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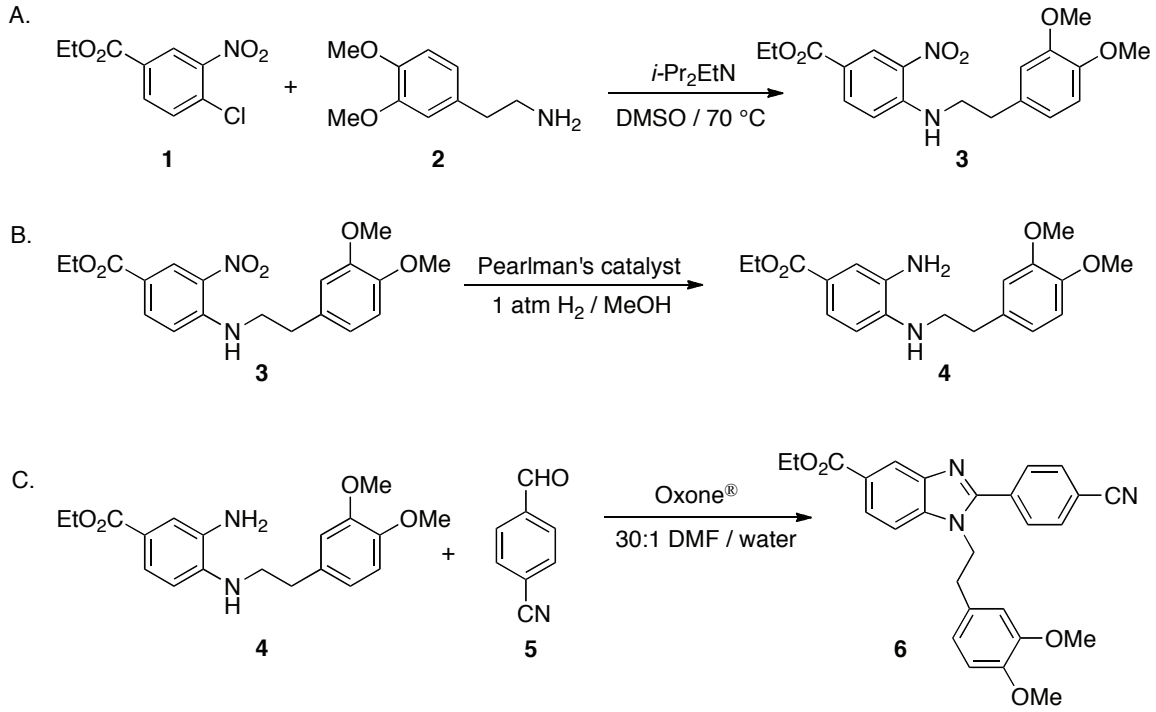
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.089.0131

Oxone®-Mediated Synthesis of Benzimidazoles from 1,2-Phenylenediamines and Aldehydes: Preparation of 2-(4-Cyano-Phenyl)-1-[2-(3,4-Dimethoxyphenyl)-Ethyl]-1H-Benzimidazole-5-Carboxylic Acid Ethyl Ester



Submitted by James R. Gillard and Pierre L. Beaulieu.[1]
Checked by York Schramm and Andreas Pfaltz.

1. Procedure

*A. 4-[2-(3,4-Dimethoxyphenyl)-ethylamino]-3-nitrobenzoic acid ethyl ester (**3**).* A 250-mL, single-necked, round-bottomed flask with a 24/40 ground-glass joint is equipped with a large egg-shaped magnetic stir bar (40 mm x 18 mm) (Note 1)**.** The flask is charged with ethyl-4-chloro-3-nitrobenzoate **1** (5.00 g, 21.8 mmol, 1.00 equiv) (Note 2) and anhydrous DMSO (20 mL) (Note 3). To this homogeneous yellow mixture, 3,4-dimethoxyphenethylamine **2** (4.04 mL, 23.9 mmol, 1.10 equiv) (Note 4) is added dropwise over 1–2 min using a Pasteur pipette. As soon has the first drop is added, the reaction mixture quickly changes to a dark reddish-orange color, but the mixture remains homogeneous throughout the addition without detectable exotherm. *N,N*-Diisopropylethylamine (5.31 mL, 30.5 mmol,

Published on the Web 10/5/2011

1.4 equiv) (Note 5) is added dropwise (1–2 min), which results in a slight cloudiness, but no exotherm is detected during or after addition. The flask is closed with a septum (Note 6) and the reaction mixture is stirred in an oil bath heated to 70 °C. During the warming process, the dark reddish-orange color lightens somewhat, but the mixture remains cloudy. The reaction is stirred for 18 h at 70 °C after which time the dark reddish-orange reaction mixture is homogeneous. The reaction is judged to be complete by the disappearance of the starting ester by TLC (Note 7). The mixture is cooled to room temperature (Note 8) and de-ionized water (2 mL) is added dropwise with a Pasteur pipette over a period of ca. 2–3 min with efficient stirring while a persistent cloudiness develops. Precipitation/crystallization of the product occurs rapidly after the addition, giving rise to a very thick dark-red suspension (Note 1). After formation of the suspension, water (150 mL) is added in 10 mL portions over a period of ca. 5 min. During the addition of water the mixture becomes slightly warm to the touch. The resulting dark-orange to dark-yellow suspension of product is stirred at room temperature for approximately 1 h. The solids are collected by suction-filtration on filter paper (Note 9) using a ceramic Büchner funnel and the solids are washed with four portions of water (20 - 30 mL each). The solids are allowed to dry for ca. 1–2 h under air suction on the filter funnel. The solids are then collected and placed under vacuum (2 mmHg) at ambient temperature until constant mass is achieved to provide 7.92–7.98 g (97–98% yield) of a red-orange to dark yellow solid (Note 10) which is suitable for use in the next step without further purification.

*B. Ethyl 3-amino-4-((3,4-dimethoxyphenethyl)amino)benzoate (**4**).* A 500-mL, single-necked, round-bottomed flask with a 24/40 ground-glass joint is equipped with a large egg-shaped magnetic stir bar (40 mm x 18 mm)**.** The flask is charged with nitro compound **3** (7.00 g, 18.7 mmol, 1.00 equiv) and methanol (285 mL) (Note 12). The flask is then fitted with a 3-way gas inlet adapter with an argon-filled balloon attached to one of the arms. While stirring the resultant yellow suspension, the flask is evacuated and back-filled with argon gas three times (Note 13). While stirring under a blanket atmosphere of argon, the adapter on the flask is briefly removed and Pearlman's catalyst (500 mg, Note 14) is added as a suspension in methanol (10 mL + 5 mL rinse). The argon balloon is then replaced with another balloon filled with hydrogen gas and, while stirring the mixture, the flask is evacuated and back-filled with hydrogen gas three times (Note 13). The dark yellow-black suspension is allowed to stir under the hydrogen atmosphere

for a period of 24 h, after which TLC analysis indicate the disappearance of compound **3** (Note 15). The hydrogen balloon is once again replaced with an argon-filled balloon and the flask is evacuated and back-filled with argon gas three times (Note 13). The 3-way stopper is then removed, Celite 545® (10g) (Note 16) is added and the suspension stirred under the argon blanket for 10 min. The solid is removed by suction filtration over filter paper (Note 17) using a ceramic Büchner funnel and the solids are washed with two portions of methanol (20 - 30 mL each). The clear, dark brown filtrate and washings are collected and combined and the volatiles removed under reduced pressure (30 °C, 5 - 10 mmHg, then at room temperature, 0.1 mmHg) to give 6.0–6.3 g (93–98% yield) of compound **4** as a dark gray-black solid (Note 18) which is suitable for use in the next step without further purification.

*C. 2-(4-Cyano-phenyl)-1-[2-(3,4- dimethoxyphenyl)- ethyl]-1 H-benzimidazole-5-carboxylic acid ethyl ester (**6**).* A 50-mL, 2-necked round-bottomed flask with 10/14 ground glass joints is equipped with an oval-shaped magnetic stir bar, a thermometer adapter and an alcohol thermometer. The flask is charged with diamine **4** (5.00 g, 14.5 mmol), 4-cyanobenzaldehyde **5** (2.10 g, 16.0 mmol, 1.10 equiv) (Note 19), DMF (30 mL) (Note 20) and de-ionized water (1 mL). The resulting dark brown homogeneous mixture is cooled to an internal temperature of 0–5 °C with the aid of an ice-water bath. Oxone® (5.80 g, 9.44 mmol, 0.65 equiv) (Note 21) is added in one portion and the resulting heterogeneous mixture is stirred while immersed in the ice-water bath. After addition of Oxone®, the following observations are made: the internal temperature of the mixture rises to ca. 6-8 °C and stays at this temperature for about 1 h; the granular Oxone® slowly loses its consistency and the mixture becomes a loose, easily stirred light brown slurry. After a period of 2 h, HPLC analysis indicates the disappearance of compound **4** (Note 11). The stirred mixture (Note 22) is allowed to warm to room temperature and is then transferred in small portions using a Pasteur pipette over ca. 15 min to a vigorously stirred solution of potassium carbonate (2.76 g, 20 mmol) (Note 23) in water (450 mL). During the addition, the desired benzimidazole product **6** precipitates as a light brown-beige solid (Note 25). The resulting slurry is stirred for an additional hour, then the solids are collected by suction filtration on a filter paper (Note 9) using a ceramic Büchner funnel. The damp filter cake is allowed to partially air-dry overnight under suction in the filter funnel and is then collected and placed under vacuum (0.03 mmHg)

(Note 26) at ambient temperature until constant mass is achieved to provide 5.88–6.04 g (89–91% yield) of a light tan solid (Notes 24 and 27). The material was further purified by dissolving the crude product in dichloromethane (250 mL), washing with diluted sodium hydroxide solution (1.0 M, 3 x 100 mL), then washing with water (100 mL) and brine (100 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered over a filter paper (Note 28) and solvents removed on the rotary evaporator (Note 29). The residue was dried *in vacuo* (0.03 mmHg) for 48 h to provide 4.9 g (74% yield) of a beige solid (Note 30).

2. Notes

1. It is important to use a large stir bar. In the subsequent precipitation step, an undersized stir bar may not adequately stir the resulting slurry, or may become jammed. On a larger scale, the authors would suggest the use of a stirring motor and paddle assembly.

2. Ethyl-4-chloro-3-nitrobenzoate was purchased from Alfa Aesar (powder, 97%, cat. no. A19338) and was used as received.

3. Anhydrous DMSO was purchased from Sigma-Aldrich Company Inc. and was used as received.

4. 3,4-Dimethoxyphenethylamine was purchased from Sigma-Aldrich Company Inc. (liquid, 97%, cat. no. D136204-100G) and was used as received.

5. *N,N*-Diisopropylethylamine was purchased from Sigma-Aldrich Company Inc. (ReagentPlus®, 99%, cat. no. D125806) and was used as received.

6. In this experiment, it is sufficient to loosely stopper the flask with a septum since all reagents and starting materials have boiling points above 70 °C. In cases where more volatile amines are used as substrate, the authors recommend the use of a reflux condenser and a larger excess of amine substrate (1.3–2 equiv) to ensure that step **A** proceeds to completion.

7. The progress of the reaction was monitored by TLC analysis on glass plates precoated (250 μm thickness) with silica gel 60 F_{254} (purchased from EMD Chemicals Inc.). The eluent was 10% EtOAc in hexane and visualization performed with UV light (254 nm). The nitroarene starting material **1** has R_f = 0.50 while phenethylamine **2** and product **3** remain at baseline.

8. After cooling to room temperature, the product may begin to crystallize to give a thick slurry or solid mass if allowed to stand. The product can be brought back into solution by reheating to 70 °C and then recooling to room temperature before proceeding as described.

9. Whatman N° 1 filter paper (7 cm diameter) was used.

10. Compound **3** has the following characteristics: R_f = 0.37 (30% EtOAc in hexane); HPLC t_R = 6.7 min, 98.5 to >99.5% homogeneity (Note 11); mp 113.6 – 115.9 °C; FTIR (thin film NaCl cm^{-1}): 3367, 2936, 1710, 1625, 1517, 1287, 1222, 1155, 1027; ^{1}H NMR (500 MHz, DMSO) δ: 1.31 (t, *J* = 7.1 Hz, 3 H), 2.89 (t, *J* = 7.0 Hz, 2 H), 3.63 (dd, *J* = 12.8, 6.5 Hz, 2 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 6.82 (d, *J* = 8.1 Hz, 1 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 6.93 (s, 1 H), 7.16 (d, *J* = 9.1 Hz, 1 H), 7.95 (d, *J* = 9.0 Hz, 1 H), 8.49 (t, *J* = 5.2 Hz, 1 H), 8.58 (s, 1 H); ^{13}C NMR (126 MHz, DMSO) δ: 14.1, 33.8, 44.1, 55.3, 55.3, 60.6, 111.9, 112.6, 114.8, 116.0, 120.6, 128.2, 130.2, 130.9, 135.6, 147.2, 147.4, 148.7, 164.3; MS (FAB, EI, 70 eV, 250°C) *m*/*z* (relative intensity): 374.2 (13.85%), 223.1 (30.54), 152.1 (30.15%), 151.1 (100%). HRMS (APPI) calcd for $C_{19}H_{22}N_2O_6$: 374.1478, found: 374.1485; Anal. calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.80; H, 5.98; N, 7.52.

11. HPLC chromatography was performed on a Waters 2695 Separation Module fitted with a Waters™ 2487 Dual Wavelength detector monitoring at 220 and 254 nm. Separations were achieved using a Waters Sunfire™ brand C18, 3.5μm, 4.6 mm x 30 mm column, employing a flow rate of 3mL/min. with a 5% to 100% water/acetonitrile gradient in 10 min with 0.10% trifluoroacetic acid added as modifier.

12. Methanol was purchased from EMD (OmniSolv® HPLC grade) and used as received.

13. CAUTION: There may be some initial frothing and/or bubbling during the evacuation.

14. Pearlman's catalyst (20% Palladium hydroxide on carbon; Pd content 20% dry weight basis. Moisture content ~50%. cat. no. 330094-10G) was purchased from Sigma-Aldrich Company Inc. and used as received.

15. The progress of the reaction was monitored by TLC analysis on silica gel (Note 7) with 30% EtOAc in hexane as eluent and visualization with UV light (254 nm). Nitroarene **3** has R_f = 0.37 while product **4** has R_f = 0.12.

16. Celite 545® was purchased from EMD and used as received.

17. Whatman N° 1 filter paper (5.5 cm diameter) was used.

18. Compound **4** has the following characteristics: R_f = 0.12 (30% EtOAc in hexane); HPLC t_R = 4.0 min (Note 11); mp 100.8 – 103.0 °C; FTIR (thin film NaCl cm^{-1}): 3397, 2935, 1694, 1600, 1516, 1294, 1143, 1027; ^{1}H NMR (500 MHz, DMSO) δ: 1.26 (t, *J* = 7.1 Hz, 3 H), 2.83 (t, *J* = 7.3 Hz, 2 H), 3.32 (dd, *J* = 13.1, 6.9 Hz, 2 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.76 (s, 2 H), 5.27 (t, *J* = 5.2 Hz, 1 H), 6.50 (d, *J* = 8.4 Hz, 1 H), 6.79 (dd, *J* = 8.1, 1.5 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.89 (d, *J* = 1.5 Hz, 1 H), 7.19 (d, *J* = 1.9 Hz, 1 H), 7.24 (dd, *J* = 8.3, 1.7 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO) δ: 14.4, 34.2, 44.9, 55.4, 55.5, 59.4, 108.0, 111.9, 112.7, 114.1, 117.0, 120.5, 120.7, 132.2, 134.2, 140.3, 147.3, 148.7, 166.4. MS (FAB, EI, 70 ev, 250°C) *m*/*z* (relative intensity): 345.2 (4.46%), 344.2 (20.57%), 194.1 (11.19%), 193.1 (100%), 165.1 (11.06%), 152.1 (11.24%), 120.1 (4.11%). Compound **4** can be partially purified in the following manner: a 50-mL Erlenmeyer flask equipped with a magnetic stir bar is charged with crude compound **4** (1.32 g) and MeOH (15 mL). The dark purple solution with a beige-colored suspension is stirred for 1 h at room temperature. The solid is collected by filtration and washed with MeOH (3 x 5 mL) at room temperature. The solid is partially dried under air suction and then dried to constant weight under vacuum (2 mmHg) to give 0.75 g of a light beige-colored solid which had comparable spectroscopic properties to the crude material (see above) in addition to: mp 101.6 – 102.8 °C; Anal. calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.20; H, 7.19; N, 8.12.

19. 4-Cyanobenzaldehyde was purchased from Alfa Aesar (98% cat. no. A14914) and used as received.

20. DMF (ACS grade) was purchased from EMD and used as received.

21. Oxone® (potassium peroxymonosulfate; $2KHSO_5.KHSO_4.K_2SO_4$) was purchased from Sigma-Aldrich Company Inc. (cat. no. 228036-100G) and used as received.

22. The authors suggest stirring the reaction mixture continuously during the transfer to avoid the settling of particles.

23. Potassium carbonate (ACS grade) was purchased from EMD and used as received.

24. Compound **6** has the following characteristics: R_f = 0.32 (50% EtOAc in hexane); HPLC t_R = 4.9 min, >98% homogeneity (Note 11); mp 125 – 130 °C; FTIR (thin film NaCl cm^{-1}): 2937, 1710, 1611, 1516, 1299, 1223, 1027; ^{1}H NMR (500 MHz, DMSO) δ: 1.36 (t, *J* = 7.1 H, 3 H), 2.82 (s,

2 H), 3.45 (s, 3 H), 3.67 (s, 3 H), 4.35 (q, J = 7.1 Hz, 2 H), 4.63 (t, J = 6.3 Hz, 2 H), 6.08 (d, J = 8.1 Hz, 1 H), 6.21 (d, J = 1.2 Hz, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 7.63 (d, J = 8.2 Hz, 2 H), 7.89 (dd, J = 12.8, 8.4 Hz, 3 H), 7.96 (d, J = 8.5 Hz, 1 H), 8.29 (s, 1 H); ^{13}C NMR (126 MHz, DMSO) δ: 14.3, 34.4, 46.1, 54.9, 55.5, 60.6, 111.5, 111.8, 112.1, 118.4, 120.4, 121.1, 123.8, 124.2, 129.5, 129.8, 132.2, 134.1, 138.8, 142.2, 147.6, 148.4, 153.8, 166.2; MS (FAB, EI, 70 eV, 250°C) *m*/*z* (relative intensity): 456.1 (8.8%), 455.1 (28.91%), 276.0 (4.41%), 151.1 (100%). HRMS (APPI) calcd for $C_{27}H_{26}N_3O_4$: 455.1845, found: 455.1858; EA by submitters: Anal. calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.23. Found: C, 70.88; H, 5.45; N, 9.19.

25. The submitters report observation of a light grey solid.

26. The submitters applied a vacuum of 2 mmHg.

27. The submitters reported that the material is analytically pure at this stage, as determined by CHN analysis. In order to obtain analytically pure product, the checkers, in consultation with the submitters, developed the purification protocol described above.

28. Whatman LS 14 1/2 filter paper (18.5 cm diameter) was used.

29. The water bath was warmed to 40 °C and a reduced pressure of 300 mmHg applied.

30. The material has the same characteristics as the crude product. mp = 132–134.5 °C. Anal. calcd for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 70.96; H, 5.48; N, 9.20.

Safety and Waste Disposal Information

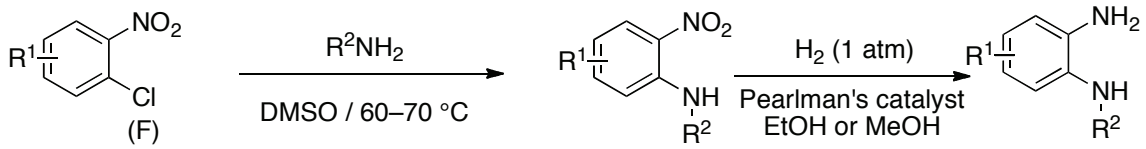
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The benzimidazole scaffold constitutes a "privileged structure" in material sciences and for drug design. It is a central constituent of many biologically active substances from both natural and synthetic origin.[2] Several methods have been described in the literature for the synthesis of substituted benzimidazole derivatives.[3] They often involve condensation of 1,2-phenylenediamine derivatives with aldehydes or carboxylic acids, performed under a variety of reaction conditions that vary in scope, yield,

harshness of reaction conditions and ease of isolation and purification of the final product. Recently, we described an Oxone®-mediated oxidative condensation of aldehydes and 1,2-phenylediamines that is suitable not only for the high-throughput synthesis of benzimidazole libraries, but can also be carried out on a large scale.[4] The method that is illustrated in this procedure is highly versatile, simple to perform, economical, metal-free and environmentally friendly. Furthermore, intermediates and the final product from this sequence are isolated in pure form and high yields by simple precipitation. While several methods for the synthesis of benzimidazoles have continued to appear in the literature since publication of the original report in 2003, attributes of this Oxone®-mediated synthesis of benzimidazoles still make the method described herein a procedure of choice for the preparation of such derivatives on small or large scale.

Table 1. Preparation of 1,2-phenylenediamine substrates[a]



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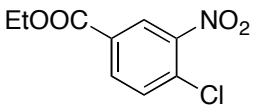
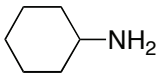
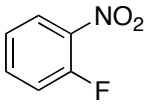
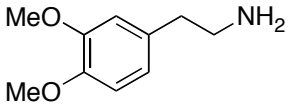
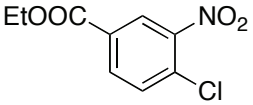
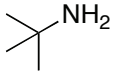
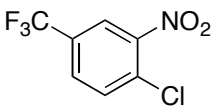
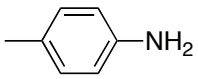
1			98%	99%
2			100%	98%
3			99%	70%
4			98%	95%

[a] See reference 4 for details

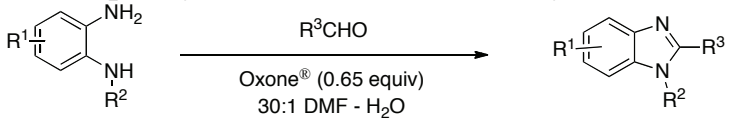
The required 1,2-phenylenediamine starting materials can be obtained from commercial sources (a search in the Symyx ACD® 2009.3 catalog

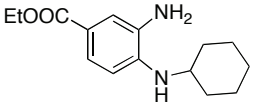
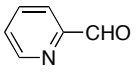
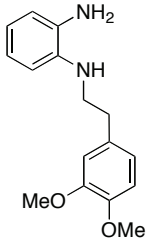
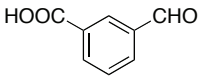
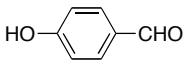
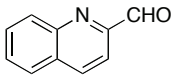
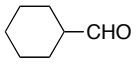
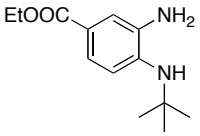
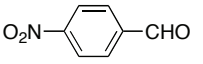
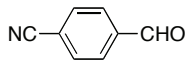
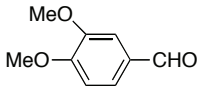
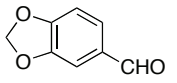
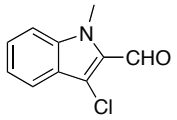
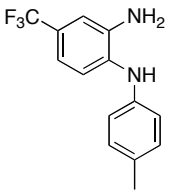
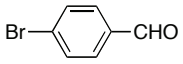
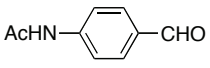
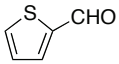
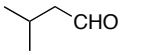
reveals >6000 hits) or prepared through a two-step sequence which involves S_NAr displacement on a 2-chloro or 2-fluoronitroarene derivative followed by reduction of the nitro functionality to the aniline. A few examples of these transformations are provided in Table 1.[4]

Condensation of 1,2-phenylenediamines with aldehydes tolerates a variety of functional groups on either substrates. The reaction can be performed on electron rich or poor systems, aromatic, heterocyclic (e.g. quinolines, pyridines, thiophenes, furans) or aliphatic aldehydes, and tolerates unprotected functionalities such as phenol hydroxyl groups, free carboxylic acids, nitriles and amides. The reaction is usually very rapid and provides good yields of pure products (>90 % homogeneity) after simple precipitation from the reaction medium with aqueous base. Table 2 is illustrative of the broad applicability of this methodology.

In the original report, the authors described a limitation of the methodology when aldehydes are sensitive to Oxone® in the acidic reaction medium (e.g. pivaldehyde, some heterocyclic aldehydes and α,ß-unsaturated aldehydes that may be susceptible to Baeyer-Villiger oxidation).[4] The authors have discovered since that in some cases, if such sensitive aldehydes are allowed to pre-form the presumed aminal intermediate by stirring with the diamine for a few hours before addition of Oxone®, these substrates can be engaged in the reaction and provide the desired benzimidazole in improved yields.

Table 2. Scope of the oxone®-mediated preparation of benzimidazoles from 1,2-phenylenediamines and aldehydes[a]



Entry	Starting material	R^3CHO	Reaction time (h)	% yield[b] (crude)	% homogeneity[c] (crude)
1			1	85	>99
2			0.5	66	98
3			1	84	>99
4			1	73	>99
5			2	80	96
6			0.5	83	>99
7			2.5	79	99
8			18	89	97
9			19	70	92
10			5	95	86
11			22	59	97
12			1.5	89	97
13			20	86	96
14			1.5	88	96
15			1.5	68	94

[a]See reference 4 for details. [b]Yield of crude material obtained after dilution of reaction mixture with 20 volumes of water and collection of the precipitate by filtration or extraction ith EtOAc. [c]Reversed-phase HPLC homogeneity of the crude products.

1. Boehringer Ingelheim (Canada) Ltd.; Research and Development; 2100 Cunard street, Laval (Québec) Canada, H7S 2G5; pierre.beaulieu@boehringer-ingelheim.com.
2. Boiani, M.; Gonzalez, M. *Mini-Reviews Med. Chem.* **2005**, *5*, 409-424.
3. Grimmet, M. R.; In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 457-498.
4. Beaulieu, P. L.; Haché, B.; von Moos, E. *Synthesis* **2003**, 1683-1692.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Ethyl-4-chloro-3-nitrobenzoate; (16588-16-2)
3,4-Dimethoxyphenethylamine: 2-(3,4-dimethoxyphenyl)ethylamine; (120-20-7)
4-Cyanobenzaldehyde; (105-07-7)
Oxone®: potassium peroxymonosulfate; (37222-66-5)

Pierre Beaulieu was born in 1957 in Canada and received his BSc and MSc degrees in chemistry from the University of Ottawa (Canada) in 1978 and 1980 respectively. He received his PhD degree in 1983 from the University of Alberta in Edmonton (Canada) working under the supervision of Professor Derrick Clive. Following Post-doctoral studies with Professor Stephen Hanessian at the University of Montréal (Canada), he was appointed Associate Director of the chemical biology and polypeptide unit at the Clinical Research Institute of Montréal from 1986 to 1988. He then joined the Research and Development division of Boehringer Ingelheim (Canada) Ltd. in 1988 as a medicinal chemist. He is currently Highly Distinguished Scientist working on the design and development of antiviral drugs for the treatment of hepatitis C virus infection.

James Gillard was born in 1965 in Nova Scotia, Canada. He received his BSc degree in chemistry from Saint Francis Xavier University, Antigonish (Canada) in 1987, and his MSc from Memorial University of Newfoundland, St. John's (Canada) in 1992, under the supervision of Professor D. Jean Burnell. He joined the Research and Development division of Boehringer Ingelheim (Canada) Ltd. in 1992 as a medicinal chemist. He is currently Research Scientist working on the development of antiviral drugs for the treatment of hepatitis C virus infection.

York Schramm was born in 1984 and received his MSc at the University of Basel (Switzerland) carrying out his master thesis at the University of Bristol (United Kingdom) under the supervision of Professor Guy Lloyd-Jones in 2009. He subsequently started his graduate studies in Basel under the supervision of Professor Andreas Pfaltz working on Mechanistic Investigations of Asymmetric Hydrogenation.

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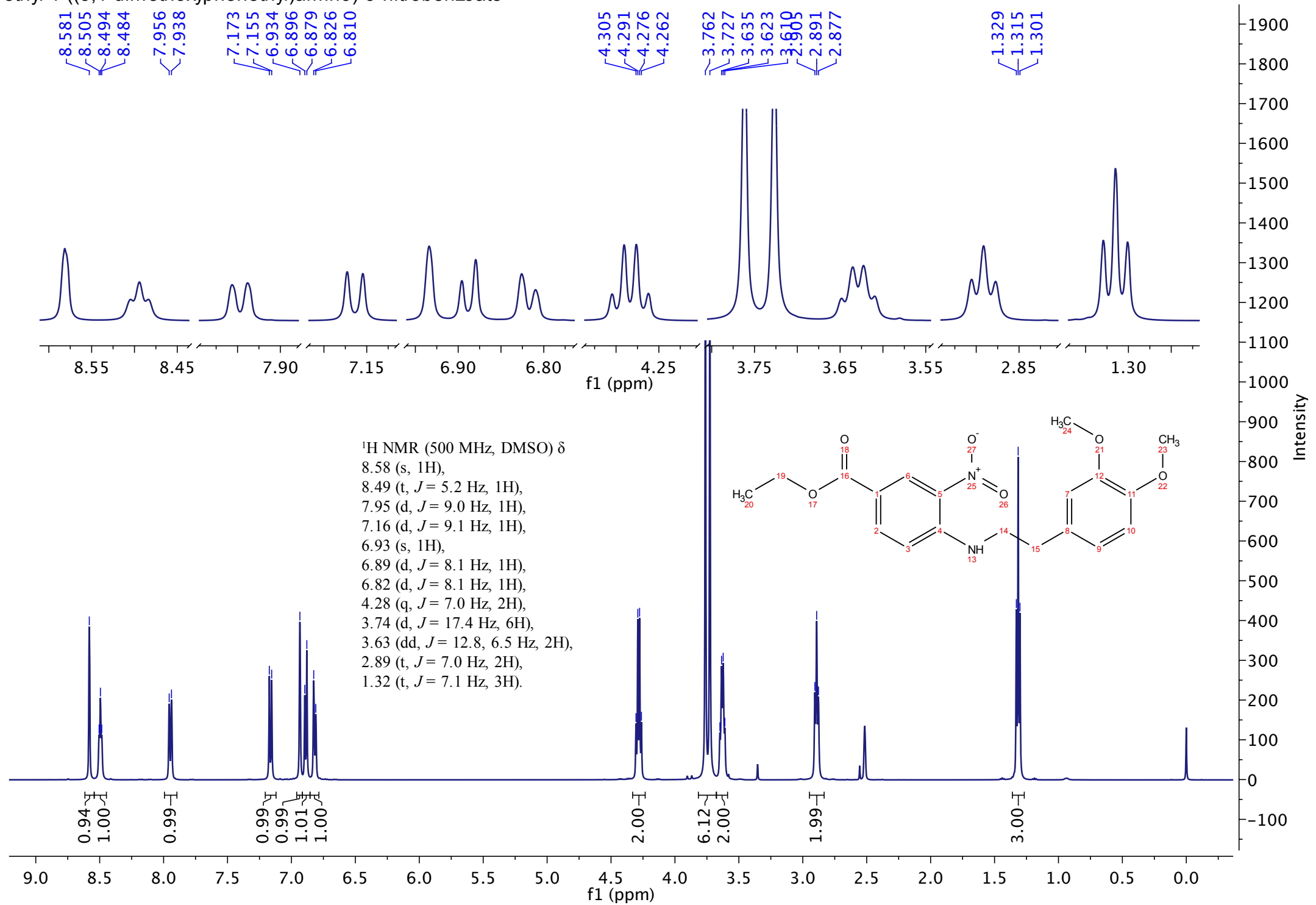
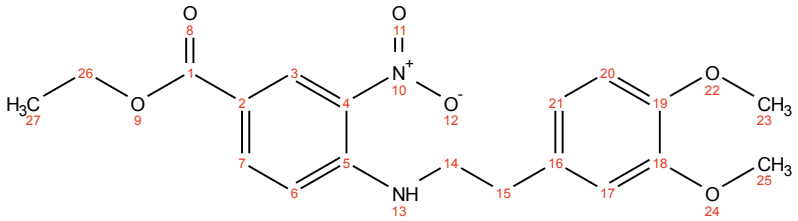
ethyl 4-((3,4-dimethoxyphenethyl)amino)-3-nitrobenzoate



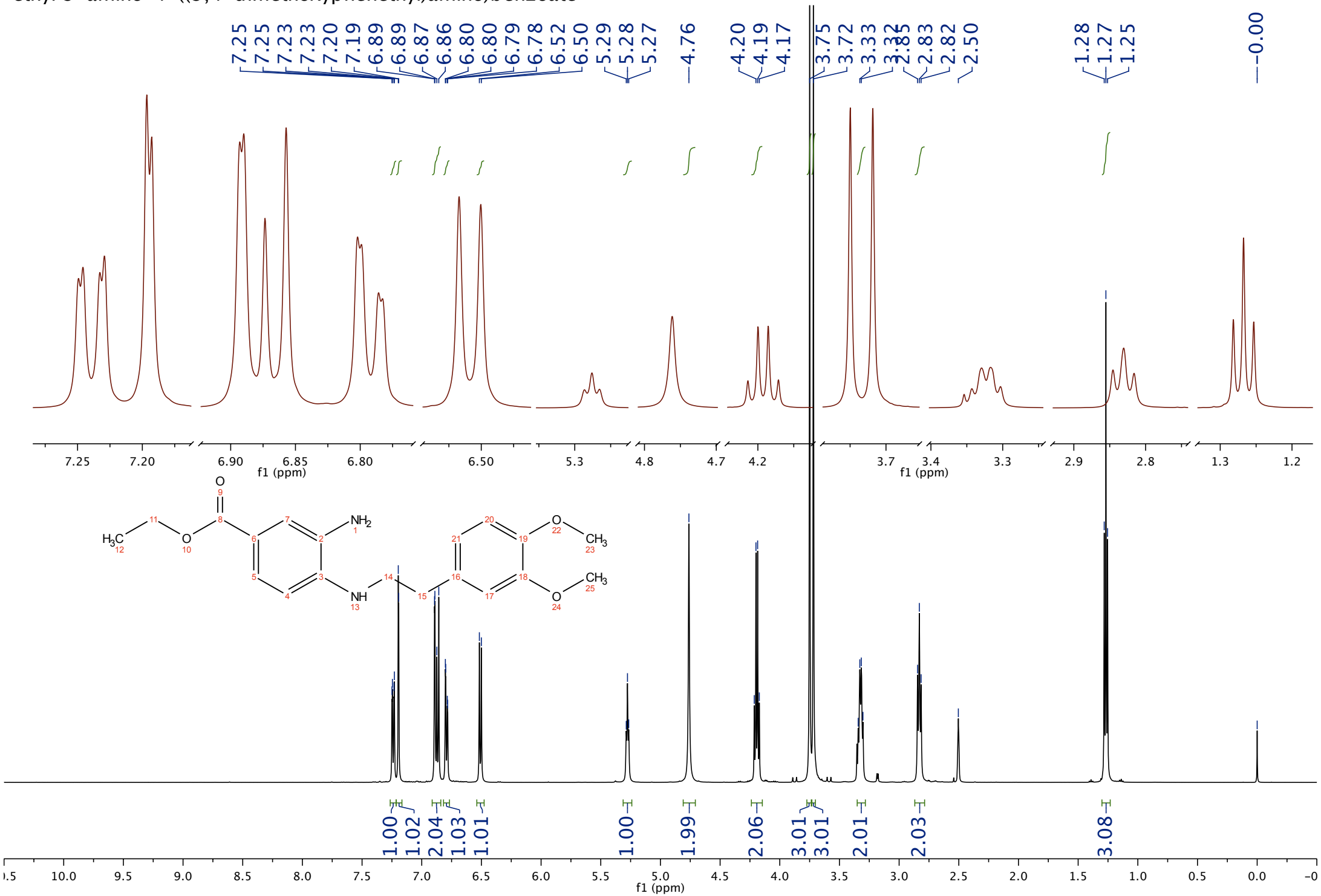
^{1}H NMR (500 MHz, DMSO) δ
8.58 (s, 1H),
8.49 (t, J = 5.2 Hz, 1H),
7.95 (d, J = 9.0 Hz, 1H),
7.16 (d, J = 9.1 Hz, 1H),
6.93 (s, 1H),
6.89 (d, J = 8.1 Hz, 1H),
6.82 (d, J = 8.1 Hz, 1H),
4.28 (q, J = 7.0 Hz, 2H),
3.74 (d, J = 17.4 Hz, 6H),
3.63 (dd, J = 12.8, 6.5 Hz, 2H),
2.89 (t, J = 7.0 Hz, 2H),
1.32 (t, J = 7.1 Hz, 3H).

4-[2-(3,4-Dimethoxyphenyl)-ethylamino]-3-nitrobenzoic acid ethyl ester

^{13}C NMR (126 MHz, DMSO) δ
164.25,
148.69,
147.44,
147.18,
135.60,
130.86,
130.24,
128.20,
120.61,
116.03,
114.79,
112.57,
111.86,
60.58,
55.43,
55.30,
44.10,
33.75,
14.13.

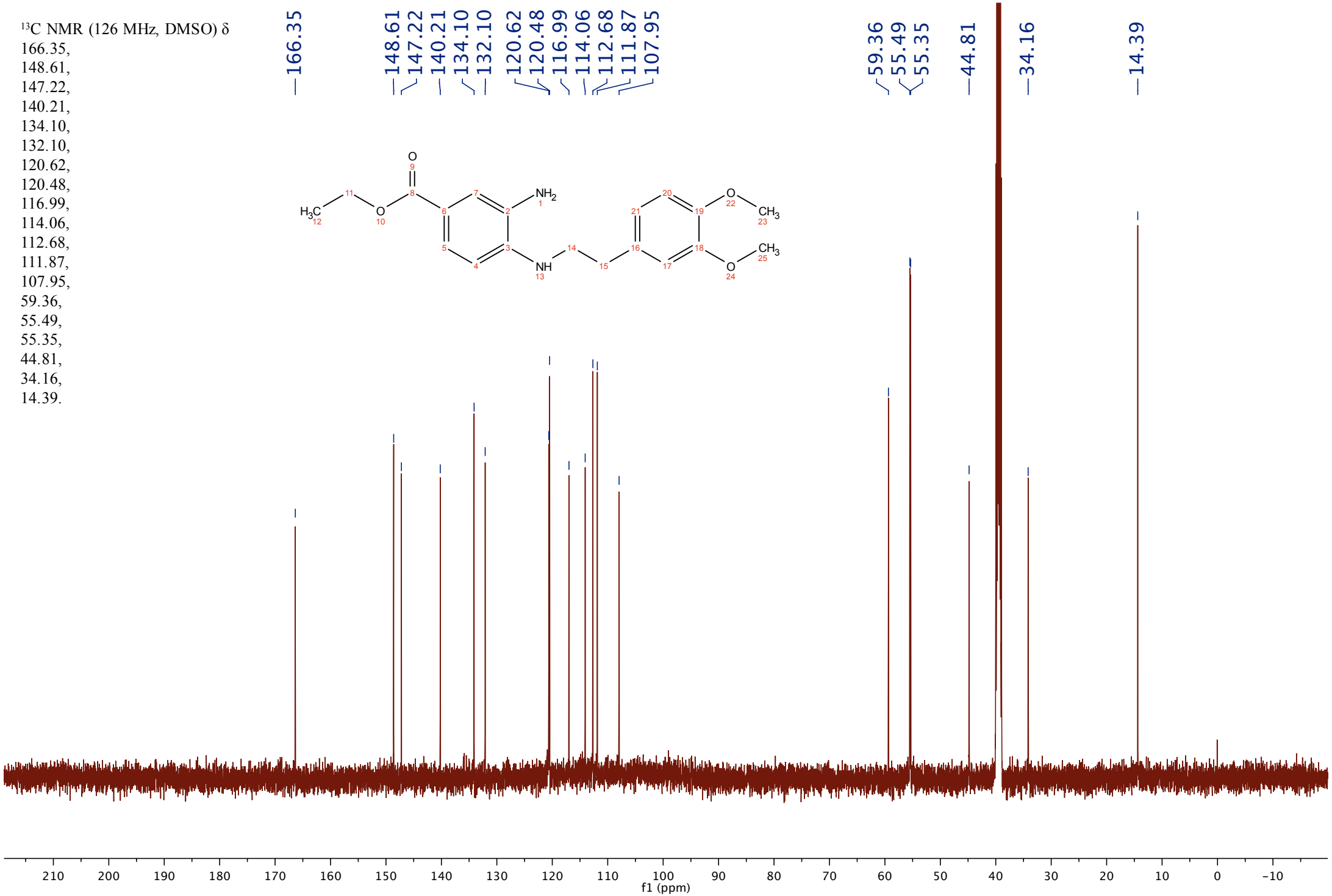


ethyl 3-amino-4-((3,4-dimethoxyphenethyl)amino)benzoate

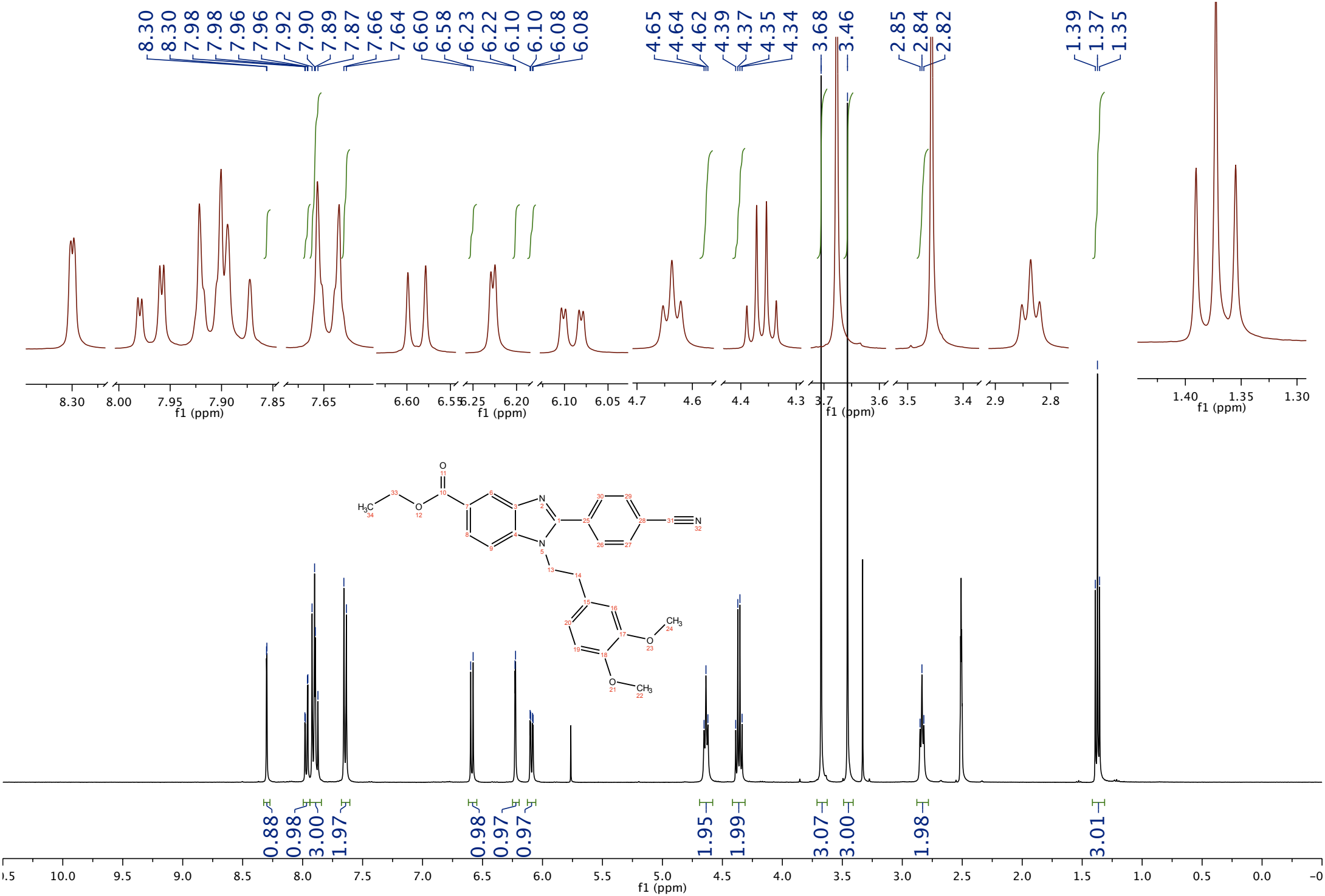


ethyl 3-amino-4-((3,4-dimethoxyphenethyl)amino)benzoate

^{13}C NMR (126 MHz, DMSO) δ
166.35,
148.61,
147.22,
140.21,
134.10,
132.10,
120.62,
120.48,
116.99,
114.06,
112.68,
111.87,
107.95,
59.36,
55.49,
55.35,
44.81,
34.16,
14.39.



2-(4-Cyano-phenyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-1H-benzimidazole-5-carboxylic acid ethyl ester



2-(4-Cyano-phenyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-1H-benzimidazole-5-carboxylic acid ethyl ester

^{13}C NMR (126 MHz, DMSO) δ
166.11,
153.74,
148.41,
147.61,
142.13,
138.71,
134.07,
132.13,
129.74,
129.47,
124.17,
123.77,
121.02,
120.35,
118.40,
112.03,
111.78,
111.52,
60.58,
55.42,
54.80,
46.11,
34.33,
14.22.