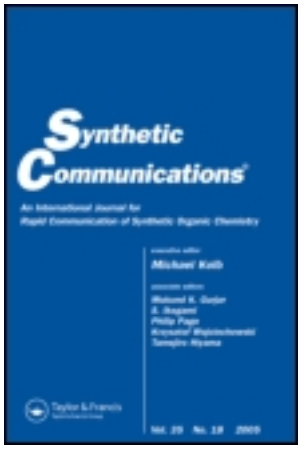

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Synthesis of 2-Aminobenzophenone Derivatives and Their Anticancer Activity

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SYNTHESIS OF 2-AMINOBENZOPHENONE DERIVATIVES AND THEIR ANTICANCER ACTIVITY

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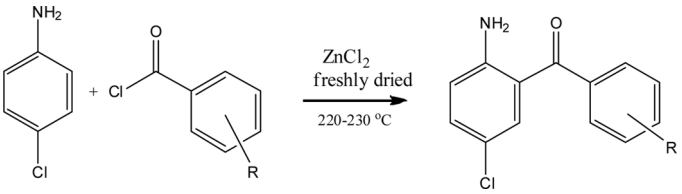
GRAPHICAL ABSTRACT



Abstract *A number of 2-aminobenzophenones have been synthesized by acylation of* para-*chloroaniline with different 2-, 3-, 4-chloro- or fluorobenzoyl chloride in solid state* via *the Friedel–Crafts reaction. Synthesized compounds were characterized by* ^{1}H *and* ^{13}C *NMR, Fourier transform–infrared, ultraviolet–visible spectroscopy, mass spectrometry, and elemental analysis. Evaluation of biological activity* in vitro *showed that the selected compounds* ***9, 10****, and* ***13*** *have potential anticancer activity. The presence of one chlorine atom in the second aromatic ring of the benzophenone molecule makes it more active.*

Keywords Aminobenzophenones; anticancer activity; benzodiazepine intermediates; biological activity; Friedel–Crafts acylation

INTRODUCTION

The development of resistance to current antibiotics continues to be an important problem in the treatment of various diseases.[1–4] Therefore, the synthesis of new drugs is a high-priority area of biochemical research. Aminobenzophenones are a new class of biologically active compounds. A great variety of aminobenzophenones and their derivatives have been synthesized. These compounds showed different types of biological activity such as antitumoral and anticonvulsive activities[5] and activity against the hepatitis C RNA virus.[6] Some aminobenzophenones showed high activity against a panel of human cancer cell lines including multidrug-resistant ones.[7,11] In addition, aminobenzophenones are intermediates in the

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synthesis of benzodiazepine derivatives,[9] more than 10,000 of which were found to have pharmacological properties. Several of them are commercially applied. Recently, it has been shown that aminobenzophenones with an amino group in the *ortho* position of the benzophenone ring show interesting biological activity characteristics.[10,11] In the present work, we report the synthesis of a series of 2-amino-5-chloro-benzophenones, chloro- or fluoro-substituted in *ortho-, meta-*, or *para*-positions, and results of their biological activity against six human cancer cell lines.

RESULTS AND DISCUSSION

Synthesis and Characterization of Aminobenzophenones

The synthesis of 2-aminobenzophenones **9–15** was achieved starting from *para*-chloroaniline and substituted benzoyl chlorides (Scheme 1) using freshly dried $ZnCl_2$ as a catalyst.[12,13] The 2-aminobenzophenones were obtained in good yields (from 40 to 50%).

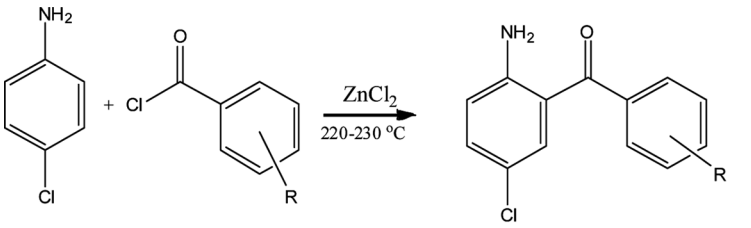
The structures of 2-aminobenzophenones **9–15** were determined by ^1H and ^{13}C NMR, Fourier transform–infrared (FTIR), ultraviolet–visible (UV-vis) spectroscopy, mass spectrometry, and elemental analysis.

When the same reaction was carried out using $ZnCl_2$ that had not been dried previously, only the amide products were obtained in most cases (Scheme 2). For example, the reaction between *para*-chloroaniline and 4-fluorobenzoyl chloride in the presence of untreated $ZnCl_2$ catalyst resulted in *N*-(4-chlorophenyl)-4-fluorobenzamide with 80% yield.

The structure of compound **16** was determined by ^1H and ^{13}C NMR, FTIR, UV-vis spectroscopy, mass spectrometry, and elemental analysis and was confirmed by x-ray diffraction analysis of a single crystal prepared by crystallization from CH_2Cl_2. The general view of the crystal structure of compound **16** is shown in Fig. 1.

Cytotoxic Activity

The cytotoxic activity of the synthesized 2-aminobenzophenones **9–15** was tested in macrophages, and three compounds [free benzophenone **9** and benzophenones with chloro- or fluoro-substituents in *ortho*-position (compounds **10** and **13**, respectively)] were chosen for the evaluation of their biological activity against

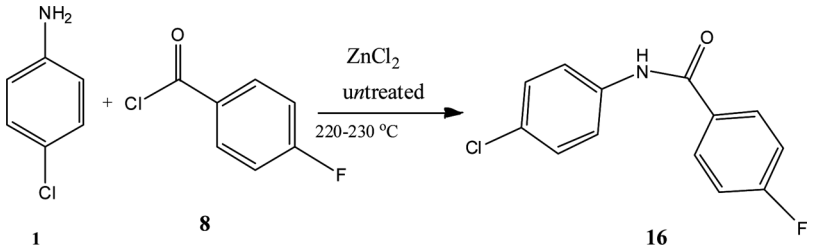


1

R= H (**2**)
R= Cl (ortho **3**, meta **4**, para **5**)
R= F (ortho **6**, meta **7**, para **8**)

R= H (**9**)
R= Cl (ortho **10**, meta **11**, para **12**)
R= F (ortho **13**, meta **14**, para **15**)

Scheme 1. Synthesis of 2-amino-5-chlorobenzophenone derivatives **9–15**.



Scheme 2. Synthesis of *N*-(4-chlorophenyl)benzamide derivative **16**.

cancer. The rest of the compounds were discarded because of lower activity. The selected compounds **9, 10**, and **13** were screened in vitro against six human cancer cell lines. K-562 (human chronic myelogenous leukemia), SKLU-1 (human lung adenocarcinoma), and HCT-15 (human colorectal adenocarcinoma) cell lines were supplied by the National Cancer Institute (NCI, USA). The human tumor cytotoxicity was determined using the protein-binding dye sulforhodamine B (SRB) in microculture assay to measure cell growth, as described in the protocols established by the NCI.[14] The cell lines were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10000 units/ml penicillin G sodium,

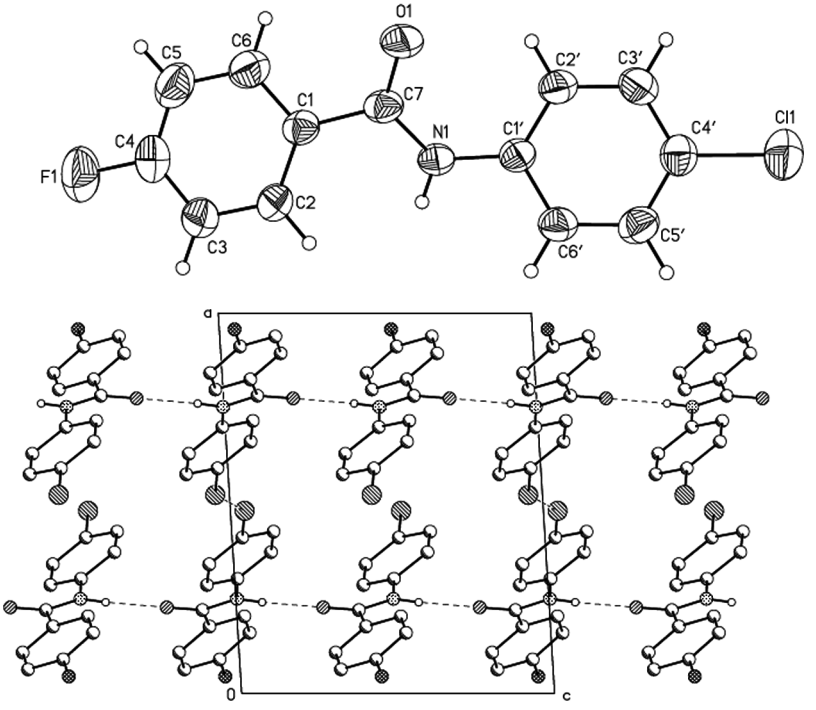


Figure 1. Crystal structure and crystal packing of **16**. Selected bond lengths (Å): N(1)–C(1′) = 1.422(2), N(1)–C(7) = 1.343(2), O(1)–C(7) = 1.226(2), F(1)–C(4) = 1.366(2), Cl(1)–C(4′) = 1.739(2). Selected bond angles (°): C(7)–N(1)–C(1′) = 126.39(16), C(7)–N(1)–H(1) = 120.7(12), C(1′)–N(1)–H(1) = 112.8(12), O(1)–C(7)–N(1) = 122.24(19), O(1)–C(7)–C(1) = 120.99(17), N(1)–C(7)–C(1) = 116.76(17).

Table 1. Inhibition on the growth (%) of human tumor cell lines for **9**, **10**, and **13** at 50 μM in DMSO

	Cell line					
Compound	U-251	PC-3	K-562	HCT-15	MCF-7	SKLU
9	16.06	21.77	49.37	66.56	73.04	25.64
10	62.04	58.6	89.92	95.43	67.84	81.47
13	52.85	40.72	98.36	75.89	78.36	76.86

Table 2. Inhibitory concentration (IC_{50}) (μM) values obtained in K-562, HCT-15, and SKLU-1 cell lines for compounds **9**, **10**, and **13** in DMSO

Compounds	K-562	HCT-15	SKLU-1
9	58.54 ± 4.6	45.43 ± 2.5	59.71 ± 2.3
10	25.48 ± 2.3	18.87 ± 0.75	15.59 ± 0.24
13	40.86 ± 1.6	33.62 ± 1.9	32.64 ± 1.0
Cis-platin	15.20 ± 1.4	13.83 ± 0.7	7.13 ± 0.2

10000 μg/ml streptomycin sulfate, 25 μg/ml amphotericin B (Gibco), and 1% non-essential amino acids (Gibco). They were maintained at 37 °C in a humidified atmosphere with 5% CO_2. The viability of the cells used in the experiments exceeds 95% as determined with trypan blue. The initially obtained cytotoxic screening data (Table 1) show that the selected compounds have good activities, especially halogen-substituted ones, and that the activity depends on the nature of the halogen substituent.

The inhibitory concentration (IC_{50}) values were only determined for those lines (K-562, HCT-15, and SKLU-1), for which almost all of the IC_{50} values were lower than 60 μM, and were compared to the results obtained with the *cis*-platin cytotoxic agent (Table 2). For the three cell lines, compound **10** was found to be the most potent among all 2-aminobenzophenones studied, exhibiting the lowest inhibitory concentrations (25.48 ± 2.3, 18.87 ± 0.75 and 15.59 ± 0.24 μM, Table 2). The comparison of the activity of chloro-derivative (compound **10**) with that of the corresponding fluoro-derivative (compound **13**) indicates that the presence of a chlorine atom in the second ring of the benzophenone gives better results for cancer inhibition.

In conclusion, in the present work it was observed that 2-aminobenzophenones with chloro- or fluoro-substituents in the second ring can be obtained in good yields from *para*-chloroaniline and benzoyl chloride using freshly dried $ZnCl_2$ as a catalyst. When untreated $ZnCl_2$ catalyst is used, only amide compounds are obtained from the same reactants. Biological activity tests showed that the synthesized 2-aminobenzophenones compounds have potential activity against cancer, which was enhanced in the presence of a chloro-substituent in the second ring of the 2-aminobenzophenones.

EXPERIMENTAL

Materials and Equipment

Solvents and chemicals were purchased from Aldrich as reagent grade and used without further purification. Column chromatography was performed on silica

gel 60 Å, Merck (70–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Varian-Unity 300-MHz instrument with tetramethylsilane (TMS) as an internal reference. Infrared (IR) spectra were measured on a Nicolet FT-SSX spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville. Electron impact (EI) mass spectra were taken on a Jeol JMS AX505 HA instrument.

Cytotoxicity Assay

The cells were removed from the tissue culture flasks and diluted with fresh media. Of these cell suspensions, 100 µl (containing 5000 or 10,000 cell per well) were pipetted into 96-well microtiter plates (Costar), and the material was incubated at 37 °C for 24 h in a 5% CO_2 atmosphere. Subsequently, 100 µl of a solution of the test compounds, obtained by diluting the stocks, were added to each well. The cultures were exposed for 48 h to the drug at concentrations ranging from 10 to 100 µM.

After the incubation period, cells were fixed to the plastic substratum by the addition of 50 µl of cold 50% aqueous trichloroacetic acid. The plates were incubated at 4 °C for 1 h, washed with tap H_2O, and air dried. The trichloroacetic-acid-fixed cells were stained by the addition of 0.4% SRB. Free SRB solution was removed by washing with 1% aqueous acetic acid. The plates were air dried, and the bound dye was solubilized by addition of 10 mM unbuffered Tris base (100 µl). The plates were placed on a shaker for 5 min, and the absorption was determined at 515 nm using an ELISA plates reader (Bio-Tex Instruments).

General Procedure for the Preparation of 2-Aminobenzophenones

To 21.0 mmol of the corresponding benzoyl chloride, 8.4 mmol of *p*-chloroaniline were added. Then the mixture was heated to about 180–200 °C, 10.08 mmol of anhydrous $ZnCl_2$ were added slowly, and the temperature was gradually increased to 220–230 °C. The reaction mixture was maintained at reflux for 3 h. Then it was cooled to 120 °C, and hot water was added to remove the benzoic acid, giving a green-brown product. The obtained green-brown product was added to a mixture of H_2SO_4, CH_3COOH, and H_2O (5.0:3.5:3.0 mL) and refluxed for 40 min. Then, about 20–25 mL of ice-water mixture was added, and the reaction mixture was subsequently extracted using dichloromethane. The organic phase was washed three times using water and a solution of 10% ammonium hydroxide to neutralize it. The organic phase was dried with anhydrous sodium sulfate. Its vacuum evaporation yielded a brown-yellow solid, which was purified by column chromatography (SiO_2, 1:2 ethylacetate/hexanes mixture as eluent).

Select Data

(2-Aminophenyl)-phenyl-methanone 9. Known compound, mp 86–88 °C.[13]

(2-Amino-5-chlorophenyl)(2-chlorophenyl)methanone 10. Known compound, mp 87–89 °C.[13]

(2-Amino-5-chlorophenyl)(3-chlorophenyl)methanone 11. Yellow solid, mp: 100–102 °C; UV-vis (CH_2Cl_2, λ nm): 394, 235, 204; FTIR (KBr, cm^{-1}): 3435, 3322, 1616, 1590, 1530, 1466, 1294, 1152, 940, 754, 633, 498; ^{1}H NMR ($CDCl_3$): 6.75 (d, 1H, Ar-3, $J = 8.8$ Hz), 7.26 (dd, 1H, Ar-4, $J = 2.4$ Hz), 7.41 (d, 1H, Ar-6, $J = 2.4$ Hz), 7.45–7.48 (m, 1H, Ar-5′), 7.52–5.55 (m, 1H, Ar-4′), 7.56 (br, 2H, NH_2), 7.62 (d, 1H, Ar-2′, $J = 2.0$ Hz), 7.63–7.67 (m, 1H, Ar-6′);^{13}C NMR ($CDCl_3$): 112.6 (Ar-1), 117.2 (Ar-3), 126.4 (Ar-5), 127.9 (Ar-6), 128.7 (Ar-3′,5′), 131.8 (Ar-2′,6′), 136.9 (Ar-1′), 137.7 (Ar-4), 138.7 (Ar-4′), 154.3 (Ar-2), 195.4 (C=O); MS m/z: 266. Anal. calcd. for $C_{13}H_9Cl_2NO$: C, 58.67; H, 3.41; N, 5.26. Found: C, 58.68; H, 3.41; N, 5.25.

(2-Amino-5-chlorophenyl)(4-chlorophenyl)methanone 12. Yellow solid, mp: 100–102 °C; UV-vis (CH_2Cl_2, λ nm): 394, 235, 204; FTIR (KBr, cm^{-1}): 3435, 3322, 1616, 1590, 1530, 1466, 1294, 1152, 940, 754, 633, 498; ^{1}H NMR ($CDCl_3$): 6.77 (d, 1H, Ar-3, $J = 8.8$ Hz), 7.26 (dd, 1H, Ar-4, $J = 2.6$ Hz), 7.41 (d, 1H, Ar-6, $J = 2.4$ Hz), 7.45–7.48 (m, 1H, Ar-5′), 7.52–5.55 (m, 1H, Ar-3′), 7.56 (br, 2H, NH_2), 7.62 (d, 1H, Ar-2′, $J = 2.0$ Hz), 7.63–7.67(m, 1H, Ar-6′); ^{13}C NMR ($CDCl_3$): 112.6 (Ar-1), 117.2 (Ar-3), 126.4 (Ar-5), 127.7 (Ar-6), 128.7 (Ar-3′,5′), 131.8 (Ar-2′,6′), 136.9 (Ar-1′), 137.7 (Ar-4), 138.7 (Ar-4′), 154.3 (Ar-2), 195.4 (C=O); MS m/z: 266. Anal. calcd. for $C_{13}H_9Cl_2NO$: C, 58.67; H, 3.41; N, 5.26. Found: C, 58.68; H, 3.41; N, 5.25.

(2-Amino-5-chlorophenyl)(2-fluorophenyl)methanone 13. Yellow solid, mp: 63–65 °C; UV-vis (CH_2Cl_2, λ nm): 392, 235, 205; FTIR (KBr, cm^{-1}): 3443, 3333, 1619, 1539, 1455, 1318, 1299, 1239, 1215, 1150, 947, 755, 645; ^{1}H NMR ($CDCl_3$): 6.71 (d, 1H, Ar-3, $J = 9.0$ Hz), 7.12 (d, 1H, Ar-3′, $J = 0.8$ Hz), 7.17 (t, 1H, Ar-5′, $J = 1.1$ Hz), 7.22–7.29 (m, 1H, Ar-4′), 7.39 (dd, 1H, Ar-4, $J = 2.0$, 1.4 Hz), 7.44–7.49 (m, 1H, Ar-6); 7.51–7.56 (m, 1H, Ar-6′); ^{13}C NMR ($CDCl_3$): 116.0, 116.4 (Ar-1), 118.7 (Ar-3), 119.0, 120.6 (Ar-3′), 124.2, 124.3 (Ar-5′), 127.6, 127.9 (Ar-1′), 129.4 (Ar-5), 129.6, 129.7 (Ar-6′), 132.1, 132.3 (Ar-6), 133.0 (Ar-4′), 135.0 (Ar-4), 148.8 (Ar-2′), 156.5 (Ar-2), 161.5 (Ar-2′), 194.3 (C = O); MS m/z: 249. Anal. calcd. for $C_{13}H_9ClFNO$: C, 62.54; H, 3.63; N, 5.61. Found: C, 62.53; H, 3.63; N, 5.60.

(2-Amino-5-chlorophenyl)(3-fluorophenyl)methanone 14. Yellow solid, mp: 106–108 °C; UV-vis (CH_2Cl_2, λ nm): 392, 235, 204; FTIR (KBr, cm^{-1}): 3462, 3348, 1630, 1580, 1540, 1471, 1436, 1243, 1162, 769, 523; ^{1}H NMR ($CDCl_3$): 6.00 (br, 2H, NH_2), 6.70 (d, 1H, Ar-3, $J = 8.8$ Hz), 7.12 (d, 1H, Ar-3′, $J = 0.8$ Hz), 7.18 (t, 1H, Ar-5′, $J = 1.1$ Hz), 7.26 (dd, 1H, Ar-4, $J = 2.0$, 1.4 Hz), 7.37 (d, 1H, Ar-6), 7.66 (d, 2H, Ar-6′), 7.68 (d, 1H, Ar-2′); ^{13}C NMR ($CDCl_3$): 115.1, 115.7 (Ar-2′,4′), 118.5 (Ar-3), 120.0 (Ar-1), 121.6, 121.7 (Ar-6′), 122.8 (Ar-6), 123.0 (Ar-5), 132.5, 132.8 (Ar-5′), 134.2 (Ar-4), 135.4, 135.7 (Ar-1′), 154.2 (Ar-2), 163.1, 166.4 (Ar-3′), 196.3 (C=O); MS m/z: 249. anal. calcd. for $C_{13}H_9ClFNO$: C, 62.54; H, 3.63; N, 5.61. Found: C, 62.53; H, 3.63; N, 5.60.

(2-Amino-5-chlorophenyl)(4-fluorophenyl)methanone 15. Yellow solid, mp: 106–108 °C; UV-vis (CH_2Cl_2, λ nm): 392, 235, 204; FTIR (KBr, cm^{-1}): 3462, 3348, 1630, 1580, 1540, 1471, 1436, 1243, 1162, 769, 523; ^{1}H NMR ($CDCl_3$): 5.98 (br, 2H, NH_2), 6.70 (d, 1H, Ar-3, $J = 9.0$ Hz), 7.16 (m, 1H, Ar-3′), 7.13–7.19 (m, 2H, Ar-3′,5′), 7.20–7.36 (m, 1H, Ar-6), 7.36 (d, 1H, Ar-4, $J = 2.4$ Hz), 7.67 (dd, 2H,

Ar-2′,6′); ^{13}C NMR ($CDCl_3$): 115.3, 115.6 (Ar-3′,5′), 118.4 (Ar-3), 118.7 (Ar-5), 120.0 (Ar-1), 131.6, 131.7 (Ar-2′,6′), 132.8 (Ar-6), 134.2 (Ar-4), 135.4 (Ar-1′), 149.2 (Ar-2), 163.1, 166.4 (Ar-4′), 196.3 (C=O); MS *m/z*: 249. Anal. calcd. for $C_{13}H_9ClFNO$: C, 62.54; H, 3.63; N, 5.61. Found: C, 62.53; H, 3.63; N, 5.60.

Crystal Structure Determination

A suitable crystal of compound **16** (obtained by crystallization from CH_2Cl_2 at room temperature) was rolled in epoxy resin and mounted on a glass fiber. Bruker Apex AXS CCD area detector x-ray diffractometer was the instrument used for determination. The data were first reduced and corrected for absorption using psi scans and then solved using the program SHELL-XS. All nonhydrogen atoms were refined using the anisotropic thermal parameters, and the hydrogen atoms were refined at calculated positions by applying thermal parameters constrained to the carbon atom on which they were attached. A summary of the key crystallographic information is given in Table 3. CCDC 778732 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk.

Table 3. Crystal data and structure refinement

Parameter	Value
Empirical formula	C_{13} H_9 Cl F N O
Formula weight	249.66
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 12.081(2) Å, α = 90° b = 9.7923(16) Å, β = 93.514(3)° c = 9.9142(16) Å, γ = 90°
Volume	1170.6(3) Å^3
Z	4
Density (calculated)	1.417 Mg/m^3
Absorption coefficient	0.320 mm^{-1}
F(000)	512
Crystal size/shape/color	0.40 × 0.10 × 0.10 mm/prism/colorless
Theta range for data collection	1.69 to 25.30°
Index ranges	−14 <= h <= 14, −11 <= k <= 11, −11 <= l <= 11
Reflections collected	9420
Independent reflections	2135 [R(int) = 0.0622]
Completeness to theta =	25.30° 100.0%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2135/1/157
Goodness of fit on F^2	0.869
Final R indices [I > 2sigma(I)]	R1 = 0.0386, wR2 = 0.0773
R indices (all data)	R1 = 0.0679, wR2 = 0.0859
Largest diff. peak and hole	0.201 and −0.144 e.Å^{-3}

ACKNOWLEDGMENTS

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