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ORIGINAL PAPER

Synthesis, Spectroscopic Characterization and X-ray Structure Analysis of 6-(2,5-Dichlorothiophen-3-yl)-2-methoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile

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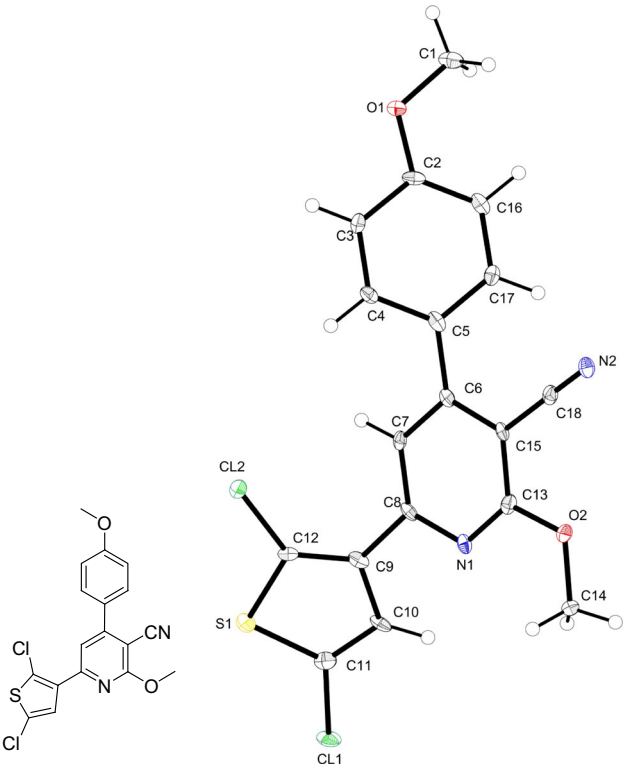
Abstract The title compound was prepared by the condensation of an equimolar mixture of 1-(2,5-dichlorothiophen-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one, malononitrile and sodium hydroxide. The molecular structure was fully characterized using different spectroscopic methods. Mass ESI–HRMS measurements were performed. The HRESIMS analysis revealed the molecular formula, $C_{18}H_{12}Cl_2N_2O_2SNa$, with $[M + Na]^+$ and $[M + Na + 2]^+$ and $[M + Na + 4]^+$ isotopic clusters characteristic for a dichlorinated compound. The compound was also thoroughly characterized by ^1H, ^{13}C, NMR spectra and 2D NMR spectra (COSY, HSQC and HMBC). The molecular structure was confirmed by X-ray single crystal analysis. The new compound crystallizes in the orthorhombic, *Pbcn* space group with unit cell dimensions: $a = 31.901(7)$ Å, $b = 15.412(4)$ Å, $c = 7.3655(14)$ Å, $V = 3621.3(13)$ Å^3 and $Z = 8$. In the title compound, the central pyridine ring carries four substituents, a thiophene ring, a methoxyphenyl ring, a carbonitrile group and a methoxy group. The dihedral angles between the planes of the pyridine ring, the thiophene ring and the methoxyphenyl ring are 36.66 and 40.18°, respectively. Intermolecular C–H···O/N, π···π and anion···π [Cl···π] interactions are found in the crystal structure. All interactions consolidate a three dimensional network.

Graphical Abstract Synthesis, characterization, crystal, molecular structure, and crystal supramolecularity of 6-(2,5-dichlorothiophen-3-yl)-2-methoxy-4-(4-methoxyphenyl) pyridine-3-carbonitrile are reported.



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Keywords Cyanopyridine · Chalcone · Spectroscopic characterization · Crystal supramolecularity · C–H···N/O · S···S interactions · Cl···π interactions · π···π interactions

Introduction

Pyridine is an integral part of B6-vitamins pyridoxine, pyridoxal, pyridoxamine, and decarboxylase. Pyridine derivatives, either natural or synthetic, possess interesting pharmacological properties [1]. Pyridine heterocyclic compounds have attracted an extensive attention due to their possible pharmacological activities, such as antimicrobial, antitumor and anti-inflammatory properties [2–6]. One class of these heterocyclic compounds, cyanopyridines, which have been used as precursor for the preparation of different types of compounds such as nicotinamide, nicotinic acid and isonicotinic acid [7, 8]. In continuation to our research in the synthesis and structural characterization of a series of compounds containing cyanopyridine derivatives, we herein report the synthesis, spectroscopic characterization, molecular and crystal structure analysis of the title compound as one compound of a series that will be published soon with biological activities.

Experimental

General Information

All reagents were purchased from Fluka and used as purchased. Solvents were dried and distilled according to standard protocols. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in $CDCl_3$ (used as an internal standard) at 300 K on Bruker spectrometers. Chemical shifts δ are given in parts per million (ppm) and were determined from the center of the respective coupling pattern (s: singlet, d: doublet, dd: doublet of doublet, t: triplet). ESI–HRMS measurements were performed on a LTQ-FT mass spectrometer (Thermo Fisher Scientific).

Thin layer chromatography (TLC) monitoring of the reaction was carried out using analytical TLC plates coated with silica gel (60 F_{254}, Merck). Preparative thin layer chromatography (PTLC) was carried out at room temperature (RT) with the mobile phase being $CHCl_3$/pentane (30:70) mixture.

Synthesis

Synthesis of Starting Materials

Scheme 1 outlines the synthesis of all starting materials and the title compound. The synthesis of 3-acetyl-2,5-dichloro-thiophene, **2**, was accomplished as described in literature [9]. A solution of 2,5-dichlorothiophene, **1,** (15.2 g, 100 mmol) in dry carbon disulfide (25 ml) was added dropwise, during 1 h, to a stirred mixture of anhydrous $AlCl_3$ (15.0 g, 110 mmol) and acetyl chloride (7.9 g, 100 mmol) in dry CS_2 (80 ml). The reaction mixture was stirred at RT for 24 h. Cold water (50 ml) was then added dropwise to the reaction with continuous stirring for 30 min the organic layer was separated, washed with water (4 × 30 ml), dried over anhydrous $CaCl_2$ and the solvent was evaporated to produce a solid product. Yield: 80 % [9].

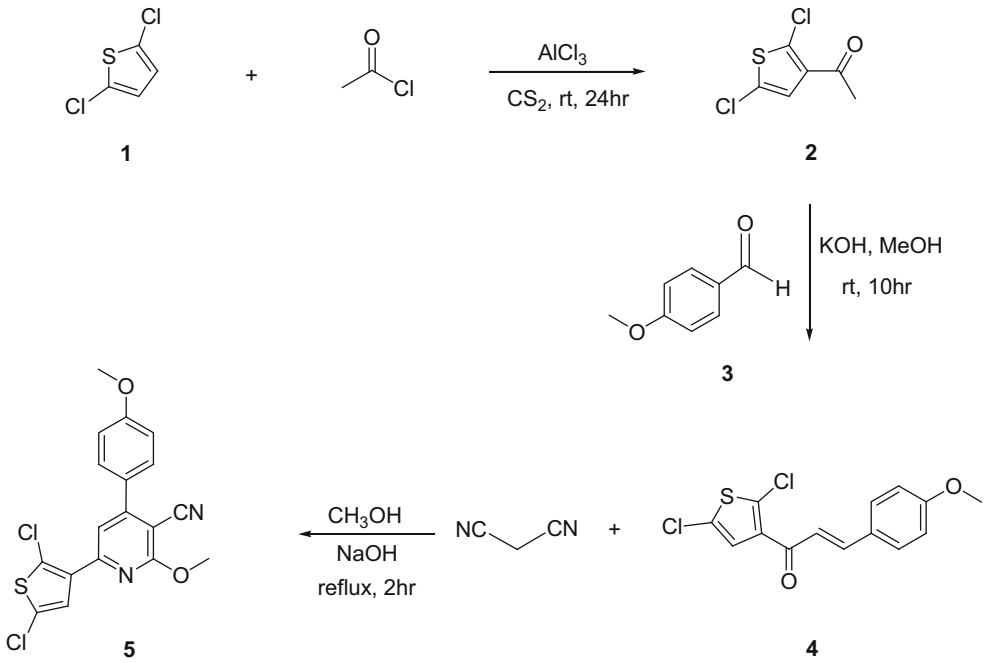
Synthesis of 1-(2,5-dichlorothiophen-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one, **4**. An equimolar mixture of the 4-methoxybenzaldehyde, KOH were dissolved in MeOH (50 ml). To this solution 3-acetyl-2,5-dichlorothiophene, **2**, in MeOH (10 ml) was added dropwise. After the addition was completed, the reaction mixture was stirred at RT for 10 h. The precipitate formed was filtered off, washed with MeOH and dried without any further purification.

Synthesis of 6-(2,5-Dichlorothiophen-3-yl)-2-Methoxy-4-(4-Methoxyphenyl)Pyridine-3-Carbonitrile, ***5***

The synthesis was done according to literature method [10]. A mixture of 1-(2,5-dichlorothiophen-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one, **4**, (0.01 mol), malononitrile (0.01 mol) and NaOH (0.01 mol) in 50 ml of MeOH was refluxed for about 2 h. The reaction mixture was cooled and then a pale yellow solid was obtained, filtered off, air-dried, and purified using PTLC (20 × 20 cm) using CH_2Cl_2: pentane (70:30 %) as a mobile phase to give the title compound, Scheme 1. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.66 (d, J = 8.70 Hz, 2H, H-2″,6″), 7.63 (s,1H, H-5), 7.42 (s, 1H, H-4′), 7.08 (d, J = 8.70 Hz, 2H, H-3″, 5″), 3.91 (s, 3H, OCH_3-4″), 4.16 (s, 3H, OCH_3-2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ = 164.91 (C-2), 161.26 (C-4″), 156.19 (C-4), 151.46 (C-6), 135.69 (C-3′), 130.00 (C-2″,6″), 128.12 (C-1″), 127.48 (C-4′), 126.76 (C-5′), 126.15 (C-2′), 115.72 (CN), 115.65 (C-5), 114.53 (C-3″,5″), 93.07 (C-3), 55.51 (OCH_3-4″), 54.88 (OCH_3-2); (+)-**ESIMS** *m/z* 391([M + H]$^+$, 48), 393 ([M + H+2]$^+$, 17), 413 ([M + Na]$^+$, 100), 415 ([M + Na + 2]$^+$, 58), 417 ([M + Na + 4]$^+$, 13)**; (+)-HRESIMS** *m/z* 412.9896 [M + Na]$^+$, 414.9867 [M + Na + 2]$^+$, 416.9837 [M + Na + 4]$^+$ (calcd for $C_{18}H_{12}Cl_2N_2O_2SNa$, 412.9889).

Structure Determination and Refinement

A Bruker D8 Quest area detector was used for X-ray crystal structure determinations. A total of 1814 frames were collected. The total exposure time was 9.58 h. The frames were integrated with the Bruker SAINT software package [11] using a narrow-frame algorithm.



Scheme 1 Reaction scheme for the synthesis of the title compound, **5**

Table 1 Crystal data and structure refinement for **5**

Empirical formula; formula weight	$C_{18.5}\ H_{13}\ Cl_3\ N_2\ O_2\ S$; 433.72
Temperature (K)	100 (2)
λ (Å)	0.71073
Crystal system, space group	Orthorhombic, *Pbcn*
Unit cell dimensions	a = 31.901 (7) Å
	b = 15.412 (4) Å
	c = 7.3655 (14) Å
	α = β = γ = 90°
V (Å^3)	3621.4 (13)
Z	8
$D_{calc.}$ (Mg/m^3)	1.591
Absorption coefficient (mm^{-1})	0.639
F (000)	1768
Crystal size (mm^3)	0.412 × 0.048 × 0.045
Theta range for data collection	2.327–25.274°
Limiting indices	$-38 \le h \le 34$, $-18 \le k \le 18$, $-7 \le l \le 8$
Reflections collected	17,368
Completeness to theta = 25.125°	99.8 %
Independent reflections	3291 [R (int) = 0.0564]
Observed reflections	2675 [II > 2 (I)]
Reflections used for refinement	3291
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3291/0/229
Goodness-of-fit on F^2	1.146
R index (all data)	wR2 = 0.1414
R index conventional [I > 2sigma (I)]	R1 = 0.0614
Extinction coefficient	0.0007 (2)
Largest diff. peak and hole	0.712 and −0.507 e Å^{-3}

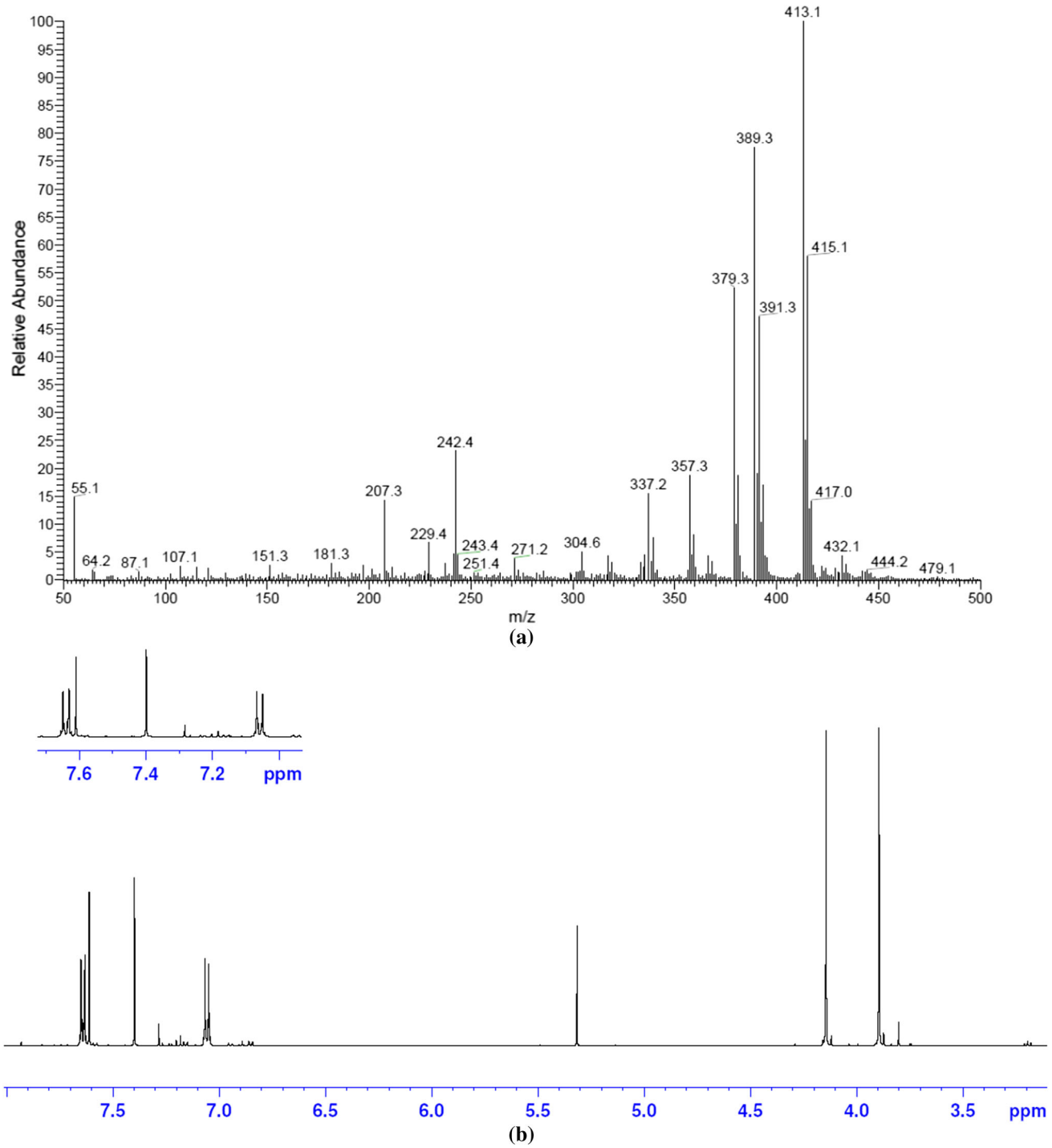
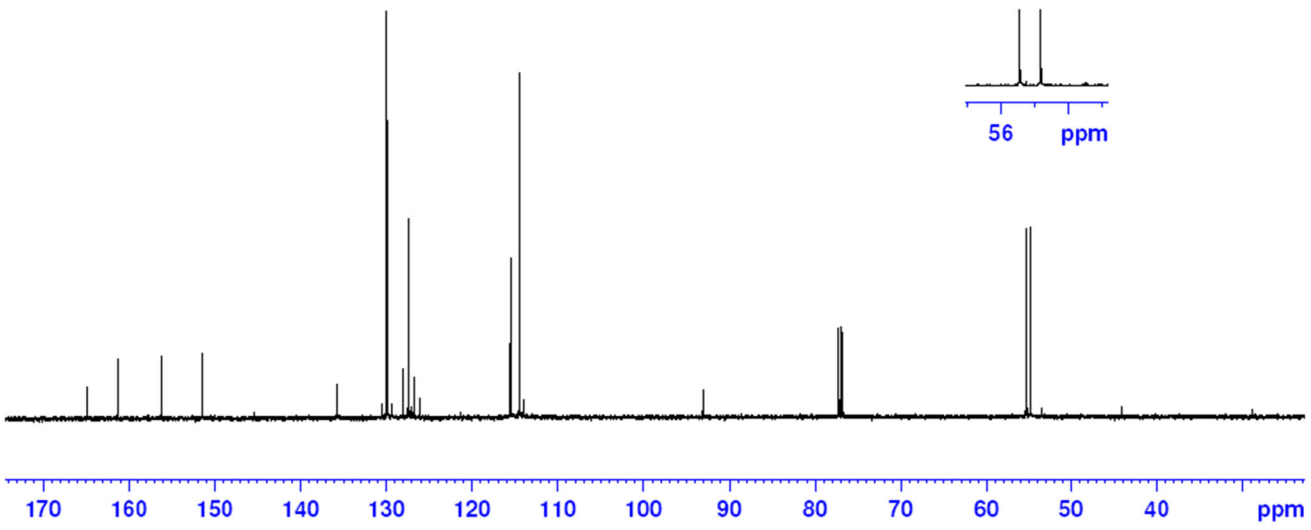
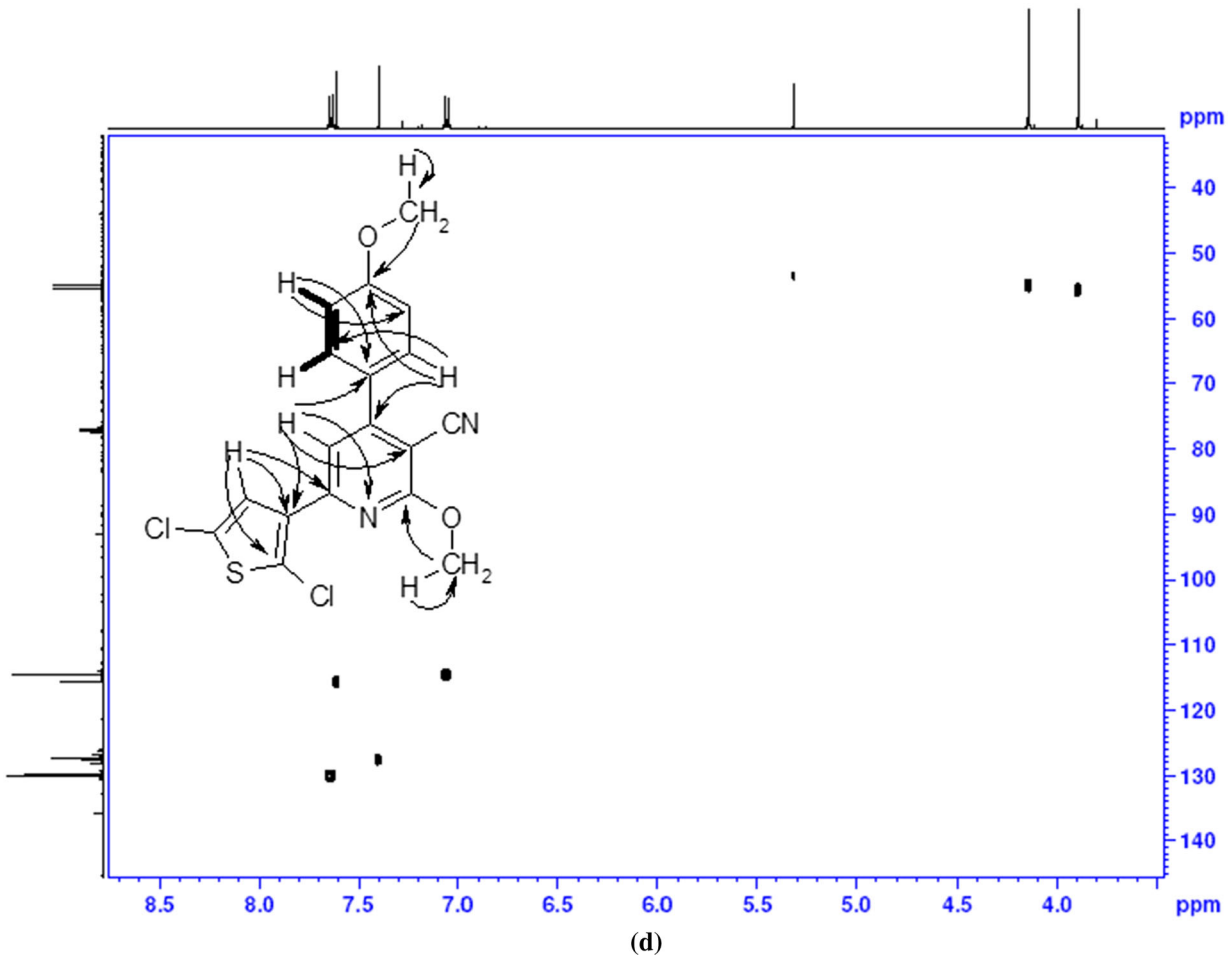


Fig. 1 **a** ESIMS analysis for **5**; **b** ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **5**. The signal at 5.32 due to the presence of traces of CH_2Cl_2; **c** ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) for **5**; **d** the HSQC spectrum for **5** with selected H,H COSY (—) and HMBC (→) correlations

The integration of the data using an orthorhombic unit cell yielded a total of 17,383 reflections to a maximum θ angle of 25.27° (0.83 Å resolution), of which 3293 were independent (average redundancy 5.279, completeness = 99.8 %, R_{int} = 5.64 %, R_{sig} = 4.43 %) and 2677 (81.29 %) were greater than 2σ (F^2). The final cell dimensions of a = 31.901 (7) Å, b = 15.412 (4) Å, c = 7.3655 (14) Å, volume = 3621.3 (13) Å^3, are based upon the refinement of the XYZ-centroids of 93 reflections above 20 σ(I) with 6.909° < 2θ < 40.64°. The systematic absence conditions leads to the space group *Pbcn*. Data were corrected for absorption effects using the multi-scan



(c)



(d)

Fig. 1 continued

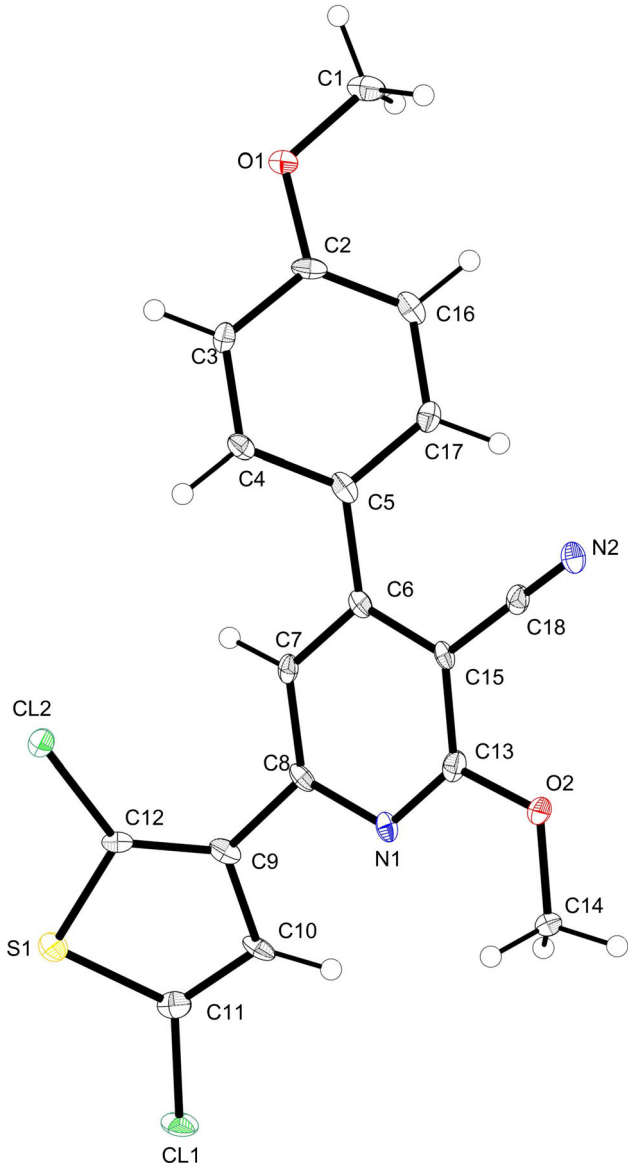


Fig. 2 Molecular structure of the title compound, with the atomic-labeling scheme. Displacement ellipsoids are drawn at the 50 % probability level

method (SADABS) [11]. The ratio of minimum to maximum apparent transmission was 0.849. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7790 and 0.9720. The final anisotropic full-matrix least-squares refinement [12] on F^2 with 229 variables converged at R1 = 0.0615, for the observed data and wR2 = 0.1414 for all data. The goodness-of-fit was 1.146. The largest peak in the final difference electron density synthesis was 0.706 $e^-/Å^3$ and the largest hole was −1.341 $e^-/Å^3$ with an RMS deviation of 0.136 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.591 g/cm^3 and F (000), 1768 e^-. The refinement of half CH_2Cl_2 (inversion symmetry) was not successful, therefor the PLATON/SQUEEZE routine [13] was used to remove the electron density of the disordered solvent (CH_2Cl_2). All H atoms were placed in their calculated positions and included in the refinement using the riding model. Crystal and experimental data for **4** are listed in Table 1.

Table 2 Selected bond distances and angles (Å, °) in **5**

Bond distances			
Cl1–C11	1.718 (5)	N1–C8	1.356 (6)
Cl2–C12	1.719 (5)	N2–C18	1.141 (6)
S1–C12	1.723 (5)	C2–C16	1.380 (7)
S1–C11	1.725 (5)	C2–C3	1.391 (7)
O1–C2	1.375 (5)	C5–C6	1.478 (6)
O1–C1	1.432 (6)	C6–C15	1.395 (6)
O2–C13	1.356 (5)	C6–C7	1.406 (6)
O2–C14	1.437 (5)	C15–C18	1.453 (7)
N1–C13	1.318 (6)	C16–C17	1.388 (8)
Bond angles			
C12–S1–C11	89.7 (2)	N1–C8–C9	113.9 (4)
C2–O1–C1	117.3 (4)	C7–C8–C9	122.7 (4)
C13–N1–C8	116.6 (4)	C10–C11–Cl1	126.2 (4)
O1–C2–C16	124.9 (4)	C10–C11–S1	113.7 (4)
O1–C2–C3	115.3 (4)	Cl1–C11–S1	120.1 (3)
O1–C2–C16	124.8 (4)	Cl2–C12–S1	118.0 (3)
C17–C5–C4	118.9 (4)	N1–C13–O2	119.7 (4)
C17–C5–C6	121.8 (4)	N1–C13–C15	124.3 (4)
N1–C8–C7	123.5 (4)	O2–C13–C15	116.0 (4)
Torsion angles			
C1–O1–C2–C16	6.6 (7)	N1–C8–C9–C12	141.9 (5)
C1–O1–C2–C3	−173.9 (4)	N1–C8–C9–C10	−33.9 (6)
C17–C5–C6–C15	41.4 (7)	C7–C8–C9–C10	146.6 (5)
C4–C5–C6–C15	−140.5 (5)	C14–O2–C13–N1	−2.5 (6)
C17–C5–C6–C7	−138.4 (5)	C14–O2–C13–C15	177.0 (4)
C4–C5–C6–C7	39.7 (6)	C5–C6–C15–C18	7.4 (7)

Results and Discussion

Synthesis and Spectroscopic Characterization

The synthesis of 3-acetyl-2,5-dichloro-thiophene, **2**, was accomplished as described in literature [9] by Friedel–Crafts acylation using 2,5-dichlorthiophene, **1**, acetyl chloride, anhydrous $AlCl_3$ as a Lewis acid mediator and CS_2 as the solvent. The chalcone, 1-(2,5-dichlorothiophen-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one, **4**, was prepared by the Claisen–Schmidt condensation of 3-acetyl-2,5-dichloro-thiophene, **2**, and 4-methoxybenzaldehyde, **3**, in the presence of KOH as indicated in Scheme 1. The reaction of 1-(2,5-dichlorothiophen-3-yl)-3-(4-methoxyphenyl)prop-2-

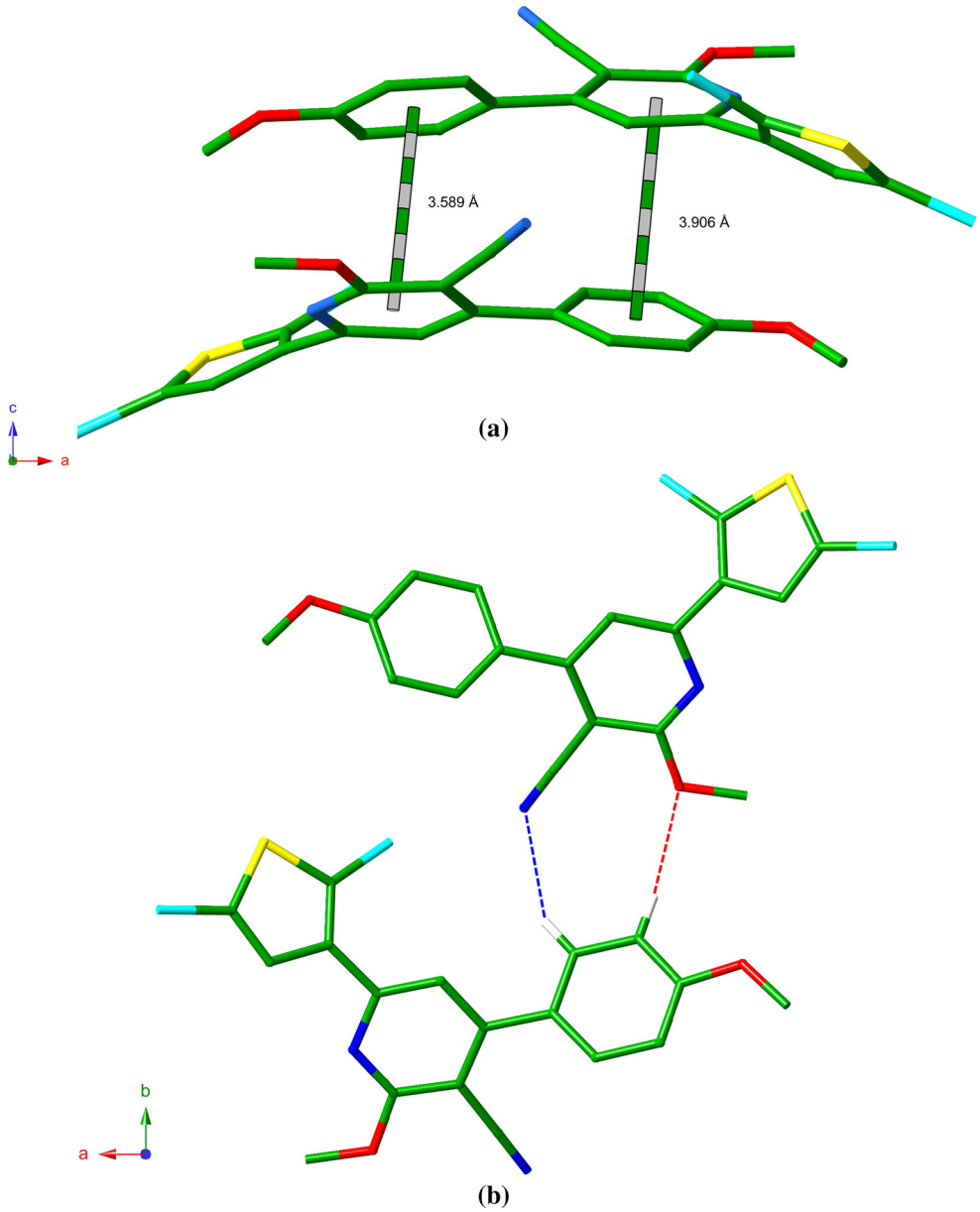


Fig. 3 Shows: **a** π···π stacking and centroid–centroid distances between two molecules; **b** C–H···O/N intermolecular interactions. π···π interactions shown as *green–gray* multi-band cylinders. Hydrogen bonds are shown by *dashed lines* (C–H···N in *blue*, C–H···O in *red*). Hydrogen atoms not involved in hydrogen bonding omitted for clarity

en-1-one, **4**, with malononitrile in the presence of methanol as solvent and sodium hydroxide as a base, yielded the title compound 6-(2,5-dichlorothiophen-3-yl)-2-methoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile, **5**, Scheme 1. The structure of **5** was established using many spectroscopic techniques and further confirmed by its single crystal structure.

Mass Spectroscopy

The ESIMS spectra of **5** exhibited a pseudomolecular ion peak at *m/z* 413 $[M + Na]^+$, 415 $[M + Na + 2]^+$, 417 $[M + Na + 4]^+$ which confirmed the presence of two chlorine atoms. The molecular formula was determined to be $C_{18}H_{12}Cl_2N_2O_2S$ from the positive ion HRESIMS at *m/z* 412.9896 $[M + Na]^+$, (calcd for $C_{18}H_{12}Cl_2N_2O_2SNa$, 412.9889), Fig. 1.

^{1}H- and ^{13}C-NMR Spectroscopy

The ^{1}H NMR spectrum of **5**, Fig. 1, show the characteristic pattern of a 1,4-disubstituted benzene ring at $\delta = 7.66$ (d, $J = 8.70$ Hz, 2H, H-2″,6″), and 7.08 (d, $J = 8.70$ Hz, 2H,

Table 3 Hydrogen bond parameters (Å, °) in **5**

D–H···*A*	H···*A*	*D*–H	D…A	*D*–H···*A*
C–H···O interactions				
(π)C3–H11···O2[a]	2.451	0.95	3.388	169
H_2C14–H3···O1[b]	2.681	0.98	3.533	145
C–H···N interactions				
(π)C4–H12···N2[a]	2.632	0.95	3.482	149

Symmetry codes: [a](1/2 − x, 1/2 + y,z); [b](1/2 − x, 1.5 − y, −1/2 + z)

H-3″, 5″), two singlets at $\delta = 7.63$ (s,1H), 7.42 (s, 1H) attributed to H-5, H-4′, respectively and two methoxy group at $\delta = 3.91$ (s, 3H, OCH_3-4″), 4.16 (s, 3H, OCH_3-2).

A detailed analysis of the ^{13}C NMR spectrum, Fig. 1, with the aid of HSQC data showed the presence of nine sp^2 quaternary carbons at δ 164.91 (C-2), 161.26 (C-4″), 156.19 (C-4), 151.46 (C-6), 135.69 (C-3′), 128.12 (C-1″), 126.76 (C-5′), 126.15 (C-2′), 93.07 (C-3), four sp^2 methine carbons at 130.00 (C-2″,6″), 127.48 (C-4′), 114.53 (C-3″,5″), 115.65 (C-5) and the signal at 115.72 was attributed to nitrile carbon. In addition the two methoxy groups were appeared at 55.51 (OCH_3-4″), 54.88 (OCH_3-2). The signal at δ 161.26 was assigned to C-4″ on the basis of its correlations observed in a HMBC experiment with the ^{1}H NMR signals at δ 7.66 (H-2″,6″), 7.08 (2H, H-3″, 5″) and 3.91 (OCH_3-4″), and the C-4 signal at 156.19 showed a correlation with the proton at 7.66 (H-2″,6″). In the HMPC spectrum the carbon at δ 164.91 (C-2) showed three bond correlation with the methoxy group at δ 4.16 (OCH_3-2), while C-6 showed correlations with the protons at 7.63 (H-5) and 7.42 (H-4′). Finally all the other carbons were assigned unambiguously based on the complete analysis of the 2D spectra (Fig. 1).

X-ray Structure Analysis

Molecular Structure

The crystallographic asymmetric unit contains one independent molecule of the title compound (Fig. 2). Selected geometrical parameters for the title compound are given Table 2, fall in normal ranges [14–16]. In the title compound, the central pyridine ring carries four substituents, a thiophene ring, a methoxyphenyl ring, a carbonitrile group and a methoxy group. The dichlorothiophene and the methoxyphenyl rings are twisted compared to the pyridine ring with dihedral angles of 36.66 and 40.18°, respectively. The two aromatic rings of the biaryl group are rotated 39.7° against each other while the thienyl group adopts a torsional angle of −33.8°. In the methoxyphenyl ring, the O1–C1 bond length [1.432 (6) Å] is significantly shorter than O1–C2 [1.375 (5) Å], indicating conjugation between oxygen and the ring (C2–C17). On the other hand, the bond angle [C16–C2–O1 = 124.9 (4)°] is larger than the bond angle [C3–C2–O1 = 115.3 (4)°], which correlates will with previously reported similar structures (see for example [14–16]), might be attributed to the steric repulsion between the aromatic rings and the methyl group.

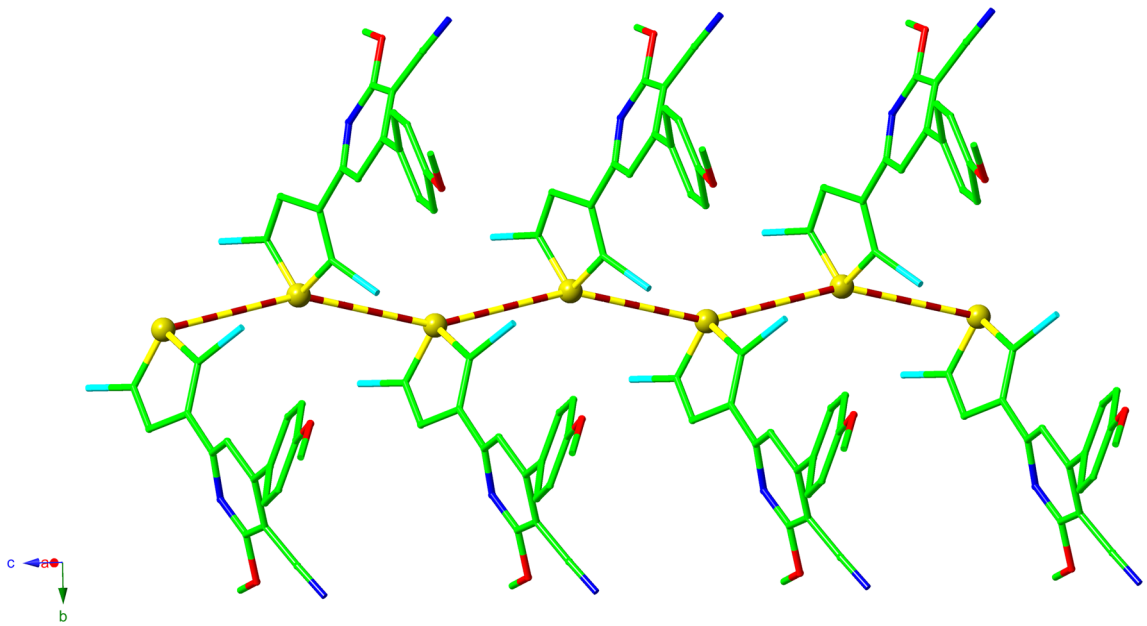


Fig. 4 Intermolecular S···S interactions (*red–yellow* rendered multi-band cylinders) between molecules. S atoms appear as *spheres*. Hydrogen atoms omitted for clarity

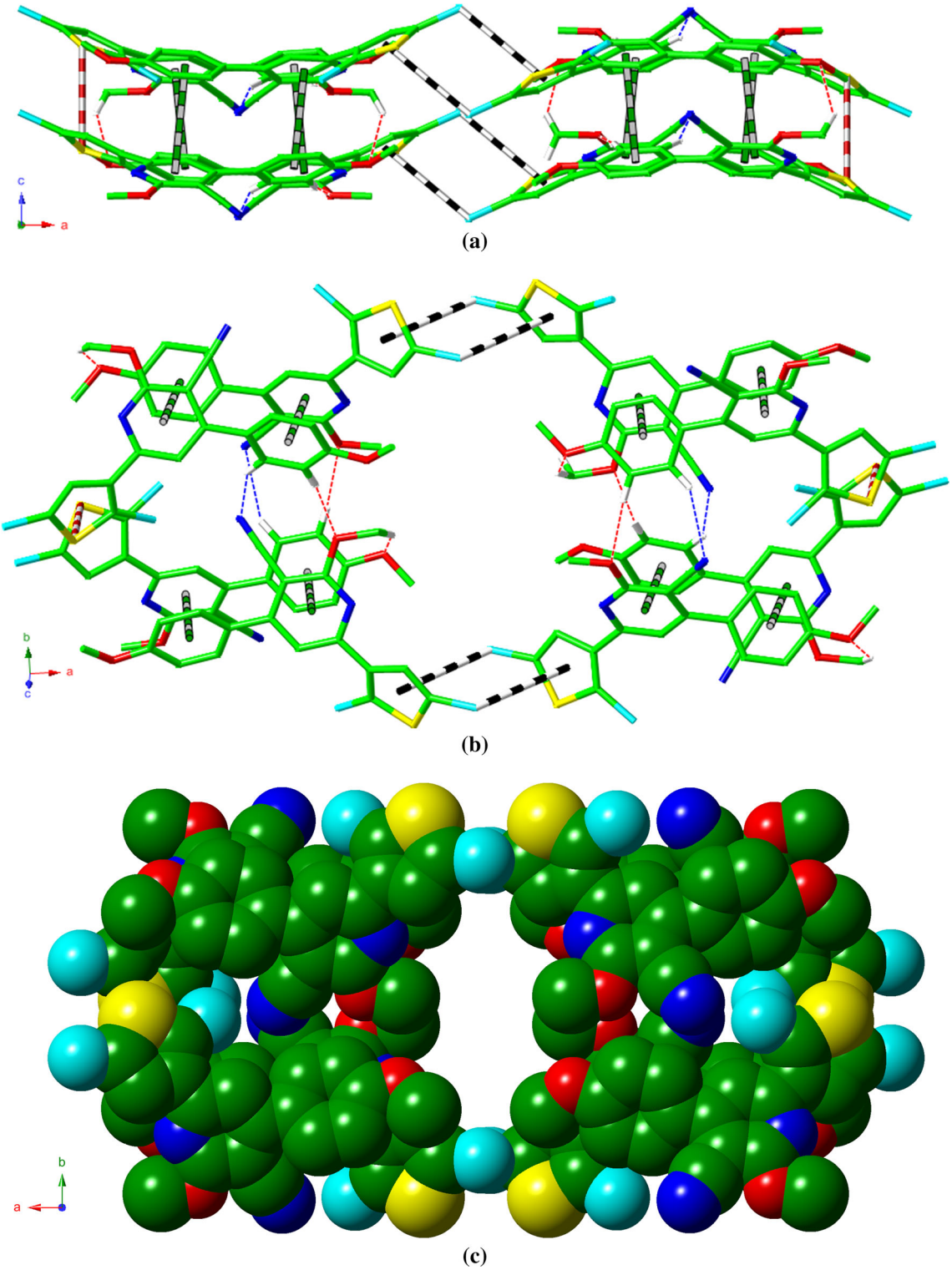


Fig. 5 Partial crystal packing of the title compound: **a** viewed down the *b* axis, showing the layers of molecules in the *bc* plane; **b** another view (*a* is horizontal and *b* is vertical) of the partial packing; **c** Sphere presentation of the packing showing the cavity. Hydrogen bonds are shown by *dashed lines* (C–H···N in *blue*, C–H···O in *red*); π···π interactions shown as *green–gray* multi-band cylinders, while S···S and Cl···π interactions shown as rendered multi-band cylinders (*black* and *white*, and *red–white*, respectively). Hydrogen atoms not involved in hydrogen bonding omitted for clarity

Crystal Supramolecularity

The molecules are interacting extensively via π···π interactions leading to chains parallel to *c*-axis. These interactions result between both the phenyl···pyridine rings where each two molecules interact by two interactions of this type with the centroid···centroid separation distances being 3.589 and 3.906 Å, Fig. 3. The electron rich phenyl ring (by OCH_3 group) and the electron deficient pyridine ring (the presence of N atom) allowing the electron-rich and electron-deficient aromatics to interact in the favored face stacking motif in this case [17]. The resulting chains are also involved in other interactions of the type C–H···O and C–H···N interactions leading to layers in the *bc* plane as depicted in Fig. 3. Detailed geometrical parameters for these interactions are listed in Table 3. Moreover, within these layers, S···S interactions add extra supramolecularity where the molecules are connected in a zigzag assembly through thiophene···thiophene S···S [Fig. 4; S···S (x, 2 − y, −1/2 + z) distance of 3.775 Å] interactions. These layers in *bc* plane interact with next layers parallel to *a*-axis through what is called anion···π interactions [18–20], Fig. 5, manipulating the (thiophene)C–Cl···thiophene (1 − x, y, ½ − z) interactions, C_{aryl}–Cl···π, [C_{aryl}–Cl···(Cg)π distance of 3.949 Å and D–Cl···Cg(π) angle of 116°]. All these intermolecular interactions result in a three dimensional network structure, Fig. 5, with a large cavity which is filled with disordered CH_2Cl_2 molecules (not shown).

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