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REVISED Manuscript Received

OCT 23 2001

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SUPPORTING INFORMATION for

Amino Acid-Derived Heterocycles: Lewis Acid-Catalyzed and Radical Cyclizations from Peptide Acetals

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Contribution from the Center for New Directions in Organic Synthesis,§

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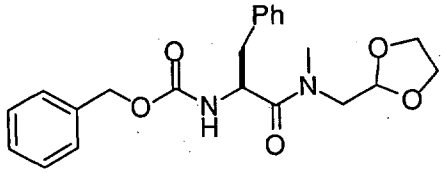
§ The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member.

General. IR spectra were obtained on thin films or mulls on a Perkin-Elmer 1600 FT-IR instrument, and NMR spectra were acquired with Bruker AM-300, AMX-400 or DRX-500 instruments in $CDCl_3$ unless otherwise stated. *Cis-trans* rotamers complicated the NMR spectra of many tertiary amides; major and minor isomers are denoted by maj and min respectively; no suffix indicates combined resonances. FAB mass spectra were obtained with NBA as matrix. All spectra and X-ray crystallographic analyses were obtained from the Analytical Services facilities of the College of Chemistry, University of California, Berkeley.

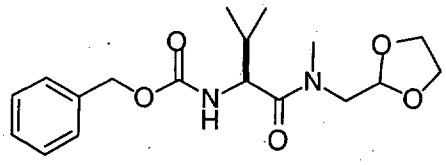
All reactions other than peptide couplings were performed under N_2. Solutions subjected to hydrogenolysis or radical reactions were deoxygenated by boiling the reaction mixture vigorously at room temperature (rt) under aspirator vacuum for 20 s, followed by purging with dry nitrogen gas, and repeating this cycle five times. Toluene was dried over 3Å molecular sieves under nitrogen for at least 24 h before use. Gradient solvent systems were usually employed for flash columns. Unless otherwise stated, crystallizations were performed by dissolving the compound in the minimum amount of toluene and allowing pentane to diffuse into the solution overnight.



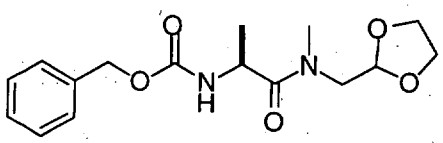
Cbz-Phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. To Cbz-phenylalanine (11.3 g, 38 mmol) and 2-methylaminomethyl-1,3-dioxolane (4.3 mL, 1 eq) in CH_2Cl_2 (300 mL) were added HOBt (5.1 g, 1 eq), EDC (7.2 g, 1 eq) and DMAP (9.2 g, 2 eq) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and water (300 mL), the layers separated and worked up with citric acid to give a straw oil (15.2 g). A portion (1.66 g) was purified by flash

column chromatography (1:1 EtOAc/pet ether → acetone) to give the Cbz-protected acetal as a clear, colorless oil (1.4 g from this portion, implying an overall yield of 12.8 g, 85%). R_F (EtOAc) 0.52; IR (film) 3285, 1715, 1644, 1602, 1529 cm^{-1}; ^1H NMR δ 7.25 (m, 10), 6.00 (d, J = 8.5), 5.96 (d, J = 9.0) (total 1), 4.95 (m, 4), 3.80 (m, 4), 3.57 (dd, J = 14.0, 4.5), 3.48 (br dd, J = 16.0, 3.5), 3.35 (dd, J = 13.5, 4.5), 3.21 (br dd, J = 16.0, 3.0) (total 2), 3.02 (m, 2), 2.94 (s), 2.83 (s) (total 3); ^{13}C NMR δ 172.5, 171.7, 155.6, 155.6, 136.7, 136.5, 136.4, 136.1, 129.5, 129.4, 128.4, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8, 126.9, 126.8, 102.0, 101.9, 66.7, 66.6, 65.1, 65.1, 64.8, 64.8, 51.9, 51.4, 50.5, 39.9, 39.7, 36.6, 35.9; MS (FAB) m/z 399 (81%, MH^+), 210 (42); HRMS (FAB) Calcd. for $C_{22}H_{26}N_2O_5$ (MH^+): 399.1920. Found: 399.1920.

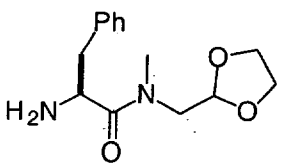
The following amides were snthesized in a similar fashion:



Cbz-Valine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. R_F (1:1 EtOAc/pet ether) 0.17; ^1H NMR δ 7.25 (m, 5), 5.78 (d, J = 9.0), 5.74 (d, J = 9.5) (total 1), 4.96 (m, 3), 4.48 (m, 1), 3.80 (m, 4), 3.57 (d, J = 17.5), 3.47 (d, J = 15.5) (total 1), 3.20 (dd, 1, J = 14.0, 4.0), 3.10 (s), 2.91 (s) (total 3), 1.92 (m, 1), 0.91 (d, J = 6.5), 0.87 (d, J = 6.5), 0.83 (d, J = 6.5) (total 6); ^{13}C NMR δ 172.6, 172.2, 156.4, 156.2, 136.6, 136.5, 128.3, 128.3, 127.9, 127.8, 102.0, 102.0, 66.6, 66.5, 65.1, 64.9, 64.7, 64.7, 55.6, 51.9, 50.2, 37.0, 35.5, 31.5, 31.2, 19.5, 19.3, 17.4, 17.2; MS (FAB) m/z 423 (14%), 351 (100, MH^+), 243 (9, M^+-OBn); HRMS (FAB) Calcd. for $C_{18}H_{27}N_2O_5$ (MH^+): 351.1920. Found: 351.1926.

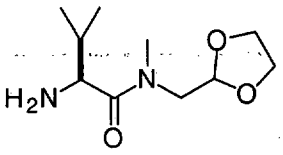


Cbz-Alanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. R_F (EtOAc) 0.5; IR (film) 1714, 1647, 1497 cm^{-1}; ^1H NMR 7.32 (m, 5), 5.84 (d, 1, J = 7.5), 5.68 (d, 1, J = 7.5), 5.58 (d, 1_{min}, J = 5.0), 5.48 (d, 1_{min}, J = 5.5), 5.24 (m, 1), 5.11 (m, 2), 5.03 (t, 1, J = 3.5), 4.97 (t, 1, J = 4.0), 4.79 (p, 1, J = 7.0), 4.69 (p, 1, J = 7.0), 3.91 (m, 4), 3.2 (m), 3.69 (d, J = 3.5), 3.66 (d, J = 3.5), 3.63 (d, J = 4.5), 3.61 (d, J = 4.0) (total 2), 3.15 (s, 3), 3.08 (s, 1), 3.02 (s, 1); ^{13}C NMR 173.6, 172.9, 155.5, 132.4, 128.4, 128.1, 127.9, 102.0, 97.3, 82.2, 66.6, 65.2, 64.9, 63.7, 51.7, 50.4, 46.9, 46.6, 36.7, 35.9, 19.2, 18.9; MS (FAB) m/z 323 (100, MH^+); HRMS (FAB) Calcd. for $C_{16}H_{23}N_2O_5$ (MH^+): 323.1607. Found 323.1605.

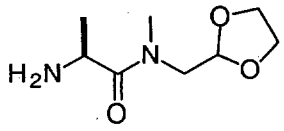


Phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. To 10% Pd/C (400 mg) suspended in absolute EtOH (400 mL) was added the N-Cbz derivative (1.4 g, 3.5 mmol) in EtOH (5 mL). The suspension was degassed, purged with hydrogen with three evacuation-hydrogen cycles, and stirred under hydrogen at rt for 105 min. The reaction vessel was purged with nitrogen, filtered through a plug of Celite, gravity-filtered through paper and concentrated *in vacuo* to yield the phenylalanine acetal as a clear, colorless oil (875 mg, 94%). Spectral data matched that reported previously (Smith, L. R.; Bartlett, P. A., *Molecules Online* **1998**, 2, 58-62).

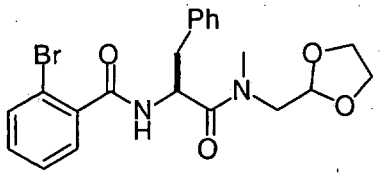
The following amines were prepared in a similar fashion:



Valine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. IR (film) 3418 br, 1639 br, 1495 br cm^{-1}; ^1H NMR δ 5.02 (br s, 2), 5.01 (dt, 1, *J* = 10.5, 3.0), 4.08 (m, 1), 3.94 (m, 4.5), 3.71 (dd, *J* = 15.5, 3.0), 3.42 (dd, *J* = 15.5, 3.0) (total 1), 3.34 (dd, 0.5, *J* = 14.0, 4.5), 3.16 (s), 3.04 (s) (total 3), 2.08 (m, 1), 1.10 (d, *J* = 7.0), 1.02 (d, *J* = 7.0) (total 6); ^{13}C NMR δ 173.3, 171.7, 101.9, 101.8, 65.3, 64.8, 64.7, 64.6, 55.7, 55.5, 51.5, 50.3, 37.1, 35.9, 31.1, 30.5, 19.4, 19.1, 17.3, 16.9; MS (FAB) m/z 217 (100%, MH^+), 118 (34); HRMS (FAB) Calcd. for $C_{10}H_{20}N_2O_3$ (MH^+): 217.1552. Found: 217.1558.



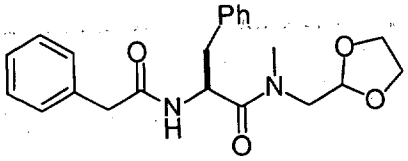
Phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. IR (film) 3361, 2974, 2893, 1638, 1487 cm^{-1}; ^1H NMR 5.00 (m, 2), 3.93 (m, 10), 3.68 (m, 3.66 (d, *J* = 4.0), 3.63 (d, *J* = 3.5), 3.61 (d, *J* = 4.5), 3.57 (ABq, *J* = 4.5, 4.0), 3.53 (d, *J* = 4.5), 3.47 (d, *J* = 3.0), 3.45 (d, *J* = 3.0) (total 4), 3.13 (s, 3), 3.03 (s, 3), 2.48 (br s, 2), 1.27 (dd, 2, *J* = 15.3, 6.5); ^{13}C NMR 176.6, 102.0, 65.2, 66.0, 64.7, 51.4, 50.5, 46.8, 46.3, 36.4, 35.8, 21.2, 21.0; MS (FAB) m/z 189 (50, MH^+).



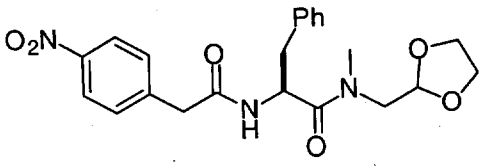
N^{α}-(2-Bromobenzoyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3a, n = 0, Y = 2-Br, R = Bn). To the free amine (200 mg, 0.76 mmol) in CH_2Cl_2 (2 mL) were added 2-bromobenzoic acid (152 mg, 1 eq), HOBt (102 mg, 1 eq), EDC (145 mg, 1 eq) and DMAP (184 mg, 2 eq), and the solution stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and water (50 mL), the layers were separated and worked up with citric acid. The residue was purified by flash column chromatography (3:1 EtOAc/pet ether → EtOAc) to give the bromobenzoyl acetal as a clear, colorless

oil (252 mg, 75%). R_F (EtOAc) 0.50; ^{1}H NMR δ 7.48 (m, 1), 7.34 (d, J = 7.5), 7.30 (d, J = 7.5) (total 1), 7.21 (m, 8), 5.39 (q, J = 7.5), 5.32 (q, J = 7.5) (total 1), 4.80 (m, 1), 3.79 (br m, 4), 3.47 (m, 1), 3.29 (dd, J = 14.0, 4.5), 3.20 (dd, J = 16.0, 3.0) (total 1), 3.11 (m, 2), 2.84 (s), 2.83 (s) (total 3); ^{13}C NMR δ 171.9, 171.2, 166.8, 166.8, 137.6, 137.4, 136.7, 136.0, 133.3, 133.2, 131.1, 131.0, 129.6, 129.5, 129.2, 129.2, 128.4, 128.3, 127.3, 127.2, 127.0, 126.8, 65.2, 65.1, 64.8, 64.7, 51.3, 50.8, 50.7, 50.4, 39.3, 39.1, 36.7, 35.9; MS (FAB) m/z 449 (100%, d, MH$^+$); HRMS (FAB) Calcd. for $C_{21}H_{24}BrN_2O_4$ (MH$^+$): 447.0919. Found: 447.0911.

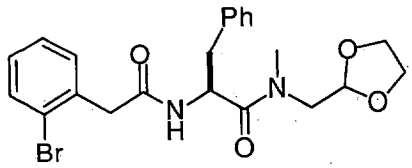
The following amides were prepared in a similar fashion:



N$^\alpha$-(Phenylacetyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3b, n = 1, Y = H, R = Bn). R_F (2:1 EtOAc/pet ether) 0.21; IR (film) 3296, 1650, 1538, 1494, 1454, 1416 cm^{-1}; ^{1}H NMR δ 7.22, (m, 10), 5.19 (m, 1), 4.84 (m, 1), 3.82 (m, 4), 3.69 (dd, J = 15.6, 3.2), 3.59 (dd, J = 14.0, 4.4) (total 1), 3.51 (s, 1), 3.47 (d, 1, J = 4.4), 3.34 (dd, J = 13.6, 4.4), 3.24 (dd, J = 15.6, 2.8) (total 1), 3.00 (m, 2), 2.97 (s), 2.88 (s) (total 3); MS (FAB) m/z 455 (9%), 383 (79, MH$^+$) 228 (17), 118 (100).

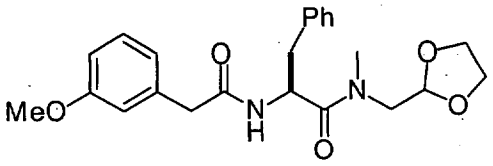


N$^\alpha$-(4-Nitrophenylacetyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3c, n = 1, Y = 4-NO$_2$, R = Bn). IR (film) 1733, 1633, 1519 cm^{-1}; ^{1}H NMR 8.06 (m, 2), 7.75 (d, J = 8.5), 7.64 (d, J = 8.5) (total 1), 7.34 (d, 1, J = 8.5), 7.20 (m, 6), 5.21 (m, 1), 4.88 (t, J = 3.3), 4.85 (t, J = 4.5) (total 1), 3.83 (m, 4), 3.53 (m, 2), 3.40 (dd, J = 15, 4.5), 3.28 (dd, J = 20, 3) (total 1), 3.01 (m, 5); ^{13}C NMR 172.9, 172.2, 169.0, 146.9, 146.8, 142.8, 142.8, 136.7, 135.9, 130.0, 129.9, 129.3, 129.3, 128.4, 128.3, 127.0, 126.8, 123.6, 123.5, 101.9, 65.1, 65.1, 64.8, 64.8, 60.3, 51.6, 50.7, 50.5, 50.5, 42.6, 39.0, 38.8, 36.8, 36.1, 14.1; MS (FAB) m/z 428 (53%, MH$^+$); HRMS (FAB) Calcd. for $C_{22}H_{26}N_3O_6$ (MH$^+$): 428.182. Found: 428.182.

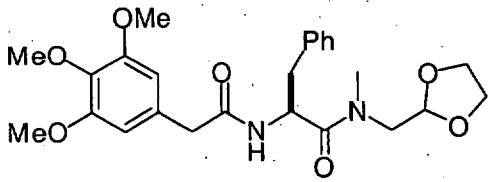


N$^\alpha$-(2-Bromophenylacetyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3d, n = 1, Y = 2-Br, R = Bn). R_F (EtOAc) 0.50; IR (film) 3296, 1659, 1650, 1644, 1633 cm^{-1}; ^{1}H NMR δ 7.50 (d, J = 8.0), 7.47 (d, J = 8.0) (total 1), 7.15 (m, 7), 6.90 (m, 1), 5.18 (qn, 1, J = 7.2), 4.82 (t, J = 4.0), 4.79 (t, J = 2.8)

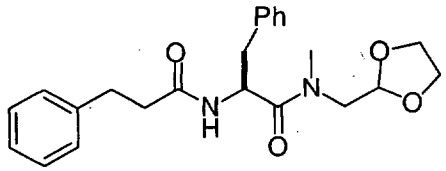
(total 1), 3.80 (m, 4), 3.30 (dd, J = 14.0, 4.4), 3.18 (dd, J = 15.6, 2.4) (total 1), 2.97 (m, 2), 2.92 (s), 2.82 (s) (total 3); ^{13}C NMR δ 172.4, 171.5, 168.9, 136.7, 136.0, 134.7, 133.0, 132.9, 131.6, 131.6, 129.5, 129.4, 129.0, 128.9, 128.4, 128.4, 127.9, 127.8, 126.9, 126.8, 102.0, 101.9, 65.2, 65.2, 64.9, 53.5, 51.4, 50.5, 50.4, 43.7, 43.6, 39.3, 39.1, 36.7, 36.1; MS (FAB) m/z 461 (73%, d, MH^+), 344 (6), 318 (14); HRMS (FAB) Calcd. for $C_{22}H_{26}BrN_2O_4$ (MH^+): 461.1076. Found: 461.1071.



N$^{\alpha}$-(2-Methoxyphenylacetyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3e, n = 1, Y = 3-MeO, R = Bn). R_F (EtOAc) 0.28; IR (film) 3297, 1644, 1633, 1601, 1584, 1538, 1489, 1454 cm^{-1}; ^{1}H NMR δ 7.18 (m, 4), 7.10 (m, 2), 6.79 (m, 3), 5.16 (m, 1), 4.83 (dt, 1, J = 14.0, 4.0), 3.85 (m, 2), 3.77 (m, 2), 3.74 (s), 3.73 (s) (total 3), 3.63 (dd, J = 16.0, 3.5), 3.57 (dd, J = 14.0, 4.5) (total 1), 3.47 (s, 1), 3.43 (d, 1, J = 4.5), 3.32 (dd, J = 14.0, 5.0), 3.23 (dd, J = 15.5, 2.5) (total 1), 2.95 (m, 2), 2.94 (s), 2.86 (s) (total 3); ^{13}C NMR δ 172.5, 171.7, 170.2, 170.1, 159.8, 159.7, 136.7, 136.3, 136.3, 136.0, 129.7, 129.7, 129.4, 129.3, 128.3, 126.9, 126.7, 121.5, 121.5, 114.7, 114.7, 112.8, 112.7, 102.0, 101.9, 65.1, 65.1, 64.8, 64.8, 55.1, 55.1, 51.4, 50.5, 50.4, 50.2, 43.4, 43.3, 39.1, 38.9, 36.6, 36.0; MS (FAB) m/z 485 (8%, M^++73) 413 (72, MH^+), 268 (20).

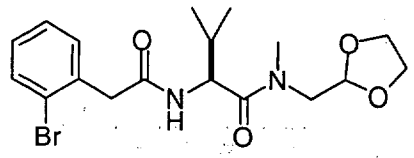


N$^{\alpha}$-(3,4,5-Trimethoxyphenylacetyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3f, n = 1, Y = 3,4,5-(MeO)$_3$, R = Bn). IR (film) 3060, 2939, 1736, 1651, 1504; ^{1}H NMR 7.06 (m, 3), 6.97 (m, 2), 6.74 (d, J = 8), 6.63 (d, J = 8) (total 1), 6.31 (s, 1), 6.25 (s, 1), 5.04 (m, 1), 4.73 (m, 1), 3.74 (br m, 13), 3.54 (dd, J = 14.3, 3.5), 3.46 (dd, J = 13.8, 4.5) (total 1), 3.24 (dd, J = 14, 4.5), 3.14 (dd, J = 15.8, 2.5) (total 1), 2.84 (br m, 7); ^{13}C NMR 172.5, 171.7, 170.2, 170.1, 153.3, 153.2, 136.9, 136.9, 136.6, 135.8, 130.5, 130.4, 129.4, 129.2, 128.2, 126.9, 126.7, 106.2, 106.1, 102.0, 101.8, 65.1, 65.1, 64.8, 64.8, 60.7, 56.0, 56.0, 53.4, 51.5, 50.5, 50.3, 50.2, 43.6, 38.9, 38.8, 36.6, 36.0; MS (FAB) m/z 473 (15%, MH^+), 355 (8), 118 (MH^+); HRMS (FAB) Calcd. for $C_{25}H_{33}N_2O_7$ (MH^+): 473.2288. Found: 473.2298.

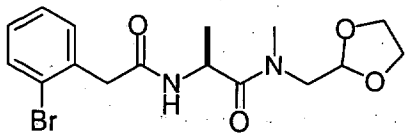


N$^{\alpha}$-(3-Phenylpropanoyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3g, n = 2, Y = H, R = Bn). IR (film) 1634, 1538 cm^{-1}; ^{1}H NMR 7.20 (m, 10), 6.73 (dd, 1, J = 15, 8.5), 5.20 (m, 1), 4.84 (t, J

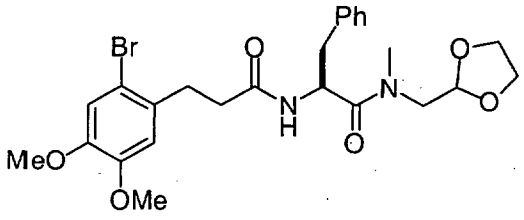
= 4.5), 4.80 (t, J = 3.3) (total 1), 3.89 (m, 1), 3.80 (m, 3) 3.56 (d, J = 4), 3.53 (d, J = 4.5), 3.50 (d, J = 3.4) (total 1), 3.35 (dd, J = 15, 4.5), 3.19 (dd, J = 15, 3) (total 1), 2.92 (br m, 7), 2.47 (m, 2); ^{13}C NMR 172.6, 171.8, 171.4, 140.8, 140.8, 136.8, 136.1, 129.5, 129.4, 128.4, 128.4, 128.3, 128.3, 126.9, 126.7, 126.1, 126.1, 102.0, 101.9, 65.1, 65.0, 64.8, 51.4, 50.5, 50.2, 50.0, 39.4, 39.2, 38.0, 37.9, 36.6, 35.9, 31.5, 31.5; MS (FAB) m/z 397 (57%, MH$^+$); HRMS (FAB) Calcd. for $C_{23}H_{29}N_2O_4$ (MH$^+$): 397.2127. Found: 397.2119.



N$^\alpha$-(2-Bromophenylacetyl)valine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3h, n = 1, Y = 2-Br, R = iPr). R_F (EtOAc) 0.30; IR (film) 3298, 1633, 1537 cm^{-1}; ^{1}H NMR δ 7.56 (dd, 1, J = 8.0, 1.5), 7.35 (dd, 1, J = 7.5, 1.5), 7.29 (td, 1, J = 7.5, 1.0), 7.13 (td, 1, J = 8.0, 2.0), 6.60 (d, J = 9.0), 6.53 (d, J = 9.0) (total 1), 5.03 (t, J = 3.5), 4.95 (t, J = 4.0) (total 1), 4.86 (m, 1), 3.92 (m), 3.82 (m), 3.72 (m), 3.54 (dd, J = 15.5, 3.5), 3.30 (dd, J = 13.5, 4.5) (total 8), 3.19 (s), 3.00 (s) (total 3), 1.99 (m, 1), 0.95 (d, J = 6.5), 0.92 (d, J = 6.5), 0.85 (d, J = 6.5), 0.84 (d, J = 7.0) (overlapping, total 6); ^{13}C NMR δ 172.4, 172.0, 169.3, 169.0, 134.9, 134.9, 132.8, 131.6, 128.9, 128.9, 127.8, 124.8, 124.8, 102.0, 102.0, 65.1, 65.0, 64.8, 64.8, 53.7, 53.6, 51.9, 50.2, 43.7, 37.1, 35.6, 31.7, 31.4, 19.6, 19.5, 17.5, 17.2; MS (FAB, glycerol/LiCl) m/z 419 (29%, d, MLi$^+$), 413 (5, d, M$^+$); HRMS (FAB) Calcd. for $C_{18}H_{25}BrN_2O_4$ (MLi$^+$): 419.1158. Found: 419.1162.

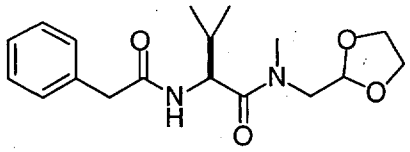


N$^\alpha$-(2-Bromophenylacetyl)alanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3i, n = 1, Y = 2-Br, R = Me). R_F (EtOAc) 0.4; ^{1}H NMR 7.54 (d, 1, J = 8.0), 7.28 (m, 2), 7.12 (dt, 1, J = 7.5, 1.5), 6.66 (d, J = 7.0), 6.53 (d, J = 7.5) (total 1), 4.93 (m, 2), 3.86 (m, 5), 3.71 (m, 3), 3.50 (d, J = 3.0), 3.47 (d, J = 3.0), 3.43 (d, J = 4.0), 3.40 (d, J = 4.5) (total 1), 3.10 (s, 3), 2.97 (s, 3), 1.28 (t, 2, J = 7.0), 1.23 (t, 2_{min}, J = 7.5); ^{13}C NMR 173.3, 172.6, 168.6, 134.7, 132.9, 131.6, 128.9, 127.8, 124.9, 101.9, 65.1, 64.8, 51.6, 50.3, 45.5, 45.1, 43.7, 36.7, 35.8, 18.7, 18.3; MS (FAB) Calcd. for $C_{16}H_{22}N_2O_4Br$ (MH$^+$): 385.0763. Found: 385.0764.

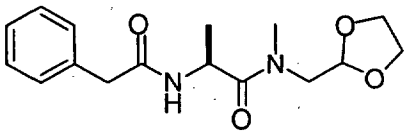


N$^\alpha$-(3-(2-Bromo-4,5-dimethoxyphenyl)propanoyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-

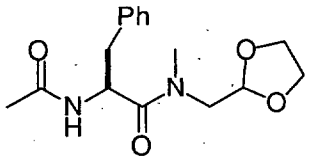
methylamide (3j, n = 2, Y = 2-Br-4,5-(MeO)$_2$, R = Bn). R_F (EtOAc/pet ether, 3:1) 0.21; IR (film) 3296, 1656, 1634 cm^{-1}; ^{1}H NMR δ 7.14 (m, 5), 6.91 (d, 1, J = 6.5), 6.84 (d, 1, J = 8.5), 6.69 (d, 1, J = 14.0), 5.14 (apparent sx, 1, J = 7.5), 4.78 (t, J = 4.5), 4.75 (t, J = 3.5) (total 1), 3.78 (m, 10), 3.52 (m, 1), 3.29 (dd, J = 14.0, 4.5). 3.17 (dd, J = 16.0, 3.5) (total 1), 2.89 (m, 4), 2.88 (s), 2.80 (s) (total 3), 2.40 (m, 2); ^{13}C NMR δ 172.5, 171.8, 171.1, 171.0, 148.3, 148.2, 148.0, 147.9, 136.8, 136.0, 132.1, 132.0, 129.4, 129.3, 128.3, 128.2, 126.9, 126.7, 115.4, 115.4, 114.5, 113.8, 113.8, 113.1, 101.9, 101.8, 65.0, 65.0, 64.7, 64.7, 56.0, 55.9, 55.9, 51.4, 50.4, 50.2, 50.1, 39.3, 39.2, 36.6, 36.3, 36.2, 35.9, 31.6, 31.5; MS (ESI) m/z 557 (38%, d, MNa$^+$), 537 (73, d, MH$^+$); HRMS (FAB) Calcd. for $C_{25}H_{31}BrN_2O_6$ (MH$^+$): 535.1444. Found: 535.1449.



N$^\alpha$-(Phenylacetyl)valine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3, n = 1, Y = H, R = iPr). R_F (EtOAc) 0.45; IR (film) 3295, 1674, 1634; ^{1}H NMR 7.25 (m, 5), 6.55 (d, 1_{maj}, J = 9.0) 6.47 (d, 1_{min}, J = 9.0), 4.99 (t, 1_{min}, J = 3.5), 4.90 (t, 1_{maj}, J = 4.0), 4.81 (m, 1), 3.87 (m, 2), 3.78 (m, 2), 3.26 (dd, 1, J = 13.8, 4.5), 3.15 (s, 3), 1.93 (q, 1, J = 6.5), 0.89 (d, J = 6.5), 0.85 (d, J = 6.5), 0.76 (d, J = 6.5) (total 6); ^{13}C NMR 172.6, 172.2, 170.8, 170.5, 135.1, 135.0, 129.2, 129.2, 128.7, 128.7, 127.1, 127.0, 102.0, 101.9, 65.1, 65.0, 64.8, 64.8, 60.3, 53.6, 53.5, 51.9, 50.2, 43.6, 43.5, 37.2, 35.6, 31.7, 31.3, 21.0, 19.5, 19.4, 17.5, 17.2, 14.1; MS (FAB) m/z 335 (59, MH$^+$), 317 (10, MH$^+$ - 18); HRMS (FAB) Calcd. for $C_{18}H_{27}N_2O_4$ (MH$^+$): 335.1971. Found: 335.1977.

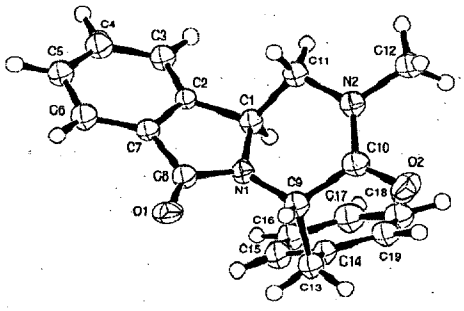


N$^\alpha$-(Phenylacetyl)alanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3, n = 1, Y = H, R = Me). R_F (EtOAc) 0.30; IR (film) 3298, 1682, 1634, 1463; ^{1}H NMR δ 7.26 (m, 5), 6.75 (d, 1_{maj}, J = 7.0), 6.69 (d, 1_{min}, J = 7.0), 4.92 (m, 2), 3.91 (m), 3.81 (m) (total 4), 3.69 (dd, 1_{min}, J = 15.5, 3.5), 3.60 (dd, 1_{maj}, J = 15.5, 3.5), 3.52 (s, 3), 1.26 (d, 3, J = 7.0); ^{13}C NMR 173.5, 172.8, 170.0, 134.9, 134.8, 129.2, 129.2, 128.8, 128.7, 127.1, 127.0, 102.0, 101.9, 65.1, 65.1, 64.8, 60.3, 51.7, 50.3, 45.4, 45.1, 43.5, 43.4, 36.7, 35.8, 18.8, 18.4, 14.1; MS (FAB) m/z 307 (52, MH$^+$); HRMS (FAB) Calcd. for $C_{16}H_{23}N_2O_4$ (MH$^+$): 307.1658. Found: 307.1661.



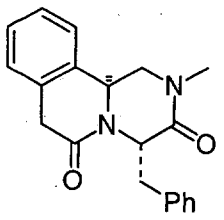
N$^\alpha$-Acetylphenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide. To the free amine (169 mg, 0.64

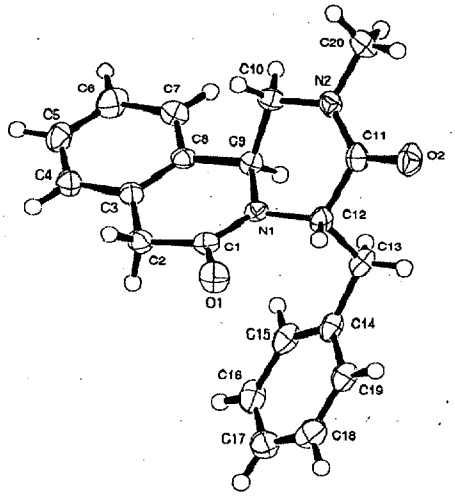
mmol) in CH_2Cl_2 (2 mL) were added DMAP (156 mg, 2 eq) and acetic anhydride (60 μL, 1 eq). After stirring at rt for 16 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and water (10 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL) and the combined organic portions were washed with 0.1 N HCl (3 × 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The light brown residue (150 mg, 77%) was not purified further. R_F (EtOAc) 0.15; ^{1}H NMR δ 7.18 (m, 5), 7.05 (d, J = 8.0), 7.00 (d, J = 8.5) (total 1), 5.15 (qn, 1, J = 7.5), 4.82 (t, J = 4.5), 4.76 (t, J = 3.0) (total 1), 3.81 (m, 4), 3.53 (m, 1), 3.33 (dd, J = 14.0, 4.5), 3.19 (dd, J = 15.5, 3.0) (total 1), 2.98 (m, 2), 2.93 (s), 2.81 (s) (total 3), 1.91 (s), 1.87 (s) (total 3); MS (FAB) m/z 307 (70%, MH$^+$), 118 (100); HRMS (FAB) Calcd. for $C_{16}H_{23}N_2O_4$ (MH$^+$): 307.1658. Found: 307.1652.



ORTEP figure of X-ray structure of tricycle **5a**.

The following derivatives were synthesized and purified as described in the paper for analog **5a**:

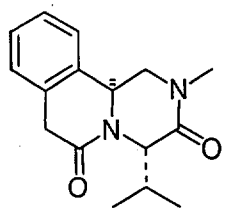




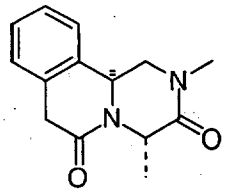
ORTEP figure of X-ray structure of tricycle **5d**.

4-Benzyl-2-methyl-1,2,7,11b-tetrahydropyrazino[2,1-a]isoquinoline-3,6-dione (5d). 96 mg (80%), as white needles; mp 189-191 °C; R_F (EtOAc) 0.17; IR (CH_2Cl_2 evap.) 1653, 1497, 1437 cm^{-1}; ^{1}H NMR δ 7.29 (t, 1, J = 9.5), 7.22 (t, 1, J = 8.0), 7.17 (m, 6), 6.95 (d, 1, J = 9.5), 5.54 (dd, 1, J = 8.5, 6.0), 4.33 (d, 1, J = 13.5), 3.65 (br s, 2), 3.22 (m, 4), 3.00 (s, 3); ^{13}C NMR δ 167.3, 166.1, 137.1, 130.6, 129.4, 128.5, 128.4, 128.0, 127.0, 126.7, 125.7, 56.5, 56.3, 54.3, 36.6, 34.8, 34.7; HRMS (FAB) Calcd. for $C_{20}H_{20}N_2O_2$

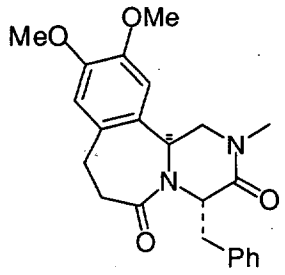
(MH+): 321.1603. Found: 321.1596.



4-Isopropyl-2-methyl-1,2,7,11b-tetrahydropyrazino[2,1-a]isoquinoline-3,6-dione (5h). 54 mg (70%), as white stars; mp 158-161 °C; R_F (EtOAc) 0.26; IR (mull) 1634 br, 1495 cm^{-1}; ^1H NMR δ 7.29 (m, 2), 7.22 (d, 1, J = 7.5), 7.18 (d, 1, J = 7.5), 5.11 (d, 1, J = 7.0), 5.02 (dd, 1, J = 11.5, 4.0), 3.73 (s, 2), 3.44 (dd, 1, J = 12.0, 4.0), 3.39 (q, 1, J = 11.5), 2.97 (s, 3), 2.44 (apparent dsept, 1, J = 7.0, 7.0), 1.15 (d, 3, J = 7.0), 0.94 (d, 3, J = 6.5); ^{13}C NMR δ 167.6, 166.8, 130.8, 128.9, 128.6, 128.1, 127.0, 126.0, 60.0, 56.3, 54.5, 35.0, 34.6, 31.0, 20.2, 19.7; HRMS (FAB) Calcd. for $C_{16}H_{20}N_2O_2$ (MH^+): 273.1603. Found: 273.1611.

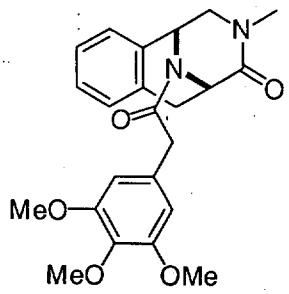


2,4-Dimethyl-1,2,7,11b-tetrahydropyrazino[2,1-a]isoquinoline-3,6-dione (5i). 53 mg (70%), as white needles; mp 186-7 °C; R_F (EtOAc) 0.13; IR (thin film) 1650, 1501, 1450; ^1H NMR 7.32 (m, 2), 7.24 (d, 1, J = 1.5), 7.18 (d, 1, J = 6.5), 5.36 (q, 1, J = 7.0), 5.01 (dd, 1, J = 10.3, 4.5), 3.73 (d, 2, J = 8.0), 3.47 (m, 2), 3.00 (s, 3), 1.52 (d, 2, J = 7.0); ^{13}C NMR 168.6, 165.4, 130.7, 128.6, 128.5, 128.2, 127.1, 125.9, 56.4, 52.9, 51.2, 34.7, 34.6, 16.4; HRMS (FAB) Calcd. for $C_{14}H_{17}N_2O_2$ (MH^+): 245.1290. Found: 245.1292.



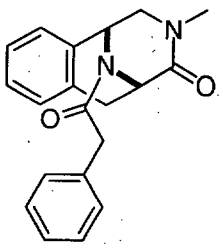
4-Benzyl-10,11-dimethoxy-2-methyl-1,7,8,12b-tetrahydro-2H-benzo[3,4]azepino[1,2-a]pyrazine-3,6-dione (5j). 26 mg (25%), as a white powder. R_F (EtOAc) 0.13; IR (film) 1651, 1519 cm^{-1}; ^1H NMR δ 7.28 (m, 3), 7.14 (m, 2), 6.76 (s, 1), 6.41 (s, 1), 4.97 (br s, 1), 4.93 (br s, 1), 3.79 (s, 3), 3.76 (s, 3), 3.63 (dd, 1, J = 13.5, 6.5), 3.41 (dd, 1, J = 14.0, 5.5), 3.26 (dd, 1, J = 14.0, 5.0), 3.11 (m, 1), 3.01 (s, 3), 2.95 (m, 2), 2.70 (m, 2); ^{13}C NMR δ 171.7, 167.2, 147.4, 145.6, 135.3, 130.7, 128.0, 126.6, 126.4, 125.2, 125.1, 111.7, 109.8, 57.2, 53.8, 53.5, 35.3, 33.9, 31.8, 26.6, 25.0; HRMS (FAB) Calcd. For $C_{23}H_{26}N_2O_4$ (MH^+):

395.1971. Found: 395.1965.



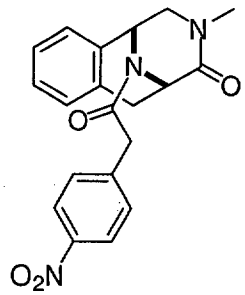
4-Benzyl-9,10,11-trimethoxy-2-methyl-1,2,7,11b-tetrahydropyrazino[2,1-a]isoquinoline-3,6-dione (5f) and **11-Methyl-13-[2-(3,4,5-trimethoxyphenyl)acetyl]-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6f)**. A solution of **3f** (n = 1, Y = 3,4,5-$(MeO)_3$, R = Bn) (150 mg, 0.317 mmol) in 1:4 methanesulfonic acid/nitromethane was stirred at 60 °C for 16 h. The reaction flask was cooled in an ice-water bath and the mixture was diluted with 5% $NaHCO_3$ solution (100 mL) and Et_2O (75 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 20 mL), and the combined organic portions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was purified by flash column chromatography (EtOAc → 1:1 EtOAc/acetone) to give the isomeric mixture of **5f** and **6f** as an orange oil (38 mg, 28%). Ratio of **5f:6f** = 2:1. R_F (EtOAc) 0.2 (streak); ^{1}H NMR 7.12 (m, 6), 6.42 (s), 6.34 (s), 6.30 (s) (total 2), 5.89 (d, 1_{maj}, J = 4.0), 5.54 (t, 1, J = 6.0), 5.46 (d, 1_{min}, J = 6.0), 5.10 (d, 1_{min}, J = 4.0), 4.80 (d, 1_{maj}, J = 6.0), 4.35 (dt, 1, J = 11.0, 1.5), 3.72 (br m, 17), 3.46 (br m, 4), 2.97 (s, 3), 2.79 (m, 1); ^{13}C NMR 168.1, 167.3, 167.2, 166.2, 154.0, 153.4, 149.8, 140.2, 137.3, 132.2, 129.5, 129.0, 128.4, 127.9, 126.9, 126.7, 126.4, 114.5, 114.2, 105.6, 105.2, 60.9, 60.8, 56.6, 56.1, 55.9, 55.4, 54.5, 53.4, 51.1, 46.9, 40.6, 36.6, 34.8, 34.7, 34.2, 32.8, 29.6; HRMS (FAB) Calcd. for $C_{23}H_{27}N_2O_5$ (MH^+): 411.1920. Found: 411.1918.

The following derivatives were synthesized and purified in a manner similar to that described for **6a**:

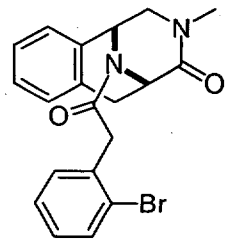


11-Methyl-13-phenylacetyl-11,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6b). 106 mg (75%), 2:5 ratio of rotamers, as a white powder. R_F (EtOAc) 0.36; ^{1}H NMR δ 7.19 (br m, 9), 5.89 (d, 1_{maj}, J = 4.5), 5.44 (d, 1_{min}, J = 6.0), 5.06 (br d, 1_{min}, J = 4.0), 4.75 (d, 1_{maj}, J = 6.5), 3.92 (dd, 1_{maj}, 11.6, 4.8), 3.77 (ABq, 2, J = 15.2), 3.43 (dd, 1_{min}, J = 12.0, 4.4), 3.14 (m, 2+1_{min}), 2.75 (m, 3+1_{maj}); ^{13}C NMR δ 168.2, 168.0, 167.9, 167.2, 134.3, 134.2, 134.0, 133.7, 133.4, 132.3, 129.5, 129.0, 128.9, 128.6, 128.4,

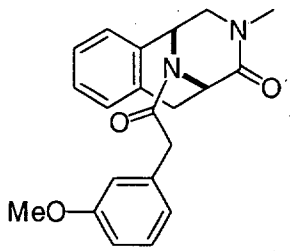
128.2, 127.8, 127.1, 127.1, 126.9, 126.7, 126.6, 125.9, 56.4, 55.9, 55.3, 52.1, 50.7, 46.9, 41.1, 40.6, 34.2, 33.9, 32.7, 31.7; HRMS (FAB) Calcd. for $C_{20}H_{21}N_2O_2$ (MH^+): 321.1602. Found: 321.1603.



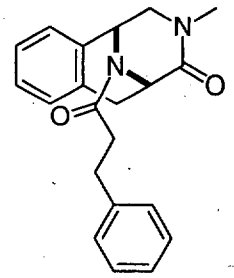
11-Methyl-13-[2-(4-nitrophenyl)-acetyl]-11,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6c). 58 mg (72%), as a straw oil. ^{1}H NMR 8.15 (m, 2), 7.39 (m, 2), 5.89 (d, 1_{maj}, J = 5.0), 5.39 (d. 1_{min}, J = 10.0), 5.14 (d, 1_{min}, J = 5.0), 4.77 (d, 1_{maj}, J = 10.0), 3.94 (d, J = 3.5), 3.91 (t, J = 4.5) (total 1), 3.87 (s, 1), 3.82 (m, 1), 3.22 (m, 1), 2.99 (dd, 1, J = 15.0, 5.0), 2.83 (s, 3 + 1_{min}); ^{13}C NMR 166.8, 166.6, 147.1, 141.5, 134.0, 131.8, 130.0, 129.8, 129.7, 129.1, 128.5, 128.1, 127.1, 126.8, 126.7, 125.8, 123.9, 123.8, 56.6, 55.9, 55.3, 53.4, 52.3, 51.0, 47.1, 40.1, 39.6, 34.3, 34.0, 33.0, 31.6; HRMS (FAB) Calcd. for $C_{20}H_{20}N_3O_4$ (MH^+): 366.1454. Found: 366.1460.



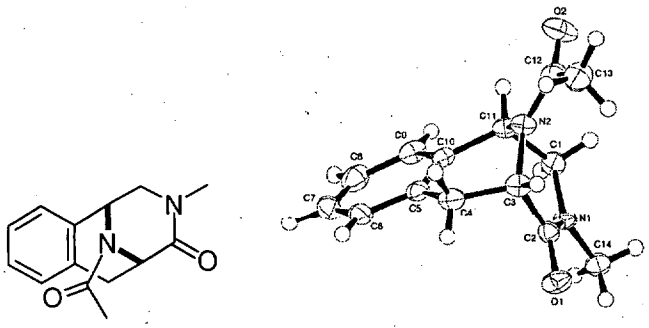
13-[2-(2-Bromophenyl)-acetyl]-11-methyl-11,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6d). 77 mg (79%), as a clear, colorless oil. R_F (EtOAc) 0.23; ^{1}H NMR (1:1.8 ratio of rotamers) δ 7.54 (m, 1), 7.21 (m), 7.09 (m) (total 1), 5.89 (d, 1_{maj}, J = 4.0), 5.43 (d, 1_{min}, J = 5.5), 5.11 (s, 1_{min}), 4.82 (d, 1_{maj}, J = 5.5), 3.95 (m, 1), 3.86 (s, 1), 3.82 (m, 1_{maj}), 3.64 (dd, 1_{min}, J = 11.5, 4.0), 3.17 (br m, 3+1_{min}), 2.82 (s, 3_{maj}), 2.78 (s, 3_{min}); ^{13}C NMR δ 168.0, 167.3, 167.2, 134.3, 134.3, 134.2, 133.7, 133.3, 132.8, 132.3, 131.0, 130.6, 129.5, 129.0, 128.9, 128.2, 127.9, 127.8, 127.6, 127.0, 126.7, 126.7, 125.9, 124.7, 124.2, 56.6, 55.9, 55.2, 52.0, 50.9, 47.1, 40.5, 40.0, 34.3, 34.0, 33.0, 31.7; HRMS (FAB) Calcd. for $C_{20}H_{20}BrN_2O_2$ (MH^+): 399.0708. Found: 399.0702.



13-[2-(3-Methoxyphenyl)-acetyl]-11-methyl-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6e). 113 mg (72%), as a clear, colorless oil. R_F (EtOAc) 0.17; ^{1}H NMR (1:2 ratio of rotamers) δ 7.16 (m, 5), 6.76 (m, 3), 5.87 (d, 1_{maj}, J = 3.5), 5.42 (d, 1_{min}, J = 6.0), 5.09 (s, 1_{min}), 4.75 (d, 1_{maj}, J = 6.0), 3.90 (dd, 1_{min}, J = 12.0, 4.5), 3.73 (m, 5), 3.51 (br m, 1), 3.12 (br m, 4), 2.77 (m, 4); ^{13}C NMR δ 168.1, 168.0, 167.8, 167.2, 159.9, 159.5, 135.7, 135.5, 134.2, 133.7, 133.3, 132.3, 129.8, 129.5, 129.4, 129.4, 129.3, 129.0, 128.4, 128.2, 128.1, 127.8, 126.9, 126.7, 126.6, 125.9, 120.9, 120.7, 114.1, 113.8, 112.8, 112.7, 56.5, 55.9, 55.3, 55.1, 55.1, 52.1, 50.7, 46.9, 41.1, 40.6, 34.2, 33.9, 32.7, 31.7; HRMS (FAB) Calcd. for $C_{21}H_{23}N_2O_3$ (MH^+): 351.17087. Found: 351.17164. The NMR spectrum indicated the presence of the isomer **5e** as a minor impurity, inseparable from the major product by chromatography.



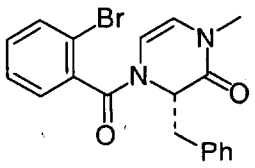
11-Methyl-13-(3-phenylpropanoyl)-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6g). 85 mg (67%), as a yellow oil. R_F (EtOAc) 0.35; IR (film) 1651, 1495 cm^{-1}; ^{1}H NMR 7.16 (m, 9.0), 5.89 (d, 1_{maj}, J = 4.5), 5.47 (d, 1_{min}, J = 6.0), 4.99 (br d, 1_{min}, J = 4.0), 4.64 (d, 1_{maj}, J = 6.0), 3.83 (dd, 2, J = 15.0, 5.0), 3.62 (dd, 1_{min}, J = 10.0, 4.5), 3.07 (br m, 5), 2.69 (m, 4); ^{13}C NMR 169.3, 167.2, 140.4, 13., 132.3, 129.0, 128.5, 128.2, 127.8, 126.9, 126.7, 126.3, 125.9, 60.3, 55.9, 54.8, 46.6, 34.2, 33.0, 31.3, 21.0, 14.1; MS (FAB) m/z 335 (92%, MH^+), 203 (48, MH^+-PhC_2H_4CO); HRMS (FAB) Calcd. for $C_{21}H_{23}N_2O_2$ (MH^+): 335.1760. Found: 335.1758.



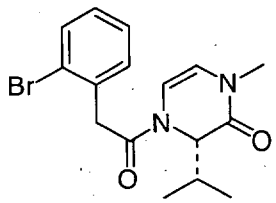
X-ray structure of bridged isomer **6 (R' = Me)**.

13-Acetyl-11-methyl-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-10-one (6, (R' = Me)). 32 mg (40%), as a straw colored oil. R_F (EtOAc) 0.11; IR (film) 1639, 1496 cm^{-1}; ^{1}H NMR (3:1 mixture of rotamers) δ 7.18 (m, 5), 5.86 (d, 1_{maj}, J = 5.5), 5.43 (d, 1_{min}, J = 8.0), 5.04 (d, 1_{min}, J = 5.5), 4.68 (m, 1_{maj}), 3.95 (dd, J = 14.5, 5.5), 3.90 (dd, J = 15.0, 6.0) (total 1), 3.22 (m, 3), 2.83 (s), 2.82 (s) (total 3), 2.15 (s), 2.13 (s) (total 3); ^{13}C NMR δ 171.4, 167.5, 156.0, 134.4, 133.7, 132.3, 129.1, 128.0, 127.1, 126.8, 126.0, 109.6, 56.1, 55.5, 46.5, 34.3, 33.0, 31.8, 20.6; HRMS (FAB) Calcd. for $C_{14}H_{16}N_2O_2$ (MH^+): 245.1290. Found: 245.1296.

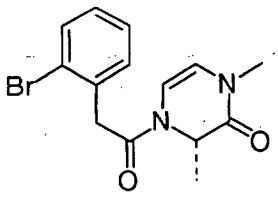
The following derivatives were synthesized and purified as described in the paper for analog **7d**:



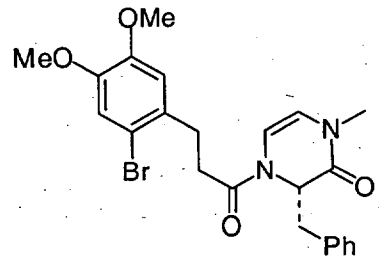
3-Benzyl-4-(2-bromobenzoyl)-1-methyl-3,4-dihydro-1H-pyrazin-2-one (7a). 39 mg (14%), as a clear, colorless oil. R_F (EtOAc) 0.59; IR (film) 1676, 1653 cm^{-1}; ^{1}H NMR δ 7.56 (br s), 7.43 (d, J = 8.0), 7.34 (td, J = 7.5, 1.0), 7.26 (br m), 7.12 (t, J = 7.5), 6.92 (m), 6.85 (dd, J = 6.0, 1.5) (total 9), 5.98 (d, J = 6.0), 5.74 (d, J = 7.5), 5.57 (t, J = 6.5), 5.44 (br s), 5.26 (br s), 5.07 (br s), 4.24 (d, J = 10.0) (total 3), 3.74 (s), 3.22 (br s), 3.19 (s), 3.07 (br s), 2.91 (dd, J = 13.5, 11.0), 2.73 (dd, J = 13.5, 3.5), 2.63 (s), 2.17 (s), 1.62 (s), 1.25 (s) (total 5); ^{13}C NMR δ 167.7, 135.8, 135.0, 135.0, 132.1, 131.0, 130.5, 130.0, 129.9, 129.1, 128.8, 128.1, 127.3, 127.2, 127.0, 119.5, 118.6, 118.6, 106.8, 61.1, 35.4, 33.7, 33.5; MS (FAB) m/z 385 & 387 (74%, MH^+), 295 & 297 (26%), 183 & 185(100%); HRMS (FAB) Calcd. for $C_{19}H_{17}BrN_2O_2$ (MH^+): 387.0531. Found: 387.0532.



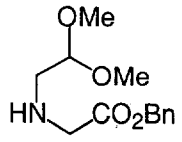
4-[2-(2-Bromophenyl)acetyl]-3-isopropyl-1-methyl-3,4-dihydro-1H-pyrazin-2-one (7h). 166 mg (87%), as a white powder. R_F (EtOAc) 0.58; IR (mull) 1674 br, 1462, 1440 cm^{-1}; ^1H NMR (major rotamer) δ 7.51 (d, 1, *J* = 8.0), 7.23 (m, 2), 7.09 (m, 1), 6.18 (dd, 1, *J* = 5.5, 1.5), 5.62 (d, 1, *J* = 6.0), 4.88 (dd, 1, *J* = 8.5, 1.5), 3.94 (d, 1, *J* = 15.0), 3.73 (d, 1, *J* = 15.0) (ABq), 3.06 (s, 3), 1.96 (sept, 1, *J* = 7.0), 0.95 (d, 3, *J* = 6.5), 0.89 (d, 3, *J* = 7.0); ^{13}C NMR δ 168.3, 164.9, 134.2, 132.7, 131.2, 128.8, 127.6, 124.7, 116.7, 108.3, 60.4, 40.6, 33.3, 30.1, 19.5, 18.8; MS (FAB, glycerol) m/z 351 & 353 (64%, MH^+), 169 & 171 (15%, $BnBr^+$), 111 (100); HRMS (FAB) Calcd. for $C_{16}H_{19}BrN_2O_2$ (MH^+): 351.0708. Found: 351.0706.



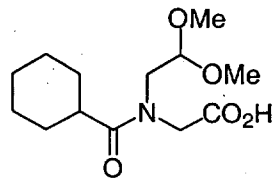
4-[2-(2-Bromophenyl)acetyl]-1,3-dimethyl-3,4-dihydro-1H-pyrazin-2-one (7i). 99 mg (88%), as a white powder. R_F (EtOAc) 0.75; ^1H NMR 7.53 (d, 1, *J* = 10.0), 7.18 (m, 3), 6.11 (d, 1, *J* = 7.0), 5.67 (d, 1_{min}, *J* = 7.5), 5.60 (d, 1, *J* = 7.0), 5.19 (m, 1), 4.0 (m, 5), 3.77 (m, 4), 1.37 (d, 1, *J* = 8.5), 1.24 (m, 2); ^{13}C NMR 171.2, 167.4, 166.7, 134.1, 132.8, 120.9, 128.9, 127.8, 124.7, 115.4, 107.2, 60.4, 51.6, 40.5, 33.5, 29.3, 21.1, 15.4, 14.2; MS (FAB) m/z 323 (100%, MH^+), 284 (74); HRMS (FAB) Calcd. for $C_{14}H_{16}BrN_2O_2$ (MH^+) 323.0395. Found: 323.0388.



3-Benzyl-4-[3-(2-bromo-4,5-dimethoxyphenyl)propanoyl]-1-methyl-3,4-dihydro-1H-pyrazin-2-one (7j). 254 mg (82%), as a white semisolid. R_F (EtOAc) 0.46; IR (mull) 1667, 1651, 1599, 1509 cm^{-1}; ^1H NMR δ 7.17 (m), 7.03 (m), 6.92 (s), 6.88 (s), 6.68 (s), 6.45 (s) (total 7), 6.65 (dd, *J* = 6.0, 2.0), 5.90 (dd, *J* = 5.6, 1.2), 5.71 (d, *J* = 6.0), 5.38 (t, *J* = 6.0), 5.25 (d, *J* = 6.0), 4.77 (s), 4.51 (m) (total 3), 3.77 (m, 6), 3.06 (s), 2.98 (s) (total 3), 2.88 (m), 2.58 (s), 2.52 (t, *J* = 7.6), 1.98 (s), 1.39 (m), 1.20 (s) (total 6); ^{13}C NMR δ 170.8, 169.7, 165.3, 164.7, 148.4, 148.2, 135.9, 135.4, 131.8, 131.6, 129.6, 129.5, 128.8, 128.1, 127.3, 126.9, 116.2, 115.4, 114.9, 113.7, 113.4, 113.1, 108.0, 107.7, 56.2, 56.1, 56.0, 36.3, 35.7, 33.6, 33.4, 33.4, 32.1, 31.1, 30.8, 29.3; MS (FAB) m/z 474 (24%, d, MH^+); HRMS (FAB) Calcd. for $C_{23}H_{25}BrN_2O_4$ (MH^+): 475.1055. Found: 475.1043.



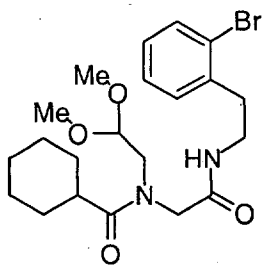
Phenylmethyl 2-[(2,2-dimethoxyethyl)amino]acetate (9). To glycine benzyl ester hydrochloride (2.0 g, 9.9 mmol) in dichloroethane (40 mL) were added glyoxal 1,1-dimethyl acetal (45% soln. in *t*-butyl dimethyl ether, 3.0 mL, 1.2 eq) and sodium triacetoxyborohydride (2.96 g, 1.4 eq). The reaction mixture was stirred at rt for 3 h, then partitioned between sat. $NaHCO_3$ (100 mL) and CH_2Cl_2 (80 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc/pet ether → 1:1 acetone-EtOAc) to give the monoalkylated amine as a light yellow oil (965 mg, 38%). R_F (EtOAc/pet ether, 1:1) 0.12; ^1H NMR δ 7.33 (m, 5), 5.14 (s, 2), 4.43 (t, 1, J = 5.0), 3.46 (s, 2), 3.34 (s, 6), 2.74 (d, 2, J = 5.5), 1.79 (br s, 1); ^{13}C NMR δ 172.1, 135.5, 128.5, 128.3, 103.7, 66.5, 53.7, 50.7, 50.4; MS (ESMS) m/z 222 (100%, MH^+-OMe); HRMS (FAB) Calcd. for $C_{13}H_{20}NO_4$ (MH^+): 254.1392. Found: 254.1396.



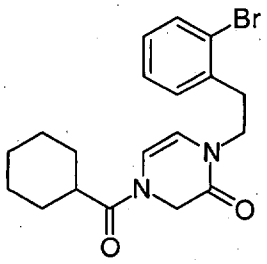
2-[N-(2,2-Dimethoxyethyl)cyclohexylcarbonylamino]acetic acid (10). To the secondary amine **9** (171 mg, 0.68 mmol) and cyclohexanecarboxylic acid (173 mg, 2 eq) in CH_2Cl_2 (2 mL) were added PyBroP (629 mg, 2 eq), HOAt (184 mg, 2 eq) and DIPEA (470 μL, 4 eq). The reaction mixture was stirred at rt for 16 h, and worked up with citric acid. Purification by flash column chromatography (1:3 EtOAc/pet ether → EtOAc) gave phenylmethyl 2-[N-(2,2-dimethoxyethyl)cyclohexylcarbonylamino]acetate as a clear, colorless oil (201 mg, 82%). R_F (EtOAc/pet ether, 1:1) 0.42; IR (film) 1749, 1649, 1452 cm^{-1}; ^1H NMR δ 7.32 (m, 5), 5.18 (s), 5.13 (s) (total 2), 4.36 (q, 1, J = 11.0, 5.5), 4.19 (s), 4.16 (s) (total 2), 3.46 (d, 2, J = 5.0), 3.35 (s), 3.33 (s) (total 6), 2.56 (tt, J = 12.0, 3.5), 2.20 (tt, J = 12.0, 3.5) (total 1), 1.71 (m, 5), 1.50 (m, 2), 1.20 (m, 3); ^{13}C NMR δ 177.1, 177.1, 169.5, 169.4, 135.5, 135.2, 128.6, 128.6, 128.5, 128.4, 128.3, 104.2, 103.9, 67.1, 66.7, 55.1, 55.0, 51.2, 51.0, 49.7, 48.9, 40.8, 40.3, 29.3, 29.3, 25.7, 25.7, 25.6; MS (ESMS) m/z 386 (20%, MNa^+), 332 (100, MH^+-OMe); HRMS (FAB) Calcd. for $C_{20}H_{30}NO_5$ (MH^+): 364.212398. Found: 364.211570.

The benzyl ester (194 mg, 0.53 mmol) was hydrogenolyzed over 10% Pd/C (150 mg) in degassed 95% EtOH (150 mL) as described below for compound **14**, to give the acid as a clear, colorless oil (144 mg, 98%). IR (film) 3000 (br), 1738, 1615 cm^{-1}; ^1H NMR δ 9.26 (br s, 1), 4.37 (s, 1), 4.13 (s), 4.07 (s) (total 2), 3.45 (s), 3.37 (s), 3.33 (s) (total 8), 2.55 (s), 2.27 (s) (total 1), 1.69 (m, 5), 1.45 (m, 2), 1.20 (m,

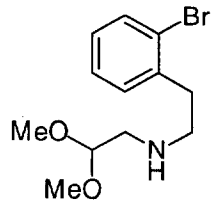
3); ^{13}C NMR δ 178.0, 177.7, 103.9, 103.7, 55.0, 55.0, 51.3, 49.7, 40.8, 40.4, 29.1, 25.6, 25.6; MS (ESMS) m/z 242 (100%, M^+-OMe); HRMS (FAB) Calcd. for $C_{12}H_{20}NO_4$ (M^+-OMe): 242.1392. Found: 242.1396.



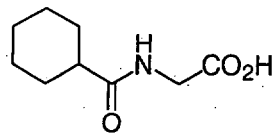
2-[N-(2,2-Dimethoxyethyl)cyclohexylcarbonylamino]-N-[2-(2-bromophenyl)ethyl] acetamide (11). To 2-[N-(2,2-dimethoxyethyl)cyclohexylcarbonylamino]acetic acid (**10**, 143 mg, 0.52 mmol) and 2-(2-bromophenyl)ethylamine (prepared by reduction of the nitrile as described by McClure, C. K., Kiessling, A. J., Link, J. S. *Tetrahedron* **1998**, *54*, 7121-26) (104 mg, 1 eq) in CH_2Cl_2 (2 mL) were added HOBt (71 mg, 1 eq), EDC (100 mg, 1 eq), and DMAP (128 mg, 2 eq). The reaction mixture was stirred at rt for 16 h and worked up with citric acid. Purification by flash column chromatography (1:3 EtOAc/pet ether → EtOAc) gave the amide as a clear, colorless oil (162 mg, 68%). R_F (EtOAc, 1:1) 0.14; IR (film) 3304, 1633, 1548 cm^{-1}; ^{1}H NMR δ 7.50 (t, 1, *J* = 8.0), 7.20 (m), 7.05 (m), 6.55 (m) (total 4), 4.58 (t, *J* = 5.0), 4.38 (t, *J* = 5.0) (total 1), 3.98 (s), 3.95 (s) (total 2), 3.52 (m, 1), 3.44 (m, 3), 3.36 (s), 3.33 (s) (total 6), 2.94 (t, *J* = 7.5), 2.90 (t, *J* = 7.5) (total 2), 2.57 (t, *J* = 11.5), 2.24 (t, *J* = 11.5) (total 1), 1.68 (m, 5), 1.43 (m, 2), 1.21 (m, 3); ^{13}C NMR δ 178.0, 177.8, 169.6, 169.3, 138.1, 137.9, 132.9, 132.8, 130.9, 130.6, 128.3, 128.2, 127.6, 127.6, 124.5, 103.4, 102.7, 55.4, 55.2, 54.0, 52.1, 51.5, 50.5, 41.0, 40.2, 39.2, 38.9, 35.7, 35.7, 29.3, 29.3, 25.7, 25.6, 25.5; MS (ESMS) m/z 425 (100%, d, MH^+-OMe); HRMS (FAB) Calcd. for $C_{20}H_{29}BrN_2O_3$ (MH^+-OMe): 424.1362. Found: 424.1313.



1-[2-(2-Bromophenyl)ethyl]-4-(cyclohexylcarbonyl)-1,3,4-trihydropyrazin-2-one (12) from Cyclization of 11. The cyclization procedure starting with the isomeric acetal, 2-[N-(2,2-dimethoxyethyl)cyclohexylcarbonylamino]-N-[2-(2-bromophenyl)ethyl] acetamide (**11**, 300 mg, 0.66 mmol) was identical to that described in the paper starting with isomer **15**. Purification was achieved by flash column chromatography (1:3 EtOAc/pet ether → EtOAc) rather than a plug of silica, to give the enediamide as a white powder (155 mg, 60%) with identical spectral characteristics to those listed in the paper.



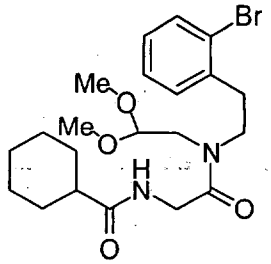
(2,2-Dimethoxyethyl)[2-(2-bromophenyl)ethyl]amine (13). To 2-(2-bromophenyl)ethylamine (prepared by reduction of the nitrile as described by McClure, C.K., Kiessling, A.J., Link, J.S. *Tetrahedron* **1998**, *54*, 7121-26) (1.0 g, 5.0 mmol) in DCE (20 mL) were added glyoxal 1,1-dimethyl acetal (45% soln. in *t*-butyl dimethyl ether, 1.8 mL, 1.4 eq) and sodium triacetoxyborohydride (1.48 g, 1.4 eq). The reaction mixture was stirred at rt for 3 h, then partitioned between sat. $NaHCO_3$ (60 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc/pet ether → 1:1 acetone-EtOAc) to give the monoalkylated amine as a light yellow oil (578 mg, 40%). R_F (EtOAc/pet ether, 1:1) 0.11; ^{1}H NMR δ 7.46 (d, 1, *J* = 8.0), 7.17, (m, 2), 6.99 (m, 1), 4.41 (t, 1, *J* = 5.5), 3.32 (s, 6), 2.84 (m, 4), 2.73 (d, 2, *J* = 5.5), 1.27 (br s, 1); ^{13}C NMR δ 139.2, 132.8, 130.6, 127.8, 127.4, 124.5, 103.8, 54.0, 50.9, 49.5, 36.7; MS (ESMS) m/z 288 (10%, d, MH^+), 256 (100, d, MH^+-OMe); HRMS (FAB) Calcd. for $C_{12}H_{19}BrNO_2$ (MH^+): 289.0667. Found: 289.0633.



2-(Cyclohexylcarbonylamino)acetic acid (14). To cyclohexanecarboxylic acid (381 mg, 1.05 mmol) and glycine benzyl ester *p*-toluenesulfonate salt (1.05 g, 1 eq) in CH_2Cl_2 (2 mL) were added HOBt (400 mg, 1 eq), EDC (568 mg, 1 eq) and DMAP (1.09 g, 3 eq). The reaction mixture was stirred at rt for 16 h and worked up with citric acid. Recrystallization of the residue from EtOAc/pet ether (1:1) gave the amide as white needles (499 mg, 61%). Mp 100-101 °C (lit. 90.5-104 °C (Alargov, D. K.; Gugova, R. G.; Denkova, P. S.; Muller, G.; Golovinsky, E. V. *Monatsch. Chem.* **1999**, *130*, 937-43)); IR (mull) 3299, 1725, 1637, 1548 cm^{-1}; ^{1}H NMR δ 7.36 (m, 5), 5.98 (br s, 1), 5.18 (s, 2), 4.08 (d, 2, *J* = 5.5), 2.15 (tt, 1, *J* = 11.5, 3.5), 1.88 (m, 2), 1.79 (m, 2), 1.67 (m, 1), 1.44 (m, 2), 1.25 (m, 3); ^{13}C NMR δ 176.2, 170.1, 135.1, 128.6, 128.5, 128.4, 67.2, 45.1, 41.2, 29.5, 25.7, 25.6; MS (ESMS) m/z 298 (35%, MNa^+), 276 (100, MH^+); $C_{16}H_{21}NO_3$ requires: C, 69.79; H, 7.69; N, 5.09% . Found: C, 69.86; H, 7.89; N, 5.19%.

A suspension of 10% Pd/C (1.2 g) and phenylmethyl 2-(cyclohexylcarbonylamino)acetate (1.33 g, 4.83 mmol) in degassed 95% EtOH (1 L) was stirred vigorously as the reaction vessel was subjected to five vacuum-N_2 cycles, followed by five vacuum-H_2 cycles. Stirring was continued under H_2 for 90 min, and the reaction vessel was purged with N_2. The reaction mixture was filtered through a plug of Celite,

filtered though paper, and finally concentrated *in vacuo* to give the acid as white needles (878 mg, 98%). Mp 150-52 °C (lit. 152 °C (Godchot, M. *Bull. Soc. Chim. Fr.*, **1911**, *9*, 261-5)). ^{1}H NMR (MeOD) δ 3.87 (s, 2), 2.25 (m, 1), 1.78 (m, 5), 1.33 (m, 5); ^{13}C NMR (MeOD) δ 178.1, 171.7, 44.7, 40.2, 29.1, 25.5, 25.3; MS (ESMS) m/z 208 (45%, MNa^+), 186 (35, MH^+), 111 (100); HRMS (FAB) Calcd. for $C_9H_{16}NO_3$ (MH^+): 186.1130. Found: 186.1130.



N-(2,2-Dimethoxyethyl)-N-[2-(2-bromophenyl)ethyl]-2-(cyclohexylcarbonylamino)acetamide (15). To 2-(cyclohexylcarbonylamino)acetic acid (**14**, 187 mg, 1 mmol) and (2,2-dimethoxyethyl)[2-(2-bromophenyl)ethyl]amine (**13**, 291 mg, 1 eq) in CH_2Cl_2 (2 mL) were added PyBroP (513 mg, 1.1 eq), HOAt (150 mg, 1.1 eq) and DIPEA (383 μL, 2.2 eq). The reaction mixture was stirred at rt for 2 d, and worked up with citric acid. Purification by flash column chromatography (1:1 EtOAc/pet ether → 1:3 acetone/EtOAc) gave the amide as a straw-colored oil (399 mg, 88%). R_F (EtOAc) 0.41; IR (film) 3396, 3324, 1643 cm^{-1}; ^{1}H NMR δ 7.46 (t, 1, J = 8.0), 7.17 (m, 2), 7.04 (m, 1), 6.58 (br s), 6.49 (br s) (total 1), 4.45 (t, J = 5.5), 4.32 (t, J = 5.0) (total 1), 4.05 (d, 1, J = 4.0), 3.99 (d, 1, J = 4.0), 3.57 (m, 1), 3.49 (m, 1), 3.39 (d, 1, J = 5.5), 3.33 (s, 3), 3.30 (s, 3), 3.16 (d, 1, J = 5.0), 2.93 (m, 2), 2.10 (m, 1), 1.83 (m, 2), 1.71 (m, 2), 1.59 (m, 1), 1.39 (m, 2), 1.18 (m, 3); ^{13}C NMR δ 175.9, 175.9, 169.0, 168.8, 138.0, 136.9, 133.0, 132.8, 131.0, 130.9, 128.7, 128.3, 127.8, 127.7, 124.3, 124.3, 103.0, 102.8, 55.0, 54.9, 49.5, 48.4, 47.9, 47.5, 45.2, 45.1, 41.1, 40.8, 35.0, 33.8, 29.5, 29.5, 25.7, 25.7, 25.6, 25.6; MS (ESMS) m/z 477 (40%, d, MNa^+), 425 (100 d, MH^+-OMe); HRMS (FAB) Calcd. for $C_{21}H_{32}BrN_2O_4$ (MH^+): 455.1545. Found: 455.1539.

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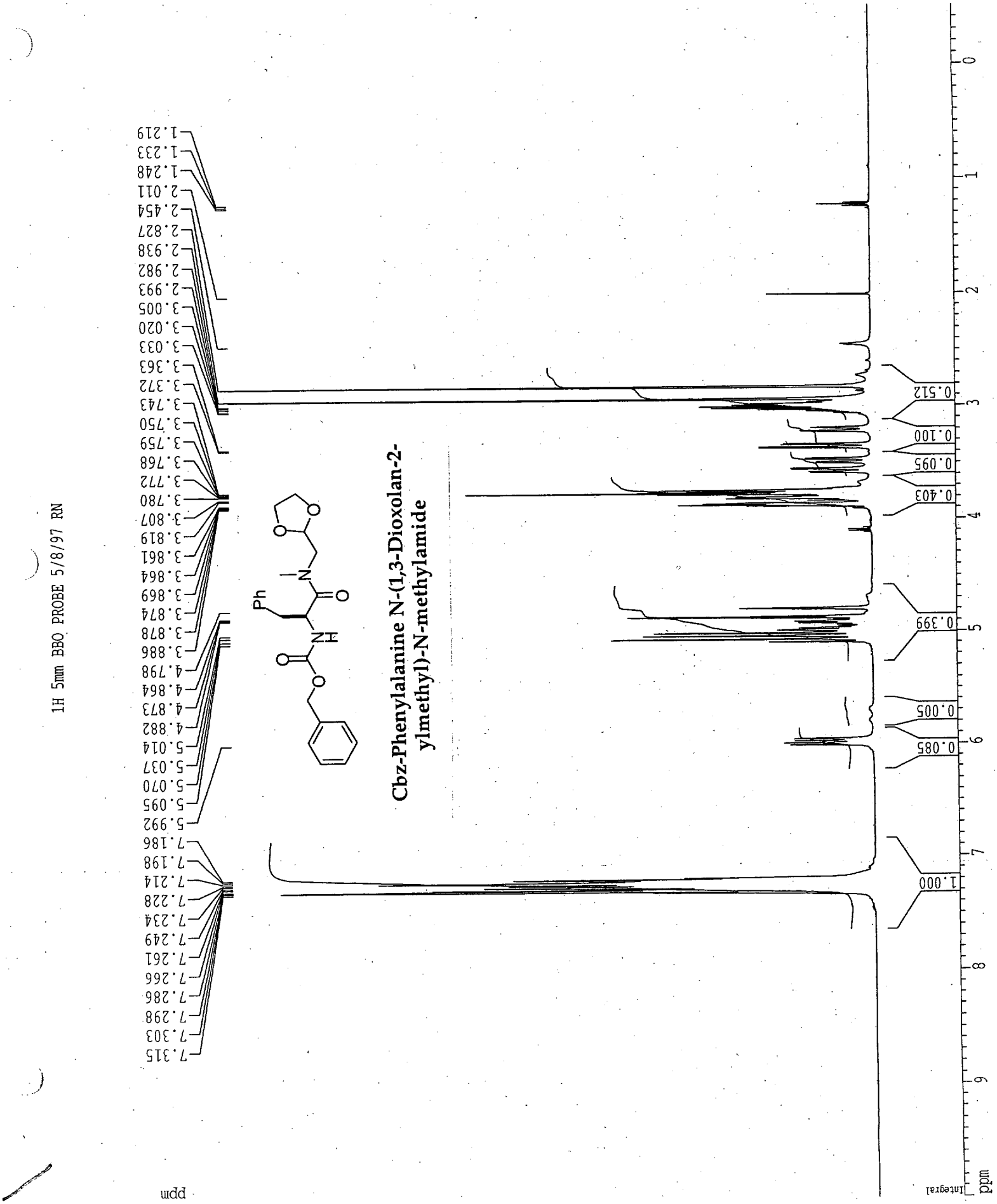

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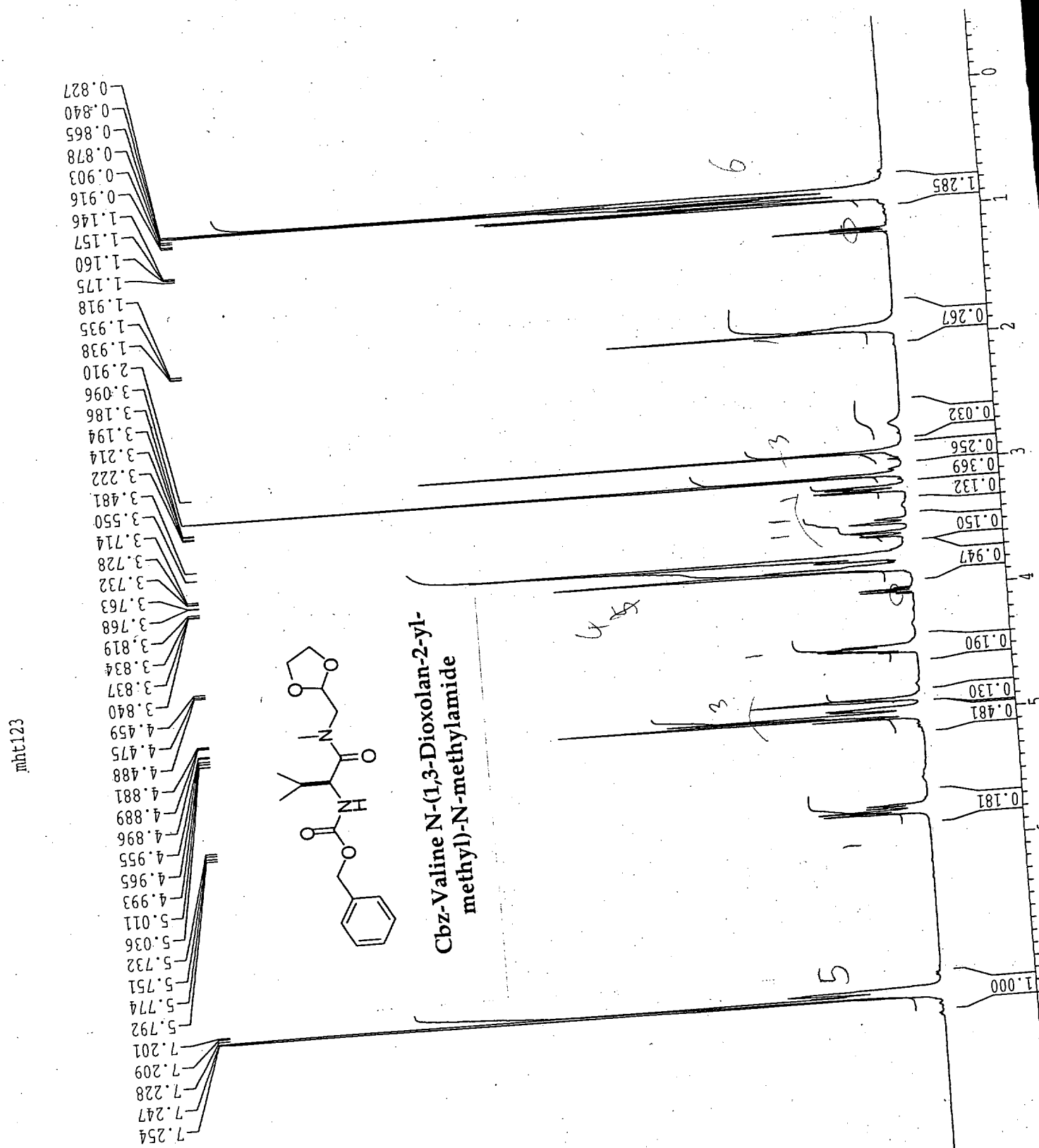

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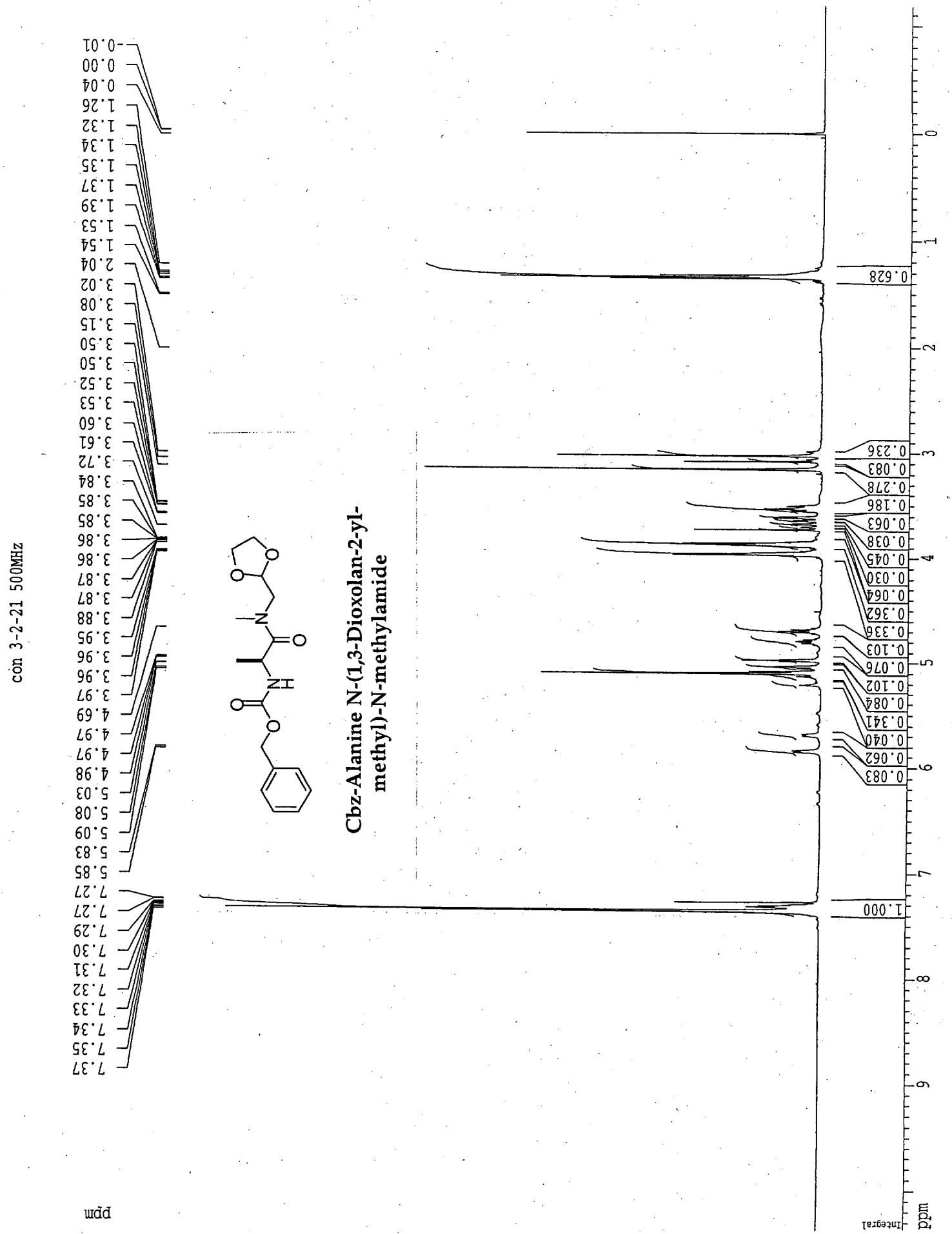

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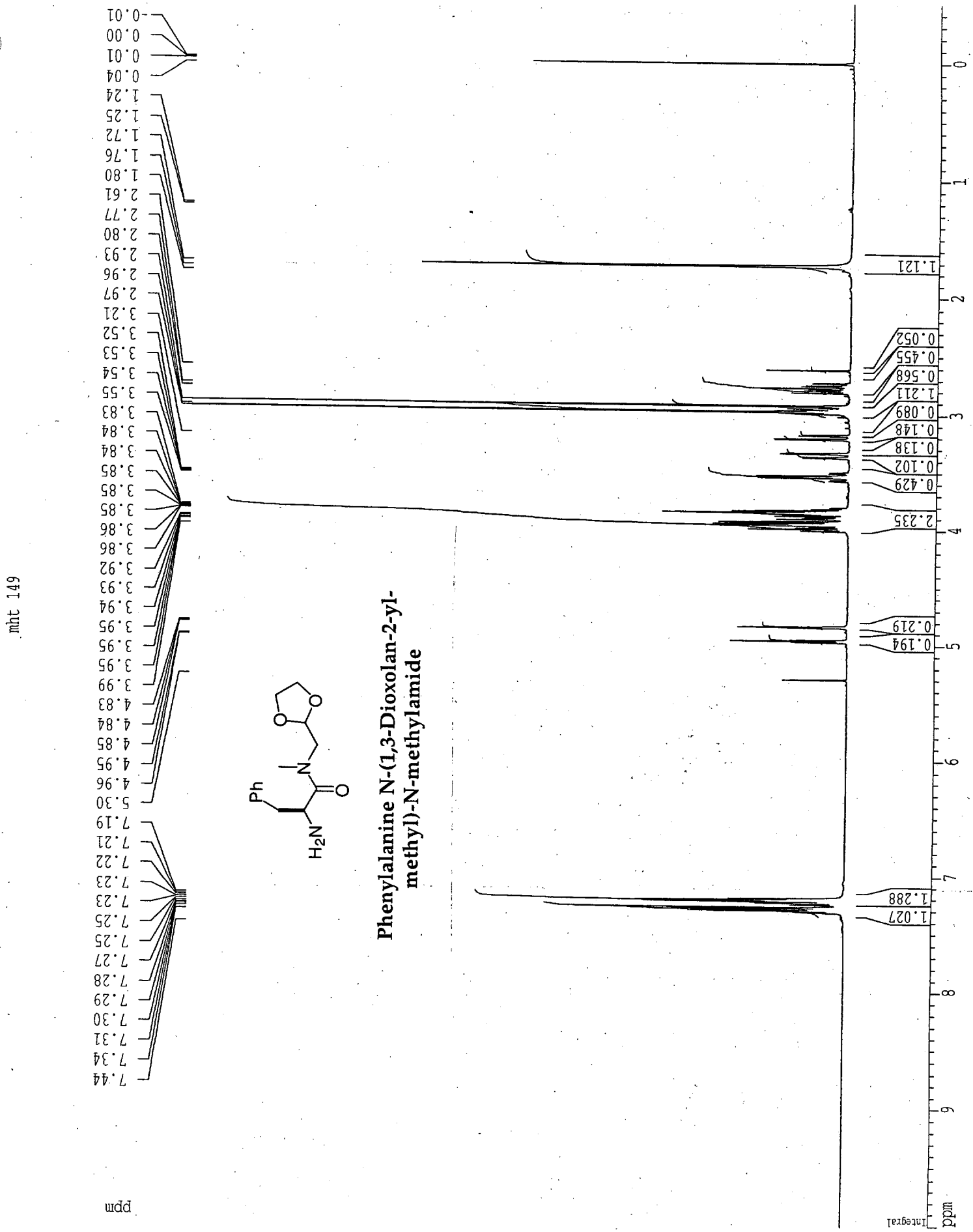

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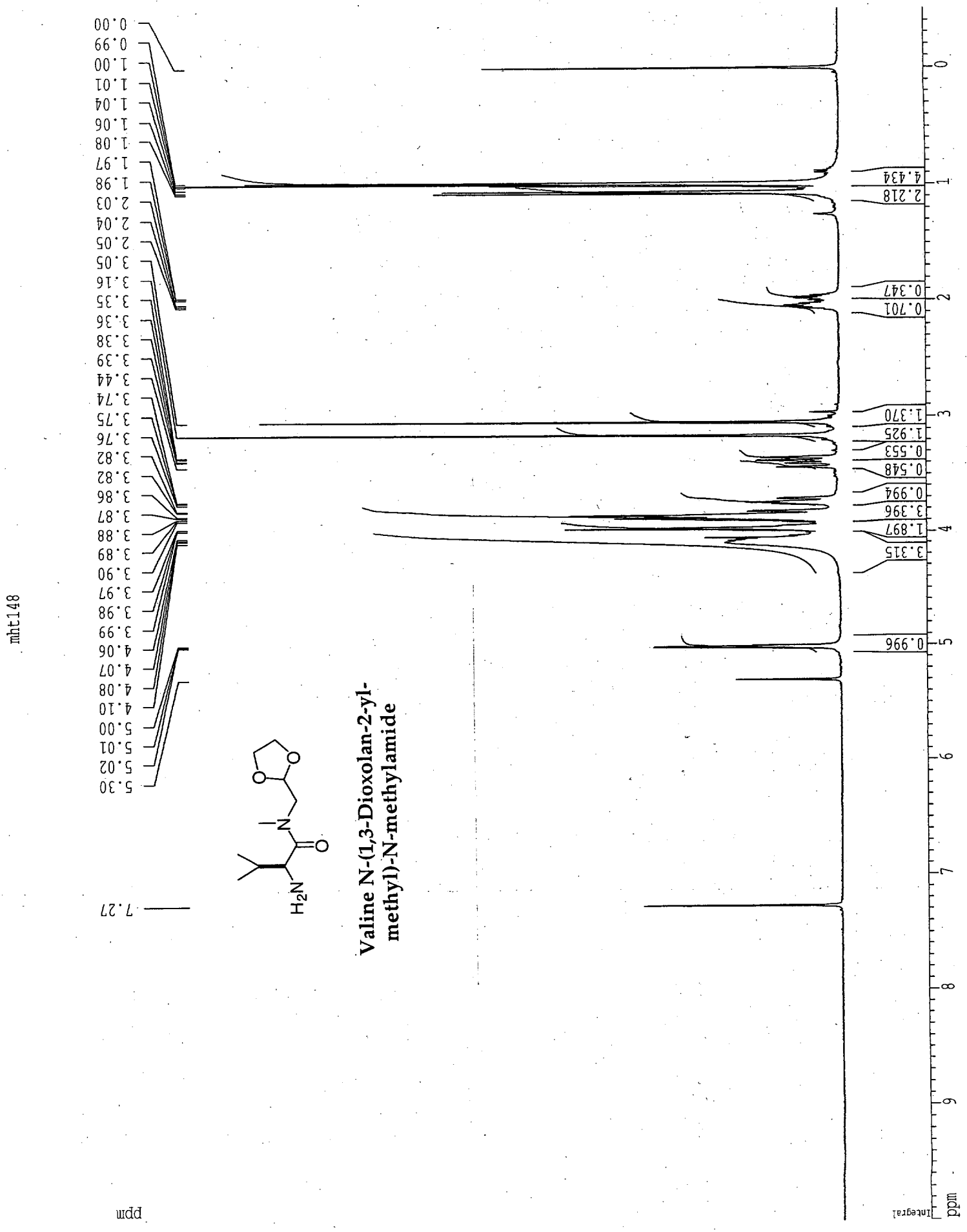

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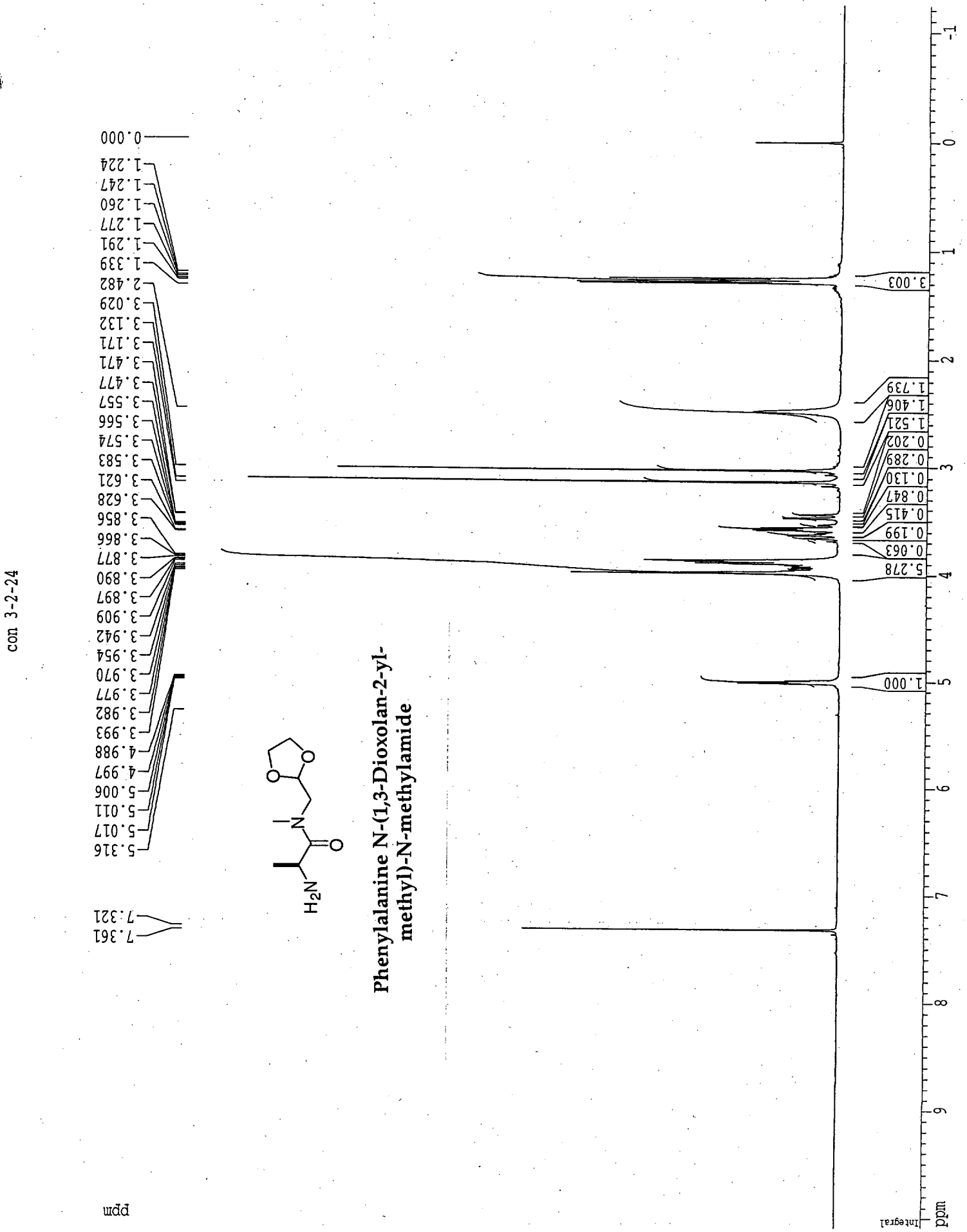

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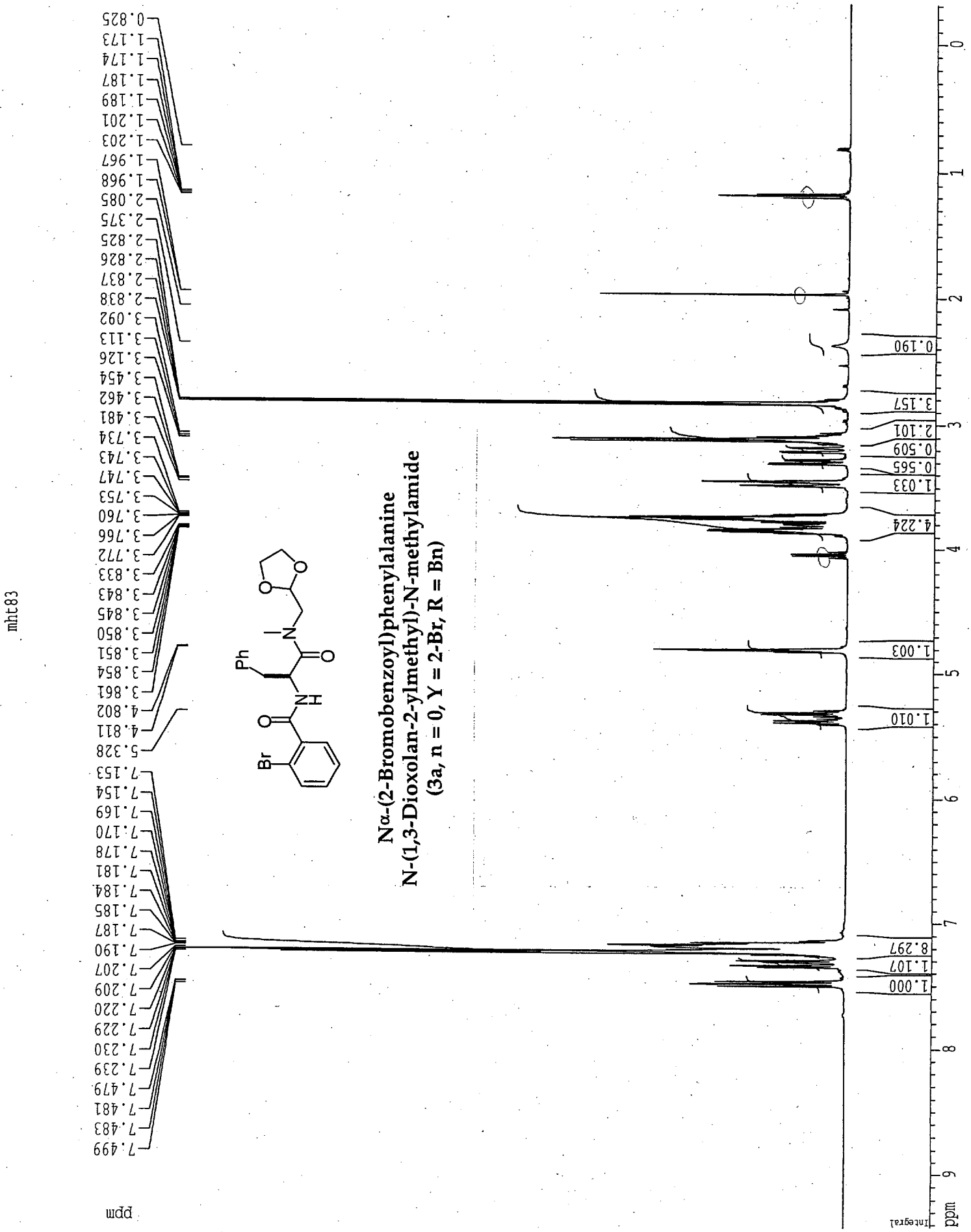

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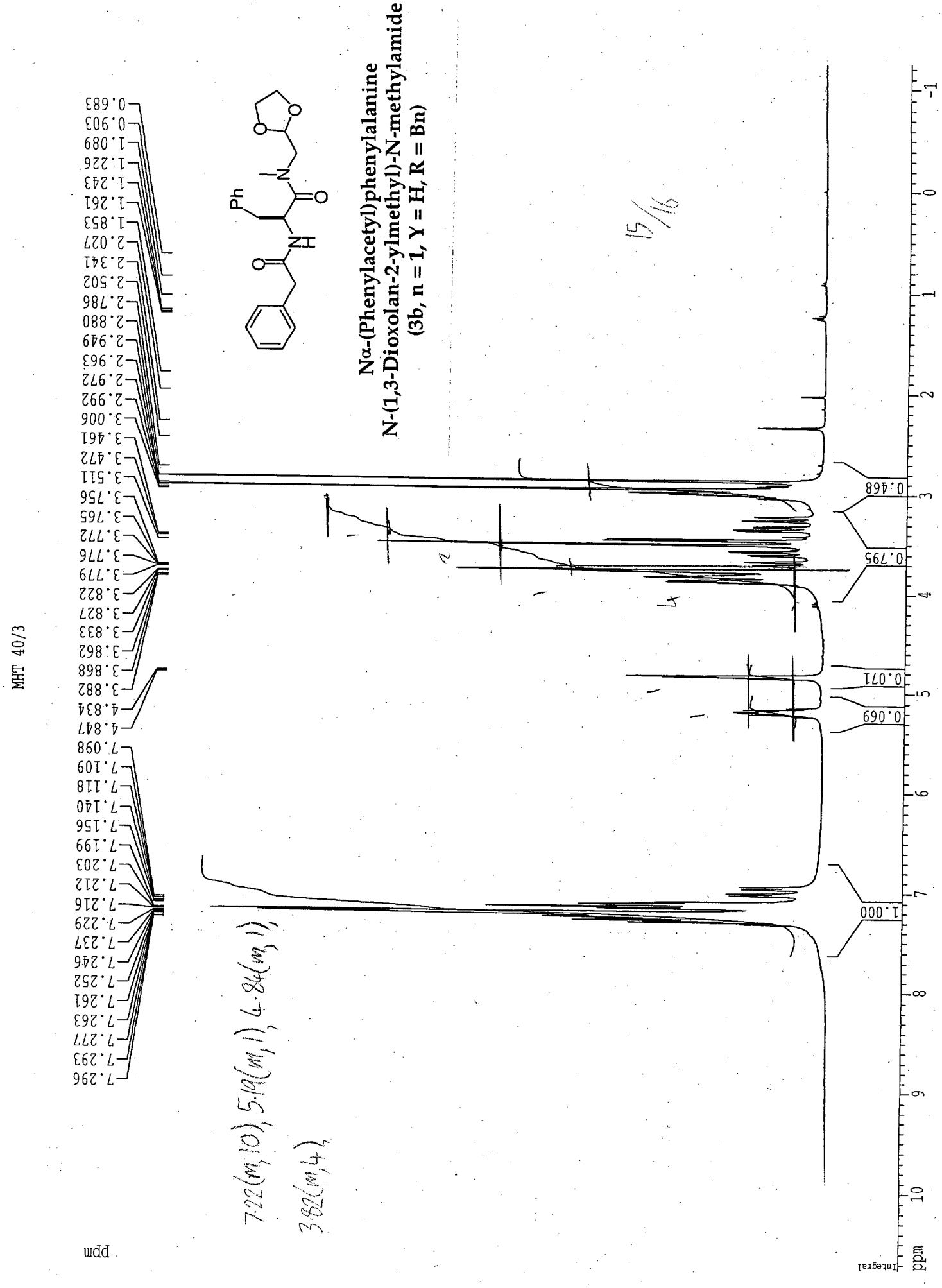

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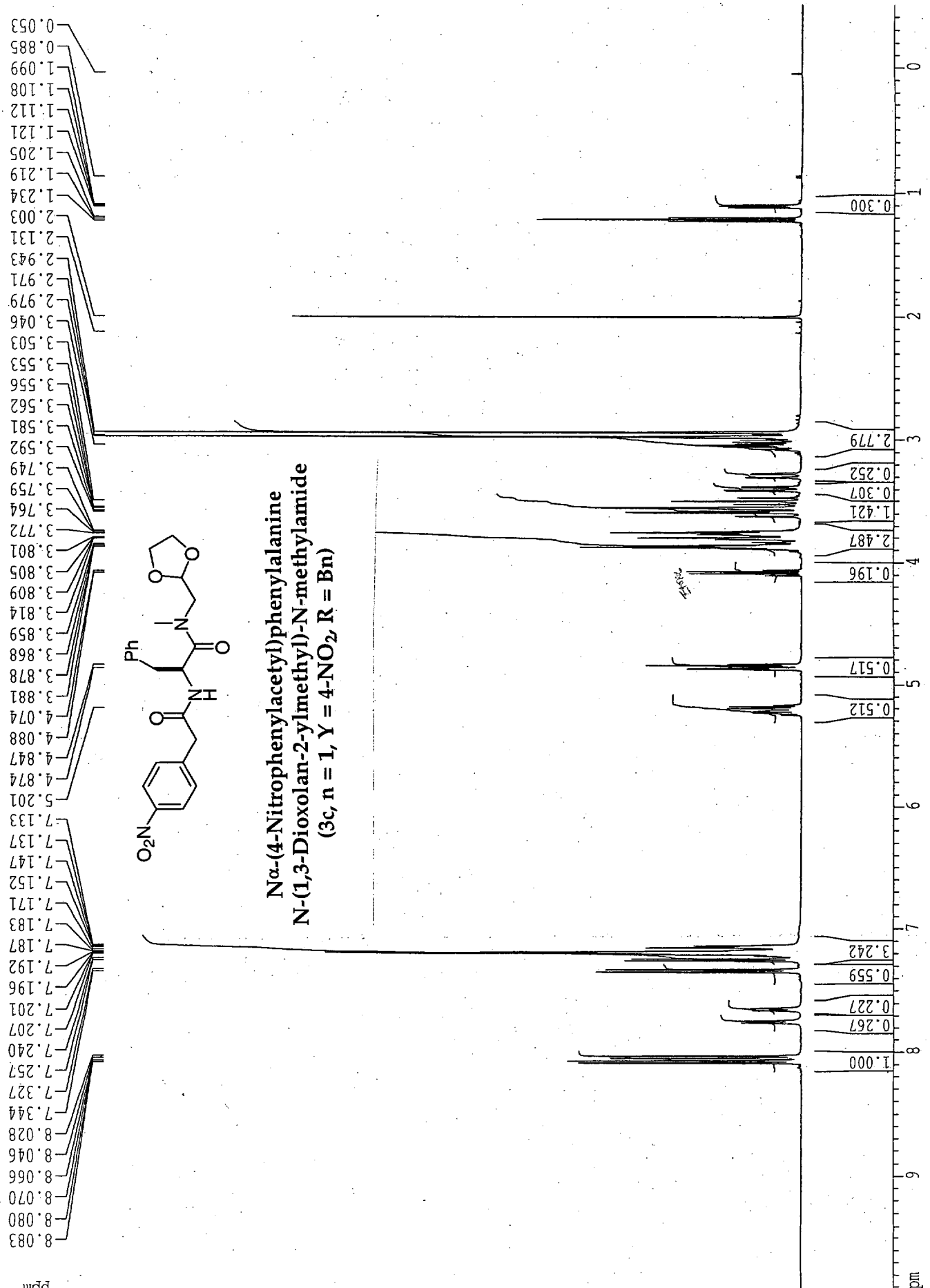

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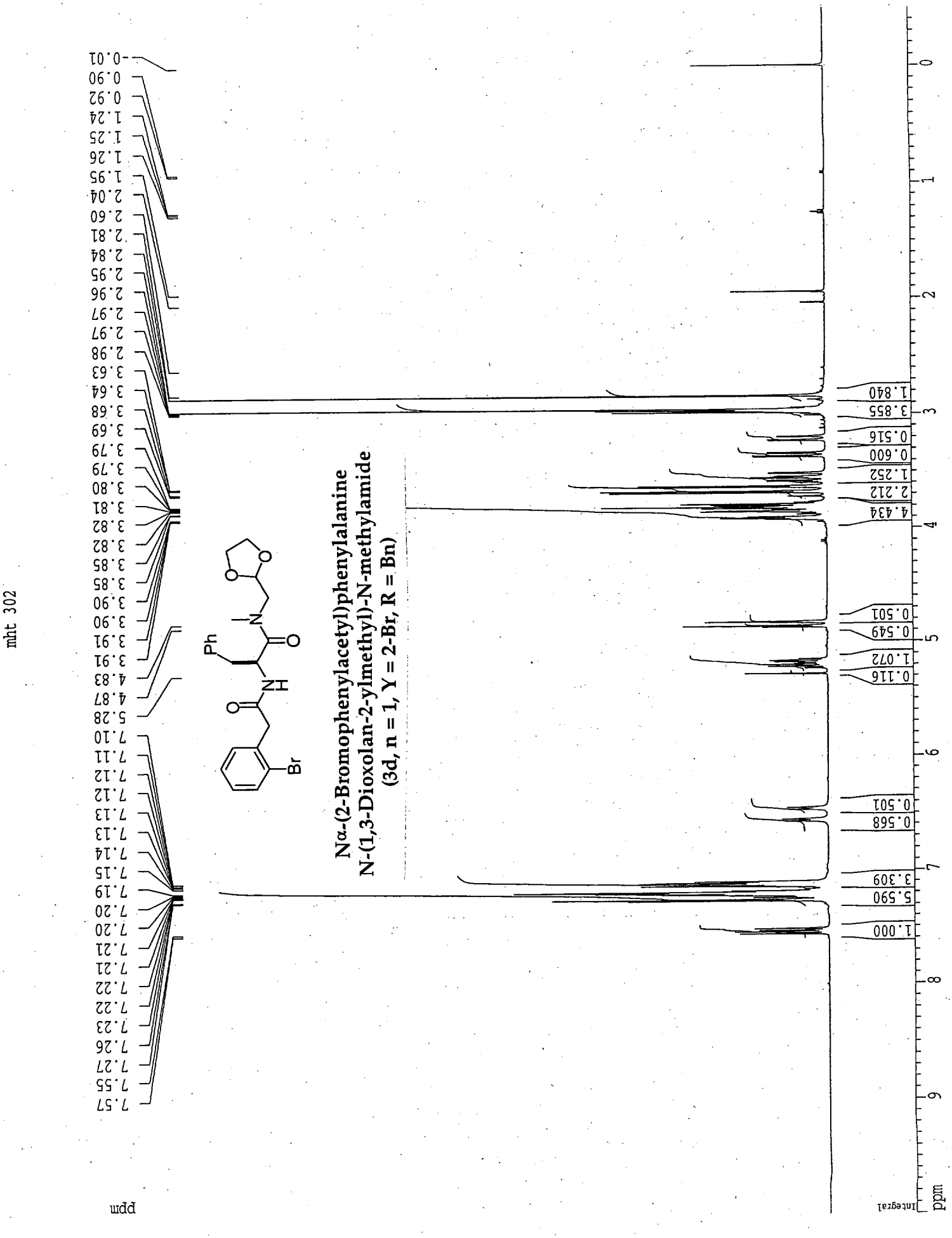

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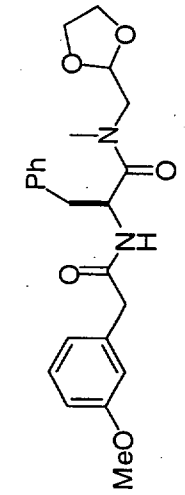
Nα-(2-Methoxyphenylacetyl)phenylalanine N-(1,3-Dioxolan-2-ylmethyl)-N-methylamide (3e, n = 1, Y = 3-MeO, R = Bn)



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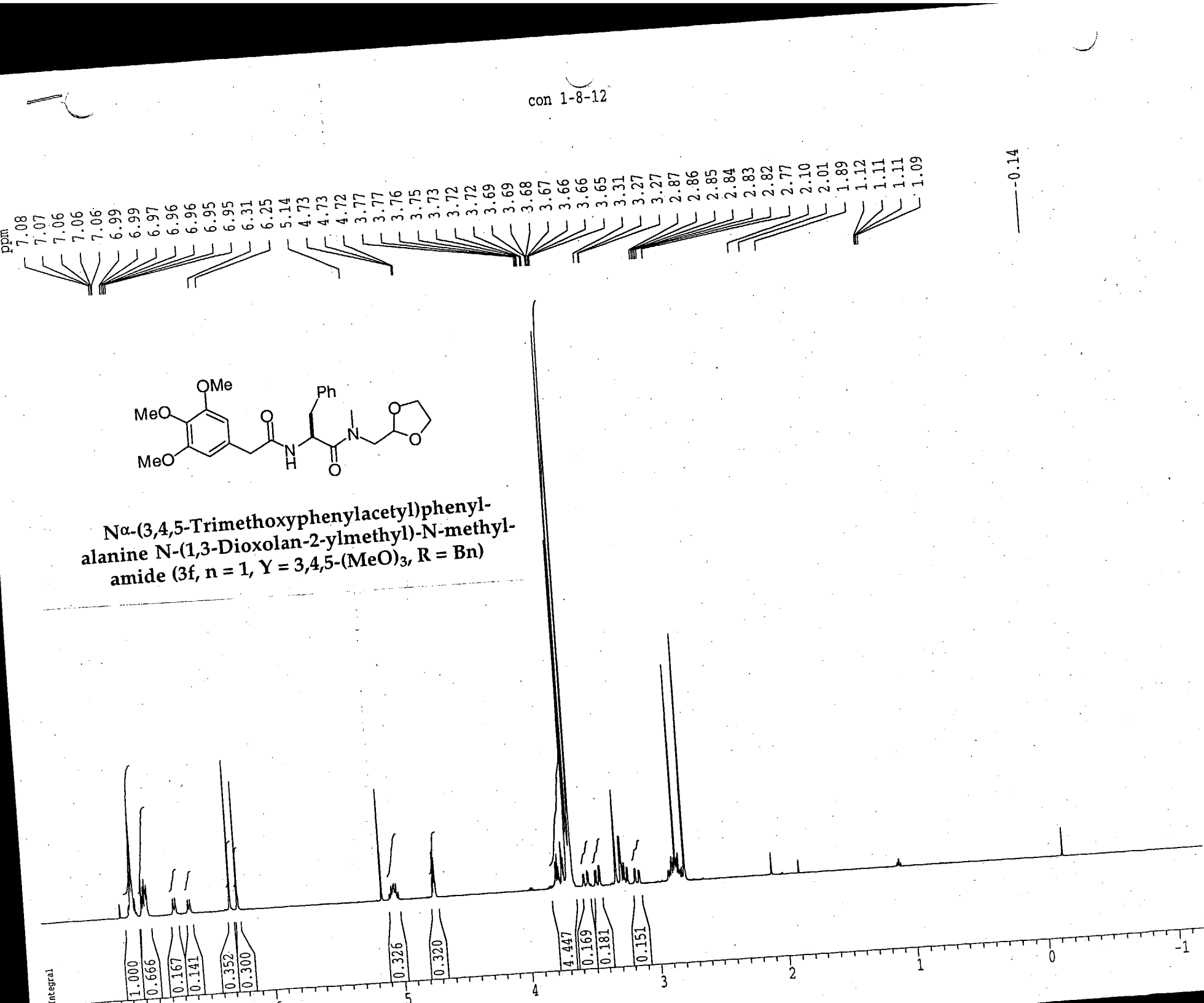

Nα-(3,4,5-Trimethoxyphenylacetyl)phenyl-alanine N-(1,3-Dioxolan-2-ylmethyl)-N-methyl-amide (3f, n = 1, Y = 3,4,5-(MeO)$_3$, R = Bn)

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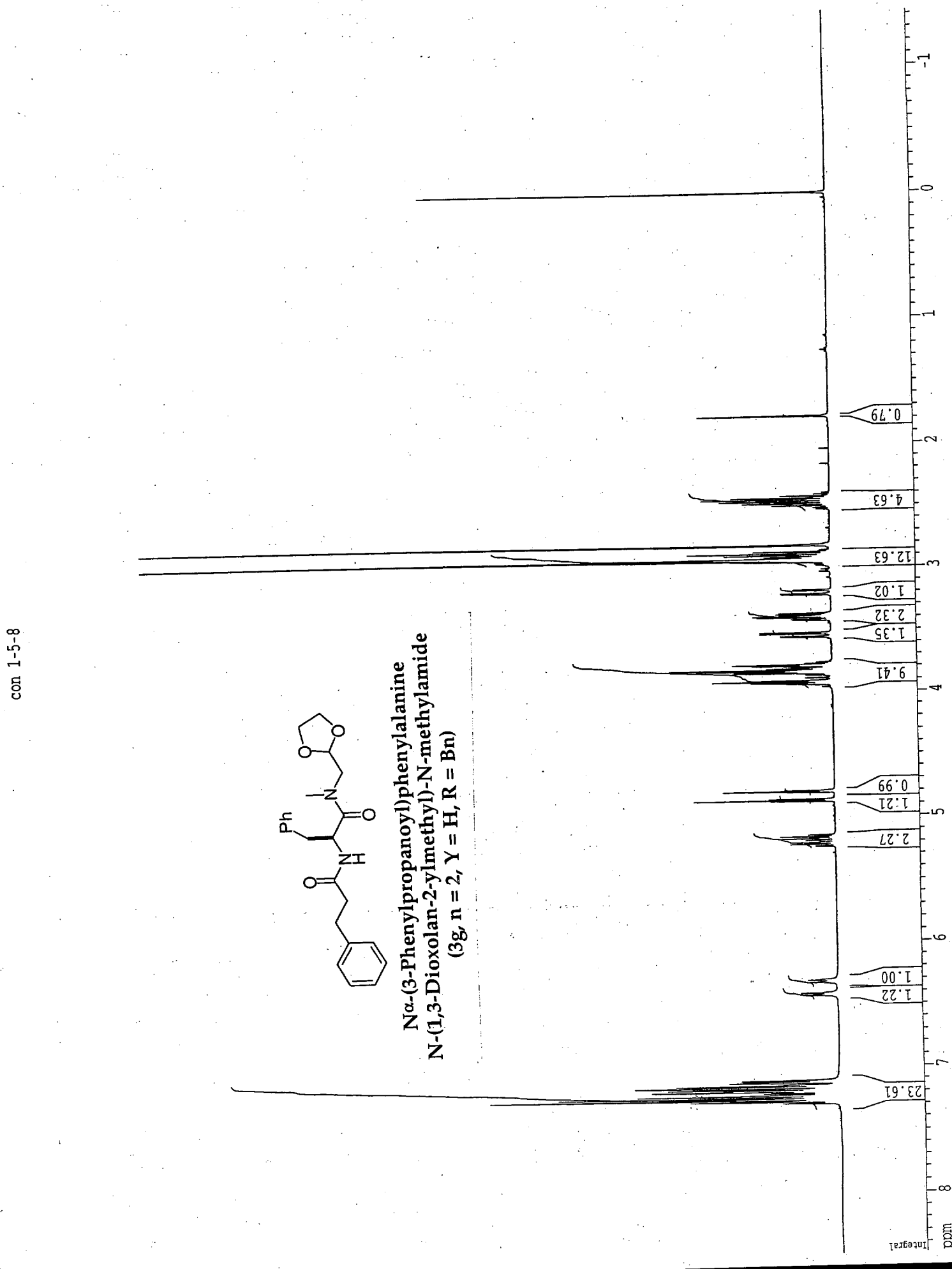

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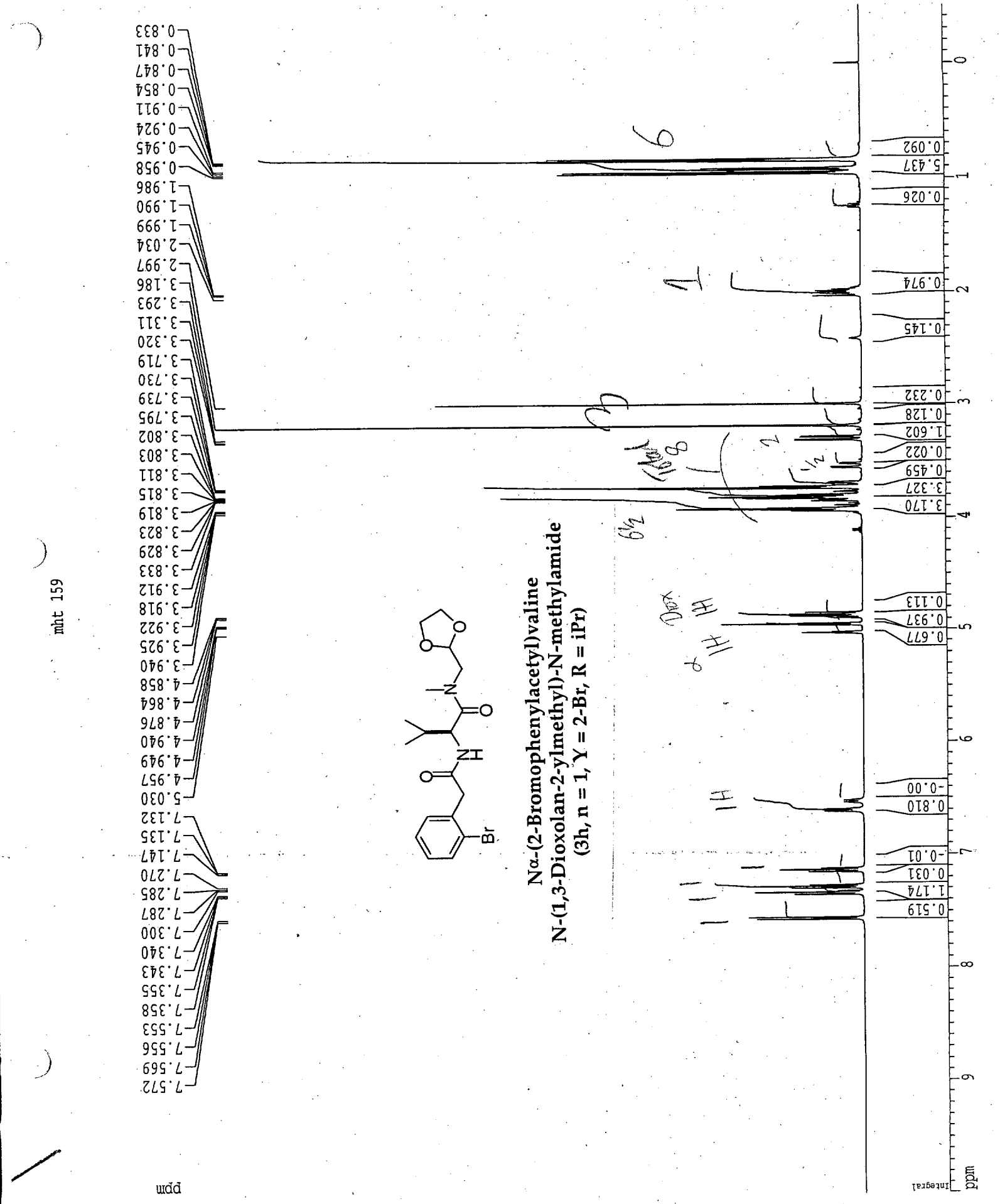

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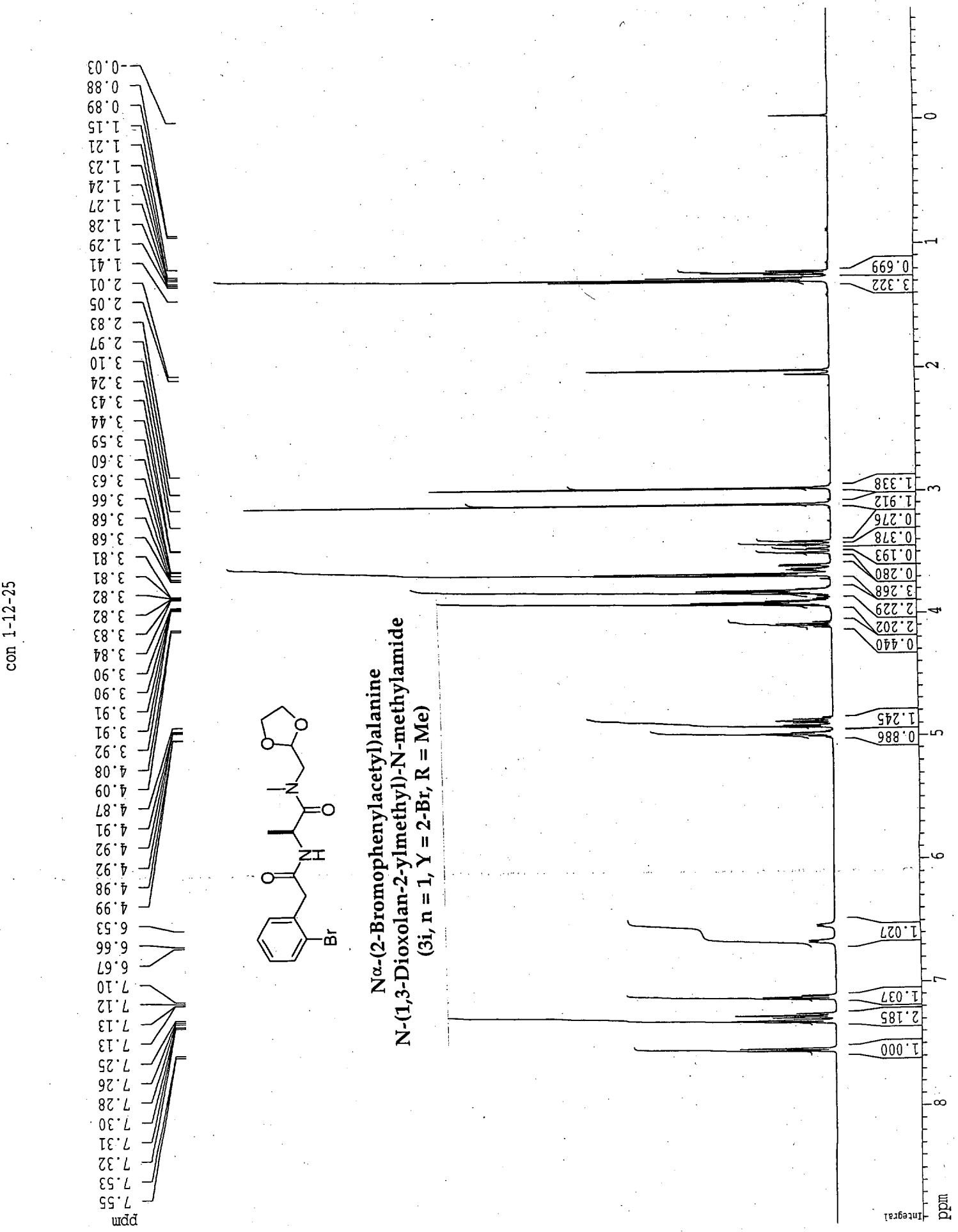

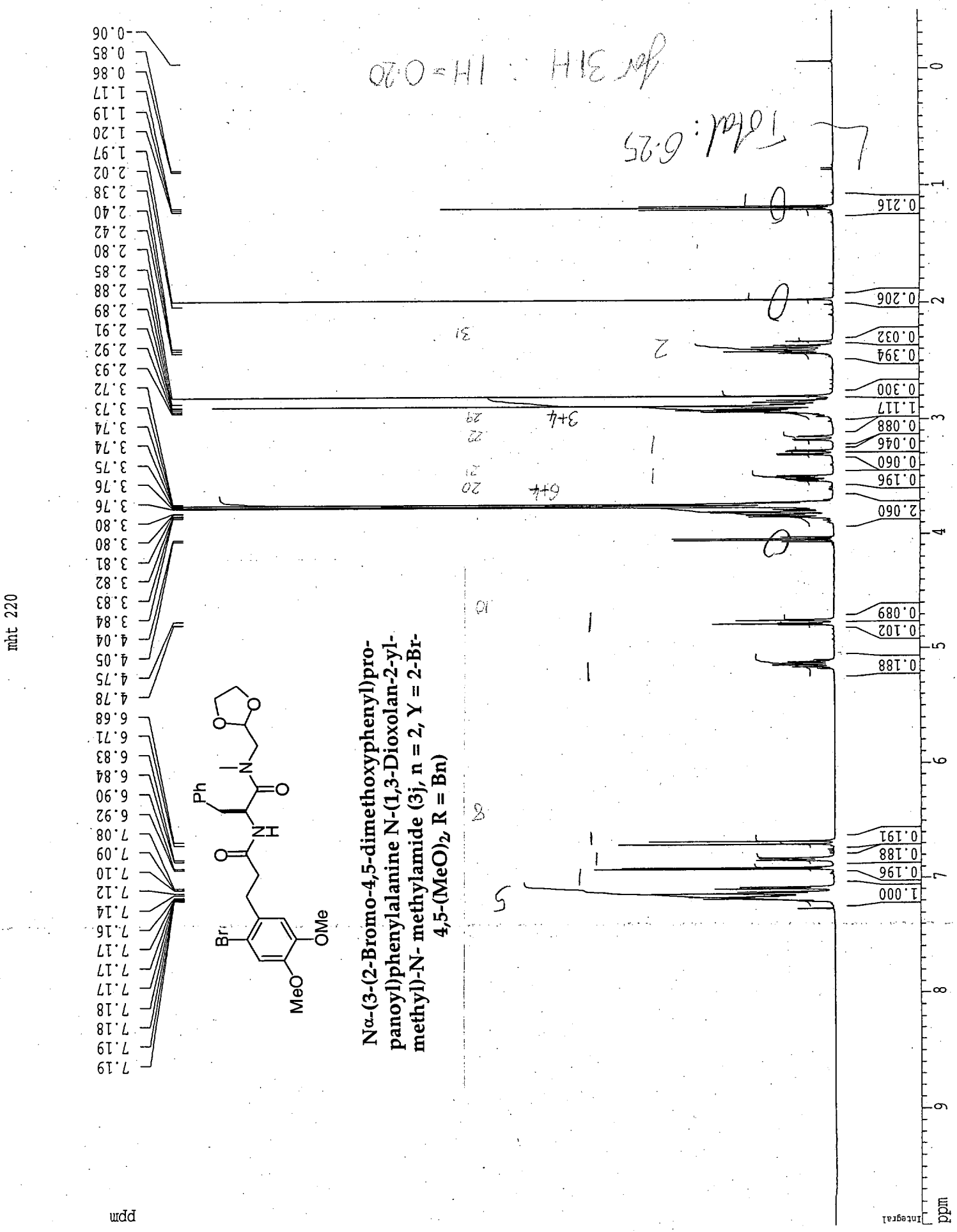
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Br
OMe
MeO

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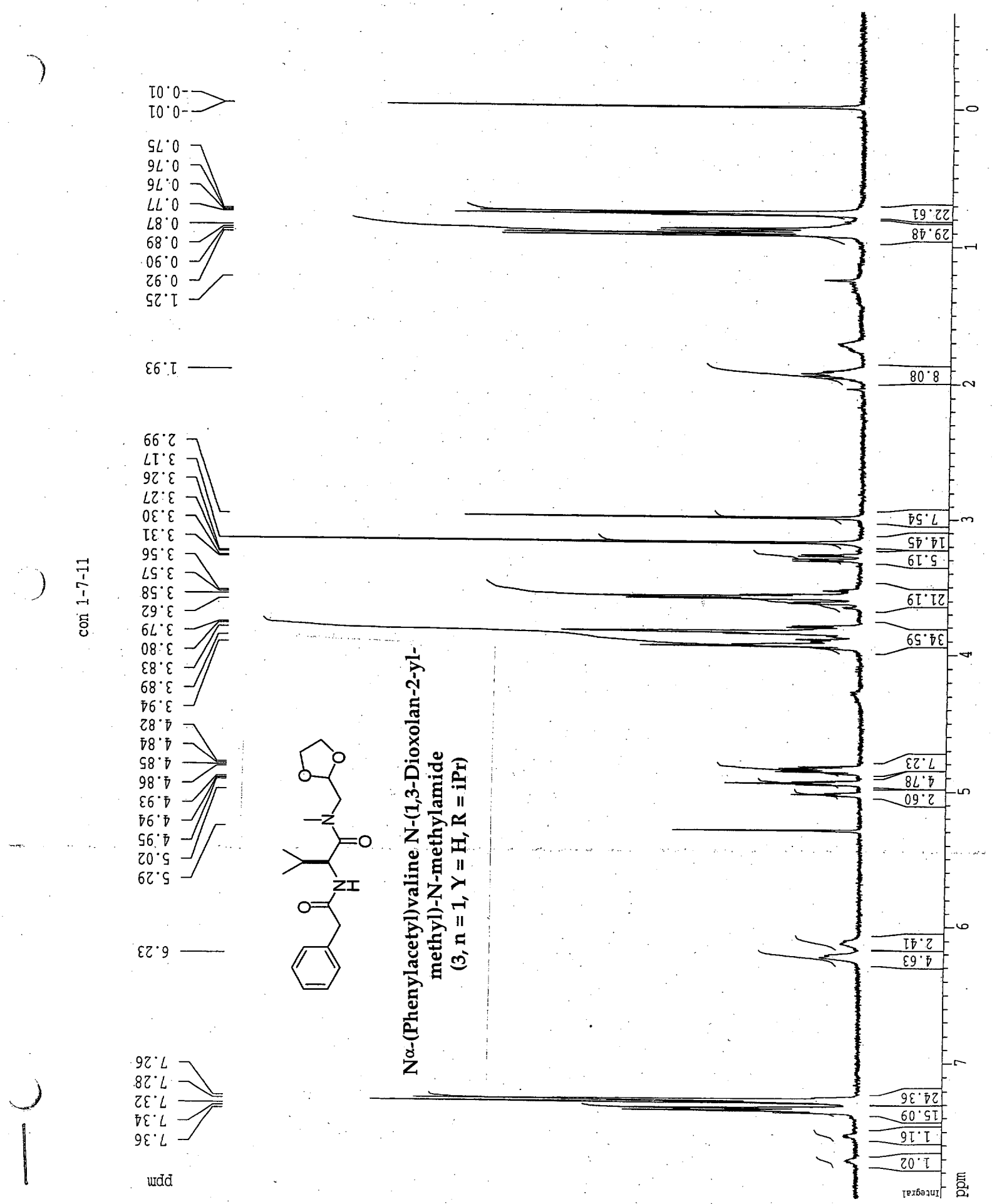

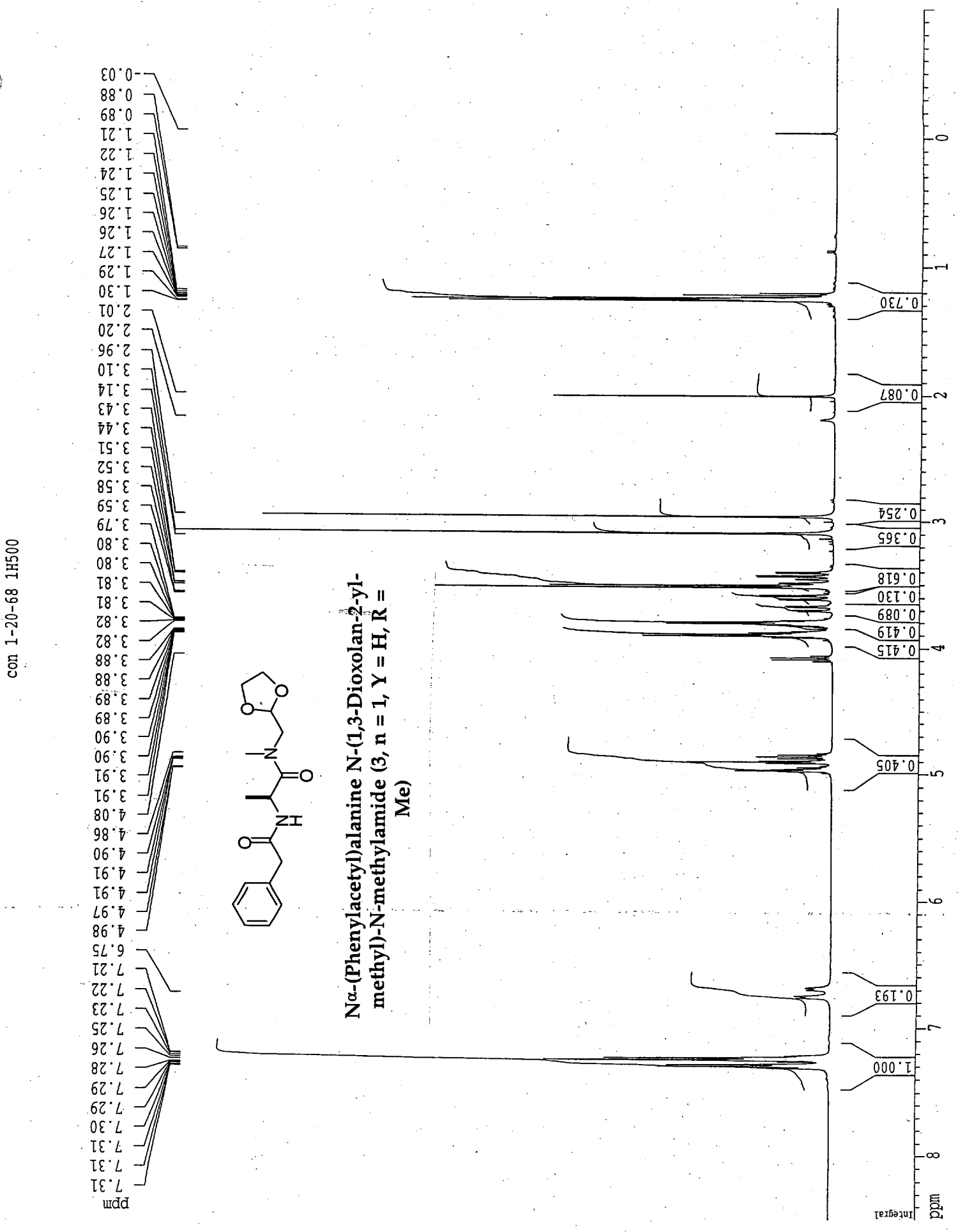
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Nα-(Phenylacetyl)alanine N-(1,3-Dioxolan-2-yl-methyl)-N-methylamide (3, n = 1, Y = H, R = Me)

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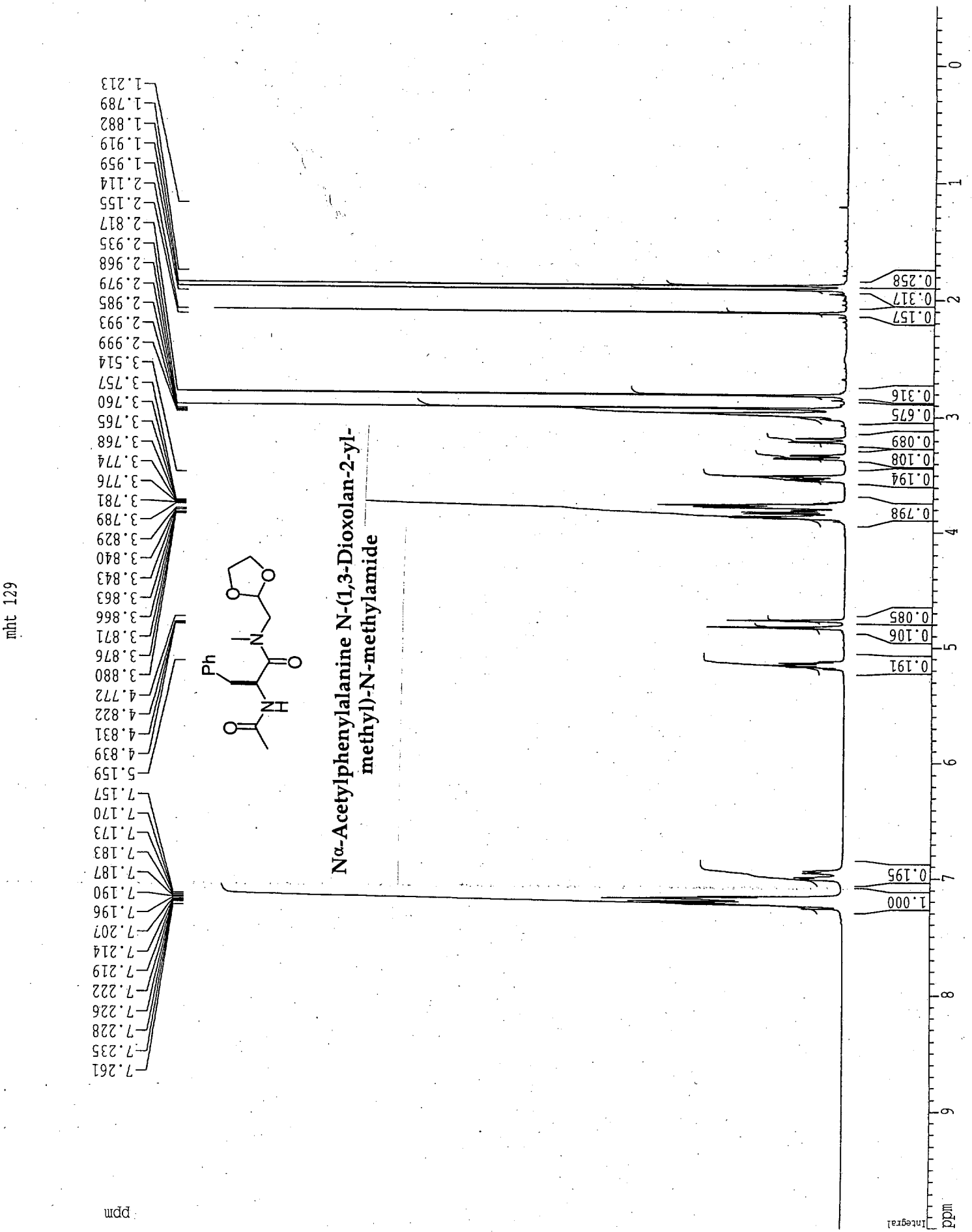

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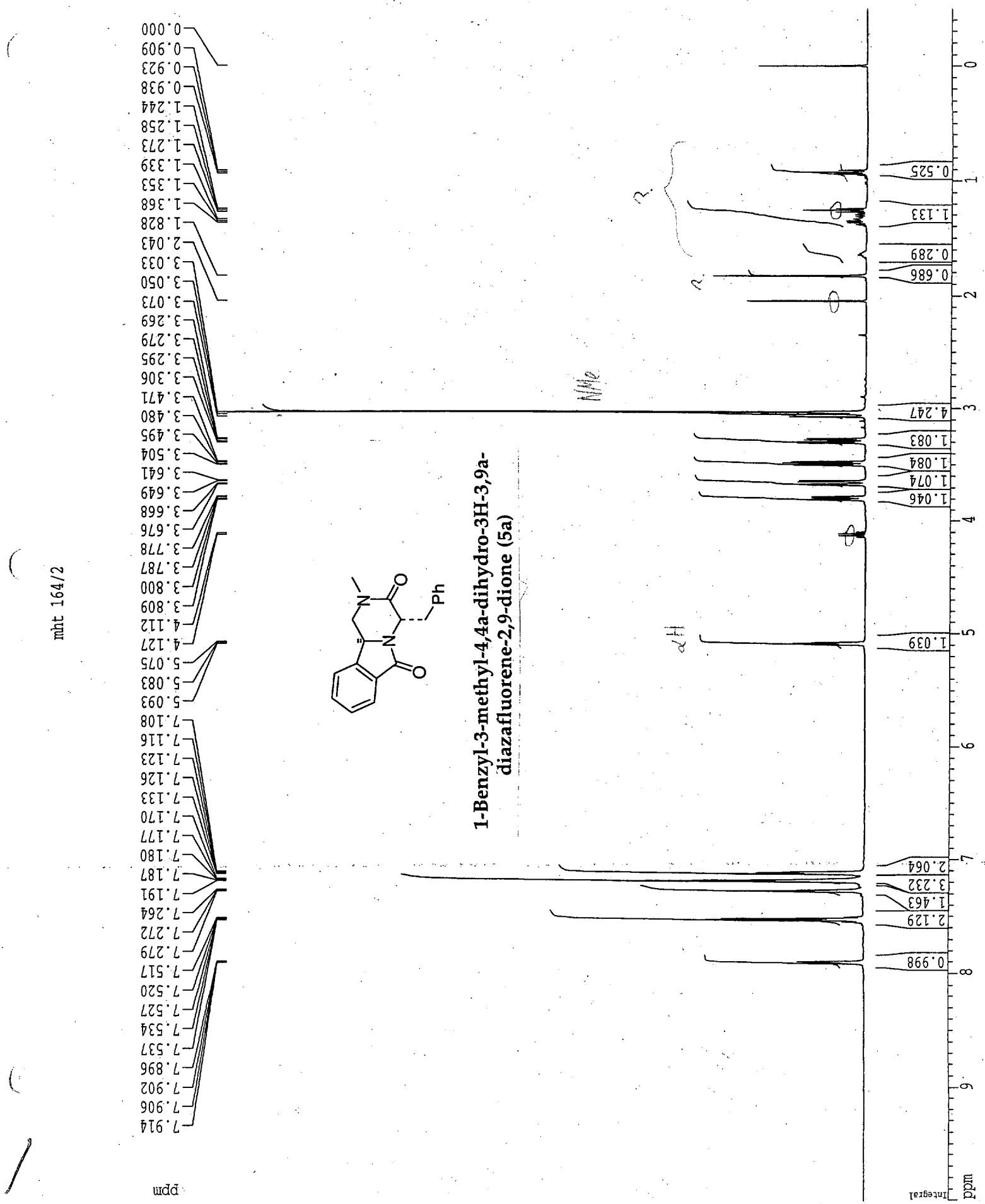

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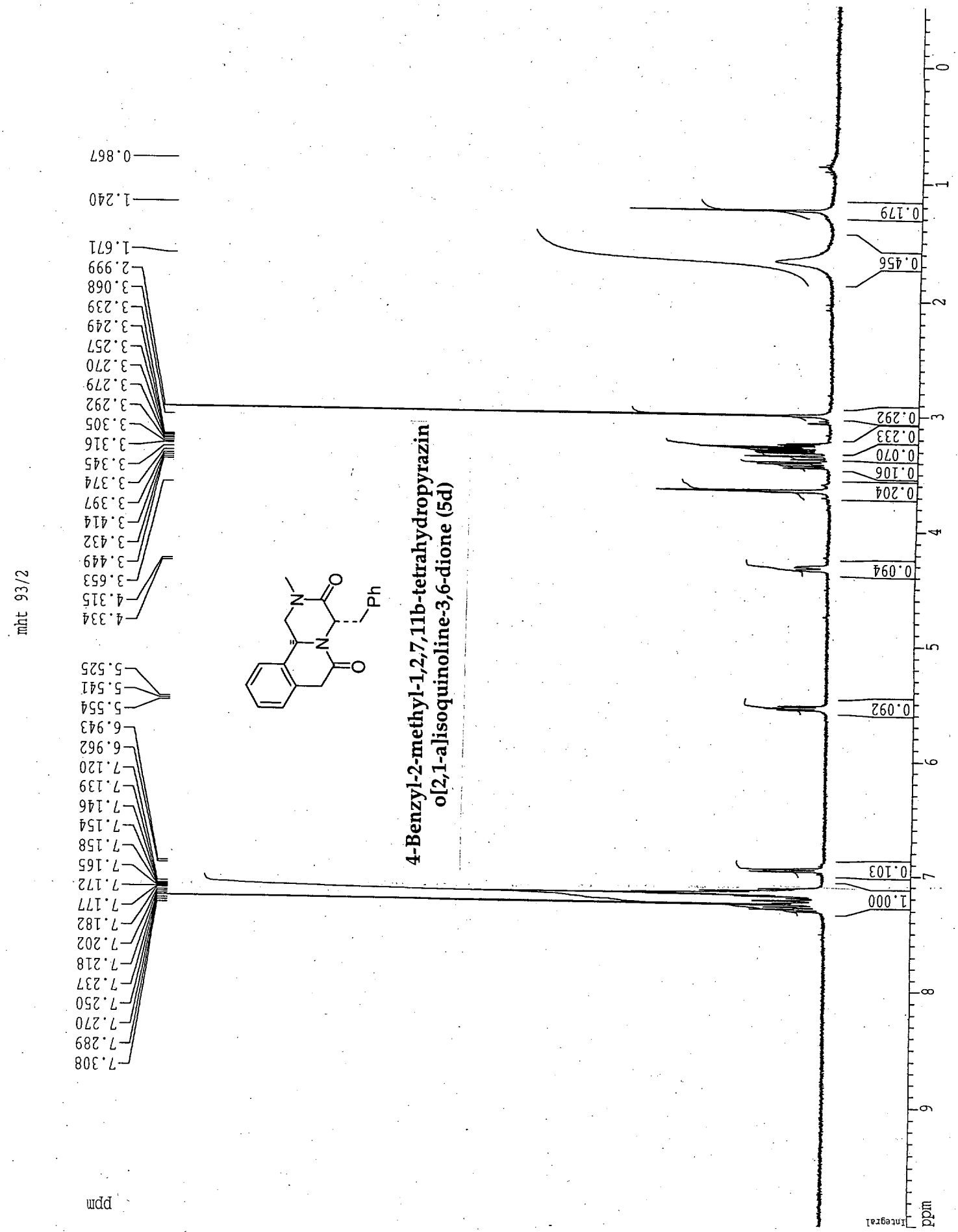

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