectrum was acquired at a concentration of 1 mg/mL and the  $^{13}\text{C}$  NMR spectrum was acquired at a concentration of 5 mg/mL.

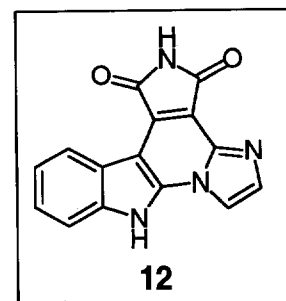
(MgSO<sub>4</sub>), and concentrated. Flash chromatography (40 g of silica gel, 40:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 79.1 mg (68 %) of **35** as a red solid that exhibited mp >240 °C (decomp.); IR (KBr) 2500-3400, 1759, 1713, 1626, 1531, 1341, 1025, 745 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.06 (bs, 1 H), 11.17 (bs, 1 H), 8.22 (d, 1 H, *J* = 3.0 Hz), 7.46 (s, 1 H), 7.41 (d, 1 H, *J* = 7.9 Hz), 7.11 (s, 1 H), 7.08 (dd, 1 H, *J* = 8, 8 Hz), 6.77 (dd, 1 H, *J* = 8, 8 Hz), 6.22 (d, 1 H, *J* = 8.1 Hz), 5.06 (s, 2 H), 3.08 (s, 3 H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 171.6, 171.4, 138.0, 137.7, 136.6, 132.7, 129.2, 124.8, 122.4, 122.0, 120.7, 120.2, 118.1, 112.1, 105.1, 76.8, 55.7; HREIMS calcd for C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub> 322.1066, found 322.1058.

**Neodidemnimide A (36).** To a stirred suspension of **35** (18 mg, 0.056 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) at rt was added BBr<sub>3</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.56 mL, 0.56 mmol) and the resulting blue mixture was heated at reflux for 5 h. The reaction mixture was cooled to rt and treated with saturated aqueous NaHCO<sub>3</sub> (5 mL), and EtOAc (10 mL) and then was stirred for an additional 0.5 h. The phases were separated and the aqueous layer was extracted with EtOAc (3 X 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (25 g of silica gel, 20:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the crude material afforded 13.5 mg (87%) of **36** as an orange solid that exhibited mp 265 °C (decomp.); IR (KBr) 3385, 3140, 1759, 1709, 1630, 1494, 1431, 1346, 1025, 1002, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR(400 MHz, DMSO-*d*<sub>6</sub> with 0.05 % TFA<sup>8</sup>) δ 12.45 (s, 1 H), 11.61 (s, 1 H), 8.37 (d, 1 H, *J* = 2.7 Hz), 7.83 (s, 2 H), 7.55 (d, 1 H, *J* = 7.8 Hz), 7.20 (dd, 1 H, *J* = 8, 8 Hz); 6.93 (dd, 1 H, *J* = 8, 8 Hz), 6.13 (d, 1 H, *J* = 7.6 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub> with 0.05 % TFA) δ 170.8, 170.2, 137.5, 137.1, 135.3, 134.6, 124.4, 122.9, 121.8, 121.3, 119.7, 112.9, 111.4, 104.5; HREIMS calcd for C<sub>15</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub> 278.0804, found 278.0797.



8. Without the use of TFA, the NMR spectra of **36** were difficult to interpret. This was also observed with didemnimide A (**8**). An improvement in the NMR spectra of both these compounds can be realized with the addition of TFA to the DMSO-*d*<sub>6</sub>. The <sup>1</sup>H NMR data for didemnimide A (**8**) in DMSO-*d*<sub>6</sub> in the presence of TFA are as follows: δ 12.13 (s, 1 H), 11.27 (s, 1 H), 8.80 (s, 1 H), 8.08 (d, 1 H, *J* = 2.7 Hz), 7.63 (s, 1 H), 7.50 (d, 1 H, *J* = 7.9 Hz), 7.15 (dd, 1 H, *J* = 8, 8 Hz), 6.93 (dd, 1 H, *J* = 8, 8 Hz), 6.67 (d, 1 H, *J* = 7.8 Hz).

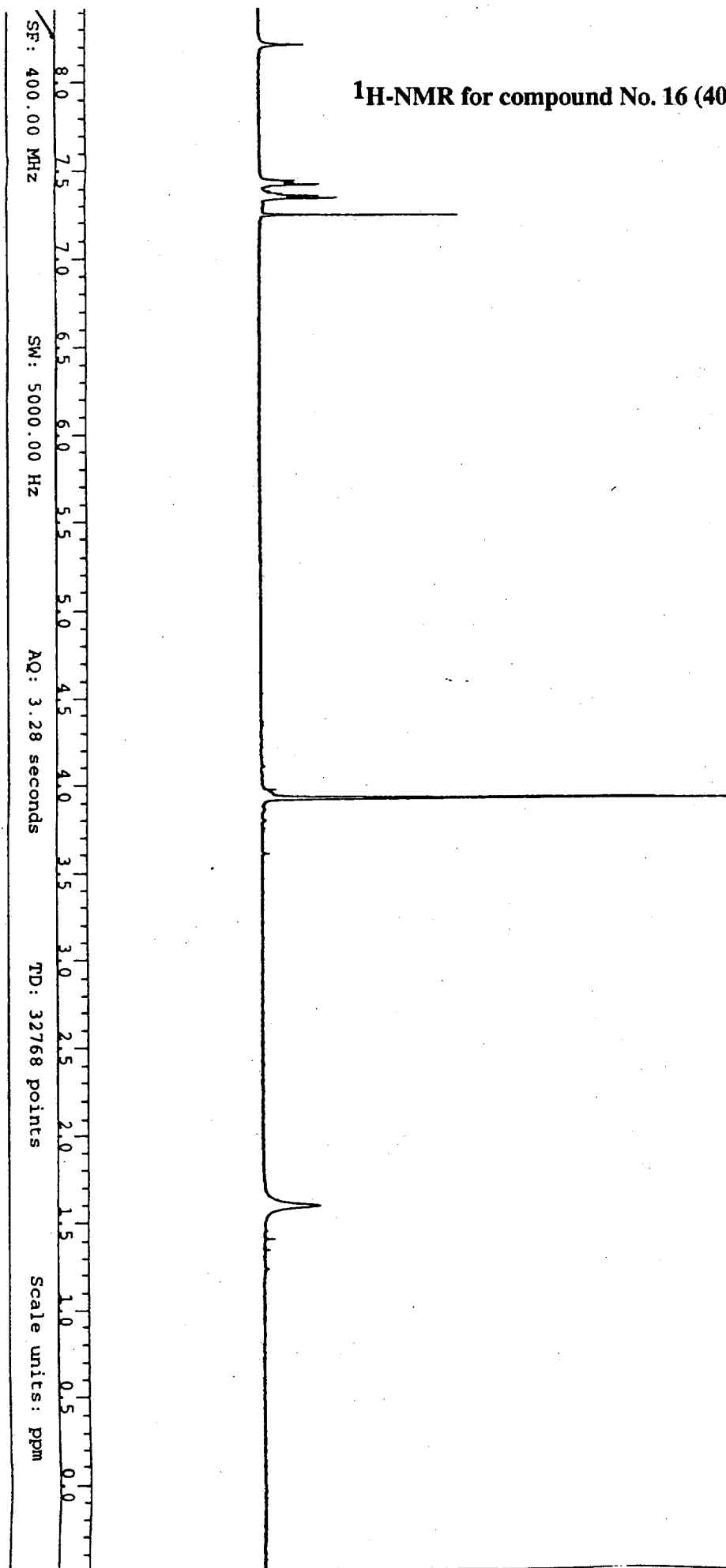
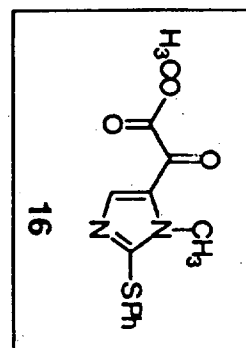
**Isogranulatimide C (12).** A stirred suspension of **36** (27 mg, 0.097 mmol) and Pd black (10 mg, 0.097 mmol) in nitrobenzene (4.0 mL) was heated to reflux for 8 h. The reaction mixture was cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and placed on a short plug of silica gel (5 g). The nitrobenzene was eluted using CH<sub>2</sub>Cl<sub>2</sub> and the reaction product was eluted with CH<sub>2</sub>Cl<sub>2</sub>-MeOH-TFA (10:1:0.05). The latter eluate was concentrated. The yellow residue was dissolved in EtOAc (50 mL). The solution was washed with



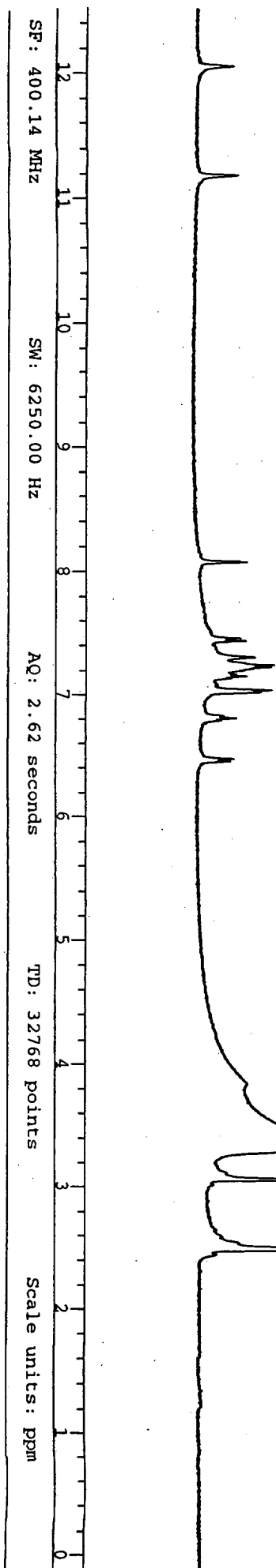
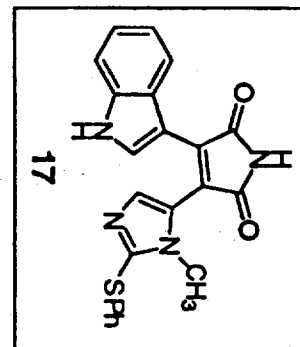
saturated aqueous NaHCO<sub>3</sub> (3 X 25 mL), water (20 mL), brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated to afford 20.1 mg (75%) of **12** as an orange solid that exhibited mp >300 °C; IR (KBr) 2600-3400, 1755, 1717, 1631, 1591, 1575, 1464, 1376, 1336, 1232, 751 cm<sup>-1</sup>; <sup>1</sup>H NMR<sup>9</sup> (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.36 (bs, 1 H), 11.13 (bs, 1 H), 8.63 (d, 1 H, *J* = 7.7 Hz), 8.40 (s, 1 H), 7.93 (s, 1 H), 7.69 (d, 1 H, *J* = 8.2 Hz), 7.48 (dd, 1 H, *J* = 8, 8 Hz), 7.38 (dd, 1 H, *J* = 8, 8 Hz); <sup>13</sup>C NMR<sup>9</sup> (100 MHz, DMSO-*d*<sub>6</sub>) δ 169.9, 168.2, 138.5, 138.3, 136.9, 135.5, 128.9, 125.4, 122.8, 121.7, 120.8, 112.5, 111.2, 109.5, 99.0; HREIMS calcd for C<sub>15</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub> 276.0647, found 276.0639.

9. The <sup>1</sup>H and <sup>13</sup>C NMR signals for **12** shift depending on the concentration. The <sup>1</sup>H NMR spectrum was acquired at a concentration of 1 mg/mL and the <sup>13</sup>C NMR spectrum was acquired at a concentration of 10 mg/mL.

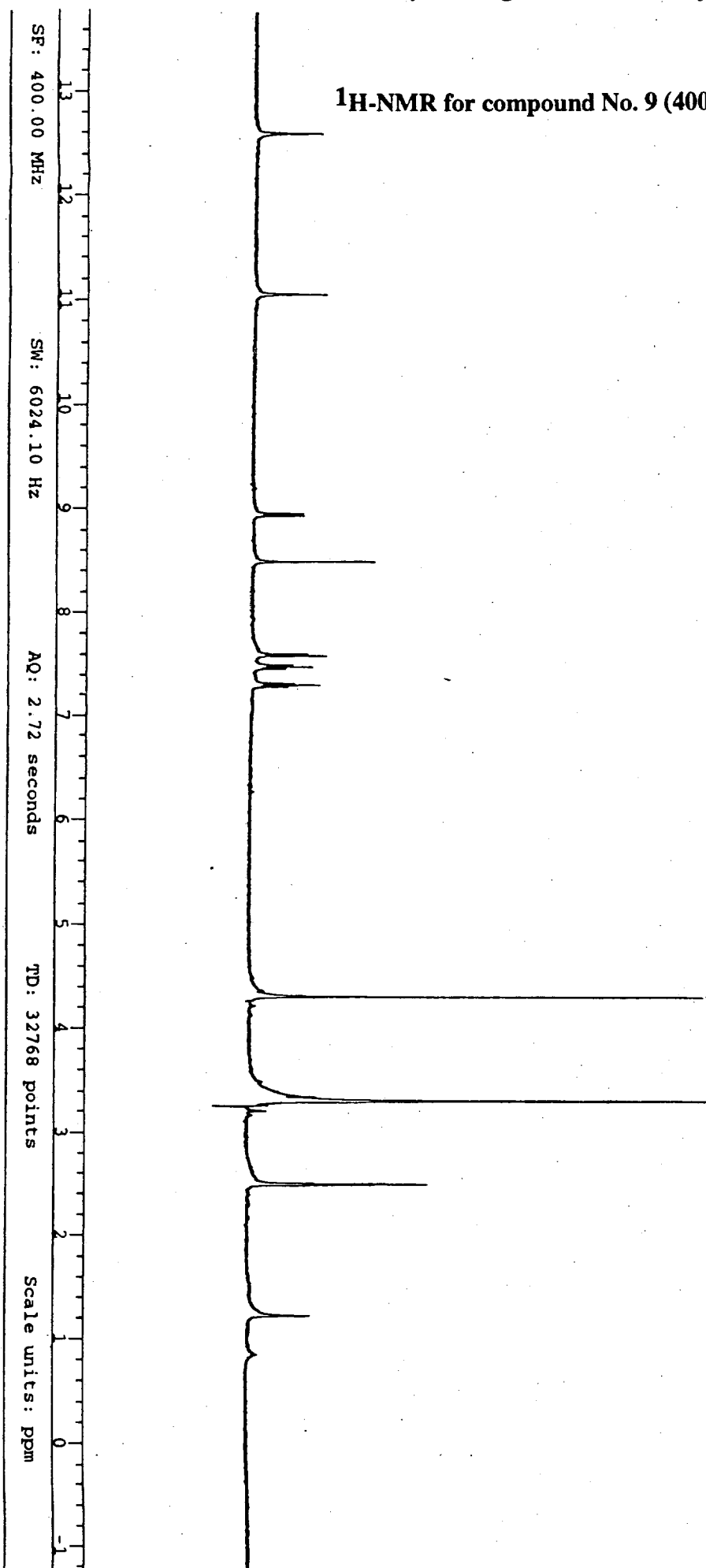
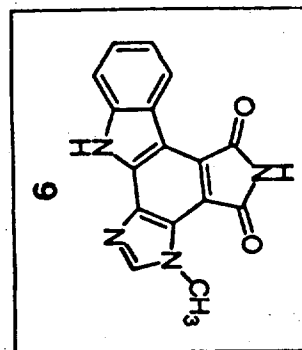
<sup>1</sup>H-NMR for compound No. 16 (400 MHz, CDCl<sub>3</sub>)



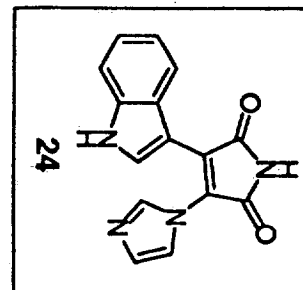
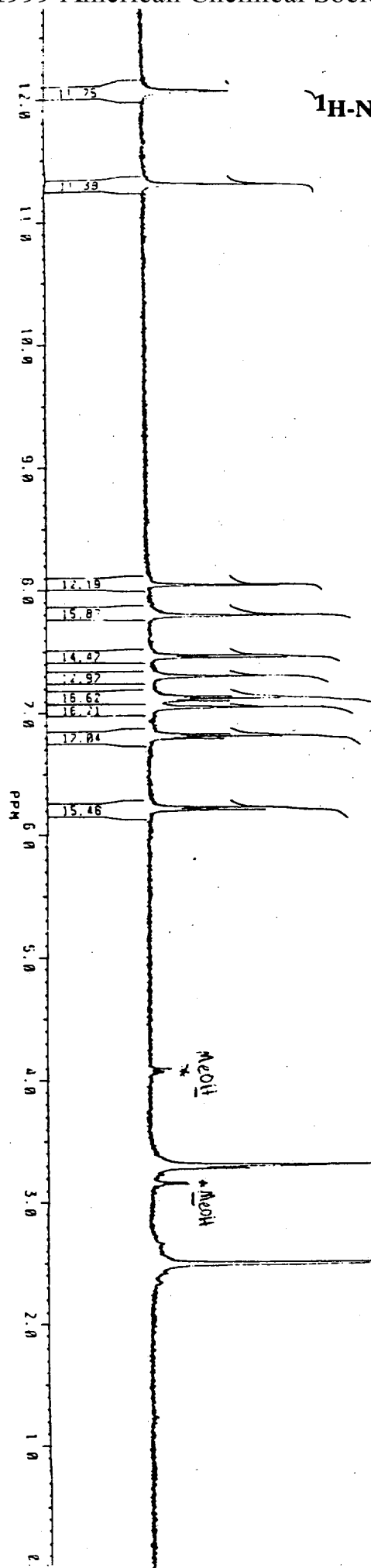
**<sup>1</sup>H-NMR for compound No. 17 (400 MHz, DMSO-d<sub>6</sub>)**



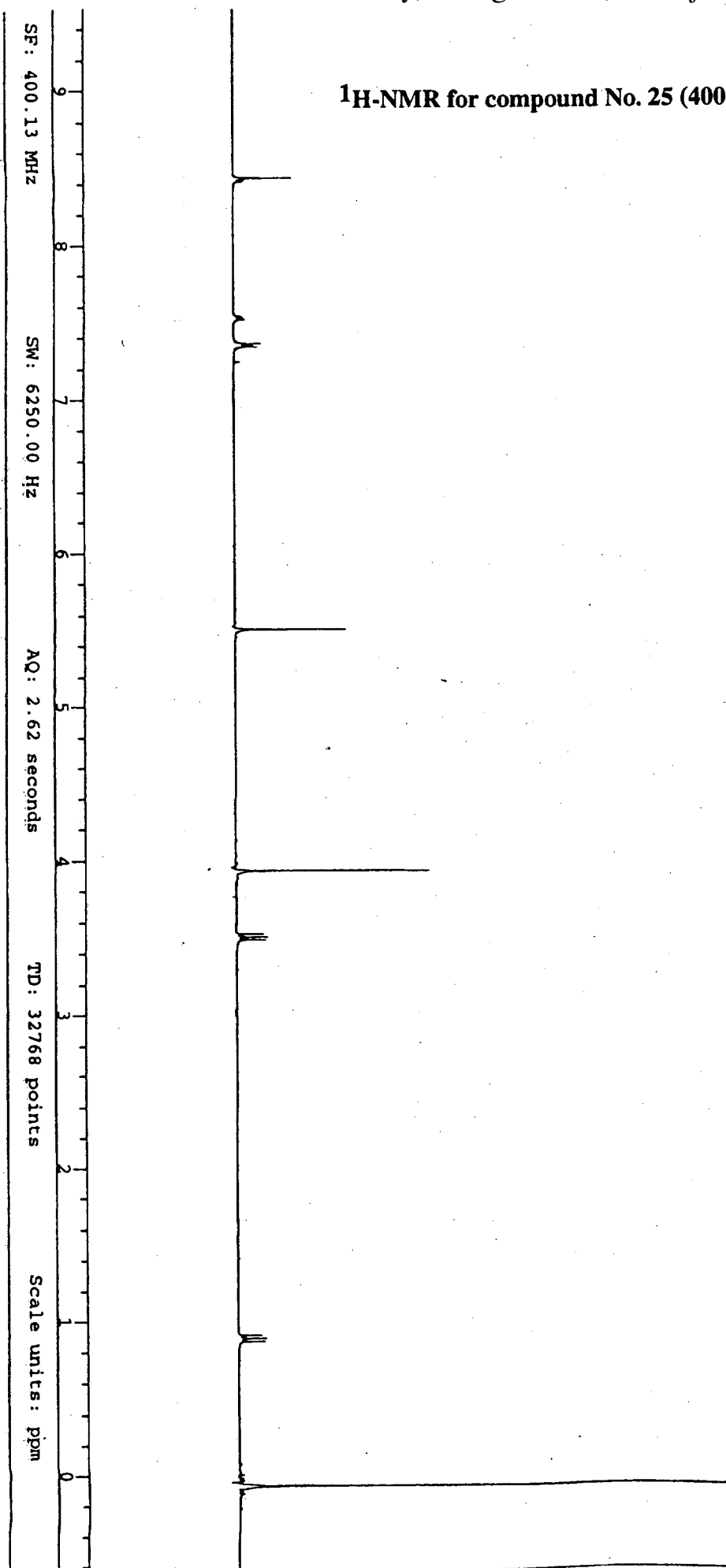
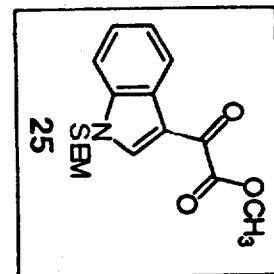
**<sup>1</sup>H-NMR for compound No. 9 (400 MHz, DMSO-*d*<sub>6</sub>)**



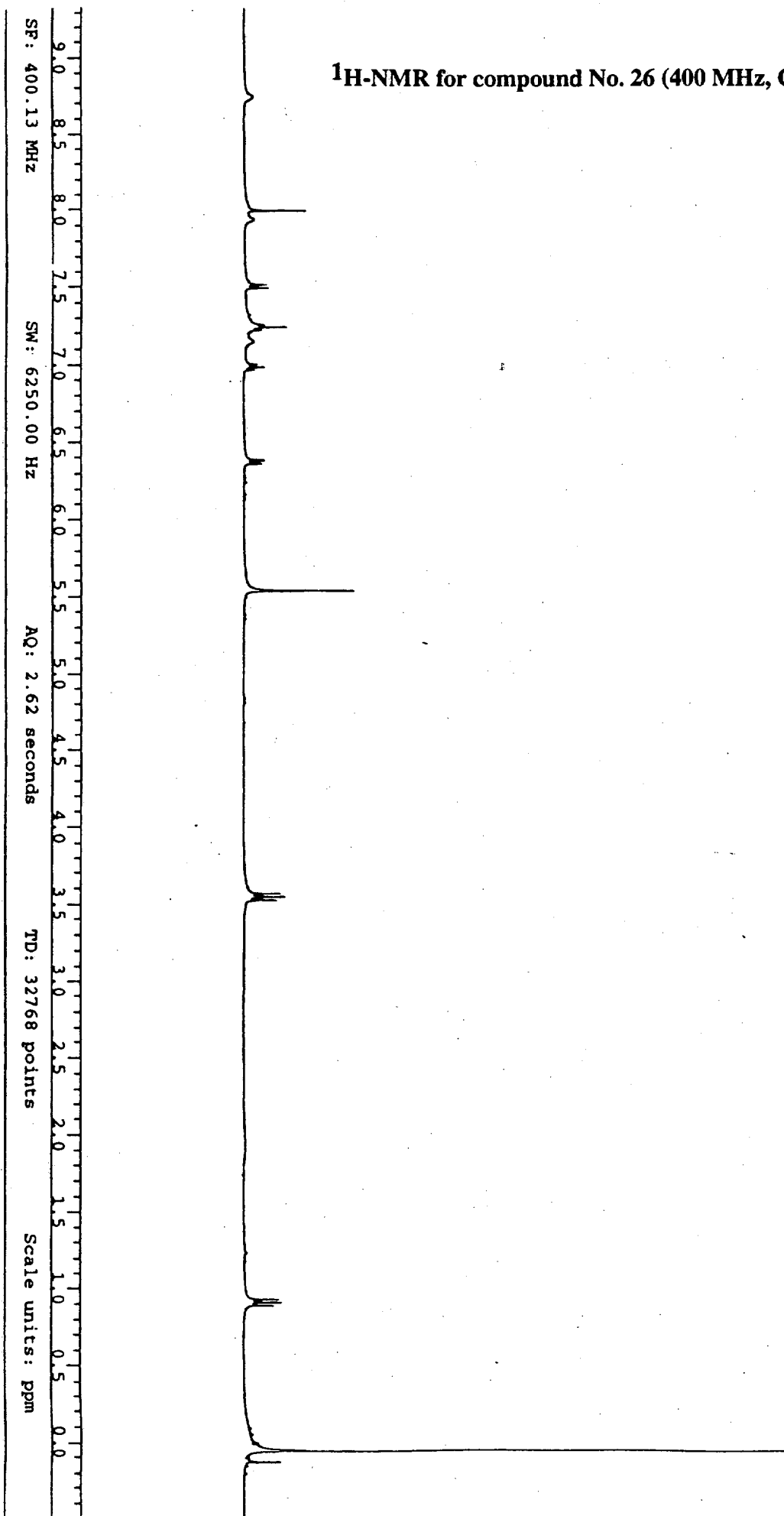
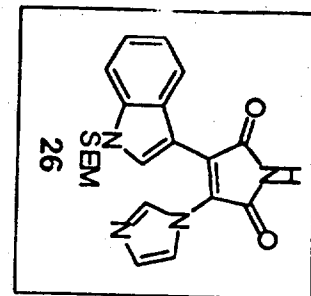
<sup>1</sup>H-NMR for compound No. 24 (400 MHz, DMSO-d<sub>6</sub>)



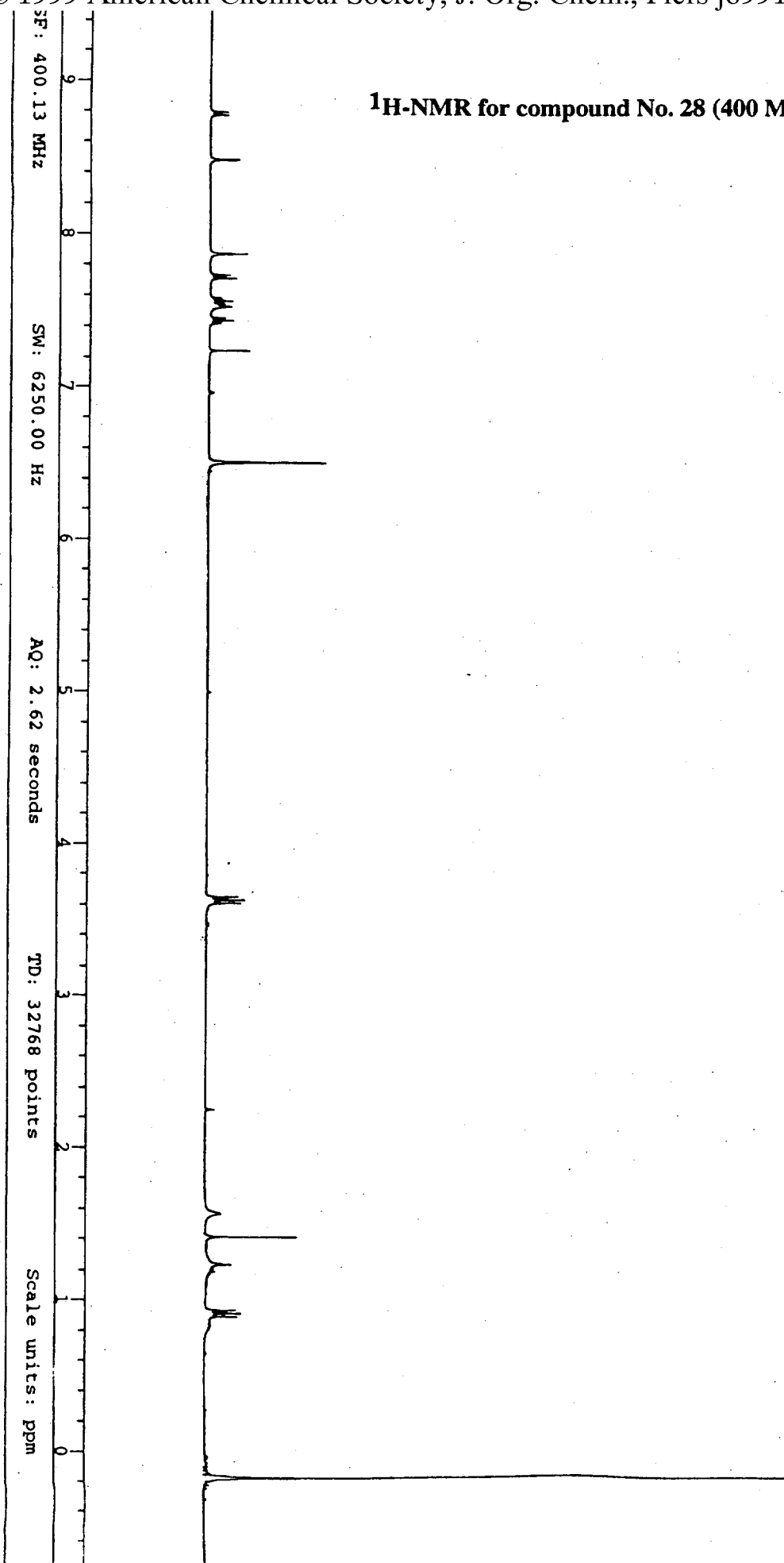
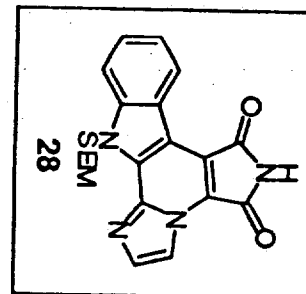
**<sup>1</sup>H-NMR for compound No. 25 (400 MHz, CDCl<sub>3</sub>)**



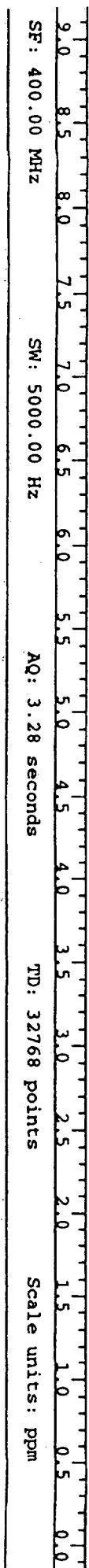
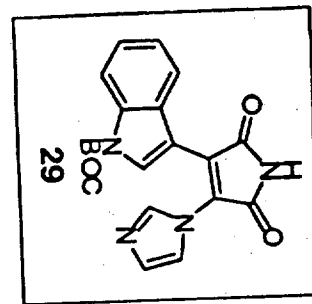
**<sup>1</sup>H-NMR for compound No. 26 (400 MHz, CDCl<sub>3</sub>)**



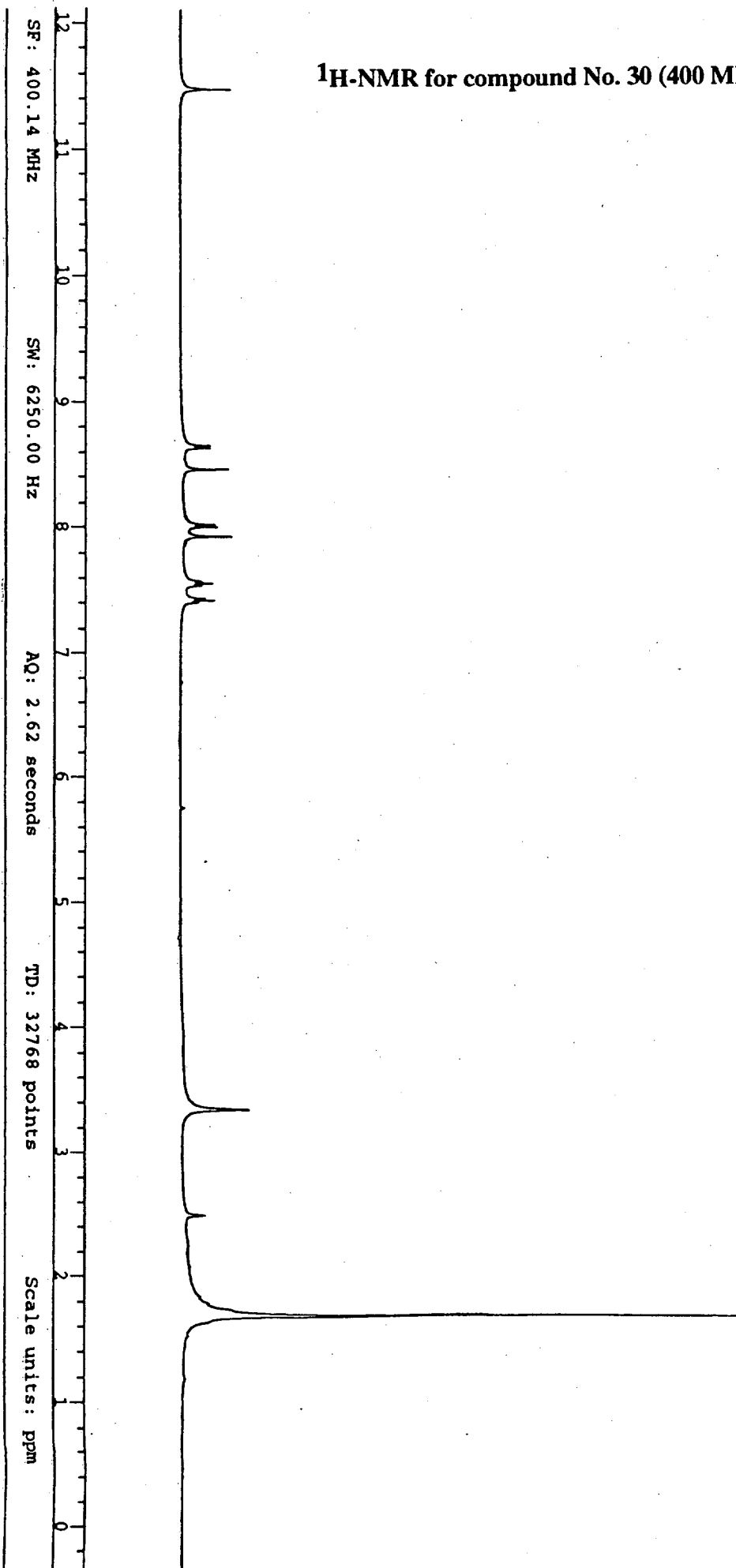
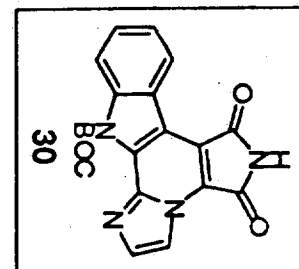
<sup>1</sup>H-NMR for compound No. 28 (400 MHz, CDCl<sub>3</sub>)



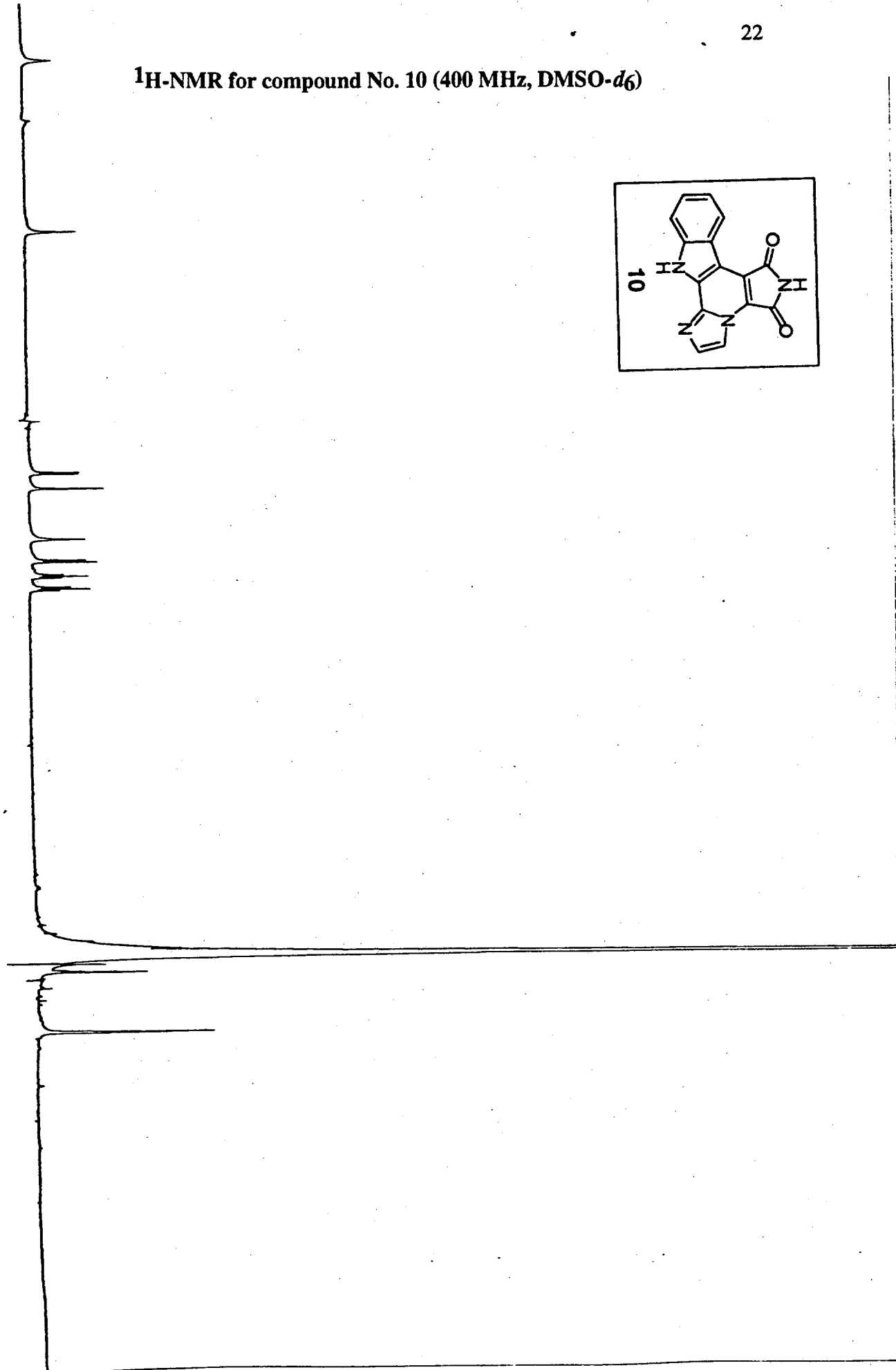
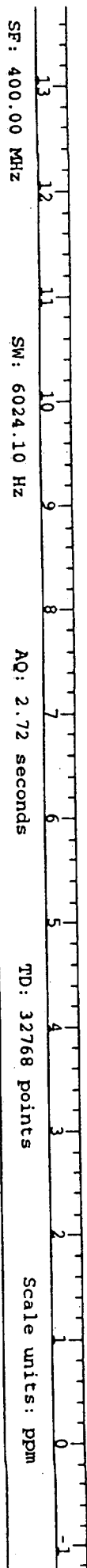
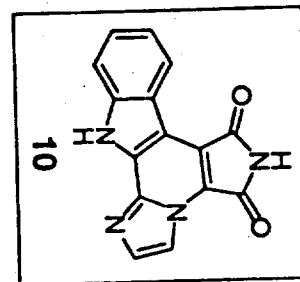
**<sup>1</sup>H-NMR for compound No. 29 (400 MHz, CDCl<sub>3</sub>)**



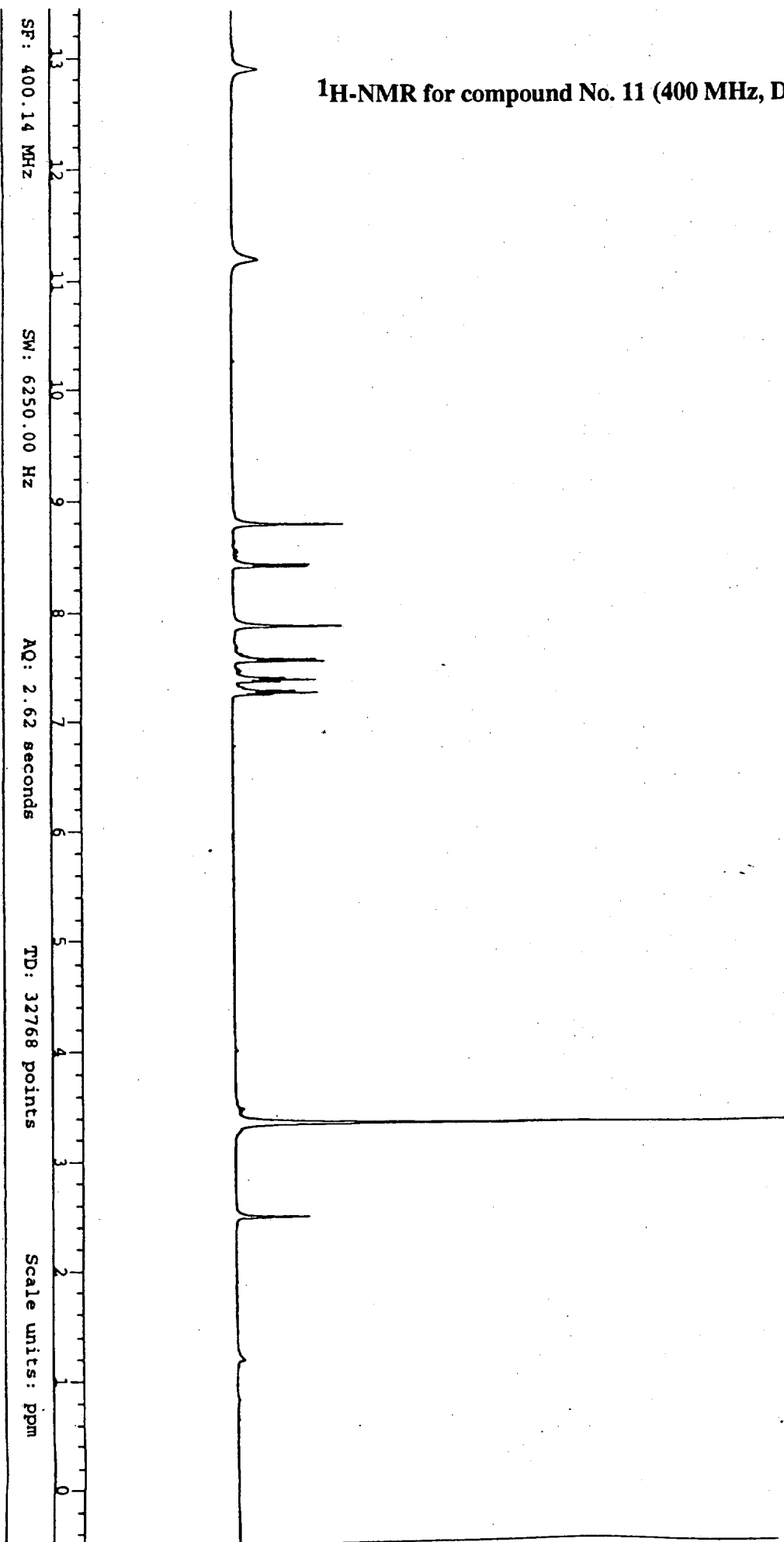
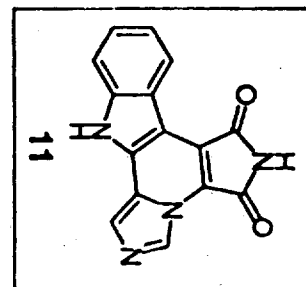
**<sup>1</sup>H-NMR for compound No. 30 (400 MHz, DMSO-*d*<sub>6</sub>)**



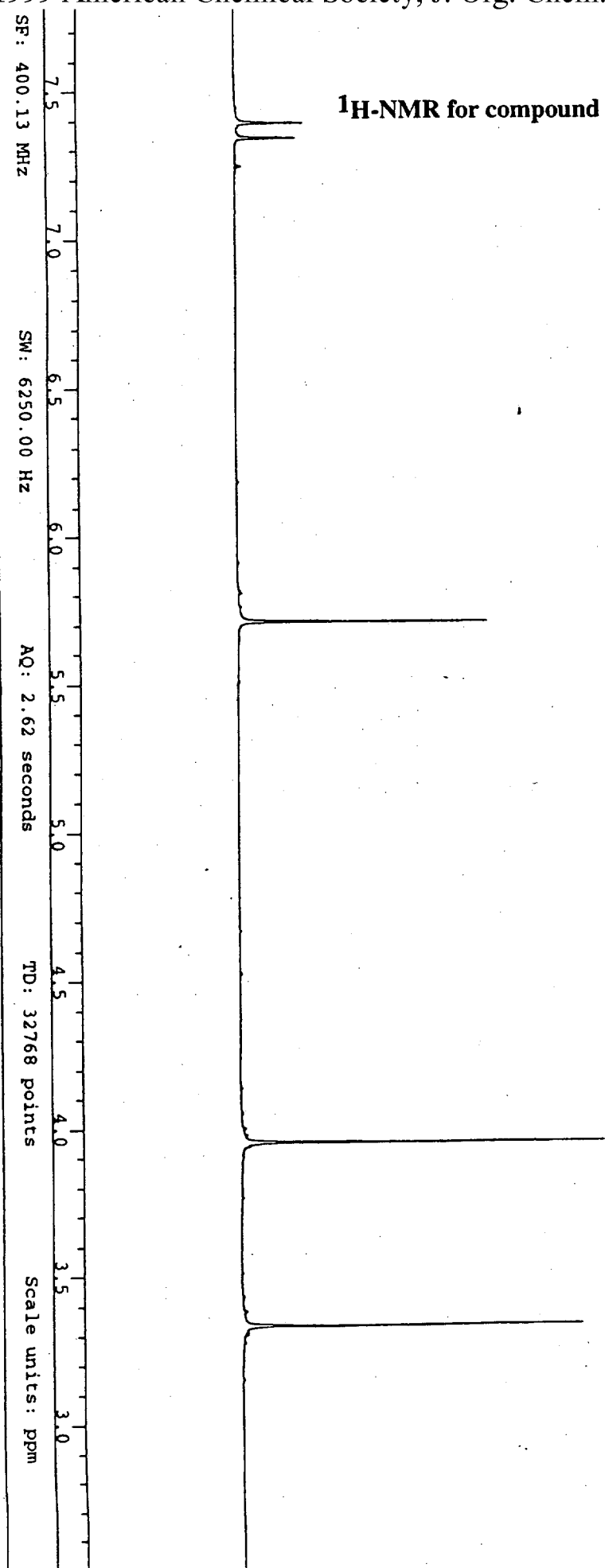
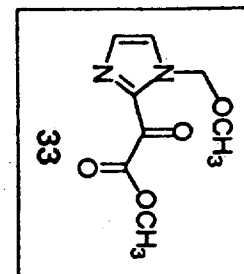
**<sup>1</sup>H-NMR for compound No. 10 (400 MHz, DMSO-d<sub>6</sub>)**



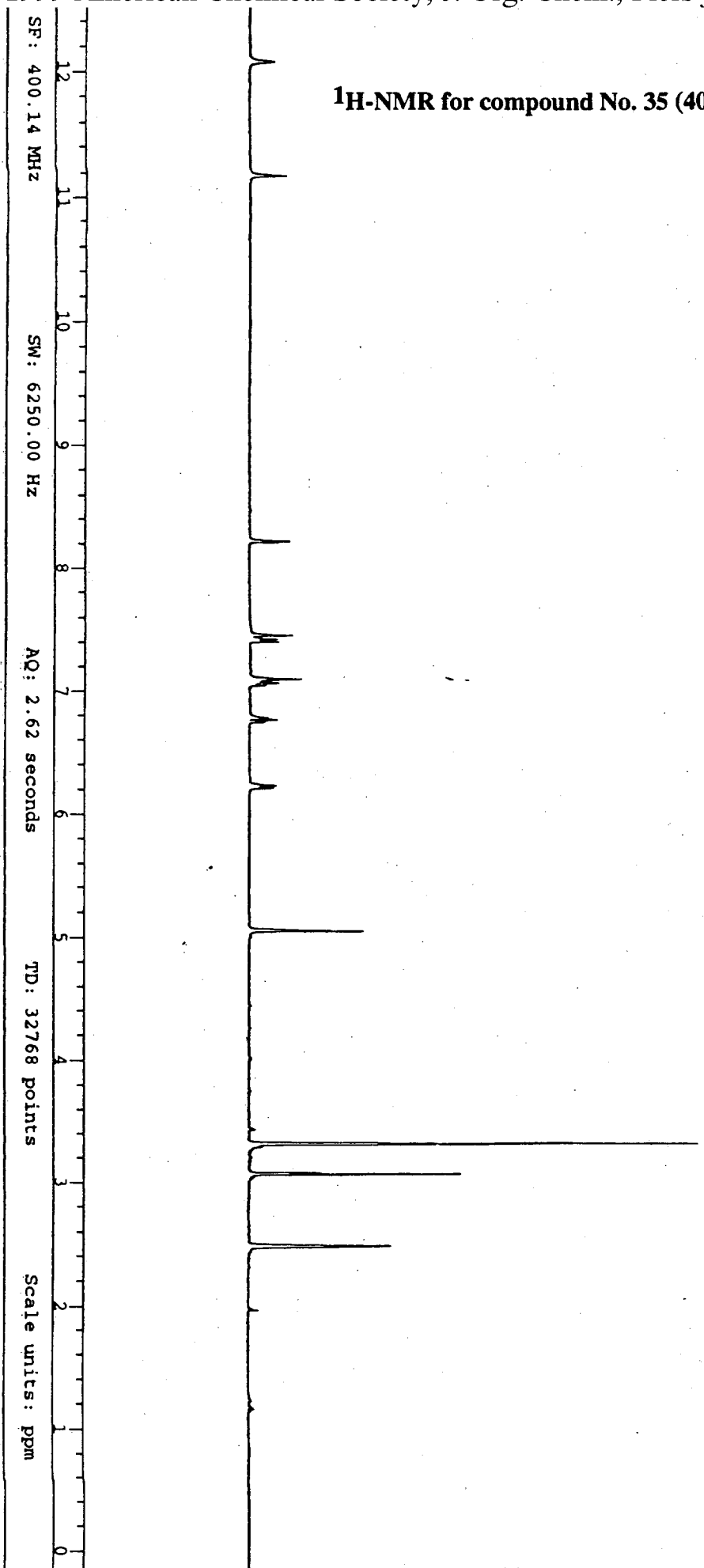
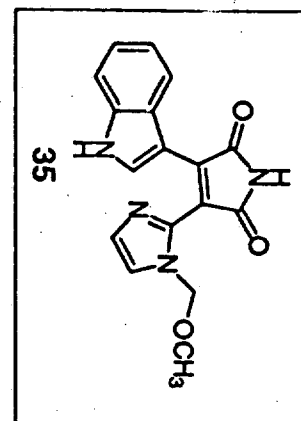
<sup>1</sup>H-NMR for compound No. 11 (400 MHz, DMSO-d<sub>6</sub>)



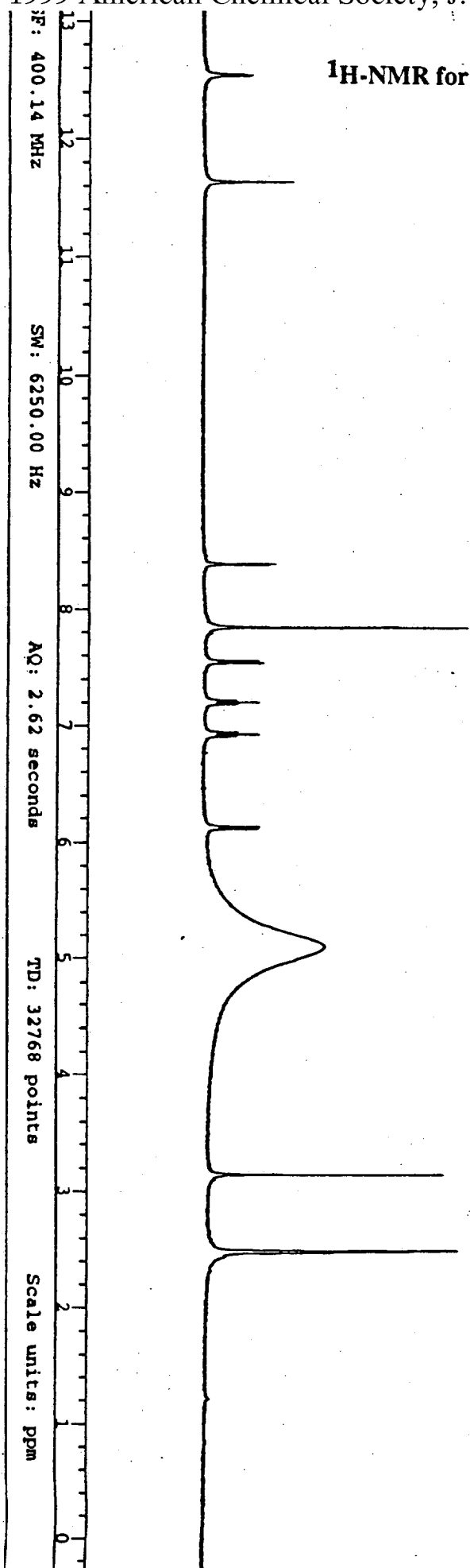
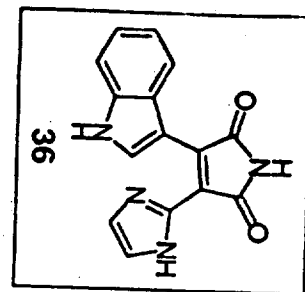
<sup>1</sup>H-NMR for compound No. 33 (400 MHz, CDCl<sub>3</sub>)



**<sup>1</sup>H-NMR for compound No. 35 (400 MHz, DMSO-*d*<sub>6</sub>)**



**<sup>1</sup>H-NMR for compound No. 36 (400 MHz, DMSO-*d*<sub>6</sub> and 0.05% TFA)**



**<sup>1</sup>H-NMR for compound No. 12 (400 MHz, DMSO-d<sub>6</sub>)**

