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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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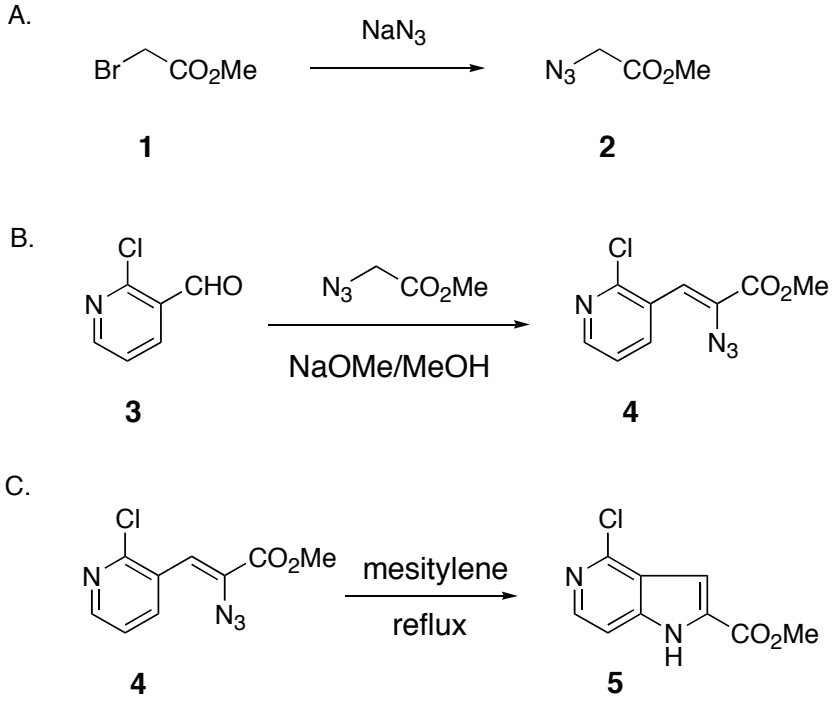
PREPARATION OF SUBSTITUTED 5-AZAINDOLES: METHYL 4-CHLORO-1*H*-PYRROLO[3,2-*C*]PYRIDINE-2-CARBOXYLATE



Submitted by Patrick Roy[1], Michel Boisvert, and Yves Leblanc.
Checked by Akiyoshi Kuramochi and Masakatsu Shibasaki.

1. Procedure

A. Methyl azidoacetate (**2**). *This reaction should be performed behind a safety shield.* To a solution of methyl bromoacetate (**1**) (51.5 mL, 0.528 mol) in MeOH (86 mL) in a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, reflux condenser, a drying tube, a septum through which is passed a metal temperature probe and a 20 °C water bath is added a slurry of sodium azide (42.3 g, 0.649 mol, 1.23 equiv) in H_2O (40 mL) via a funnel in one portion. The residual sodium azide is rinsed into the round-bottomed flask with water (2 x 6 mL). The suspension is stirred for 20 min in the water bath and a mild exotherm occurs (Note 2). The solution is then brought to gentle reflux with a heating mantle for 2 h. After cooling to room temperature, the solvent is removed carefully on the rotary evaporator (40 mmHg, 25 °C water bath), as the heterogeneous mixture has a tendency to bump. The residue is partitioned between Et_2O (100 mL) and H_2O (100

mL), transferred to a separatory funnel and the aqueous phase is further extracted with of Et_2O (3 x 30 mL). The combined organic layer is dried with $MgSO_4$, filtered, and evaporated to give methyl azidoacetate (53.9–54.5 g, 89–90%) as a slightly yellow oil.

B. Methyl (2Z)-2-azido-3-(2-chloropyridin-3-yl)acrylate (**4**). *This reaction should be performed behind a safety shield.* A 2-L three-necked, round-bottomed flask (24/40 ground glass joints) is fitted with a drying tube, a 125-mL addition funnel, a magnetic stir bar (Note 3), and a septum through which is passed a metal temperature probe. To the flask is added 2-chloro-3-pyridine carboxaldehyde (20.0 g, 141 mmol) (Note 1), MeOH (200 mL), and methyl azidoacetate (32 mL, 349 mmol, 2.5 equiv) (Note 4). A slightly positive pressure of nitrogen is placed on the system via a needle through the septum. The flask is placed in an acetone bath, and dry ice is added slowly to the bath until the internal temperature reaches –10 to –12 °C (Note 5). At that point, a 25% solution of NaOMe in MeOH (80 mL, 4.37 M, 349 mmol, 2.5 equiv) is slowly added using the addition funnel over a period of 25 to 30 min. Dry ice is occasionally added to the cold bath during this time to maintain the internal temperature at approximately –9 to –12 °C. The reaction color changes from clear pale brown to cloudy orange/yellow as the addition proceeds, and mild bubbling is noted. When the addition is completed, the mixture is stirred an additional 15 min at –10 °C. The flask is then transferred to an ice bath, and stirring is continued for 2.5 h, during which time the internal temperature rises to 1.5 to 2 °C (Note 6). A tan-colored precipitate gradually forms (product), and slow bubbling is observed. The reaction is then placed in an ice bath in a 4 °C cold room, and is stirred overnight (16 h) with the drying tube in place. The flask is covered in aluminum foil to exclude light. The next morning, a 4-L Erlenmeyer flask is placed in an ice bath and the flask is then charged with 500 g of ice and 1.5 L of saturated NH_4Cl solution. A stir bar is transferred to the Erlenmeyer flask, and the tan-colored suspension is poured onto the stirring mixture over approximately 20 sec. The reaction flask is rinsed with 3 x 50 mL of ice water to ensure that any remaining solid is transferred. The final pH of the suspension is approximately 7.5. After stirring for an additional 5 min, the product is collected on a 12-cm Büchner funnel using a standard vacuum filtration setup, washing with ice-cold water (3 x 100 mL) (Note 7). The tan-colored solid is air-dried for 10 min on the Büchner funnel under suction from an aspirator, and is then transferred to a 1-L single-necked round-bottomed flask and placed under high vacuum for 30 min. Dichloromethane

(250 mL) is then added to dissolve the product, and $MgSO_4$ (approximately 3–4 g) is added to dry the solution. The pale brown solution is filtered through a 2-cm thick pad of silica gel 60 on a 4-cm sintered glass funnel, which removes some dark brown baseline material. The pale yellow solution is concentrated to dryness on the rotary-evaporator (approximately 15 mmHg) at 25 °C to give the product as a pale yellow solid (17.7–18.8 g, 53–56%) (Note 8).

C. Methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**5**). *This reaction should be performed behind a safety shield.* The product (**4**) from Step B (17.7 g, 74.2 mmol) is suspended in 740 mL of mesitylene (0.1 M) in a 2–L, single-necked round-bottomed flask equipped with a magnetic stir bar and a reflux condenser with a drying tube. The reaction mixture is stirred while being heated in an oil bath at 185 °C (Note 9), and after approximately 3 min, the starting material dissolves. At 5 min, bubbling occurs for several min as N_2 is extruded from **4**. After 30 min, the mixture is gently refluxing, which is maintained for 1 h. The clear deep yellow solution is then allowed to stand at room temperature for 1 h, during which time a thick pale yellow precipitate forms. After cooling to 0 °C for 1 h, the product is collected on a 12–cm Büchner funnel, washing with 4 x 50 mL of cold hexanes. The solid is then suspended with vigorous stirring overnight in 200 mL of EtOAc:hexanes (1:20, vol/vol). The product is then collected on a 12–cm Büchner funnel and washed with 2 x 50 mL of hexanes to give a pale yellow solid (10.7 g, 69%) (Note 10).

2. Notes

1. Methyl bromoacetate (97% purity) was obtained from Lancaster Synthesis. Sodium azide (>99.5% purity), 2-chloro-3-pyridine carboxaldehyde (97% purity), 25% NaOMe/MeOH and mesitylene (98% purity) were obtained from the Aldrich Chemical Co. MeOH was Optima D.I.G. grade (4 L, 0.07% H_2O) from Fisher.

2. A mild exotherm to approximately 45 °C was observed, although this exothermic behaviour never showed any sign of loss of control. Differential scanning calorimetry indicated an endotherm at 58 °C. This reaction was carried out at this scale or greater without incident. The characterization of **2** is as follows: ^{1}H NMR (500 MHz, acetone-d_6) δ: 3.77 (s, 3 H), 4.04 (s, 2 H). ^{13}C NMR (126 MHz, acetone-d_6) δ: 50.47. 52.64, 169.87; IR (neat): cm^{-1} 2108, 1751.

3. Mechanical stirring was not necessary, although for other substrates such as 2-methoxy-3-pyridine carboxaldehyde[2] the reaction became a thick paste overnight at 0 °C. This thickening, however, did not appear to affect the yield.

4. In the original papers using methyl azidoacetate for the condensation step (Monatshefte Chemie **1969**, 100(5) 1599), the authors used 4 equivalents of the reagent, which was reduced to 2.5 equivalents in the above procedure. The excess was felt to be necessary since the reagent slowly decomposed with time, as indicated by the gentle bubbling during the condensation step.

5. The addition was also carried out successfully at –30 °C for this substrate. However, for 2,4-dichloro-3-pyridine carboxaldehyde[2] addition at –30 °C followed by warming to 0 °C resulted in an exotherm to >12 °C, which led to the mixture frothing out of the flask. No product was recovered. As a *precaution* when carrying out the reaction, the flaps on the septa are not folded down in order to minimize problems arising from any build-up of pressure in the event of an exotherm.

6. If a non-insulated container such as a plastic bowl is used for the ice bath, care must be taken to maintain enough ice to prevent the internal temperature from rising too high. Internal temperatures of 4 °C have been noted with ice floating in water in the bath.

7. The filtration can require 15–20 min due to the fine nature of the crystals. A larger Büchner funnel reduces this filtration time. The aqueous/MeOH filtrate soon turned a dark red after filtration.

8. The product was best stored in the refrigerator or freezer, covered in aluminum foil, although we noted no change in the NMR spectra after several days at room temperature. Depending on the substitution pattern on the pyridine ring, the intermediate **4** gradually darkened over several weeks/months in the refrigerator. The material was repurified by dissolution in CH_2Cl_2 and filtration through a small plug of silica gel to remove baseline material. Differential scanning calorimetry of this material indicated that an exotherm occurred at approximately 120 ºC. The characterization for **4** is as follows: mp = 107–109 ºC (dec, gas bubbles); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (s, 3 H). 7.16 (s, 1 H), 7.26 (dd, J = 7.9, 4.8 Hz, 1 H), 8.29 (dd, J = 4.8, 1.7 Hz, 1 H), 8.50 (dd, J = 7.9, 1.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 53.54, 118.65, 122.50, 128.29, 129.22, 139.48, 149.35, 151.33, 151.33. IR (KBr): cm^{-1} 2129, 1708. MS (ESI+): *m/z* 260.7 (M+1) (100%)

9. The reaction was also carried out through use of a heating mantle, but some dark brown solid material formed on the walls of the flask. The yield was not greatly affected.

10. The characterization for **5** prior to chromatography was as follows: mp = 210–212 ºC (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.91 (s, 3 H), 7.19 (s, 1 H), 7.43 (d, J = 5.8 Hz, 1 H), 8.09 (d, J = 5.8 Hz, 1 H), 12.77 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 52.29, 105.97, 107.87, 122.08, 129.15, 141.51, 141.85, 144.23, 160.81; IR (KBr): cm^{-1} 1718. MS (ESI+) *m/z* 210.8 (M+H) (58%), M+Na 232.7 (100%). Anal. Calcd. for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.31; H, 3.41; N, 13.11. Although further purification was not necessary, the product was purified on small scale (100 mg) by flash chromatography on silica gel 60 (EMD), eluting with 30 % EtOAc/hexanes. The crude solution in mesitylene was applied directly to the column before the product precipitated.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes the preparation of methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate, a 4-Cl-5-azaindole, via thermolysis of an intermediate azidopyridine acrylate (Hemetsberger-Knittel reaction).[3] The product is isosteric with the analogous indole template, and represents an interesting scaffold from the point of view of medicinal chemistry. Furthermore, with four sites available for selective functionalization, one could envisage a wide range of chemical diversity in the construction of libraries based on this core structure. Table 1 shows the results obtained for the preparation of a variety of 5, 6, and 7-azaindoles. Procedure A (100 mg of pyridine acrylate at 0.1 M) involves bulb-to-bulb distillation of the mesitylene followed by chromatography. Procedure B is used for amounts greater than 500 mg of the pyridine acrylate and is performed as described in the current preparation. Procedure C is for the synthesis of 6-azaindoles (entries 13 and 14) and involves adding the pyridine acrylate to a refluxing

solution of decalin (190 ºC) at a concentration of 2 g/ 500 mL and refluxing 10 min before cooling and filtering.

Of the unsubstituted pyridine acrylates (entries 1-3), only the 7-azaindole was obtained, albeit in low yield (25%). For the two 6-azaindole precursors listed in entries 13 and 14, decomposition/poor yields were observed upon thermolysis at 160 ºC, whereas use of refluxing decalin gave acceptable yields (44%, 51%). There appears to be a minimum threshold below which the desired cyclization does not readily take place for these substrates. The best results were obtained with 5-azaindoles (entries 4-12). The thermolysis proceeds smoothly at 160 ºC with halogen, ether, thioether, methylsulfone, and alkyl substituents on the pyridine ring to give good yields (66–93%) with the exception of the methoxychloro-substituted entry 12 (32%).

Table 1. Thermolysis of 2-Azido-3-pyridine Acrylates

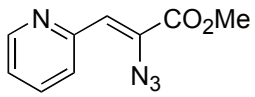
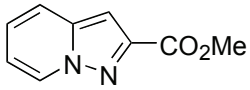
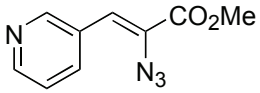
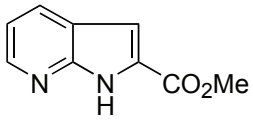
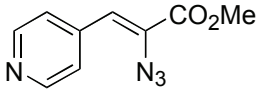
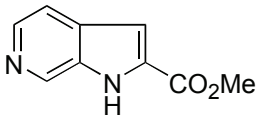
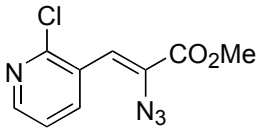
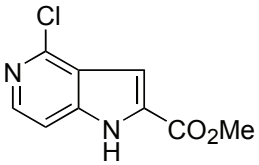
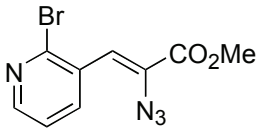
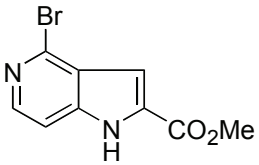
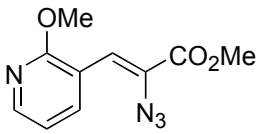
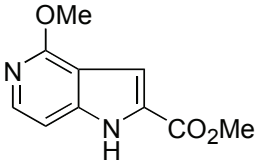
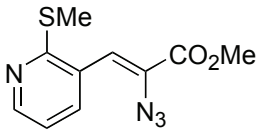
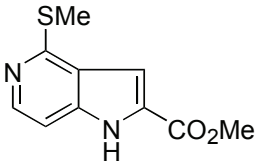
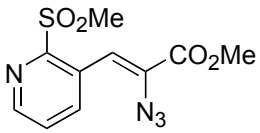
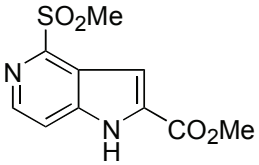
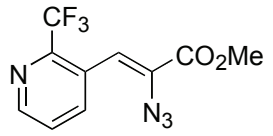
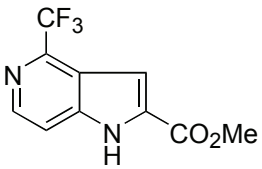
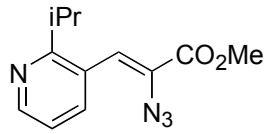
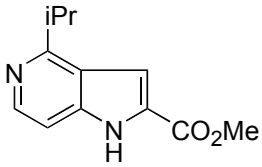
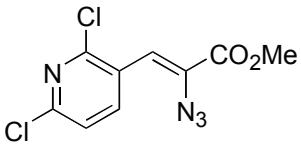
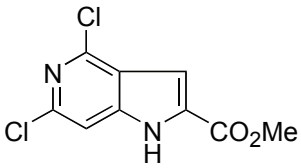
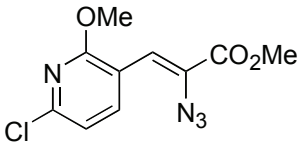
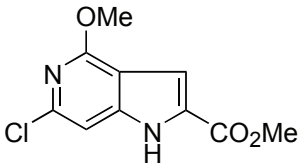
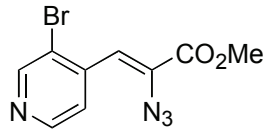
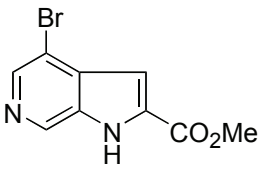
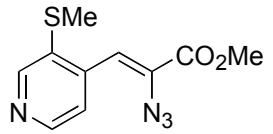
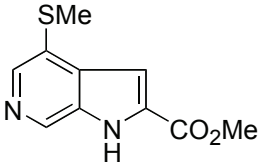
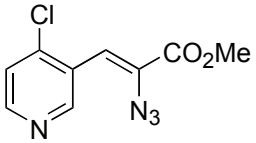
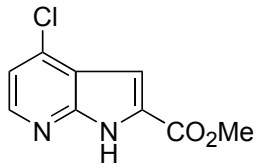
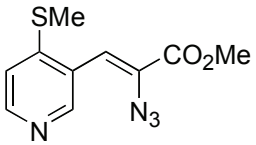
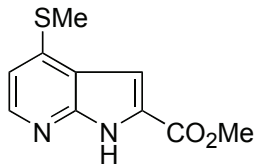
Entry	Azidopyridine acrylate	Procedure	Product	Yield(%)
1		B		67
2		B		25
3		B		0
4		B		72
5		A		78
6		A		93
7		A		84
8		A		69

Table 1. (continued) Thermolysis of 2-Azido-3-pyridine Acrylates

Entry	Azidopyridine acrylate	Procedure	Product	Yield(%)
9		B		66
10		B		75
11		A		77
12		A		32
13		C		44
14		C		51
15		A		40
16		B		56

1. Merck Frosst Centre for Therapeutic Research, C.P. 1005, Pointe Claire-Dorval , Québec H9R 4P8, Canada.
2. Roy, P.J.; Dufresne, C.; Lachance, N.; Leclerc, J-P.; Boisvert, M.; Wang, Z.; Leblanc, Y. *Synthesis* **2005**, *16*, 2751-2757.
3. a) Hemtsberger, H.; Knittel, D.; Wiedmann, H. *Monatshefte Chemie* **1970**, *101*, 161-165. For references on the preparation of azaindoles via this reaction, see b) Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett*. **2000**, *41,* 4777-4780 and c) Lomberget, T.; Radix, S.; Barret, R. *Synlett* **2005**, *13*, 2080-2082.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Methyl azidoacetate: Acetic acid, azido-, methyl ester; (1816-92-8)
Methyl bromoacetate: Acetic acid, bromo-, methyl ester; (96-32-2)
Sodium azide; (26628-22-8)
Methyl (2*Z*)-2-azido-3-(2-chloropyridin-3-yl)acrylate: 2-Propenoic acid, 2-azido-3-(2-chloro-3-pyridinyl)-, methyl ester; (688357-18-8)
2-Chloro-3-pyridinecarboxaldehyde; (36404-88-3)
Methyl 4-chloro-1*H*-pyrrolo[3,2-c]pyridine-2-carboxylate: 1*H*-Pyrrolo[3,2-c]pyridine-2-carboxylic acid, 4-chloro-, methyl ester; (688357-19-9)
Mesitylene: 1,2,3-Trimethylbenzene; (108-67-8)

Patrick Roy was born in Deep River, Canada, in 1960. After completing a Co-operative Chemistry B.Sc. at the University of Waterloo in 1984 with an emphasis on organic chemistry, he joined a custom synthesis group in the fine chemical industry. In 1985 he resumed his studies, in Prof. Hanessian's group at Université de Montréal where he obtained his M.Sc. During this time he completed a formal synthesis of dihydromevinolin. He joined Merck Frosst Canada Inc. in 1988 where he is currently a Research Associate.

Michel Boisvert was born in 1983 in Ottawa, Canada. He started his undergraduate studies at University of Sherbrooke in 2002 and received a B.S. degree in Chemistry in 2006. In 2006, Michel began his M.Sc. studies at Université de Montréal and joined the research group of Professor Stephen Hanessian. Since starting his graduate studies, his research has focused on the total synthesis of Calyciphylline B, a natural product isolated from the leaves of Daphniphyllum calycinum.

Yves Leblanc was born in 1959 in Montreal, Canada. After undergraduate studies at Université de Montréal from 1978-1981, he joined the group of Prof. Stephen Hanessian where he obtained his M.Sc. degree in 1982. His work there was focused on phosphorus chemistry including diazaphospholanes and asymmetric olefination and alkylation. In February 1983 he joined Merck Frosst Canada Inc., where he is currently a Senior Research Fellow. During his 24 year career he has been involved in several projects, including leucotriene synthesis, LTD4 antagonist, and cyclooxygenase programs.

Akiyoshi Kuramochi was born in 1981 in Yokohama, Japan. He received B.S. in 2003 and M.S. in 2005 from The University of Tokyo. Presently, he is pursuing his Ph.D. degree at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, under the guidance of Professor Masakatsu Shibasaki. His research interests are in the area of total synthesis of complex natural compounds.

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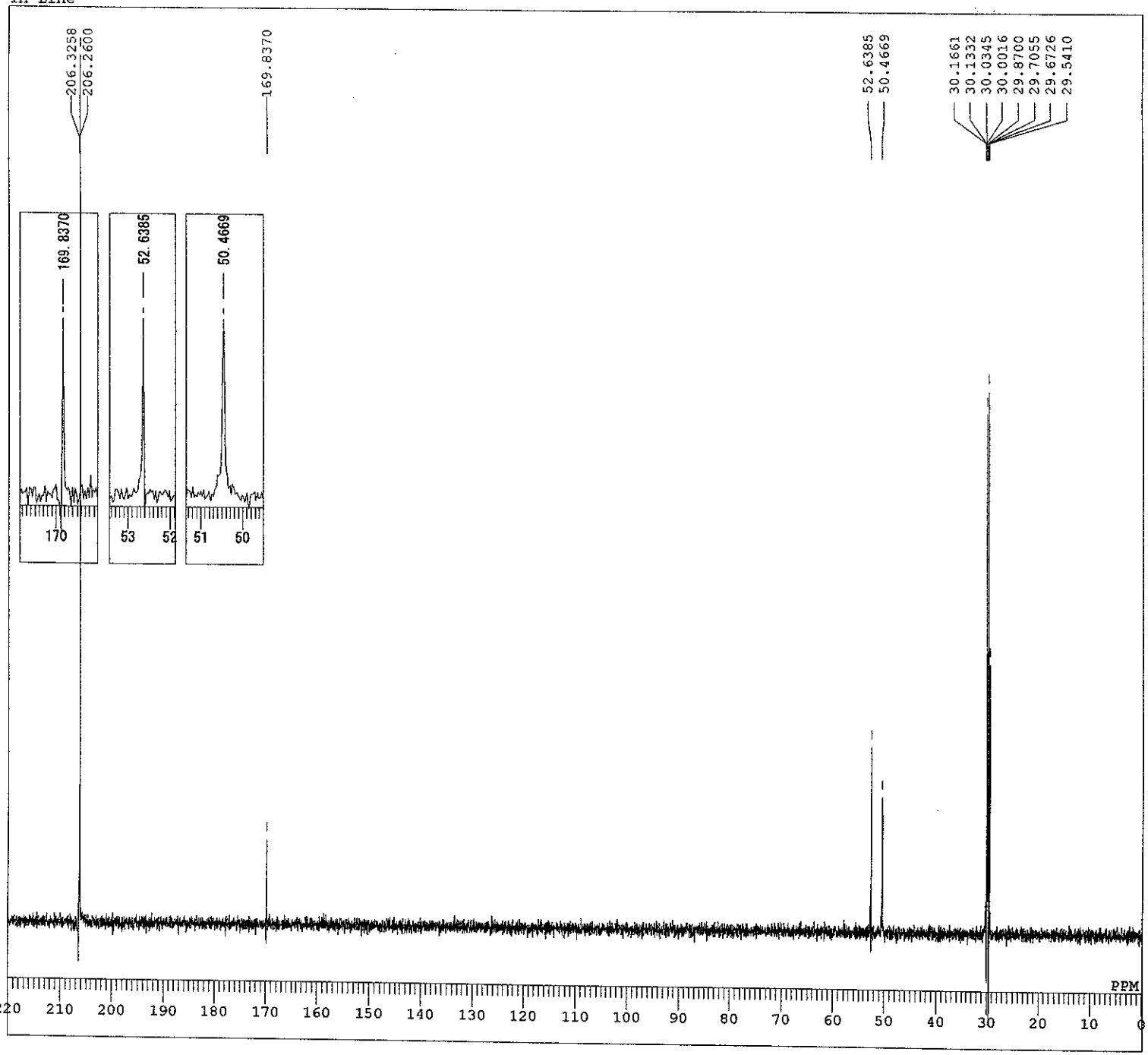

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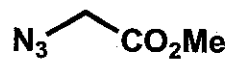

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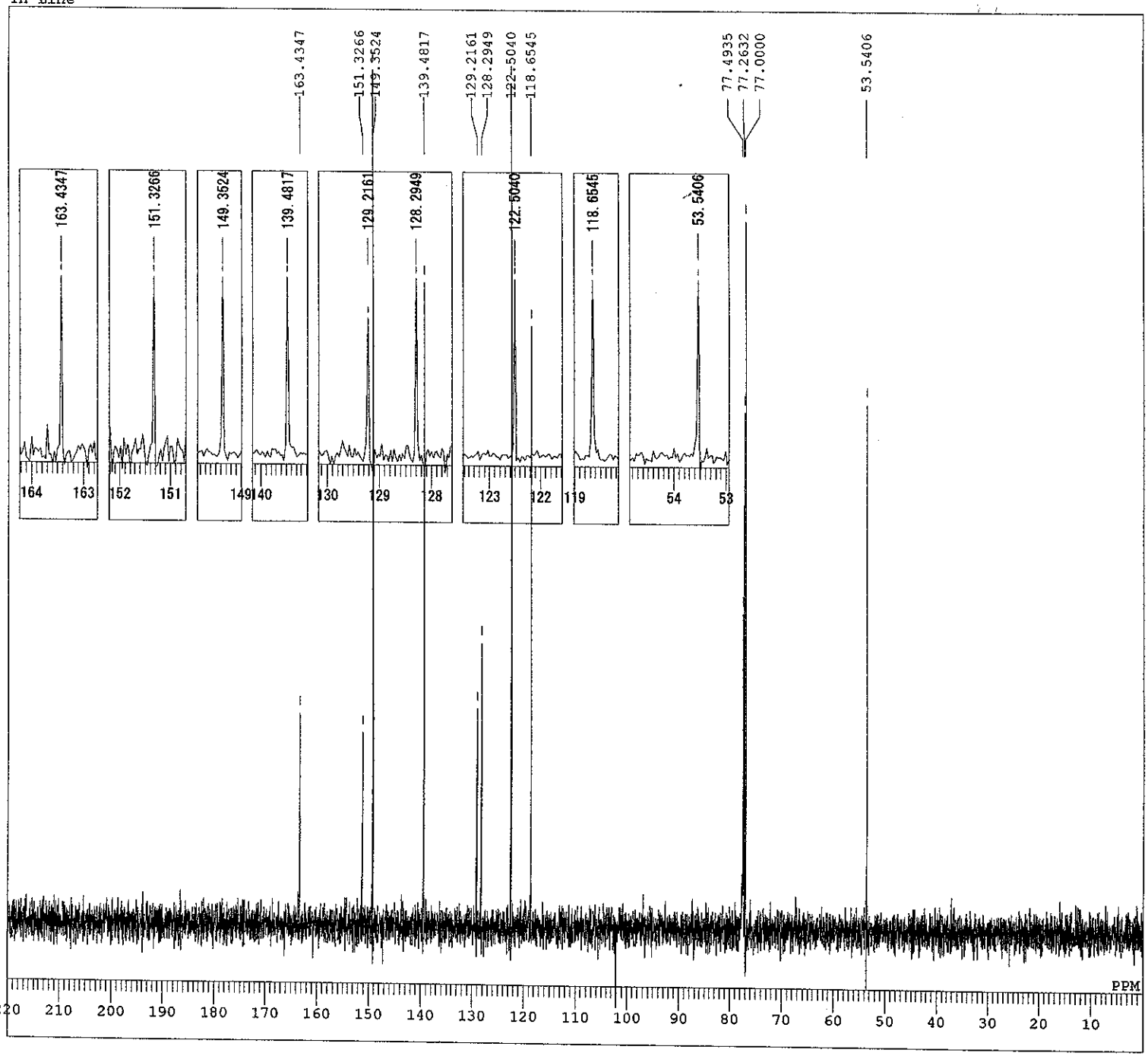

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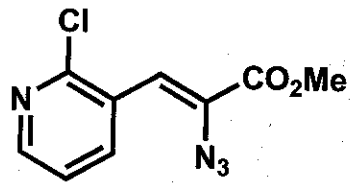

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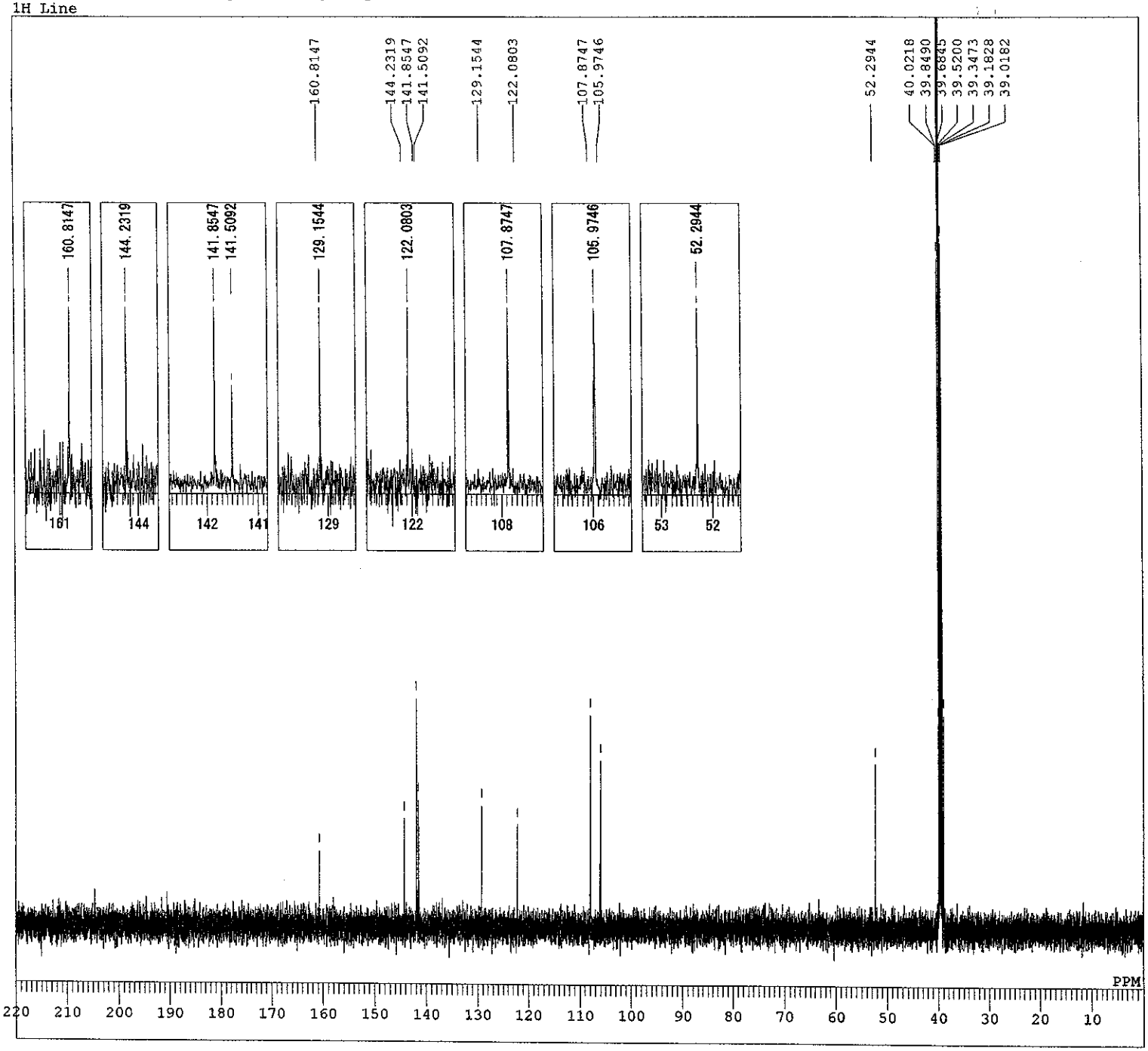

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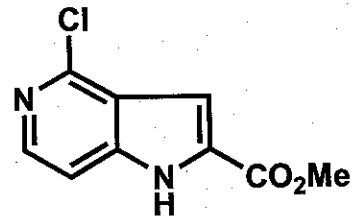

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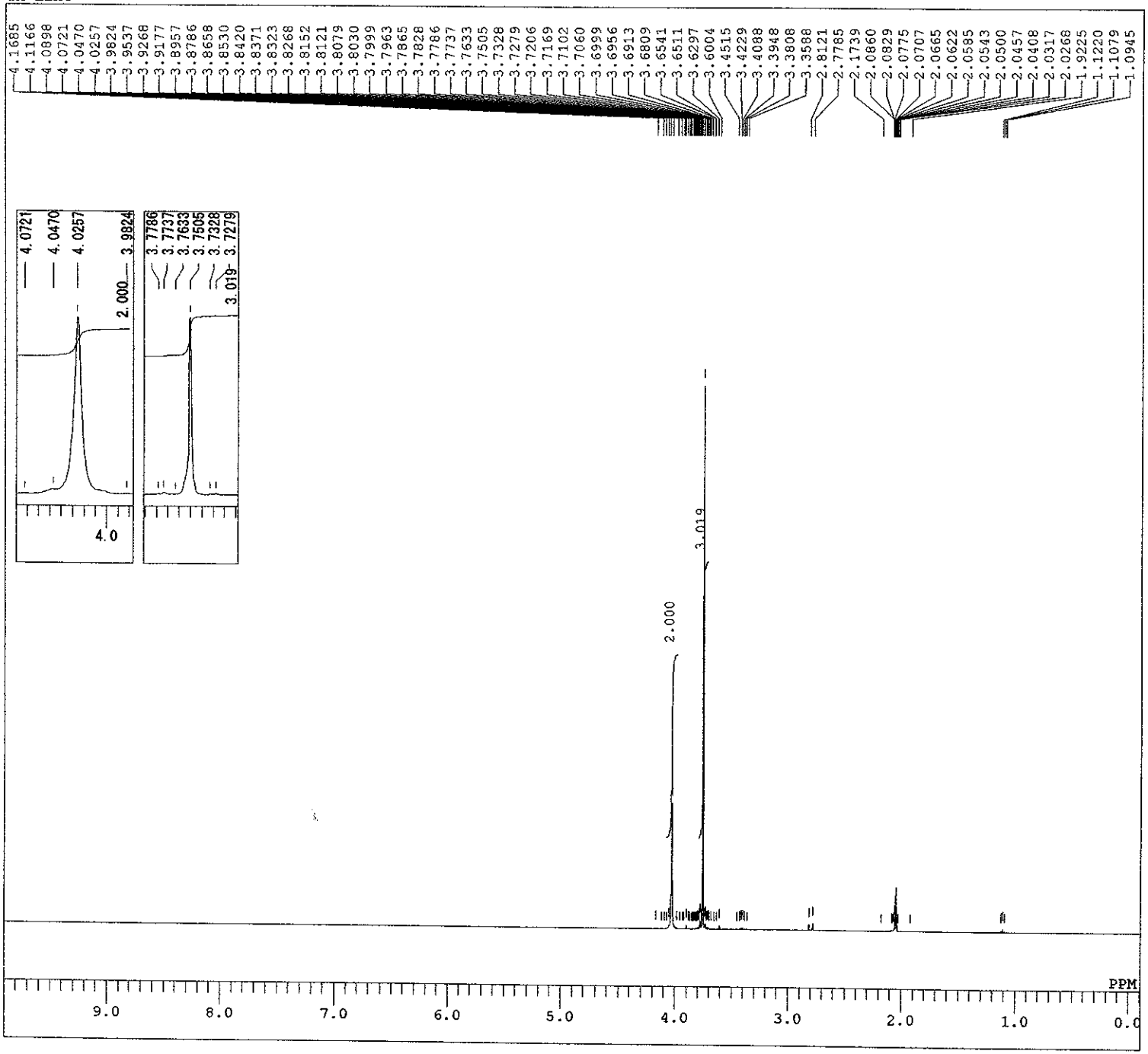

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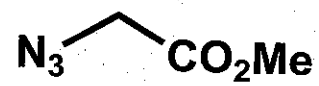

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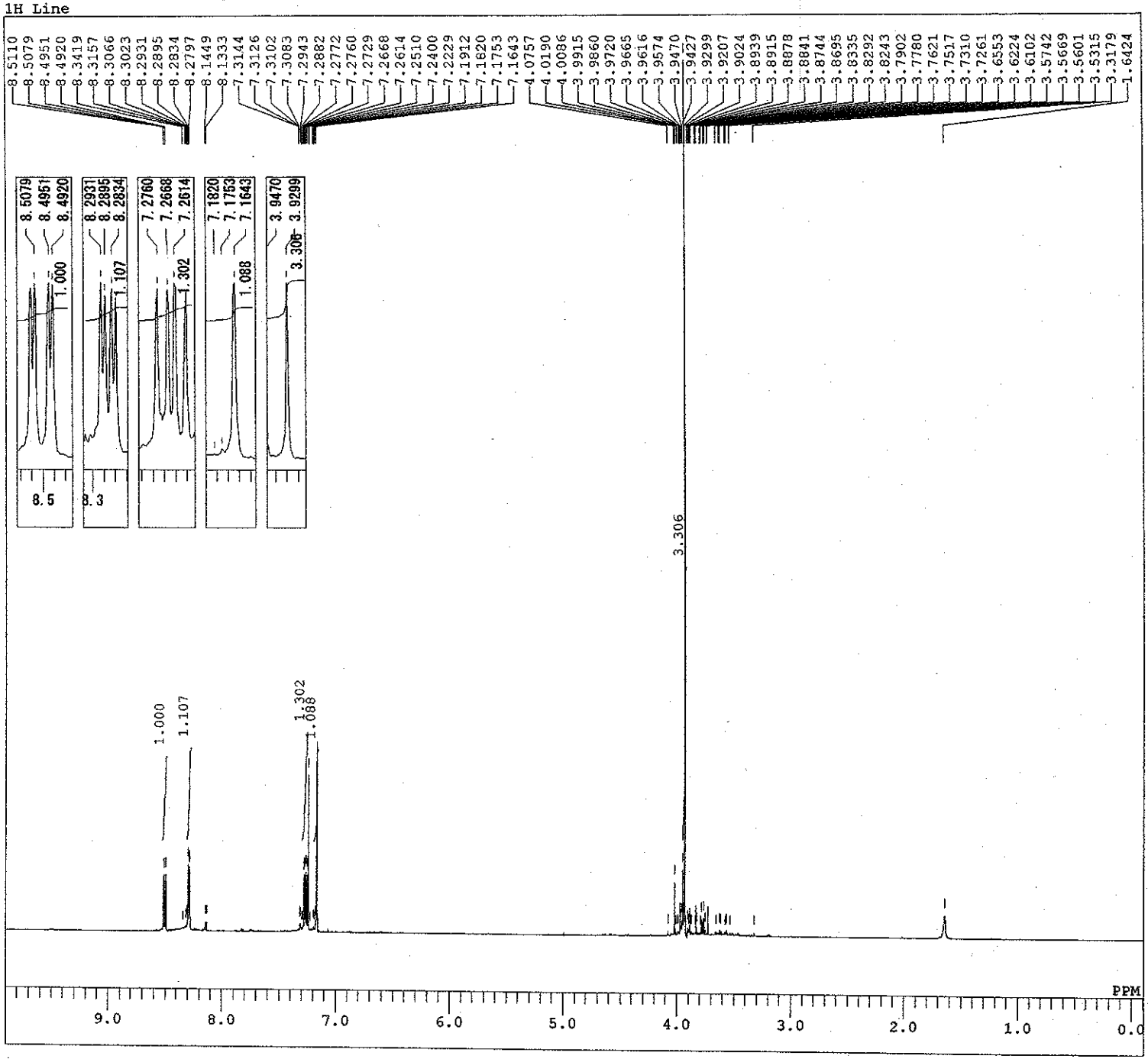

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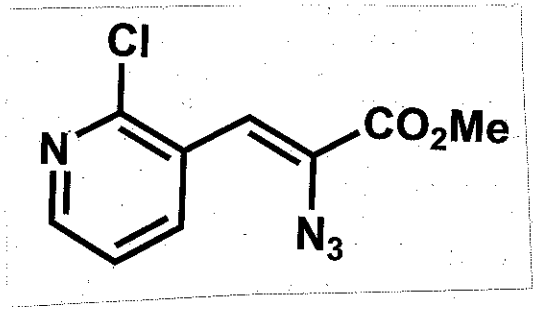

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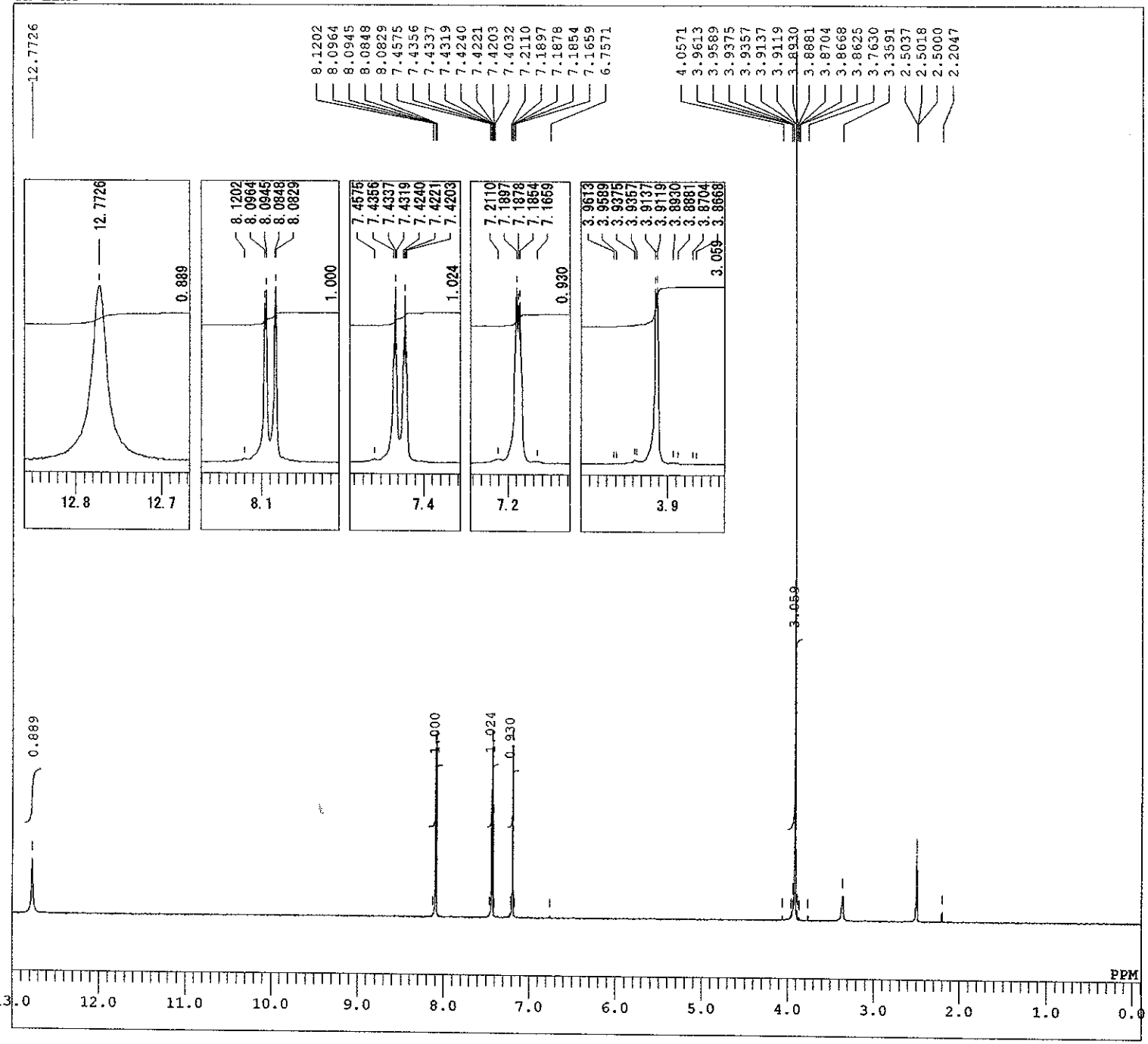

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