PAPER DETAILS

TITLE: Synthesis, Spectroscopic and Computational Studies of (E)-2-(2,3-dihydroxy)-benzylidene)amino)-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

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Synthesis, Spectroscopic and Computational Studies of (E)-2-(2,3-dihydroxy)-benzylidene)amino)-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

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Abstract

Heteroaromatic Schiff base was synthesized by the reaction of 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile with 2,3-dihydroxybenzaldehyde. Titled compound was characterized by elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C/APT-NMR and X-ray diffraction methods. Imine compound was crystallized in triclinic crystal system with space group P-1. X-ray studies reveal that our molecule is stabilized by O-H···N and C-H···O hydrogen bonds and intermolecular π···π interactions. The molecular structure of Schiff base was optimized by density functional theory (DFT) method using B3LYP/6-311+G(2d,p) quantum set in Gaussian 09W software program. The chemical shifts and geometrical parameters were also computed by the same quantum level and compared with the experimental results of (E)-2-(2,3-dihydroxy)-benzylidene)amino)-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile.

1. INTRODUCTION

Numerous reports on the synthesis of aminothiophenes in literature have been emerged, recently. Substituted alkyl 2-aminothiophene-3-carbocylate are versatile main constituent for the synthesis of agrochemicals, dyes [1], and pharmacologically active compounds [2−4]. A lot of substituted thiophene derivatives are important heterocycles used in drug design [5], biodiagnostics [6], conductivity-based sensors [7] and biological studies [8-11] such as antioxidant [12], antifungal [13], antitumor [14], antibacterial [15], anti-inflammatory [16] and antitubercular activities. However, some studies have been done on Imine compounds and complexes derived from aminothiophenes including cycloalcylthiophene [17]. Imine compounds have been extensively used as starting materials in the synthesis of important drugs such as antibiotics, anti-allergic, anticancer and enzyme inhibitor owing to their biological activities [18–27]. Computer-aided drug design uses computational chemistry to discover, develop or investigate drugs and related biologically active molecules. The most important aim is to predict whether molecule will bind to a target and, if so, how strongly [28].

In this study, a novel Schiff base was prepared by the reaction of 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile with 2,3-dihydroxybenzaldehyde and characterized by using elemental analysis, ^{1}H-NMR, ^{13}C/APT-NMR, FT-IR and X ray diffraction methods. Theoretical calculations invoking structural optimization, geometrical parameters (bond lengths and angles) and chemical shifts for the title compound were performed at the B3LYP methods with the 6-311+G(2d,p) basis set. These studies are precious for providing insight into molecular properties of Schiff base.

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2. EXPERIMENTAL

2.1. Physical Measurements and Chemicals

Elemental analyses (C, H, N and S) was carried out on a LECO-CHNS-O 932 instrument. Melting points were measured without corrections on a Gallenkamp apparatus using a capillary tube, Infrared spectra (4000–400 cm^{-1}) were recorded using a Thermo Nicolet 6700 FT-IR spectrometer on ATR. ^{1}H-NMR spectra was recorded with a Bruker AVANCE III 400 MHz and ^{13}C/APT-NMR spectra was recorded with a Bruker AVANCE III 100 MHz using TMS as an internal standard in d_6-$CDCl_3$. The reagents of analytical grade were purchased from Sigma-Aldrich and used without any further purification.

2.2. The synthesis of 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (1)

Amine compound was prepared according to the procedure described by Gewald [29,30]. A mixture of malononitrile (0.66 g, 0.01 mol), 4-methylcyclohexanone (1.12 g, 0.01 mol) and sulfur (0.32 g, 0.01 mol), morpholine (0.87 g, 0.05 mol) and 15 mL of ethanol were mixed at 50 °C until crude product was precipitated. The reaction mixture was poured into the water, then the resulting solid was collected and recrystallized from ethanol. Yield: 74. Mp: 138-140 °C [31].

2.3. The synthesis of 2-((2,3-dihydroxybenzylidene)amino)-6-methyl-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carbonitrile: general procedure (2)

A mixture of 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (1.92 g, 0.010 mol) and 2,3-dihydroxybenzaldehyde (1.38 g, 0.01 mol) in 15 mL of ethanol was refluxed for 2 hours at 50 °C and cooled at room temperature. The precipitated solid was collected, then washed with cold ethanol and recrystallized from ethanol. The general synthetic route used to prepare imine compound is illustrated in Figure 1.

Yield: 66 %, Mp: 220-221°C. FW: 312.39 g/mol. Anal. Calc. for $C_{17}H_{16}N_2O_2S$ (%): C 65.36, H 5.16, N 8.97, S 10.26. Found: C 68.84, H 4.88, N 8.33, S 9.97. **FT-IR** (ATR, cm^{-1}): 3399 cm^{-1} –OH, 2970 cm^{-1} and 2919 cm^{-1} aliphatic C-H, 2220 cm^{-1} CN, 1619 cm^{-1} C=N. **^{1}H NMR** (400 MHz, $CDCI_3$, ppm): 12.22 (b, 2H, OH), 8.49 (s, 1H, CH=N), 7.10 (dd, 1H, Ar-H), 6.97 (dd, 1H, Ar-H), 6.88 (t, 1H, Ar-H), 2.54-2.85 and 2.33 (m, 4H, CH_2CH_2), 1.95 (m, 2H, CH_2), 1.45 ppm (m, 1H, CH), 1.11 ppm (d, 3H, CH_3). **^{13}C APT NMR** (100 MHz, $CDCI_3$, ppm): **Positive amplitude**: 24.20, 30.20, 33.12, 106.88, 114.01, 117.99, 132.69, 134.98, 144.96, 147.90, 156.81. **Negative amplitude**: 21.24, 29.27, 118.99, 119.99, 123.32, 160.79 ppm.

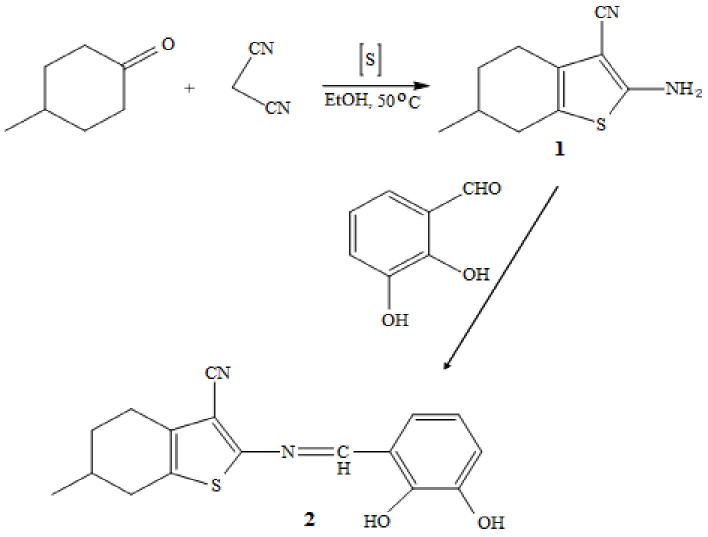


Figure 1. *Synthesis route of Schiff base*

2.4. X-Ray diffraction analysis

Suitable crystals of Schiff base were selected for data collection which was performed on a D8-QUEST diffractometer equipped with a graphite-monochromatic Mo-K_α radiation at 100 K. The structures were solved by direct methods using SHELXS-97 [32] and refined by full-matrix least-squares methods on F^2 using SHELXL-97 from within the WINGX [33] suite of software. All non-hydrogen atoms were refined with anisotropic parameters. H atoms of hydroxyl groups were located in a difference map refined subject to a DFIX restraint. Other H atoms were located from different maps and then treated as riding atoms with C-H distances of 0.93-0.98 Å. The large s.u. values and displacement parameters of some C atoms are caused by the disorder of the benzothiophene. This disorder was modeled as two different orientations with occupancy factors of 0.605(5) and 0.395(5), respectively. Molecular diagrams were created by using MERCURY [34]. Supramolecular analyses were made and the diagrams were prepared with the aid of PLATON [35].

2.5. Computational methods

Computational studies were performed by density functional theory (DFT) by Becke's three-parameter hybrid functional combined with the Lee–Yang–Parr correlation functional (B3LYP) [36-38]. The optimized geometries, chemical shifts and geometrical parameters (bond lengths and angles) were determined using 6-311+G(2d,p) basis set. All calculations were performed with Gaussian 09 software package and GaussView molecular visualization program.

3. RESULTS AND DISCUSSION

This study has been occurred in two stages. In the first stage, we synthesized 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile as amine compound (**1**). In the second stage, we obtained Schiff base by the reaction of 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile with 2,3-dihydroxybenzaldehyde.

3.1. FT-IR spectra

Vibrational spectroscopy is one of the most useful tools for characterization of the chemical compounds in terms of experimental studies. In the FT-IR spectra of Schiff base; (E)-2-((2,3-dihydroxy benzylidene)amino)-6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile, OH stretching band was observed at 3399 cm^{-1}, the aliphatic C-H band was observed at 2970 cm^{-1} and 2919 cm^{-1}, the C-N band was observed 2220 cm^{-1}, the C=N band was observed at 1619 cm^{-1}. In the FT-IR spectra of imine compound, the absorption bands at 1622 cm^{-1} and 1619 cm^{-1} which is typical for the stretching vibrations of imine (CH=N) groups [39]. The FT-IR spectra and wavenumbers of Schiff base are given in Figure 2.

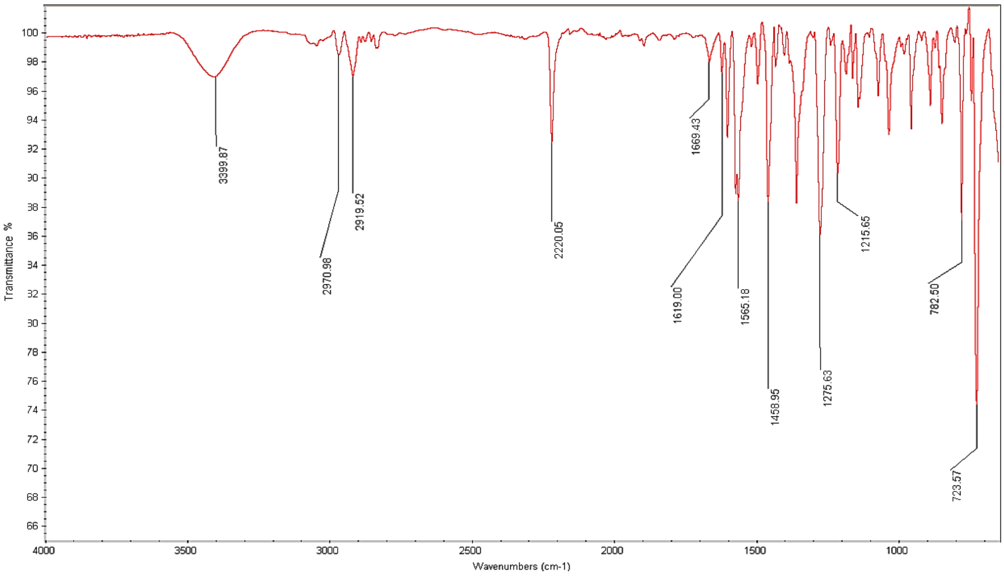
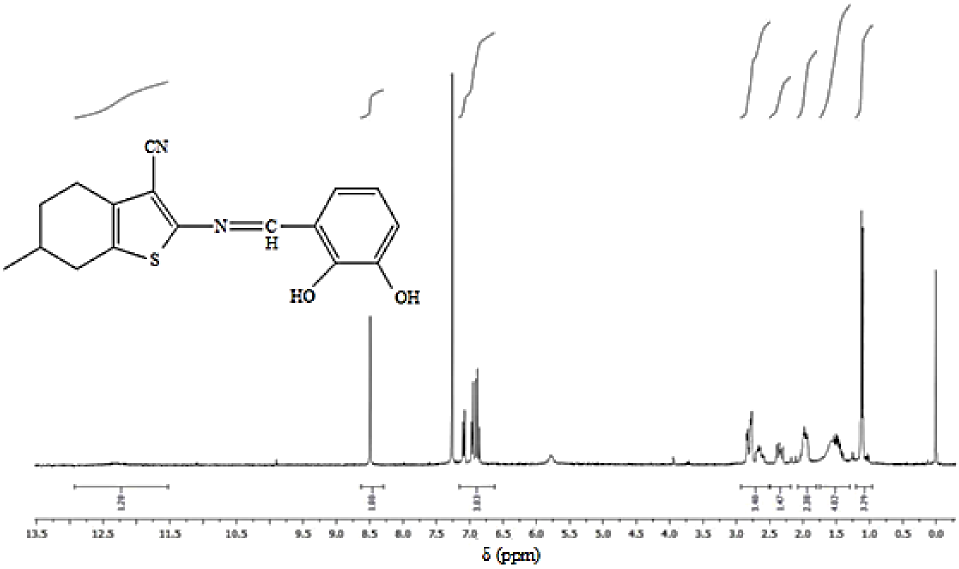


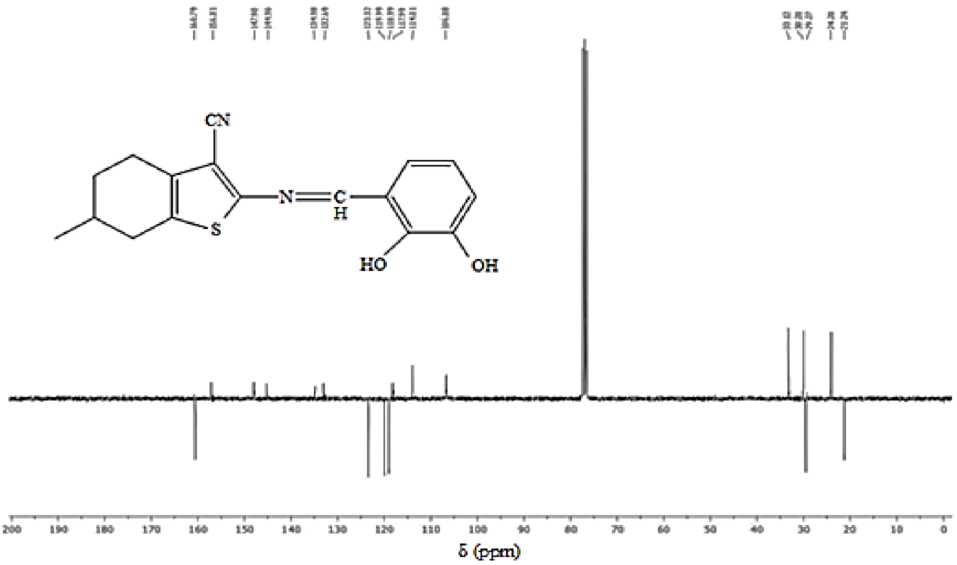
Figure 2. *FTIR spectra of Schiff base*

3.2. NMR spectra

The ^{1}H-NMR and ^{13}C/APT-NMR spectrum of newly synthesized Schiff base has been carried out in d$_6$-CDCl$_3$ at room temperature (Figure 3) The chemical shift values were resoluted for each group for the first time by us. The OH protons at 12.22 ppm as broad peak, imine (CH=N) proton at 8.49 ppm as a singlet [40], aromatic protons at 7.10-6.88 ppm, aliphatic protons at 2.85-1.11 ppm are observed, respectively. The attached proton test (APT) experiment is used as an aid to assignment by separating carbons signals. In ^{13}C NMR spectra, C and CH$_2$ are observed at positive amplitude, CH and CH$_3$ are observed at negative amplitude. The experimental ^{1}H and ^{13}C/APT-NMR spectral data of imine compound are summarized in Table 1.



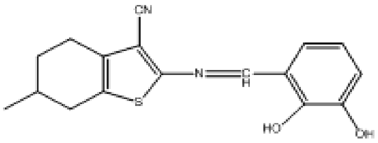
(a)



(b)

Figure 3. *^{1}H-NMR (a) and ^{13}C/APT-NMR (b) spectrum of Schiff base*

Table 1. *The experimental ^{1}H and ^{13}C/APT- NMR data of Schiff base*

	
	Experimental chemical shifts δ (ppm)
^{1}H NMR	12.22 (b, 2H, OH), 8.49 (s, 1H, CH=N), 7.10 (dd, 1H, Ar-H), 6.97- 6.88 (m, 2H, Ar-H), 2.54-2.85 and 2.33 (m, 4H, CH_2CH_2), 1.95 (m, 2H, CH_2), 1.45 (m, 1H, CH), 1.11 (d, 3H, CH_3)
^{13}C-APT NMR	*Positive amplitude:* 24.20, 30.20, 33.12, 106.88, 114.01, 117.99, 132.69, 134.98, 144.96, 147.90, 156.81 *Negative amplitude:* 21.24, 29.27,118.99, 119.99, 123.32, 160.79
	Theoretical chemical shifts (δ, ppm)
^{1}H NMR	9.30 (2H, OH), 8,33 (1H, CH=N), 6.95 (1H, Ar-H), 6.73 (2H, Ar-H), 2.58-2.84 and 2.30 (4H, CH_2CH_2), 1.82 (2H, CH_2), 1.30 (1H, CH), 1.03 (3H, CH_3)
^{13}C-APT NMR	*Positive amplitude:* 28.10, 35.45, 36.85, 113.98, 117.46, 128.43, 141.02, 144.12, 147.98, 152.57, 152.82 *Negative amplitude:* 22.97, 34.07, 118.23, 123.05, 125.65, 171.32

3.3. Description of the crystal structure

The molecular structure of Schiff base with the atom numbering schemes are shown in Figure 4. The N2-C16 bond distance [1.151 (3) Å] is typical N≡C triple bond while the N1-C7 bond distance 1.293 (2) Å is typical N═C double bond.

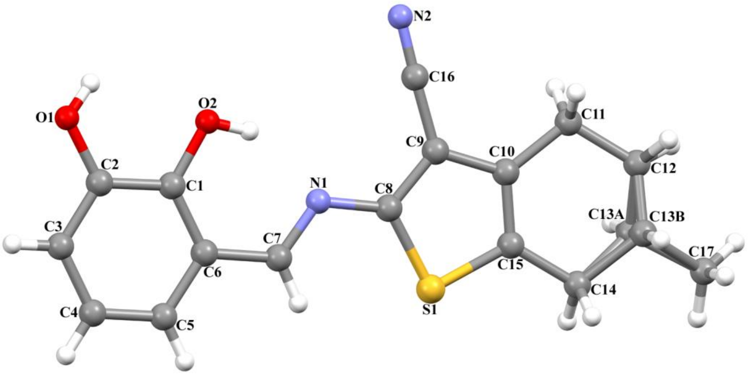


Figure 4. *The crystal structure of Schiff base showing the atom numbering scheme*

Crystal data and structure refinement parameters of Schiff base are given in Table 2. The experimental and calculated bond lengths and bond angles of compound are presented in Table 3. Schiff base is connected to other molecules through O-H···N and C-H···O atoms by hydrogen bonds (Table 4) [41]. Atom O1 atom acts as hydrogen-bond donor via atom H1 to atom N2 in the molecule at (-x+1, -y, -z), forming a centrosymmetric $R_2^2(22)$ ring centered at (1/2, 0, 0). Similarly, C3 atom acts as hydrogen-bond donor via atom H3, to atom O1 in the molecule at (-x, -y, -z-1), forming centrosymmetric $R_2^2(8)$ ring centered at (n+1, 0, n+1/2) (n = zero or integer). The combination of hydrogen bonds generate edge-fused $R_2^2(8)R_2^2(22)$ rings which is running parallel to the [101] direction (Fig. 5). The imine compound also contains two $\pi\cdots\pi$ interactions and all of $\pi\cdots\pi$ interactions give one-dimensional framework which is running parallel to the [001] direction (Fig. 6 and Table 5).

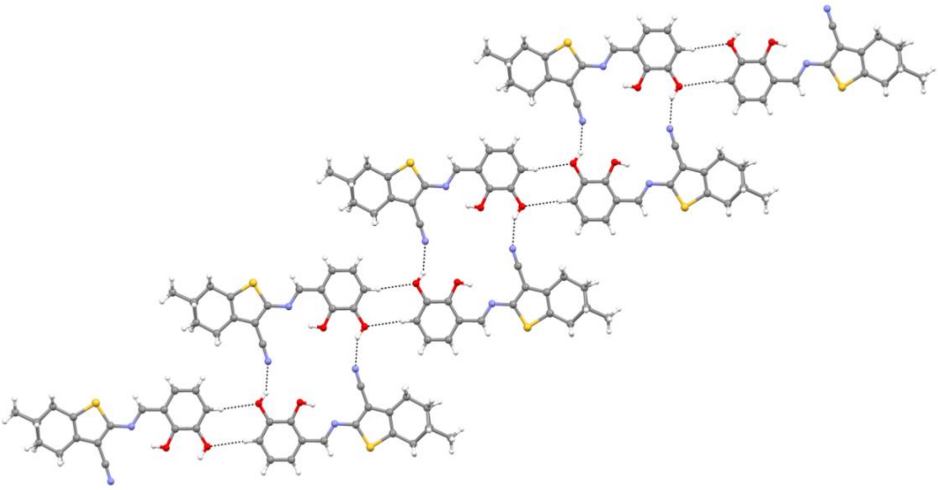


Figure 5. *Crystal structure of Schiff base with the formation of edge-fused* $R_2^2(8)R_2^2(22)$

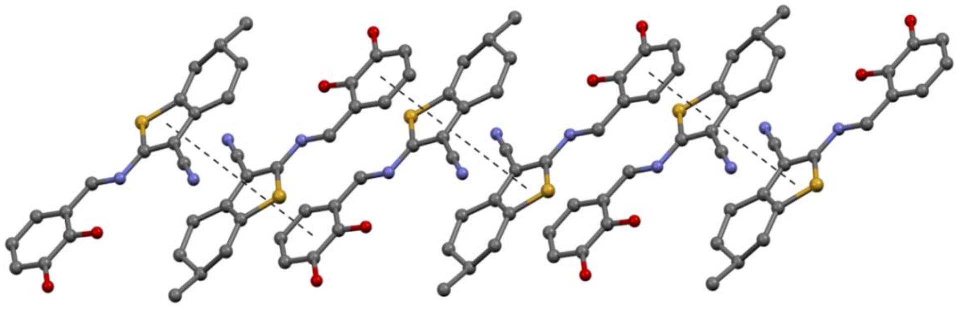


Figure 6. *Crystal structure of Schiff base with formation of chain along [001]generated by* $\pi\cdots\pi$ *interactions*

Table 2. *Crystal data and structure refinement parameters of Schiff base*

Empirical formula	$C_{17}H_{16}N_2O_2S$	Z	2
Formula weight(g/mol)	312.38	D_c (g cm^{-3})	1.394
Crystal system	Triclinic	μ (mm^{-1})	0.23
Space group	P-1	T (K)	100
a (Å)	8.4285 (5)	θ range (º)	3.4-28.3
b (Å)	9.3960 (5)	Measured refls.	28673
c (Å)	10.5957 (5)	Independent refls.	2916
α (º)	115.317 (2)	R_{int}	0.024
β (º)	95.932 (3)	S	1.08
γ (º)	95.944 (2)	R1/wR2	0.046/0.111
V (Å^3)	744.21 (7)	$\Delta\rho_{max}/\Delta\rho_{min}$ (eÅ^{-3})	0.67/-0.68

Table 3. *Selected bond lengths and angles of Schiff base*

Assign.	Exp.	Calc.*	Assign.	Exp.	Calc.*	Assign.	Exp.	Calc.*
				bond lengths (Å)				
C1—O2	1.358 (2)	1.361	C5—C6	1.408 (3)	1.407	C8—N1	1.385 (2)	1.362
C1—C2	1.402 (3)	1.400	C6—C7	1.445 (3)	1.455	C15—S1	1.7324 (18)	1.744
C1—C6	1.409 (3)	1.402	C7—N1	1.293 (2)	1.285	C8—S1	1.7381 (19)	1.768
C2—O	1 1.369 (2)	1.378	C14—C15	1.498 (3)	1.499	C16—N2	1.151 (3)	1.154
C2—C3	1.384 (3)	1.382	C8—C9	1.377 (3)	1.385	C10—C15	1.360 (3)	1.362
C3—C4	1.395 (3)	1.398	C9—C10	1.430 (2)	1.434	C10—C11	1.504 (2)	1.505
C4—C5	1.376 (3)	1.380	C9—C16	1.433 (3)	1.421	C11—C12	1.521 (3)	1.5348
				bond angles (º)				
O2—C1—C2	116.82 (17)	119.84	C5—C6—C1	119.13 (17)	118.75	C10—C15—C14	125.07 (17)	125.21
O2—C1—C6	123.26 (16)	120.19	C5—C6—C7	119.51 (17)	121.67	C15—C10—C9	111.77 (16)	123.40
C2—C1—C6	119.92 (17)	119.97	C1—C6—C7	121.36 (17)	119.58	C10—C15—S1	112.31 (14)	112.21
O1—C2—C3	119.35 (17)	124.54	N1—C7—C6	122.49 (17)	121.75	C15—C10—C11	122.34 (17)	122.20
O1—C2—C1	120.90 (17)	114.86	C9—C8—N1	124.51 (17)	123.95	C14—C15—S1	122.59 (14)	122.59
C3—C2—C1	119.74 (18)	120.59	C9—C8—S1	110.18 (14)	109.51	C9—C10—C11	125.89 (16)	125.40
C2—C3—C4	120.58 (17)	119.71	N1—C8—S1	125.30 (14)	126.54	N2—C16—C9	177.0 (2)	177.39
C5—C4—C3	120.31 (18)	120.19	C8—C9—C16	123.00 (17)	122.69	C10—C11—C12	111.88 (16)	111.43
C4—C5—C6	120.31 (18)	120.71	C10—C9—C16	123.09 (16)	123.14	C15—S1—C8	91.81 (9)	91.71

* by DFT/ B3LYP/6–311+G(2d,p) quantum set

Table 4. *Hydrogen bonds parameters (Å) for Schiff base*

D-H···A	D-H	H···A	D···A	D-H···A
C3-H3···O1^{i}	0.93	2.58	3.497 (2)	168
O1-H1···N2^{ii}	0.83 (2)	2.17 (2)	2.907 (2)	148
O2-H2···N1	0.834 (2)	1.91 (2)	2.655 (2)	149

Symmetry codes: (i) −x, −y, −z−1; (ii) −x+1, −y, −z

Table 5. *π···π interactions distances (Å) for Schiff base*

Cg(1)	Cg(1)^{i}	4.094	3.569
Cg(1)	Cg(2)^{ii}	3.505	3.366

Symmetry codes: (i) 1-x, 1-y, 1-z; (ii) 1-x, 1-y, -z; Cg(1)=S1/C8/C9/C10/C15; Cg(2)=C1-C6

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SUPPLEMENTARY MATERİAL

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1420259. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors

REFERENCES

[1] Yen, M. S., Wang, I.J. “Synthesis and absorption spectra of hetarylazo dyes derived from coupler 4-aryl-3-cyano-2-aminothiophenes”, Dyes Pigm., 61: 243-250, (2004).

[2] Nikolakopoulos G, Linden J, Figler H, Scammells P. J. “2-Aminothiophene-3-carboxylates and Carboxamides as A1 Adenosine Receptor Allosteric Enhancers”, Bioorg. Med. Chem., 14: 2358–2365, (2006).

[3] Lütjens, H., Zickgraf, A., Figler, H., Linden, J., Olsson, R. A., Scammells P.J. “2-Amino-3-benzoylthiophene allosteric enhancers of A1 adenosine agonist binding: new 3,4-,and 5-modifications”, J. Med. Chem., 46: 1870-1877, (2003).

[4] Pillai, A. D., Rani, S., Rathod, P. D., Xavier, F.P. Vasu, K. K., Padh, H., Sudarsanam, V. “QSAR studies on some thiophene analogs as anti-inflammatory agents: enhancement of activity by electronic parameters and its utilization for chemical lead optimization”, Bioorg. Med. Chem., 13: 1275-1283, (2005).

[5] Wu, C., Decker, E. R., Blok, N., Bui, H., You, T. J., Wang, J., Bourgoyne, A. R., Knowles, V., Berens, K. L., Holland, G. W., Brock, T. A., Dixon, R. A. F. “Discovery, modeling, and human pharmacokinetics of N-(2-Acetyl-4,6-dimethylphenyl)-3-(3,4-dimethylisoxazol-5-ylsulfomayl)thiophene-2-carvoxamide (TBC3711), a second generation, ETA selective, and orally bioavailable endothelin antagonist.”, J. Med. Chem., 47: 1969-1986, (2004).

[6] Doré, K., Dubus, S., Ho, H., Alévesque, I., Brunette, M., Corbeil, G., Boissinot, M., Boivin, G., Bergeron, M. G., Boudreau, D., Leclerc, M. “Fluorescent polymeric transducer for the rapid, simple and specific detection of nucleic acids at the zeptomole level”, J. Am. Chem. Soc., 126: 4240-4244, (2004).

[7] Vriezema, D. M., Hoogboom, J., Velonia, K., Takazawa, K., Christianen, P. C. M., Maan, J. C., Rowan, A. E., Nolte, R. J. M. “Vesicles and polymerized vesicles from thiophene-containing rod-coil block copolymers”, Angew. Chem., 42: 772-776, (2003).

[8] Noack, A., Hartmann, H. “Synthesis and characterization of N,N-disubstituted 2-amino-5-acylthiophenes and 2-amino-5-acylthiazoles”, Tetrahedron, 58: 2137-2146, (2002).

[9] (a) Jagodzinski, T. S. “Thioamides as useful synthons in the synthesis of heterocycles” Chem. Rev., 103: 197-227 (2003). b) Heyde, C., Zug, I., Hartmann, H. “A simple route to N,N-dialkyl derivatives of 2-amino-5-thiophenecarboxylates”, Eur. J. Org. Chem., 3273-3278, (2000).

[10] Zeika, O., Hartmann, H. "Preparation and characterization of 3,4-diaryl substituted 2-diarylaminothiophenes" Synthesis, 3: 377-380, (2004).

[11] Zeika, O., Hartmann, H. "On the oxidative coupling of N,N-disubstituted 2-aminothiophenes synthesis of N,N'-persubstitited 5,5'-diamino-2,2'-bithiophenes", Tetrahedron 60: 8213-8219, (2004).

[12] Kumar, K. P., Mohan, S., Saravanan, J., Prakash, K. V., Raju, N. A., Rao, J. V. Int. J. Chem. Sci., 5 (2007) 1284–1290.

[13] Katada, J., Iijima, K., Muramatsu, M., Takami, M., Yasuda, E., Hayashi, M., Hattori, M., Hayashi, Y. "Cytotoxic effects of NSL-1406, a new thienopyrimidine derivative, on leukocytes and osteoclasts", Bioorg. Med. Chem. Lett., 9(6):797-802, (1999).

[14] Narlawar, R., Lane, J. R., Doddareddy, M., Lin, J., Brussee, J., Jzerman, A. P. "Hybrid ortho/allosteric ligands for the adenosine A1 receptor", J. Med. Chem., 53: 3028–3037, (2010).

[15] Kemnitzer, W., Sirisoma, N., May, C., Tseng, B., Drewe, J., Cai, S. X. "Discovery of 4-anilino-N-methylthieno[3,2-d]pyrimidines as potent apoptosis inducers", Bioorg. Med. Chem. Lett., 19: 3536–3540, (2009).

[16] Fakhr, I. M. I. Radwan, M. A. A., El-Batran, S., Omar, M. E., El-Salam, A. El-Shenawy, S. M. "Synthesis and pharmacological evaluation of 2-substituted benzo[b]thiophenes as anti-inflammatory and analgesic agents", Eur. J. Med. Chem., 44: 1718–1725, (2009).

[17] Mohanan, K., Devi, S. N. Murukan, B. "Complexes of copper(II) with 2-(N-salicylideneamino)-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[b]thiophene containing different counter anions", Synth. React. Inorg. Met.-Org. Nano-Met. Chem., 36: 441–449, (2006).

[18] Desai, S. B., Desai, P. B., Desai, K. R. "Synthesis of some Schiff bases, thiazolidones, and azetidinones derived from 2,6-diaminobenzo[1,2-d:4,5-d′]bisthiazole and their anticancer activities", Heterocyclic Commun., 7(1):83–90, (2001).

[19] Karia, F. D., Parsania, P. H. "Synthesis, biological and thermal properties of Schiff bases of bisphenol-C", Asian J. Chem., 11: 991-995, (1999).

[20] Aktan, E., Balaban Gündüzalp, A., Özdemir Özmen, Ü. "Structural, physicochemical characterization, theoretical studies of carboxamides and their Cu(II), Zn(II) complexes having antibacterial activities against E. Coli", J. Mol. Struc., 1128: 775-784, (2017).

[21] Singh, W. M., Dash, B. C. "Synthesis of some new Schiff bases containing thiazole and oxazole nuclei and their fungicidal activity", Pesticides, 22: 33-37, (1988).

[22] Murhekar, MM. and Khadsan, RE."Synthesis of Schiff bases by organic free solvent method." J. Chem. Pharm. Res., 3(6):846-849, (2011).

[23] Salman, S. R., Shawkat, S. H., Al-Obaidi, G.M. "Tautomerism in o-hydroxy Schiff bases: effect of alkyl group", Canadian J. Spect. 35: 25-27, (1990).

[24] Gavranić, M., Kaitner, B., Meštrović, E. "Intramolecular N−H···O hydrogen bonding, quinoid effect and partial π-electron delocalization in N-aryl Schiff bases of 2-hydroxy-1-naphthaldehyde: the crystal structures of planar N-(α-naphthyl)- and N-(β-naphthyl)-2-oxy-1-naphthaldimine." J. Chem. Cryst., 26: 23–28 (1996).

[25] Ünver, H., Zengin, D. M., Güven, K. "Intramolecular hydrogen bonding and tautomerism in 1-[N-(4-bromophenyl)] aminomethylidene-2(1H)naphthalonene", J. Chem. Crystallogr., 30: 359–364, (2000).

[26] Cannor, J. A., Fine, D. J. "Studies of chelation. Part 9. Cobalt complexes of 1-[(substituted phenyl)azo]-2-naphthol and 1-[(substituted phenylimino)methyl]-2-naphthol ligands. Tautomerism and Reactivity", J. Chem. Soc., Dalton Trans., 559–566, (1981).

[27] Özmen, Ü. Ö., Aktan, E., Balaban Gündüzalp, A., Özbek, N., Sarı, M., Çelik, Ö., Saydam, S. "Characterization, antibacterial, anticarbonic anhydrase II isoenzyme, anticancer, electrochemical and computational studies of sulfonic acid hydrazide derivative and its Cu(II) complex", Inorg. Chim. Acta, 423: 194-203, (2014).

[28] Geromichalou, E.G., Trafalis, D. T., "Overview on the current status on virtual high-throughput screening and combinatorial chemistry approaches in multi-target anticancer drug discovery; Part II", J. Buon, 21:1337-1358 (2016).

[29] Peet, N. P., Sunder, S., Barbuch, R. J., Vinogradoff, A. P. "Mechanistic observations in the Gewald syntheses of 2-aminothiophenes", J. Heterocyclic Chem., 23: 129–134, (1986).

[30] Altundaş, A., Sarı, N., Çolak, N., Öğütçü, H. "Synthesis, biological activity of new cycloalkylthiophene-Schiff bases and their Cr(III) and Zn(II) Complexes", Med. Chem. Res., 19: 576-588, (2010).

[31] Nitinkumar, S. S., Lamani, R. S., Imtiyaz, A. M. K. "Synthesis and antimicrobial activity of some novel thienopyrimidines and triazolothienopyrimidines", J. Chem. Sci., 121: 301-307, (2009).

[32] Sheldrick, G. M. "A short history of SHELX", Acta Cryst. A64: 112-122, (2008).

[33] Farrugia, L. J. "WinGX suite for small-molecule single-crystal crystallography", J. Apply. Cryst., 32: 837-838, (1999).

[34] Mercury, version 3.0; CCDC, available online via ccdc.cam.ac.uk/products/mercury.

[35] Spek, A. L. "PLATON-a multipurpose crystallographic tool." Utrecht University, Utrecht (2005).

[36] Çatıkkaş, B., Aktan, E., Yalçın, E. "Vibrational and electronic investigations, NLO, FMO analysis on a hetarylazoindole disperse dye by density functional theory", J. Mol. Struc. 1117: 216-226 (2013).

[37] Aktan, E., Çatıkkaş, B. "Infrared and Raman spectra, DFT investigation of the tautomerism, conformational equilibrium, structure and vibrational assignment of 1-(2-benzothiazolyl)-3-methyl pyrazol-5-one." Vib. Spec. 67:92-100 (2013).

[38] Aktan E., Elmaci G., Aktan E., Seferoğlu N., Hökelek T., Seferoğlu Z. "Synthesis, molecular structure and computational study of (Z)-2-((E)- 4-nitrobenzylidene)hydrazone)-1,2-diphenylethan-1-one." J. Mol. Struc. 1099: 83-91 (2013).

[39] Uddin, M. N., Chowdhury, D. A., Rony, M., Halim, E. "Metal complexes of Schiff bases derived from 2-thiophenecarboxaldehyde and mono/diamine as the antibacterial agents", Modern Chem. 2: 6-14 (2014).

[40] Ahmed, R. M., Yousif, E. I., Al-Jeboori, M. J. "Co(II) and Cd(II) Complexes Derived from Heterocyclic Schiff-Bases:Synthesis, Structural Characterisation, and Biological Activity", 2013: 1-6 (2013).

[41] Aziz, A. N., Taha, M., Ismail, N. H., Anouar, El-H., Yousuf, S., Jamil, W., Awang, K., Ahmat, N., Khan, K. M., Kashif, S. M "Synthesis, Crystal Structure, DFT Studies and Evaluation of the Antioxidant Activity of 3,4-Dimethoxybenzenamine Schiff Bases", Molecules 19: 8414-8433 (2014).