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Synthesis, identification, thermal analysis, computational, and antibacterial studies of *Z*-N'-(5-bromothiophen-2-yl)methylene)nicotinohydrazide

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Abstract:

N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide Schiff base was isolated and characterized as Z-isomer. Ethanoic reflux condensation of equivalent amount of nicotinohydrazideand with 5-bromothiophene-2-carbaldehyde produced the desired compound in good yield. The condensation reaction was monitored by FT-IR and UV-visible as well as DFT calculation. The structure of desired compound wasexperimentally analyzed based on: elemental analysis, EI-Ms, UV-visible, FT-IR spectral, TG/DTG and ^{1}H-NMR.DFT-computational calculation supportedZ- isomer as favorited product over E one, good accordance between experimental and theoretical calculated were recorded. The antibacterial results obtained using the desired compound indicates a promising result against human pathogenic bacteria.

***Keywords**: FT-IR, condensation, TG, Schiff bases, DFT.*

1. Introduction

Schiff bases ligands as organic azomethine [–RC=N–] ligand prepared classically by condensation of ketones or aldehydes with 1^{o} amines under acidic reflux condition [1]. In the last years, such of ligand have been studied broadly and have received high attention because of their attractive chemical and physical properties [2-8]. Versatile Schiff base ligands have many applications, such as: catalysts in hydrogenation and oxidation of olefins [8–10], in photochromic industry [11-14] and as fluorescent sensors for toxic metal ions [12-16].

It is known that the coordination ability of such compounds was enhanced due to the presence of >C=N– group, mono, di or poly-dentate modes were recorded [15-19], for the same reason Schiff base have been extensively served as good ligands for transition metal ions complexes, moreover, due to their facile syntheses, electronic properties, strong electron donation, good solubility and easily tunable steric [10].

In recent years, complexes have gained much importance as medicinal drugs. They are in use, as medicines for the treatment of anti-inflammatory, diabetes, cancer, and cardiovascular disease [2–7]. The extensive applications of Schiff bases and their complexes including the biological activities are as antifungal, antibacterial, antioxidant, anti-inflammatory, antitumor, tubercular and antiviral agents [10-16].

Recently we prepared a series of Schiff base ligands for their own structural analysis [20-23], some of these compounds have served as chelate ligands to prepare metal ion complexes for structural and biological analysis [16-22].

In this work, we have point our efforts across the synthesis, structural characterization, computational analysis and antibacterial properties of Z-N'-((5-bromothiophen-2-yl)methylene)-nicotinohydrazide (Scheme 1). The synthetic reaction was monitored by both FT-IR and UV-visible to follow up the condonation reaction. The described product here also can be used as novel bidentate ligands which will be future work.

2. Materials and methods

2.1. Reagents and measurements

Nicotinohydrazide, 5-bromothiophene-2-carbaldehyde were from Aldrich, all solvents were used as received and without any purification. Melting points were obtained by a Thermo Scientific 9100 apparatus. EI-MS data was obtained on a Finnigan 711A (8 kV) (PerkinElmer Inc., Waltham, MA, USA). ^{1}HNMR spectra were recorded on 300 MHz Bruker Advance spectrometer using $CDCl_3$ solvent; chemical shifts (d) are given in ppm. The IR spectra for samples were recorded using Perkin Elmer Spectrum 1000 FT-IR Spectrometer. The UV-visible spectrum was measured by using a TU-1901 double-beam UV–visible spectrophotometer. TG spectrum was measured by using a TGA-7 PerkinElmer thermogravimetric analyzer (PerkinElmer Inc., Waltham, MA, USA).

2.2. Theoretical measurements

Full geometry TD-DFT, HOMO/LUMO and optimization of N'-((5-bromothiophen-2-yl)methylene)-nicotinohydrazidewere carried out using density functional theory (DFT) at the B3LYP level [23]. All calculations were carried out using the GAUSSIAN 09 program package with the aid of the GaussView visualization program [24]. GaussView was used to calculate the fractional contributions of various groups to each molecular orbital [25].

2.3. General procedure to synthesis

N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazidewas prepared following literature [15-22]: to the stirred solution of 5-bromothiophene-2-carbaldehyde (1.1mmol) in absolute ethanol (10 mL) was added dropwise a solution of nicotinohydrazide(1mmol) in absolute ethanol (15 mL) and the resulting colorless solution refluxed for 5 h. The product separated on evaporation of the solvent was filtered, washed with n-hexane.

2.4 Biological evaluation

The antimicrobial activity of the prepared compound were tested against the following microbial strains: Escherichia coli (ATCC 25922), Staphylococcus aureus (ATCC 25213),) Klebsiella pneumoniae (ATCC 13883), Bacillus subtilis (ATCC 6633), Bacterial strains were stocked onto nutrient agar slant. All slants were stored at 4 °C. Disc diffusion method was used to study the antimicrobial activity. Stock of the desired

compound was initially dissolved in ethanol and sterilized by filtration using 0.45 μm membrane filters. Sterile 6 mm diameter filter paper disc was soaked with 0.1 mg/disc of the sterile compound and was placed in triplicates onto Muller–Hinton agar (Oxoid, England) plates for bacterial strains. These plates were previously inoculated separately with 100 μL (1.0×10^8 CFU m L^{-1}) of fresh culture of bacteria suspension. The plates were incubated for 24 h at 37 °C. After incubation, the inhibition zone around each disc was measured and recorded. Reported inhibition zones are the average calculated from three replicates. Discs soaked with sterile water were used as a negative control. While standard antibacterial tetracycline (30 μg/disc) and (Oxoid, Basingstoke, UK) were used as positive controls in the assay.

3. Results and Discusions

3.1. Synthesis of N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide

Z-N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazidewas synthesized by condensing equimolar amounts of nicotinohydrazide with 5-bromothiophene-2-carbaldehyde in absolute ethanol at reflux condition for 4h, as shown in Scheme 1.

Scheme 1. Synthesis of Z/(E)- N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide

The product is gray powder with110 ^{o}C melting point, complete soluble in dichloromethane and THF, partially soluble in ROH, insoluble in water and non-polar solvents like *n*-hexane.To enhance the yield of reaction slightly excess amount of aldehyde was added to the mixture, the unreacted residue was washed out at the end of the reaction by excess *n*-hexane solvent. The expected Z/E isomer formation was judged by molecular geometry computational calculation.

3.2. Molecular geometry

In order to identify the favored isomer (Z or E) of N'-((5-bromothiophen-2-yl) methylene) nicotinohydrazidestructure optimizationmolecular structure of desired compound was obtained by DFT-B3LYP/6-311+G(d,p) levelalong with numbering of atoms is shown in Fig. 1.

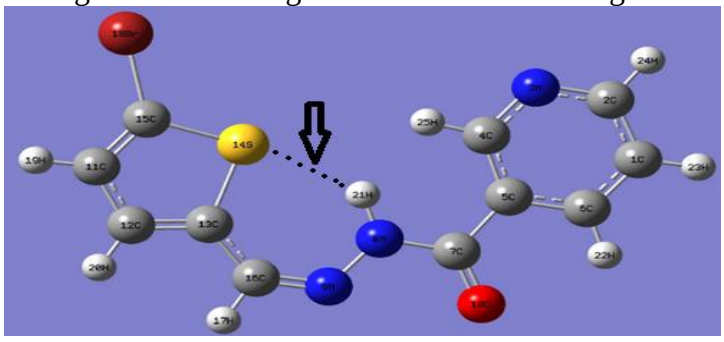

Fig. 1. Optimized geometrical structure of Z/(E)- N'-((5-bromothiophen-2-yl)methylene)-nicotinohydrazide.

Z-isomer was found to be the optimized molecular structure of desired compound, this may be due to the farther stabilization of such isomer due to formationof intra H-bond between N-H….S withsemi six-member ring cyclic stabilization, as libeled in Fig. 1

3.3. The elemental analysis and mass spectroscopy

The elemental analysis of N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide is consistent with the proposed molecular formula (Calcd. for $C_{11}H_8BrN_3OS$: C, 42.60; H, 2.60; N, 13.55. Found: C, 42.42; H, 2.74; N, 13.45). EI-MS of the compound is in good agreement with the assigned structure, the experimental molecular ion [M^+] *m/z* = 308.2 (310.2 theoretical).

3.4. FT-IR investigation

In order to monitor the reaction with IR, the starting materials before and after it react to produce the desired compound were subjected to IR measurements, as seen in Fig. 2.

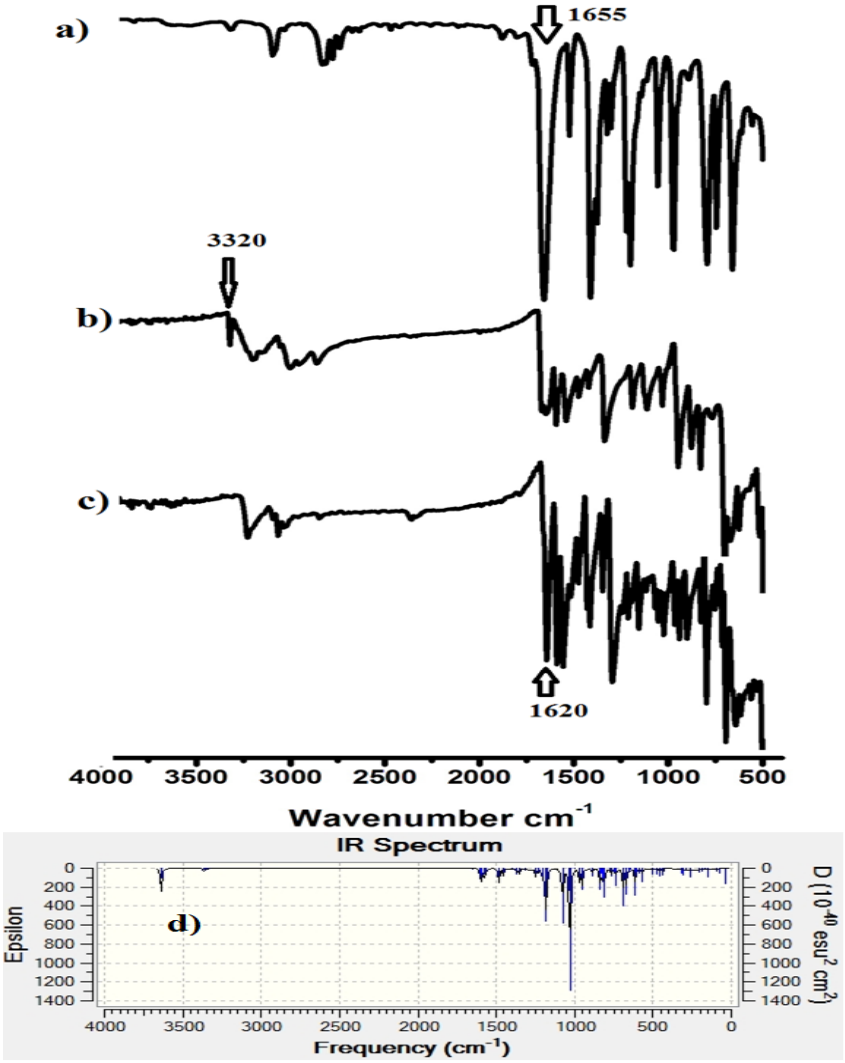

Fig.2. IR spectra of: a) 5-bromothiophene-2-carbaldehyde (starting material), b) nicotinohydrazide (starting material) and c) Z-N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide (product) d) calculated with B3LYP 6-31G(d,p).

The formation of the product was easily monitored by: disappearance of N-H_2stretching vibration belongs to nicotinohydrazide at 3320 $cm^{-1}$when condensate with 5-bromothiophene-2-carbaldehyde, as in Fig. 2b and

2c. The C=O of 5-bromothiophene-2-carbaldehyde at 1655 cm^{-1}shifting down to 1620 cm^{-1} due to formation of C=N function group belongs to N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide, as seen in Fig. 2a and 2c. The harmonic vibrational frequencies calculated for the desired compound at B3LYP level using the 6-31G(d,p) basis sets along with infrared intensities. Comparison of the experimental frequencies with calculated at B3LYP was represented in Fig. 2c and 2d. As expected the calculated vibration modes revealed higher values compared with experimental, in general the calculated result is in a good agree with experimental.

3.5. Frontier molecular orbital analysis

The ability of the molecule to donate an electron is associated with the HOMO and the characteristic of the LUMO is associated with the molecule's electron affinity. The HOMO and LUMO energies are very useful to gauge the chemical reactivity of the molecule and are very important terms in quantum chemistry [26, 27]. The electronic absorption corresponds to the transition from the ground to the first excited state and is mainly described by one electron excitation from the HOMO to the LUMO. The pictorial representation of the HOMO and the LUMO in the gaseous phase is shown in Fig. 3.

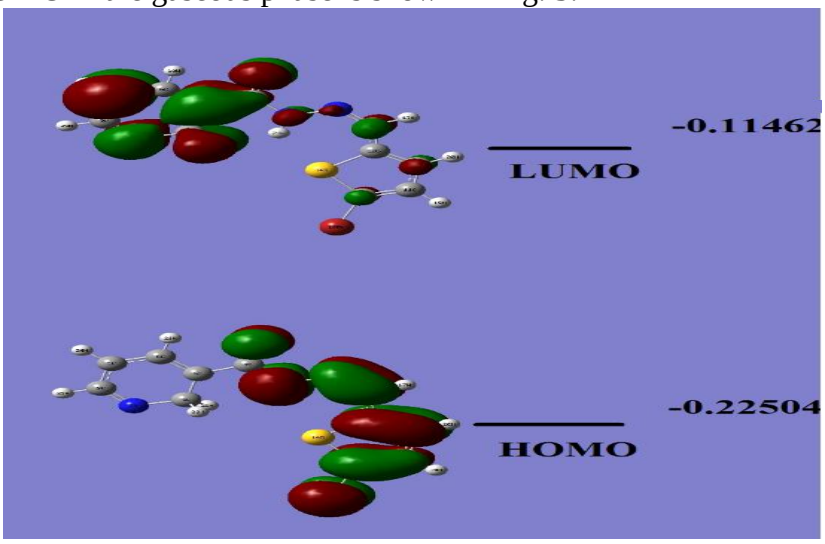

Fig. 3. HOMO and LUMO plots of N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide.

The HOMO lies at -0.22504 a.u and whereas the LUMO is located at -0.11462 a.u with 0.110 a.u the frontier orbital energy gap. It is more easily are the electrons excited from the ground to the excited state with this low energy gap. The energy gap explains the eventual charge transfer interaction within the molecule and is useful in determining molecular electrical transport properties [26, 27].

3.6. Electronic absorption

The electronic absorption spectra of the starting materials and prepared compound in EtOH was monitored before and after reflux by Uv-visible, as seen in Fig. 4a-c.Before refluxa) nicotinohydrazide which revealed broad electron transition maxima at 260 nm,b) 5-bromothiophene-2-carbaldehyde with two electron transition maxims at 255 and 300 nm, after refluxedc) new electron transfer maxims at 265 and 330 nm was observed due to formation of *Z*-N'-(5-bromothiophen-2-yl)methylene)nicotinohydrazide. All electron absorbance in both starting and product material were resonated π-n or π-π* electron transition.

Ultraviolet spectra analysis of the product have been investigated by TD-DFT/B3LYP/3-311 method in ethanol. As can be seen from Fig. 4d the UV–vis spectra absorption maxima values havebeen found to be less than 400 nm, which in agree with the experimental value as seen in Fig. 4c.

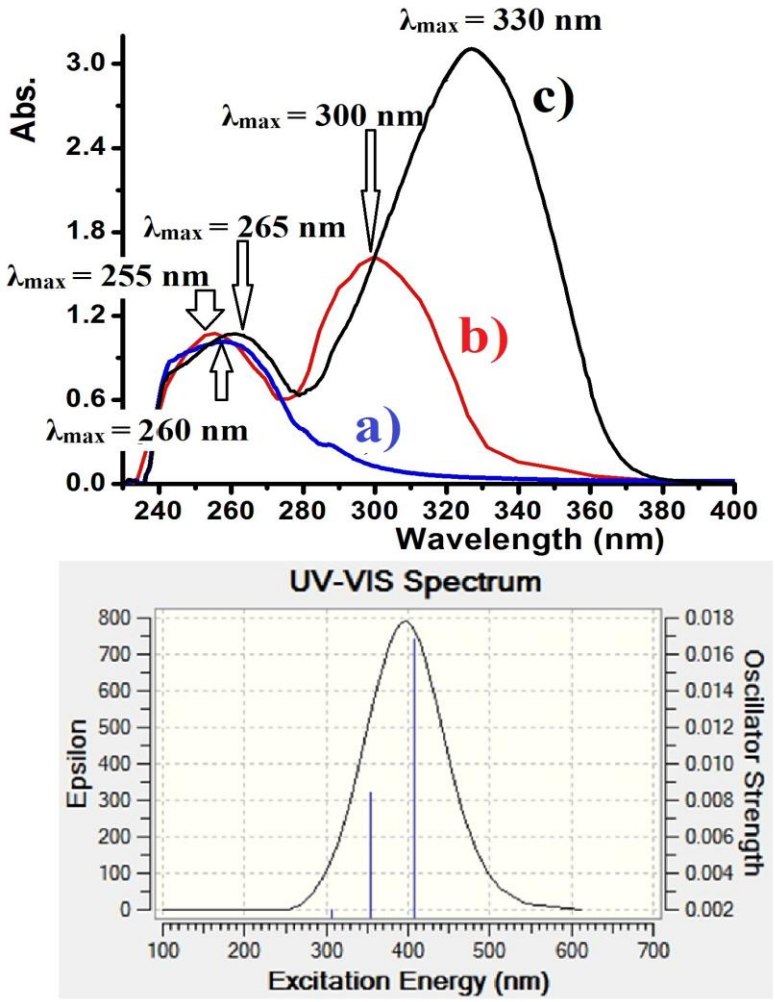

Fig. 4. UV–Vis spectra of a) nicotinohydrazide, b)5-bromothiophene-2-carbaldehyde and c)Z-N'-(5-bromothiophen-2-yl)methylene)nicotinohydrazidein EtOH at RT, d)TD-DFT/B3LYP/3-311(product).

3.7.^{1}H NMR spectral analysis

In the ^{1}H-NMR spectrum (in $CDCl_3$) of the desired compound revealed several types of protons as seen in Fig. 5, all of these protons were sited to high chemical shifts 6.7-10.5 ppm. The ^{1}H-NMR chemical shifts and their splitting supported the combination of thiophene and nicotino parts to form Z-N'-(5-bromothiophen-2-yl)methylene)nicotinohydrazide product without any other impurities or strange signals. The high chemical shift of N-H at ~ 10.5 ppm may be resonated to the H-bond formation with S of thiophene (N….H….S, see Fig. 1 above) due to Z-isomer formation. The ^{1}H-NMR chemical shifts and their splitting of each protons were libeleddirectly to their position as seen in Fig 5

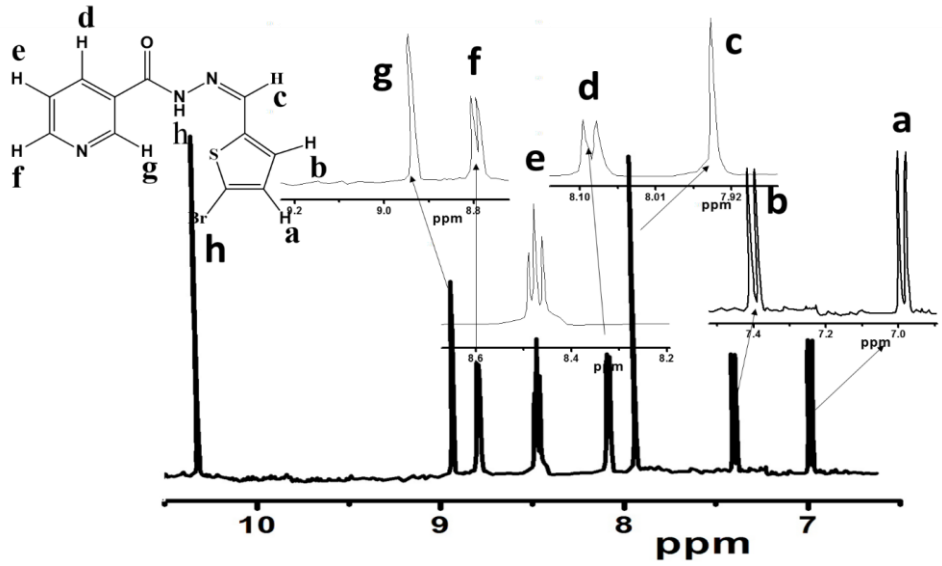

Fig. 5. ^{1}H NMR spectrum of Z-N'-(5-bromothiophen-2-yl)methylene)nicotinohydrazidein $CDCl_3$ at RT.

3.8. TG/DTG analysis

The thermal properties TG/DTG of the Z-N'-(5-bromothiophen-2-yl)methylene)nicotinohydrazide was investigated under an open atmosphere in the range of 0–260 °C and heating rate of 10 °C/min. Fig. 6 showed simple decomposition process with one broad step typical decomposition, started from 100 °C and end at 150 °C with weight loss ~98% and without intermediate decomposition step.

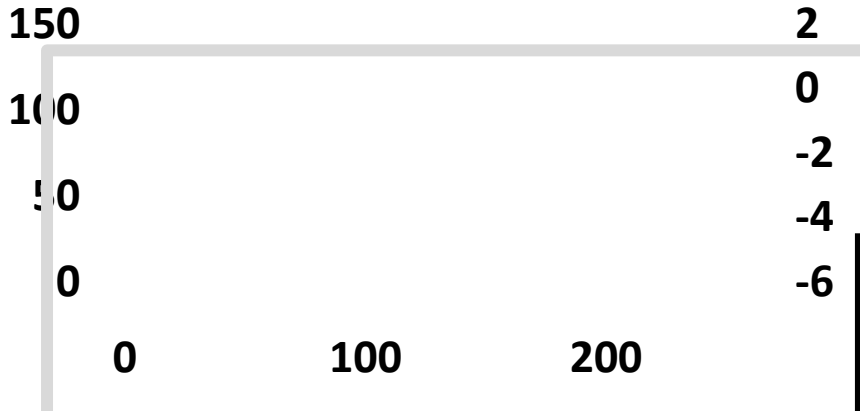

Fig.6. TG/DTG thermal curve of the desired compound at heating rate of 10 °C/min.

3.9. Antibacterial assay

In order to evaluate the antimicrobial activity of the compound, the synthesized compound was tested against several microbial strains (E. coli, S. aureus, K. pneumoniae and B. subtilis). The highest activity of the compound was against S. aureus with inhibition zone of 16.7 mm. The same compound exhibited moderate activity against E. coli, K. pneumonia and B. subtilis; with inhibition zones of 15.4, 13.8 and 11.9 mm, respectively. Weak activity of the tested compound was observed against B. subtilis with inhibition zones less than 12 mm as in Fig. 7. The compound was able to target Gram positive and Gram-negative bacteria indicating a broad-spectrum antimicrobial activity

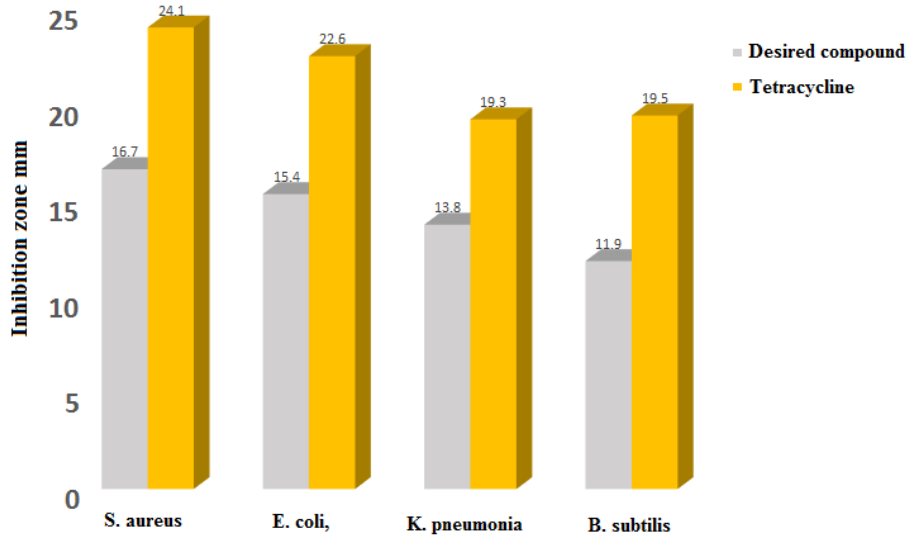

Fig. 7. Antimicrobial activity (mm inhibition zone diameter) of 0.1 mg/ml of the desired compound.

4. Conclusion

New Schiff bases of Z-N'-((5-bromothiophen-2-yl)methylene)nicotinohydrazide was synthesized by condensing of nicotinohydrazide with 5-bromothiophene-2-carbaldehyde in good yield. The desired compound was characterized by various spectroscopic, thermal techniques and comupoutorial calculation. Theoretical calculations carried out by B3LYP level of theory. Based on the theoretical calculation and experimental physical measurements Z- isomer is favored formed over E one. The results show a good accordance between experimental and calculated values. The compound was also in vitro evaluated for the antibacterial activities against human pathogenicbacteria.

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References

[1] H. Schiff, *Ann. Chem.*, 131 (1864) 118–119.
[2] S. Ghozlan, M. Al-Omar, A. Amr, K. Ali, A. El-Wahab, *J. Heterocycl. Chem.*, 48 *(*2011) 1103-1110.
[3] V. Kuz'min, A. Artemenko, R. Lozytska, A. Fedtchouk, V. Lozitsky, E. Muratov, A. Mescheriakov, *Environ. Res*., 16 (2005) 219–230.
[4] J. Costamagna, J. Vargas, R. Latorre, A. Alvarado, *Coord. Chem. Rev.*, 119 *(*1992) 67–88.
[6] L. Shi, H. Ge, S. Tan, H. Li, Y. Song, H. Zhu, R. Tan, *Eur. J. Med. Chem.*, 42 *(*2007) 558–564.
[7] G.Huang, Y. Liang, X. Wu, W. Liu, Y. Ma, *Appl. Organomet. Chem.*, 17 *(*2003) 706–710.
[8] M. Behpour; S. Ghoreishi; M. Salavati-Niasari, *Mater. Chem. Phys*., 107 (2008) 153–157.
[9] Y. Elerman, M. Kabak, A. Elmali, *Z., Naturforsch. B Chem. Sci.*, 57 *(*2002) 651– 656.
[10] M. Sonmez, A. Levent, M. Sekerci, Russ. *J. Coord. Chem*. 30 (2004) 655–659.
[11] S.P. Fricker, *Dalton Trans*. 43 (2007) 4903–4917.
[12] R.R. Crichton, D.T. Dexter, R.J. Ward, *Coord. Chem. Rev*. 252 (2008) 1189–1199.
[13] R. Cini, G. Tamasi, S. Defazio, M.B. Hursthouse, *J. Inorg. Biochem*. 101 (2007) 1140–1152.
[14] H. L. Singh, M. Sharma, A.K. Varshney, *Synth. React. Inorg. Met.-Org. Chem*. 30 (2000) 445–456.

[15] Z. H. Chohan, M. Praveen, A. Ghaffer, *Synth. React. Inorg. Met.-Org. Chem*. 28 (1998) 1673–1687.
[16] M. Azam, I. Warad, S. Al-Resayes, N. Alzaqri, M. Khan, R. Pallepogu, S. Dwivedi, J. Musarrat, M. Shakir, *J. Molec. Strut.*, 104 (2013) 48–54.
[17] I. Warad, A. Khan, M. Azam, S. Al-Resayes, S. Haddad, *J. Molec. Strut.*, 1062 *(*2014) 167–173.
[18] I. Warad, A. Khan, M. Azam, S. Al-Resayes, M. Khan, P. Ahmad, M. Al-Nuri, Sh. Jodeh, A. Husein, S. Haddad, B. Hammouti, M. Al-Noaimi, *Inorg. Chem. Comm.*, 43 (2014) 155–161.
[19] S. Resayes, I. Warad, M. Choudhary, A. Wahab, S. Rasheed, *USA Patent office*, (2014) *USA 2014/0221429A1*., P4.
[20] I. Warad, S. Haddad, M. Al-Noaimi, B. Hammouti, T. Ben Hadda, *Acta Cryst.*, E69 (2013) o 1442.
[21] I. Warad, M. Al-Noaimi, S. Haddad, Y. Al-Demeria, B. Hammouti, *Acta Cryst.*, E69 (2013) o1075.
[22] M. Abdoh, I. Warad, S. Naveen, , N. Lokanathd, R. Salghi, *Acta Cryst.*, E71 *(*2015) o431.
[23] C. Lee, W. Yang, R. Parr, *Phys. Rev. B.*, 37 (1988) 785–789.
[24] P. Hay, W. Wadt, *J. Chem. Phys.*, 82 (1985) 270–283.
[25] R. Bauernschmitt, R. Ahlrichs, *Chem. Phys. Lett.*, 256 (1996) 454–464.
[26] K. Fukui, *Science*, 218 *(*1982) 474–754.
[27] S. Gunasekaran, R. Balaji, S. Kumaresan, G. Anand, S. Srinivasan, *Can. J. Anal. Sci. Spectrosc*., 53 (2008) 149–162.