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Synthesis, crystal structure, characterization, and microbial evaluation of (*E*)-*N*-(4-isopropylbenzylidene)thiophene-2-carbohydrazide

A. Rajavel[a], T. Jeyakumar[b], M. L. Sundararajan[b], T. Srinivasan[c], and D. Velmurugan[d]

[a]Department of Chemistry, Annamalai University; [b]Chemistry Section, Faculty of Engineering and Technology, Annamalai University, Annamalainagar, Tamil Nadu, India; [c]Department of Physics, Vel Tech University, Avadi, Chennai, Tamil Nadu, India; [d]Centre for Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai, Tamil Nadu, India

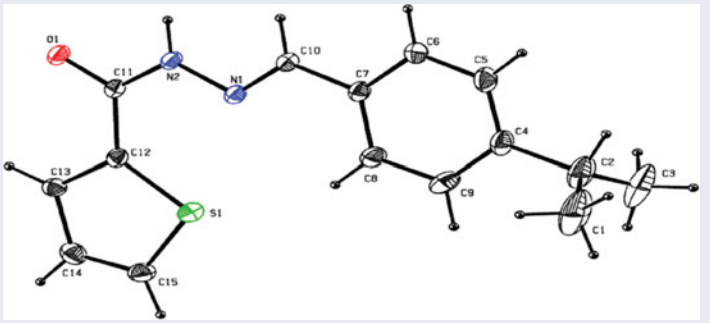
ABSTRACT

(*E*)-*N*-(4-isopropylbenzylidene)thiophene-2-carbohydrazide (L) was prepared and characterized using elemental analysis, UV-visible, IR, ^{1}H and ^{13}C NMR, mass spectra. The crystal structure of L was determined by single-crystal X-ray diffraction method. The compound L crystallizes in monoclinic space group $P2_1/n$ with $a = 16.676(5)$ Å, $b = 5.475(5)$ Å, $c = 17.022(5)$ Å, and $Z = 4$. Antimicrobial and antifungal activity was assayed against four bacterial and four fungal microorganisms. The antioxidant behavior of L was also investigated.

KEYWORDS

Cuminaldehyde:2-thiophene-carboxylic acid hydrazide; mass spectra Anti oxidant properties

GRAPHICAL ABSTRACT



Highlights

- A new hydrazide with thiophene moiety has been synthesized and characterized by spectral techniques.
- The compound was also characterized by single-crystal X-ray diffraction technique.
- Antimicrobial and antioxidant activity of the compound were tested.

CONTACT T. Jeyakumar rvel46@gmail.com

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CCDC No. 1037203 contains the supplementary crystallographic data for this paper. Copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EQ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

1. Introduction

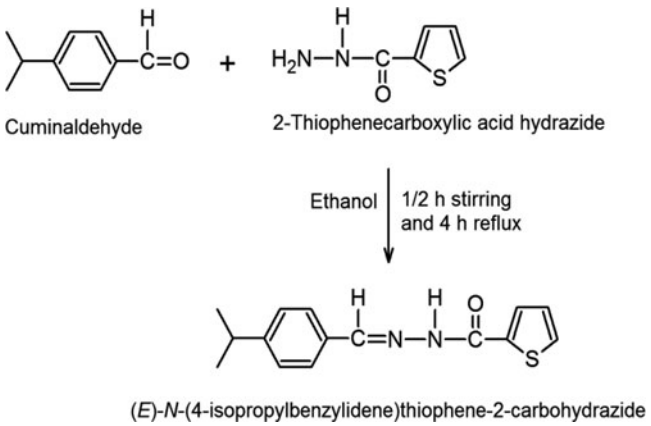
Hydrazides have received special interest due to their potential applications as building blocks in the synthesis of hydrazones, Schiff bases and coordination compounds [1–3]. Hydrazides with thiophene moiety have attracted considerable attention due to the interesting biological and pharmacological activities of 2-thiophene moiety. Several derivatives of thiophenes are used as antibacterial [4–6], anti-inflammatory [7], anticancer [8,9], and antiviral agents [10]. Cuminaldehyde is an important phytochemical and possesses many health benefits. Cuminaldehyde is the major active component of cumin (45–50%), which is a seed spice belonging to the family Umbelliferae. Cumin exhibits strong antioxidant activity superior to known antioxidant ascorbic acid [11]. Cumin has proven antibacterial activity [12], hypolipidemic [13], and antihyperglycemic [14] effects. The antibacterial activity of cumin was found to be comparable with that of standard antibiotics [15]. Cuminaldehyde, isolated from cumine, found to have chemo preventive effects [16].

In view of above, we thought it was worthwhile to synthesis hydrazide with thiophene moiety. Nevertheless, no work has been undertaken concerning the biochemical characterization of hydrazide with thiophene moiety derived from cuminaldehyde. In the present study, we describe synthesis of (*E*)-*N*-(4-isopropylbenzylidene)thiophene-2-carbohydrazide (L) and characterization by elemental analysis, UV-Vis, FT-IR, ^{1}H, ^{13}C NMR, mass spectra, single crystal X-ray diffraction, antibacterial, antifungal, and antioxidant activities of the title compound were also reported.

2. Synthesis

2.1. Synthesis of (E)-N-(4-isopropylbenzylidene) thiophene-2-carbohydrazide (L)

The compound L was prepared by condensation of cuminaldehyde (5 mmol, 0.741 g) and 2-thiophenecarboxylic acid hydrazide (5 mmol, 0.711 g) in 50 mL of absolute ethanol. The resulting mixture was stirred well and refluxed for 4 h. Yellow product was separated by filtration after the mixture concentrated to its half volume and cooled. The product was recrystallized using hot ethanol. Brownish yellow single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of the product dissolved in 10 mL of ethanol at room temperature over a period of five days (Scheme 1). Yield 80%; m.p. 108.7°C MW: 272,



Scheme 1. Synthetic route of Ligand (L).

2-Thiophenecarboxylic acid hydrazide, cuminaldehyde, and 2,2-diphenyl-1-picrylhydrazide (DPPH) were purchased from Sigma Aldrich Chemical Co and used without further purification. A digital Gallenkamp melting point apparatus was used to determine the melting point of the compound. A FT-IR spectrum of the title compound was recorded using Avatar 330 FT-IR spectrophotometer in the range 4000–400 cm^{-1} with KBr disk. ^{1}H and ^{13}C NMR spectra were recorded using Bruker reagent system (400 MHz/84 mm) instrument in $CDCl_3$ solvent and TMS as an internal standard. Perkin Elmer 240 (USA) elemental analyzer was used to carry out elemental (C, H, N, and S) analysis. UV-Vis spectrum was recorded on Shimadzu UV-2450 spectrophotometer. The mass spectrum was recorded on JEOL GCMATE II GC-MS.

X-ray diffraction intensity data was collected for the compound on Bruker AXS SMART APEX II single crystal X-ray diffractometer equipped with graphite monochromated MoKα ($\lambda = 0.7103$ Å) radiation and CCD detector. Crystals were cut to suitable size and mounted on a glass fiber using cyanoacrylate adhesive. The unit cell parameters were determined from 36 frames measured (0.5° phi-scan) from three different crystallographic zones and using the method of difference vectors. The intensity data were collected with an average four-fold redundancy per reflection and optimum resolution (0.75 Å). The intensity data collection, frames integration, Lorentz and polarization correction and decay correction were done using SAINT-NT (version 7.06a) software. Empirical absorption correction (multi-scan) was performed using SADABS program [17].

Well diffusion method [18] was followed to screen the biological activity of the compound against bacterial strains such as *Salmonella typhi, Klebsiellapneumoniae, Pseudomonas aeruginosa*, and *Escherichia coli*. *Candida albicans, Mucor* sp., *Rhizophus* sp. and *Aspergillus fumigatus* as fungal strains. Ciprofloxacin and Amphotericin-B were used as reference. Muller–Hinton agar was used for bacterial and fungal cultures growth. The compound was DMSO soluble. Wells were punched on the agar medium using cork borer with 4 mm of diameter. 10 mg mL^{-1} compound in DMSO were carefully placed into the well using sterile L rod and the plates were incubated for 24 h at 37°C in case of bacteria and for 72 h at 30°C in case of fungi. The inhibition zone diameter was measured in millimeter.

In antioxidant activity determination of the compound, the stable free radical 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) was used as a scavenging agent. Experimental method to determine the antioxidant activity of the compound was followed according with literature [19–21]. Antioxidant ability of the compound was revealed in terms of % inhibition.

3. Results and discussion

The compound L was prepared by condensation of cuminaldehyde and2-thiophenecarboxylic acid hydrazide. The purity of L has been checked with TLC technique using 3:1 benzene/ethyl acetate as the eluent. The elemental analysis data are consistent with the proposed structure of L Anal. Calc. for $C_{15}H_{16}N_2OS$ (%): C (66.15), H (5.92), N (10.29),S (11.74); found (%): C (66.14), H (5.84), N (10.24), S (11.74); the schematic representation of synthesis of L has been depicted in Scheme 1. In this study, we also confirmed the structure by IR, ^{1}H and ^{13}C NMR, mass spectra, and single-crystal X-ray analysis.

3.1. IR, ^{1}H and ^{13}C NMR spectra

The FT-IR spectrum of the compound shows (Fig. 1) a sharp band at 1605 cm^{-1} attributed to azomethine>C = N stretching. The bands appeared at 3163, 3047 and 2959 cm^{-1} are assigned

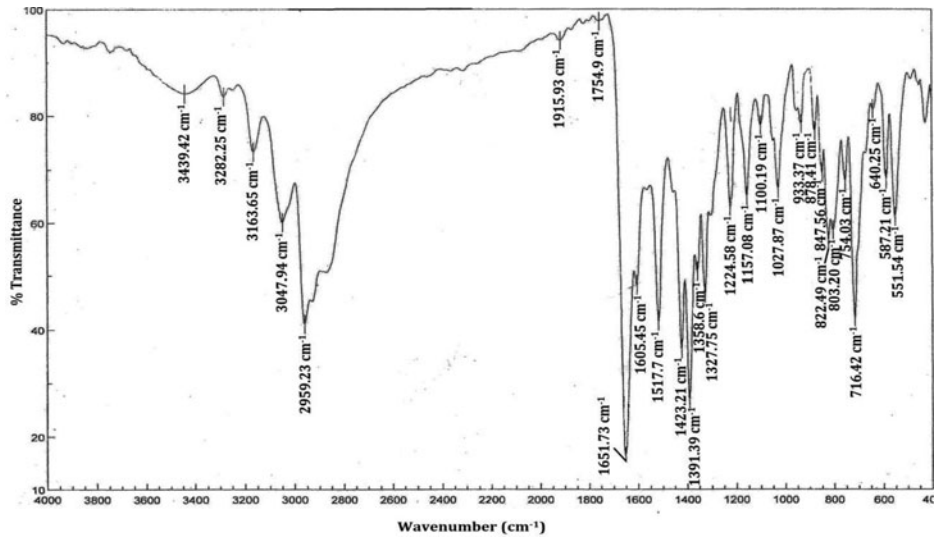


Figure 1. IR spectrum of L.

to ν (N–H), ν (C–H aromatic) and (C–H aliphatic), respectively. A strong band at 1651 cm^{-1} is due to ν (C = O). A sharp band at 847 is assigned to the characteristic ν (C–S –C) thiophene ring [20]. The asymmetric and symmetric stretching of C-S is appeared as sharp band at 754 and 716 cm^{-1}, respectively [21] Formation of L was confirmed by ^{1}H, ^{13}C NMR spectra and is shown in Fig. 2 and 3. A sharp singlet observed at 9.948 ppm is assigned to N–H proton. Theazomethine proton (–C = N–) is appeared as a singlet at 8.249 ppm. The multi signals exhibited at 7.261, 7.744 and 7.922 ppm are attributed to the protons of thiophene ring. Aromatic protons are observed as multi signals at 7.724, 7.327, 7.308 and 7.183 ppm. ^{13}C NMR spectrum of the compound L shows characteristic signal at 163.27 and 145.00 ppm are due to

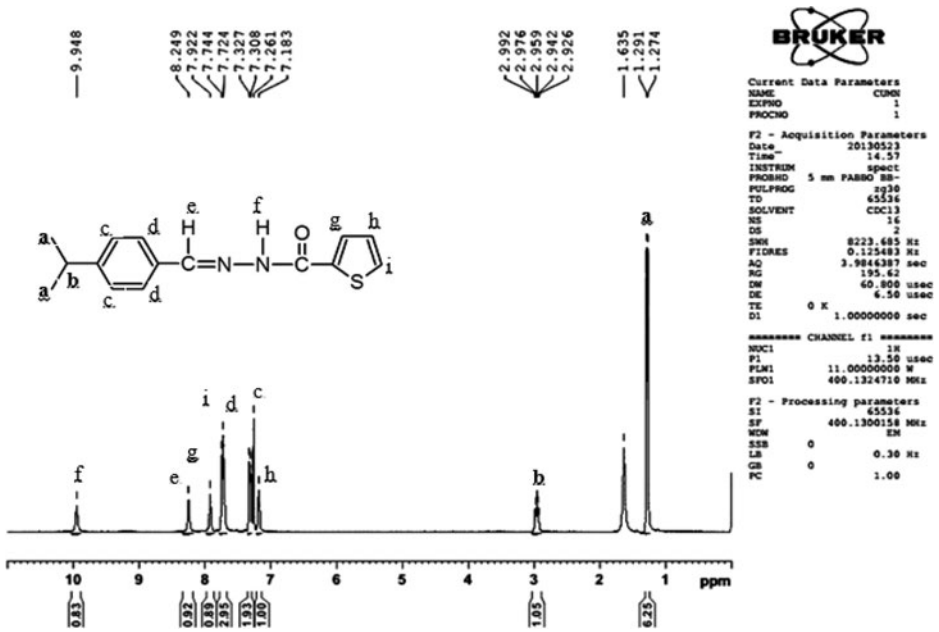


Figure 2. ^{1}H NMR spectrum of L in $CDCL_3$.

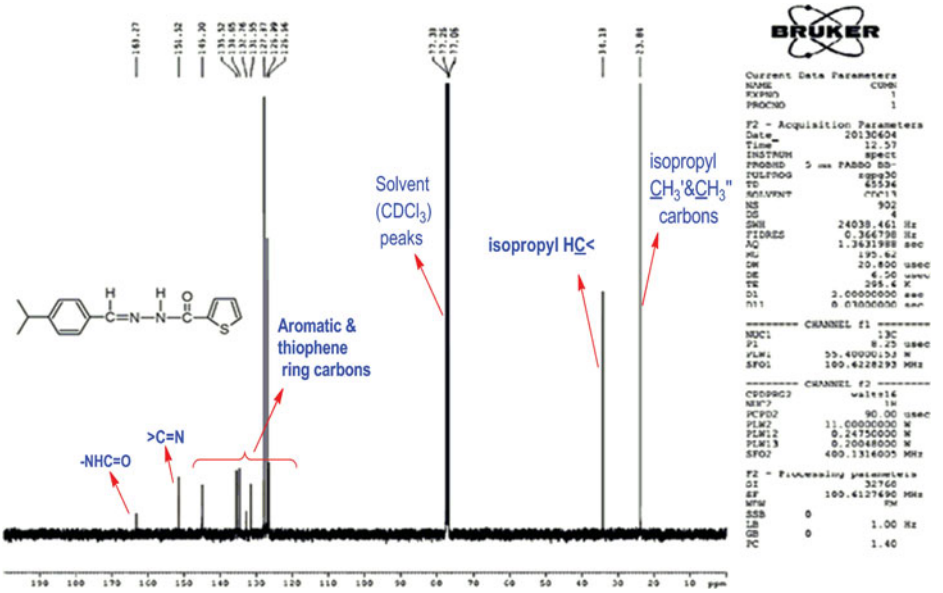


Figure 3. ^{13}C NMR spectrum of L in $CDCL_3$.

>C = O and >C = N carbon, respectively. The aromatic and thiophene ring carbon signals observed at 145.30 to 126.36 ppm. Two isopropyl methyl carbons ($\underline{C}H_3'$ & $\underline{C}H_3''$) are merged together appeared at 23.84 ppm. Another up filed peak at 34.18 ppm is due to isopropyl >$\underline{C}$H carbon atom at *para* position of the phenyl ring.

3.2. Mass spectrum

The mass spectrum of the title compound is shown in Fig. 4. The spectrum confirms the proposed formula by showing peaks at *m*/*z* 273 [M+1] and *m*/*z* 274 [M+2]

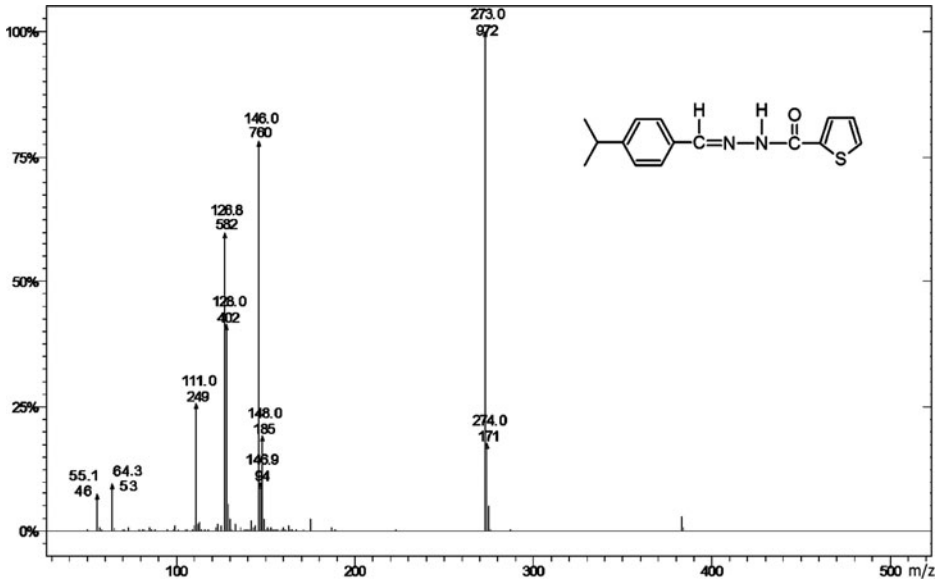
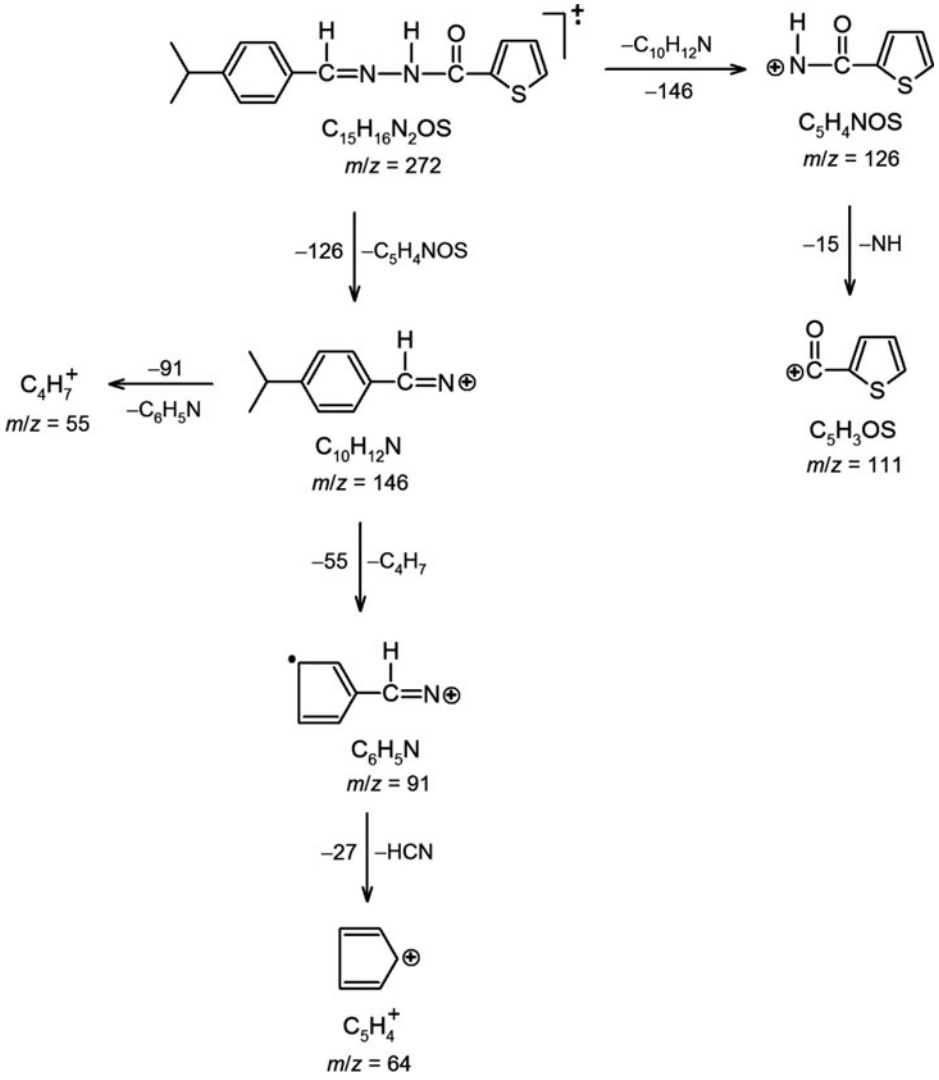


Figure 4. Mass spectrum of L.



Scheme 2. Mass fragmentation pattern of L.

Corresponding to the compound ($C_{15}H_{16}N_2OS$: atomic mass 272). Here the molecular ion peak (*m*/*z* 272) is hiding behind the base peak (100%) [M+1] (*m*/z 273). While, fragmentation, the molecular ion undergoes tow major fragments include (**A**) isopropyl benzylidene ion ($C_{10}H_{12}N^+$; *m*/*z* 146, 80%) and (**B**) thiophene-2-carbohydrazide ion (C_5H_4NSO; *m*/*z* = 126, 60%) (Scheme 2). The fragment ion **A** undergoes further fragmentation to give ion peak at *m*/*z* 55 (2%) which can be attributed to $C_4H_7^+$ ion. Also give another ion radical ($C_6H_5N^+$) at *m*/*z* 91 (3%). This radical ion further loses HCN molecule and form $C_5H_4^+$ at *m*/*z* 64 (3%) [22]. Meanwhile the fragment **B** on further fragmentation gives a molecular ion $C_5H_3OS^+$at *m*/*z* 111 (25%) by losing –NH of mass 15.

3.3. X-Ray crystallography

Fig. 5 shows the molecular structure of the title compound with atom numbering scheme and the displacement ellipsoids are drawn at 30% probability level. The title compound,

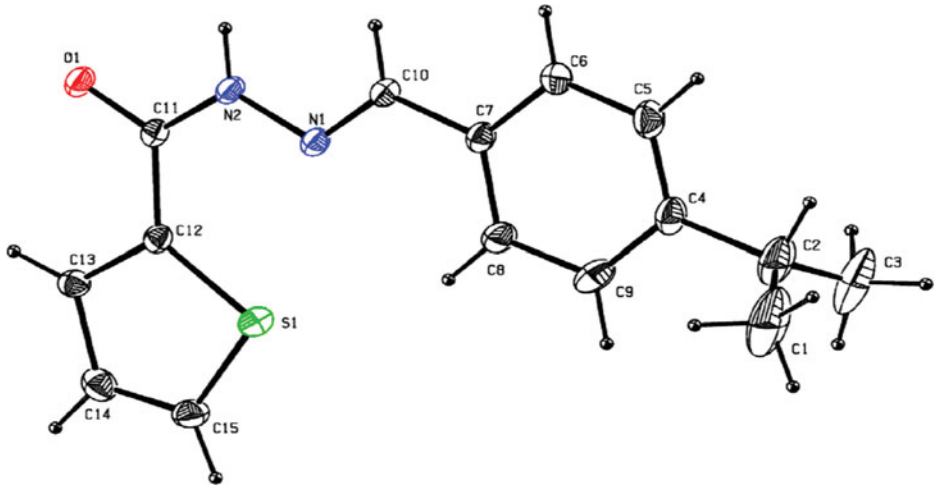


Figure 5. ORTEP of L with atomic numbering scheme.

$C_{15}H_{16}N_2OS$ crystallizes in the monoclinic crystal system with the space group of $P2_1/n$. The thiophene ring (S1/C12–C15) makes a dihedral angle of 5.53(18)° with the phenyl ring(C4–C9). The isopropyl group (C1/C2/C3) makes a dihedral angle of 88.29(34)°with the phenyl ring to which it is attached. The molecule adopts an extended conformation about C10 = N1 bond which is evident from the torsion angles (C11–N2–N1–C10 = 175.4(3)° and C7–C10–N1–N2 = –178.9(3)°). The crystallographic data for the compound is given in Table 1. The

Table 1. Crystal data and structure refinement parameters of L.

Empirical formula	$C_{15}H_{16}N_2OS$
Formula weight	272.36
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	16.676(5)
b (Å)	5.475(5)
c (Å)	17.022(5)
α (°)	90.000(5)
β (°)	109.396(5)
γ (°)	90.000(15)
Volume (Å^3)	1465.9(15)
Z	4
Calculated density (g cm^{-3})	1.234
Absorption coefficient(mm^{-1})	0.215
F(000)	576
Crystal size (mm)	0.35 × 0.30 × 0.25
θ Range for data collection (°)	1.48–28.42
Limiting indices	$-22 \leq h \leq 22$; $-6 \leq k \leq 7$; $-22 \leq l \leq 22$
Reflections collected/unique	13720/3648 [R(int) = 0.0316]
Completeness to θ = 28.42	98.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9483 and 0.9287
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3648/0/174
Goodness-of-fit on F^2	1.030
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0656$, $wR_2 = 0.2033$
R indices (all data)	$R_1 = 0.1232$, $wR_2 = 0.2494$
Largest diff. peak and hole (e Å^{-3})	0.370 and –0.345

Table 2. Bond lengths, bond angles and torsional angles for L.

Atom	Bond length (Å)	Atom	Bond angle (°)	Atom	Torsional angle (°)
C(1)–C(2)	1.364(8)	C(1)–C(2)–C(3)	119.8(6)	C(1)–C(2)–C(4)–C(5)	112.2(7)
C(2)–C(3)	1.447(8)	C(1)–C(2)–C(4)	116.5(5)	C(3)–C(2)–C(4)–C(5)	− 101.8(7)
C(2)–C(4)	1.528(5)	C(3)–C(2)–C(4)	113.9(4)	C(1)–C(2)–C(4)–C(9)	− 68.7(9)
C(4)–C(5)	1.342(6)	C(5)–C(4)–C(9)	117.7(3)	C(3)–C(2)–C(4)–C(9)	77.3(7)
C(4)–C(9)	1.385(6)	C(5)–C(4)–C(2)	122.4(4)	C(9)–C(4)–C(5)–C(6)	− 3.8(7)
C(5)–C(6)	1.387(5)	C(9)–C(4)–C(2)	119.9(4)	C(2)–C(4)–C(5)–C(6)	175.3(4)
C(6)–C(7)	1.385(5)	C(4)–C(5)–C(6)	122.0(4)	C(4)–C(5)–C(6)–C(7)	2.2(6)
C(7)–C(8)	1.380(5)	C(7)–C(6)–C(5)	120.7(4)	C(5)–C(6)–C(7)–C(8)	1.1(5)
C(7)–C(10)	1.459(4)	C(8)–C(7)–C(6)	118.2(3)	C(5)–C(6)–C(7)–C(10)	− 179.0(3)
C(8)–C(9)	1.398(5)	C(8)–C(7)–C(10)	122.0(3)	C(6)–C(7)–C(8)–C(9)	− 2.5(6)
C(10)–N(1)	1.263(4)	C(6)–C(7)–C(10)	119.8(3)	C(10)–C(7)–C(8)–C(9)	177.7(3)
C(11)–O(1)	1.243(3)	C(7)–C(8)–C(9)	119.4(4)	C(5)–C(4)–C(9)–C(8)	2.4(7)
C(11)–N(2)	1.340(4)	C(4)–C(9)–C(8)	121.9(4)	C(2)–C(4)–C(9)–C(8)	− 176.7(4)
C(11)–C(12)	1.471(4)	N(1)–C(10)–C(7)	122.5(3)	C(7)–C(8)–C(9)–C(4)	0.7(6)
C(12)–C(13)	1.436(4)	O(1)–C(11)–N(2)	118.7(3)	C(8)–C(7)–C(10)–N(1)	− 2.4(5)
C(12)–S(1)	1.712(3)	O(1)–C(11)–C(12)	119.3(3)	C(6)–C(7)–C(10)–N(1)	177.7(3)
C(13)–C(14)	1.419(5)	N(2)–C(11)–C(12)	121.9(2)	O(1)–C(11)–C(12)–C(13)	− 1.6(4)
C(14)–C(15)	1.334(5)	C(13)–C(12)–C(11)	120.6(2)	N(2)–C(11)–C(12)–C(13)	178.0(3)
C(15)–S(1)	1.689(4)	C(13)–C(12)–S(1)	112.4(2)	O(1)–C(11)–C(12)–S(1)	177.2(2)
N(2)–N(1)	1.372(3)	C(11)–C(12)–S(1)	127.0(2)	N(2)–C(11)–C(12)–S(1)	− 3.2(4)
		C(14)–C(13)–C(12)	107.8(3)	C(11)–C(12)–C(13)–C(14)	179.3(3)
		C(15)–C(14)–C(13)	115.2(3)	S(1)–C(12)–C(13)–C(14)	0.4(3)
		C(14)–C(15)–S(1)	113.3(3)	C(12)–C(13)–C(14)–C(15)	− 0.1(4)
		C(11)–N(2)–N(1)	121.9(2)	C(13)–C(14)–C(15)–S(1)	− 0.1(4)
		C(15)–S(1)–C(12)	91.25(18)	O(1)–C(11)–N(2)–N(1)	− 179.9(2)
		C(10)–N(1)–N(2)	116.2(2)	C(12)–C(11)–N(2)–N(1)	0.5(4)
				C(14)–C(15)–S(1)–C(12)	0.3(3)
				C(13)–C(12)–S(1)–C(15)	− 0.4(2)
				C(11)–C(12)–S(1)–C(15)	− 179.2(3)
				C(7)–C(10)–N(1)–N(2)	− 178.9(3)
				C(11)–N(2)–N(1)–C(10)	175.4(3)

selected bond length, bond angle, and the torsional angles are represented in Table 2. The packing of the crystal is stabilized by intermolecular N2–H2A···O1 hydrogen bonds which generate $R^2_2(8)$ ring motifs (Fig. 8 and Table 3).

Scanning electron microscopic images were displayed in Fig. 6 at different magnifications, which confirm the external morphology and surface roughness of the as-grown crystals. The photographs showed that the L has appears to be stone-shaped rock-like structures at 3500x level while it is seems to be rod and plate like shaped structures at 1000x and 2000x, respectively. Further, bulk formation of the material has analyzed using powder X-ray diffractions patterns. Sharp peaks indicate the good crystallinity of the material. The experimental pattern was compared with simulated pattern; these were displayed in Fig 7. Almost all the peaks were matches with simulated one and small intensity variations were due to the difference in preferred orientations in both measurements procedures (23,24).

Table 3. Hydrogen bond geometry (Å and °) for L.

Distance (Å)				Angle (°)
D–H···A	D–H	H···A	D···A	D–H···A
N2–H2A···O1^{i}	0.86	2.00	2.861(4)	175

Symmetry codes: 1−x, 1−y, 2−z.

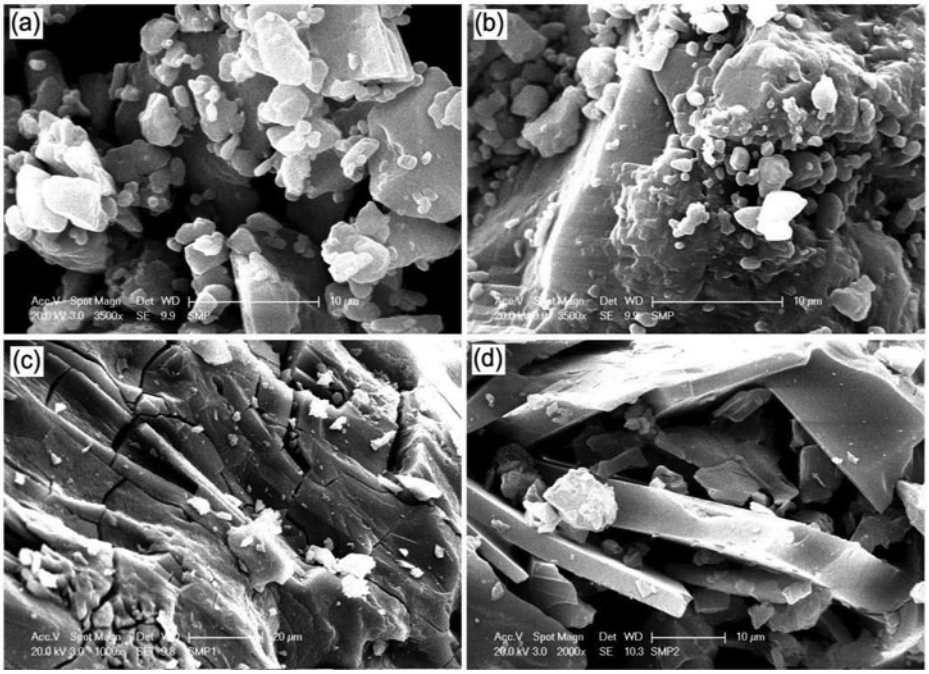


Figure 6. SEM photographs of L at different magnifications: (a, b) 3500×, (c) 1000×, and (d) 2000×.

3.4. Antimicrobial and antioxidant activity

Data on *in vitro* antimicrobial activities of the compound L are presented in Table 4. Four bacterial strains *viz., S. typhi, K. pneumoniae, P. aeruginosa, E. coli* and four fungal strains *C. albicans, Mucorsp*., *Rhizopussp*., and *A. fumigatus* were used to evaluate the antimicrobial

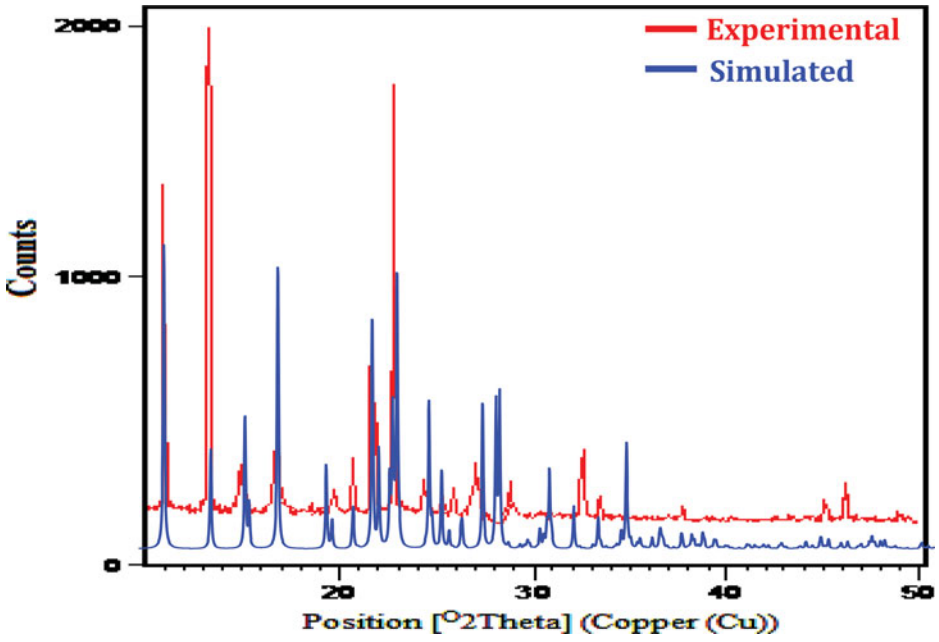


Figure 7. Experimental and simulated powder XRD patterns of L.

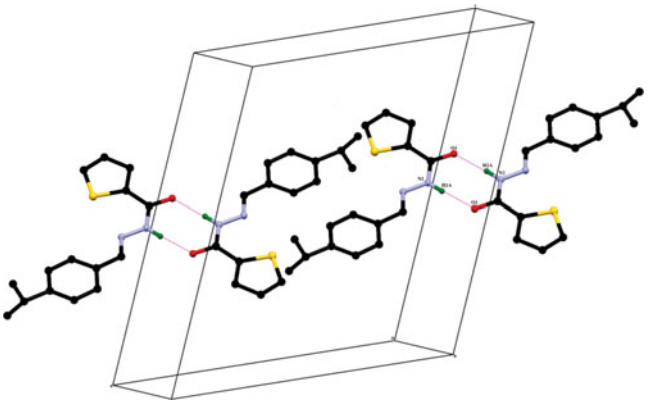


Figure 8. The crystal packing diagram of L.

Table 4. The in *vitro* antibacterial and antifungal activity of L.

	Diameter zone of inhibition (mm)		MIC (μg mL^{-1})	
Microorganism	Reference	L	Reference	L
Antibacterial				
S. typhi	11	7	5.20	100
K. pneumoniae	15	7	4.25	100
P. aeruginosa	15	8	6.25	25
E. coli	16	10	7.25	100
Antifungal				
C. albicans	15	9	6.20	25
Mucor sp.	13	10	4.75	100
Rhizopus sp.	12	11	6.25	100
A. fumigatus	15	8	7.85	25

activity of the compound. Here we used Ciprofloxacin and Amphotercin-B as standards (reference). The activity of the compound towards the bacterial and fungal strain is judged by measuring the zone of inhibition in mm. The results reveal that compound L shows less activity towards the screened microorganisms compared with standards. Furthermore, L shows moderate activity with two bacterial (*P. aeruginosa* and *E. coli*) and two fungal strains (*Mucor* sp. and *Rhizopus* sp.) include MIC values. This remarkable activity of the compound may be due to the presence of thiophene moiety.

Stable free radical DPPH$^{\bullet}$ was used to determine the antioxidant activity of the compound L in terms of radical scavenging capability by using UV-vis spectrophotometer. The color change of DPPH$^{\bullet}$ solution by mixing with the known quantity of the compound in solution from purple to yellow was follow by the decrease in absorbance of the solution at 517 nm. We obtained 60% inhibition, which was moderate when compared with the compound contain OH group [**25**].

4. Conclusion

In summary, a compound (*E*)-*N*-(4-isopropylbenzylidene)thiophene-2-carbohydrazide has been synthesized and characterized. X-Ray crystallographic analysis of this compound suggests that the packing of the crystal is stabilized by intermolecular hydrogen bonds (N2–H2A···O1) and the isopropyl group makes a dihedral angle with the phenyl ring to which it is attached. IR, 1H, 13C NMR and mass spectral fragmentation also supported the

confirmation of the structure L. The antimicrobial activities against four bacterial and four fungal strains showed remarkable results due to the thiophene moiety. The compound L also possessed moderate antioxidant nature.

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