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Synthesis, Theoretical and Antimicrobial Activity Study of New Benzimidazole Derivatives

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A VARIETY of synthetic routes to benzimidazole derivatives have been reported based on different hetero-cyclic rings such as Schiff bases, 2-azetidinone, 4-thiazolidinone and 1,3-oxazepan. Additionally, HOMO-LUMO and vibrational wavenumbers which represents the quantum mechanical calculations of energies, were conducted by Density functional theory (DFT) method at the level of B3LYP with 6-31G(d,p) basis set. FTIR, ^{1}H NMR spectroscopy and spectral mass spectrometry were used to characterize these compounds; this was followed by measuring the biological activities for gram-negative, gram-positive bacteria and fungi by using diffusion protocol. The outcomes of DFT calculations showed consistency between the experimental values and theoretical of the vibrational and NMR spectroscopy.

Keywords: Benzimidazole, 2-Azetidinone, 4-thiazolidinone, DFT, HOMO-LUMO, Antimicrobial activity.

Introduction

Benzimidazole is considered a heterocyclic organic compound which is benzene ring moiety fused with an 4, 5 position of imidazole ring[1]. Scientists pointed great concern to benzimdazole derivatives which they are extremely beneficial intermediates in evolution of pharmaceutical and biological activities of these molecules for many diseases. Many studies show that most benzimidazole compounds can find in nature, such as vitamin B_{12} [2]. The first Benzimidazole has been synthesized in 1872 by Hobrecker [3]. This unique structure considered to be one of significant compounds in organic and industrial chemistry, especially against the corrosion [4], and their medical uses such as: *anti*-inflammatory, anti-cancer, anti-fungal and antioxidant [5-8]. The benzimidazole derivatives like Schiff base or known as imine group (C=N) [9].The special property of C=N group gave it especial role in biological, pharmacological, analytical and industrial applications [10].While the thiazolidin-4-one is five-membered heterocyclic containing nitrogen (N) and sulfur (S) in 1, 3 position [11]. Thiazolidine derivatives are reported to show of natural product such as (vitaminB1) and exhibit numerous biological and antimicrobial activities and industrial applications [12,13].

Furthermore, the structure of these derivatives that containing 2-azetidinone (B-Lactam) which consists of a four-membered heterocyclic ring with three carbon atoms and one nitrogen atom, this unique structural system has been found in living organisms, natural products, medicine and in most chemistry fields [14].

Also oxazepin derivatives are seven-membered heterocyclic ring with nitrogen and oxygen heteroatoms that are available in medicinal chemists and in many pharmaceutical applications [15]. The aims of this study are to synthesize novel benzimidazole derivatives (scheme 1), that can be

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used as an antimicrobial material. The final part of this work is the structural optimization of these prepared compounds by DFT calculations which have been performed, the results were compared with experimental data, simulated vibrationaly and NMR spectra.

Experimental

Materials and physical measurements

All the chemicals that applied in our study are obtainable from [Fluka co. And Sigma□Aldrich] were annular graded and used without further purification. The melting points (m.p) have been specified by capillary Electro thermal apparatus. Completing of the reaction was monitored by thin layer chromatography (TLC) using Merck silica coated plates and as mobile phase a mixture of hexane and ethylacetate. Recorded the FT-IR spectra by using (ATR) technicality SHIMADZU 8400S, the wavelength ranges between (500-4000) cm^{-1}which has been made in Japan. Fourier Transform Infrared spectroscopy have been done at Chemistry department; College of Science; Mustansiryah University. ^{1}H-NMR spectra were recorded on a Bruker, type ultra-shield 300 MHz spectrometers in University of Al-Al-Bayt in Jordan, Amman. All spectra were obtained in DMSO-d6 (as a solvent) with tetramethylsilane (TMS) as inner reference. The compounds were analyzed by mass spectra which were recorded on SHIMADZU type QP 1000EX (SCI)at Chemistry department; College of Science; Mustansiryah University.

2-(thiophen-2-yl)-1H-benzo[d]imidazole (1).

A mixture of thiophene-2-carbaldehyde (0.05mol, 9.25g), o-phenylendiamine (0.05mol, 5.4g) and (0.05mol, 5.20g $NaHSO_3$) were dissolved in DMF (50ml). The reaction mixture was refluxed for (20 h). TLC technique ethylacetat: hexane (3:7) was used to monitor the perfecting the reaction. This reaction mixture was poured in cold water, filtrated off, washed in cold water, and then recrystallized from ethanol [16].

Ethyl 2-(2-(thiophen-2-yl)-1H-benzo[d]imidazol-1-yl) acetate (2).

A mixture of compound (1) (0.03mol, 8.1g), anhydrous K_2CO_3 (0.07mol, 10g) bromoethylacetate (0.035mol, 6g) were dissolved in acetone (50ml). The mixture was refluxed for (6h), and the solvent was removed *in vacuo*, the final products were crystallized using ethanol 95% [17]. Yield: 87%; m.p: 139-141°C; F-TIR (ATR. Cm-1), ν_{max} : (3064, arom. C-H), (2926, 2866, C–H aliph.), 1739 (C= O, aceter); ^{1}H-NMR (DMSO-d6), δ, ppm. 7.24-7.28 (m,7H,Ar-H) , 5.4 (s,2H,-CH_2) ,4.13-4.20 (q,2H , -OCH_2) , 1.14-1.19 (t, 3H ,-CH_3). The MS for $C_{15}H_{14}N_2O_2S$, is m/z = 286 (M+, 100%).

2-(2-(thiophen-2-yl)-1H-benzo[d]imidazol-1-ylcacetohydrazide(3).

A mixture of hydrazine hydrate 80% and compound (2) (0.093 mol) were dissolved in ethanol (99.9 %)(20ml).The reaction mixture was refluxed for (10 h). The resulting precipitate product; filtrated and then washed in cold water (10 ^{O}C). The final product was dried and recrystallized using ethanol 95% [18]. 95% . Yield: 71%; m.p: 237-239°C;F-TIR(ATR, cm−1), ν_{max}: 3342,3294(NH2),3167(NH) ,1689(C=O ,amide),1600 (C = N); ^{1}H-NMR (DMSO-d6) S, ppm : 9.58 (s, 1H ,NH), 7.28-7.81 (m, 8H, Ar-H), 4.85 (s, 2H, CH2), 4.37 (s, 2H, NH2). And the MS for $C_{13}H_{12}N_4OS$, m/z = 272 (M+, 100%).

General procedure for the Schiff bases synthesized (4-6):

A mixture of acetohydrazides(3) (0.0043mol), (0.0042mol) of the variousaldehydenamely4-nitrobezaldehyde,4-bromobezaldehyde,4-chlorobezaldehyde and glacial acetic acid (0.1ml) in methanol(50ml) has been refluxed for (8 h). The reaction mixture was filtrated off, then dried and recrystallized using ethanol.

N'-(4-nitrobenzylidene)-2-(2-(thiophen-2-yl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (4).

Yield: 89%; m.p: 312-314°C; F-TIR (ATR, cm−1), ν_{max} : 3192(NH),1683 (C= O amid), 1610 (C=N), ^{1}H-NMR (DMSO-d6), ppm δ : 8.23 (s,1H, NH) 8.03-7.31 (m, 12H, Ar-H, CH=N), 5.10(s, 2H, CH2). The MS for $C_{20}H_{15}N_5O_3S$, m/z = 405 (M+, 100%) .

2-(2-(thiophen-2-yl)-1H-benzo[d] imidazol)-N'-(4-bromobenzylidene) cetohydrazide (5).

Yield: 81%; M. p: 321-423°C; F-TIR (ATR, cm−1), ν max: 3203(NH), 1672 (C= O), 1599(C=N); ^{1}H-NMR. (DMSO-d6,) δ, ppm: 8.24 (s, 1H, NH) 8.04-7.26 (m, 12H, Ar-H, CH=N,), 5.06(s, 2H, CH2).

2-(2-(thiophen-2-yl)-1H-benzo[d] imidazol) -N'-(4-chlorobenzylidene) acetohydrazide (6).

Yield: 51%; m. p: 317-318°C; F-TIR (ATR, cm−1), ν_{max}: 3161(NH), 1672 (C= O), 1614 (C= N); ^{1}H-NMR (DMSO-d6,) δ, ppm: 8.09 (s, 1H, NH), 7.91 -6.65 (m, 11H, Ar-H,CH=N), 5.01 (s, 2H, CH2) .

N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)-2-(2-(thiophen-2-yl)-1H benzo[d]imidazol-1-yl) acetamide (7):

A mixture of compounds (4-6) (0.001mol),(0.005mol) of thioglycolic acid and with $ZnCl_2$ (0.01g) were dissolved in chloroform (25ml). The reaction mixture was refluxed for (10h).TLC technique ethylacetat: hexane (3:7) was used to monitor the completion of the reaction, then the solvent was removed *in vacuo*, to remove the excess of mercaptoacetic acid, then the product treated by 10% $NaHCO_3$, and then washed with water. The drying reagent was filtered off and recrystallize from chloroform Yield: 67%; m. p: 178-180°C; F-TIR(ATR, cm−1), ν max : 3178(NH),1728 (C=O), 1683 (C=O ;of amide); 1H-NMR (300 MHz, DMSO-d6, δ, ppm): 7.92 (s, 1H, NH),7.76-6.75 (m, 12H, Ar-H), 5.5 (s, 1H, N-CH), 4.98 (s, 2H, CH2), 3.86-3.68 (d-d, 2H, S-CH2 C=O thiazolidin, geminal proton).

N-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-2-(2-(thiophen-2-yl)-1H-benzo[d]imidazol-1-yl) acetamide (8):

Compounds (4-6) (0.001mol) andtriethyl amine Et_3N (0.025 mol) were dissolved in (10ml) dioxane, and allowed to stir in warm bath (0-5°C), then $ClCH_2COCl$ (0.01mol) was added slowly over a period of (3h), and then the mixture was stirred for (6 h). The resultant was filtrated off and the solvent removed *in vacuo*. The final product was washed with water; crystallized using chloroform [19]. Yield: 42%; m .p: 77-80°C; F-TIR(ATR, cm−1), ν max : 3170 (NH),1730 (C=O, β-Lactam), 1680 (C=O, amide); ^{1}H-NMR (300 MHz, DMSO-d6, δ, ppm):8.35(s, 1H, NH), 8.31 -7.27 (m, 11H, Ar-H), 5.6 (d, 1H, CH-Cl) , 5.11(s, 2H, CH2), 4.5 (d, 1H, N-CH). The MS for $C_{21}H_{15}ClN_5O_4S$, m/z = 468 (M+, 100%) .

N-(4-nitrophenyl)-4,7-dioxo-1,3-oxazepan-3-yl)-2-(2-(thiophen-2-yl)-1H-benzo[d] imidazol-1-yl)acetamide (9):

A mixture of Schiff bases (4-6) (0.001 mol) and (0.001 mol, succinicanhydride) were dissolved in(20ml) $CHCl_3$. The mixture was refluxed for (24 h). The resultant has been filtrated off, and the solvent removed *in vacuo* and recrystallizaed using ethanol [19]. Yield: 51%; m. p: 241-243°C; F-TIR(ATR, cm−1), ν max : 3146 (NH), 1714,1689(C= O), 1614 1H-NMR (DMSO-d6,) δ, ppm:8.09 (s, 1H, NH), 7.91 -6.65 (m, 11H, Ar-H,CH=N), 5.01 (s, 2H, CH2).

Biological activities

The biological activity (antimicrobial) of benzimidazole derivatives was estimated for four bacterial strains. The antimicrobial activity was determined by using the well diffusion method as agar [20]. Dimethyl sulfoxide has been used as a control. The trial was outright at 100mg/ml by adding 50µl to each disc (i.e.5µg/disc) concentration by using (DMSO) as solvent. The fungi and 4 bacteria were subculture in Agra. The plates have been incubated at 37 °C and checking after 24 h for bacteria and 27°C (48 h) for fungi Table (1).

TABLE 1. Antimicrobial evaluation of compounds (3-Amoxicillin) .

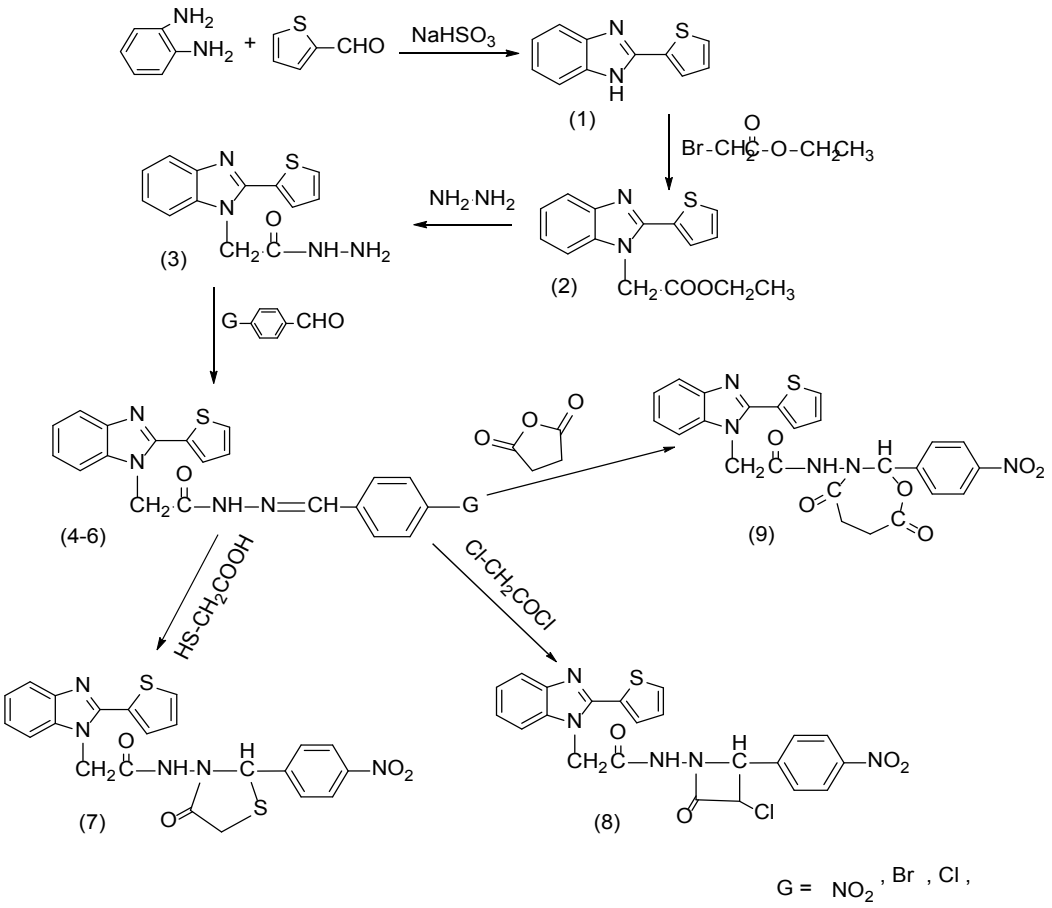
Heterocyclic derivatives	Inhibition zone (mm) at 100 mg/ml				
	Gram-positive		Gram-negative		Fungi
	S. aureus	*S.epidermidis*	*E.coli*	*Klebsiellaspp*	*C.albicanus*
3	-	5	10	8	10
4	-	14	12	-	15
5	11	12	20	13	12
6	13	10	18	-	14
7	22	15	14	19	11
8	14	17	14	12	18
9	18	20	12	20	20
Amoxicillin	21	20	18	19	21

Computational details

The current study focuses on the application of DFT. The vast majority of computational studies were carried out by using DFT methods at B3LYP/6-31G (d, p) levels of theory. The computational study of these compounds has been carried out by utilizing the Gaussian 09 code and Gauss-View molecular visualization program package on PC [21]. The gradient-corrected B3LYP functional form (i.e. Becke's 3-parameter hybrid exchange functional [22] and Lee, Yang, and Parr correlation functional [23]) was used in the process of the calculations. It is worth noting that DFT is the considered one of the best methods to calculate ground state structures and the electronic variables. The polarized continuum model (PCM) has been applied to examine the effects of DMSO solvent. Structural optimization was gained by restricted closed-shell formalism and without any symmetry restriction. Hence, the dipole moment μ calculated by DFT is an important property that is essentially used to study the intermolecular interactions which involve the non-bonded type dipole–dipole interactions, where the higher value of the dipole moment leads to the strong intermolecular interactions [24].

Results and Discussion

The derivatives of Benzimidazole were synthesized in the scheme (1) and all the structures of compounds have been characterized on the base of their (TLC) thin layer chromatography, FT-IR, ^{1}H-NMR and MS spectroscopy of some of them, then compared with theoretical (DFT) calculations. DFT using B3LYP functional combined with 6-31G (d, p) basis set carried out to calculate energies, geometry optimization, vibrational wavenumbers, NMR and electronic transitions.



Scheme .1.

Vibration analysis.

Successful attempts were conducted to synthesized the thiazolidenone generation (7) by treated of Schiff bases (4-6) with mercaptoaotic acid in chloroform, the structures of these compounds (4-6) were fully elucidated by the presence of carbonyl stretching. Also, FT-IR spectra show peak at 1734 cm^{-1}assigned to thiazolidinone ring. From these findings, it can be concluded that the cyclization step was successful as shown in Table 2.

Furthermore, azetidinyl derivative (8) was obtained by reaction of compounds (4-6) with Et_3N and chloroacetyl chloride ($C_2H_2OCl_2$) in dioxone. The F-TIR spectra show peak assigned to a carbonyl group(C=O) at 1730 cm^{-1}due to *β*-lactam which is consistent with experimental results 1807.4 cm^{-1}. Also, FT-IR assignment revealed the disappearance of imine group (N=CH)at 1610 cm^{-1} (Table 2).

Finally, the FT-IR spectra analysis confirmed the structural assignment of compound (9) by existence of. C=O stretching.band at 1714cm-1. Also, IR spectra show an extra peak assigned to a carbonyl group belongs to oxazepine ring, all these outcomes consistent with the experimental results 1718.9 cm^{-1} (Table 2).

It is worth to mention that the theoretical IR spectra analysis of entitled compounds was gained by using the same level of DFT. All band assignments are shown in Table 3. At this point, the calculated frequencies for the compound 7,8 and 9 are higher than the comparable experimental quantities because the basis set truncation and the negligence of the mechanical anharmonicity [25]. Therefore, a scale factor was introduced to recompense these shortcomings; and an explanation of this approach was discussed [26]. The used scaling factor is 0.961 for 6-31G (d,p) basis set. Figure (1-a, b) and table 2 showed the experimental and theoretical FTIR spectrum of the compounds under study.

FT-NMR Analysis

The 1H NMR spectra of compound (8) was reported (internal standard), TMS; solvent, DMSO-d6) (Figure. 2a,b) and carried out by the GIAO method through applying B3LYP/6-31G (d,p) levels and the PCM method of density functional calculations. The theoretical 1H chemical shift values are compared with the experimental values. These results are presented in Table 3. The experimentally aliphatic protons appeared in the upfield region at δ 2.968-3.392 but the calculated chemical shift values at δ 2.96-4.567. The phenyl ring protons are shown at δ 7.126-8.57 and the theoretical calculation was also in the range of δ 7.433-8.878.

TABLE 2. Experimental and Theoretical of IR spectral data for compounds (7-9).

Comp. No.	Characteristic bands (ATR, υ, cm^{-1})					
	N-H	**C=O oxazepine ring**	**C=O β-lactam**	**(C=O) Amide**	**C=O Thiazolidi-non**	**C-H Aliph**
7	3117 Exp. 3626.1 DFT 3484.6 SF-DFT	-	-	1695 Exp. 1767.9 DFT 1698.9 SF-DFT	1734 Exp. 1804.3 DFT 1733.9 SF-DFT	-
8	3170 Exp. 3586.2 DFT 3446.3 SF-DFT	-	1730 Exp. 1880.6 DFT 1807.4 SF-DFT	1680 Exp. 1776.5 DFT 1707.2 SF-DFT	-	(2850-2956) Exp. (3091.7 -3156.1) DFT (2971.1-3032.1) SF-DFT
9	3146 Exp. 3550.9 DFT 3412.4 SF-DFT	1714 Exp. 1788.67 DFT 1718.9 SF-DFT	-	1689 Exp. 1757.3 DFT 1688.8 SF-DFT	-	(2868-2956) Exp. (3188.2-3213.2) DFT (3063.8-3081.3) SF-DFT

SF-DFT:Scaling Factor –DFT

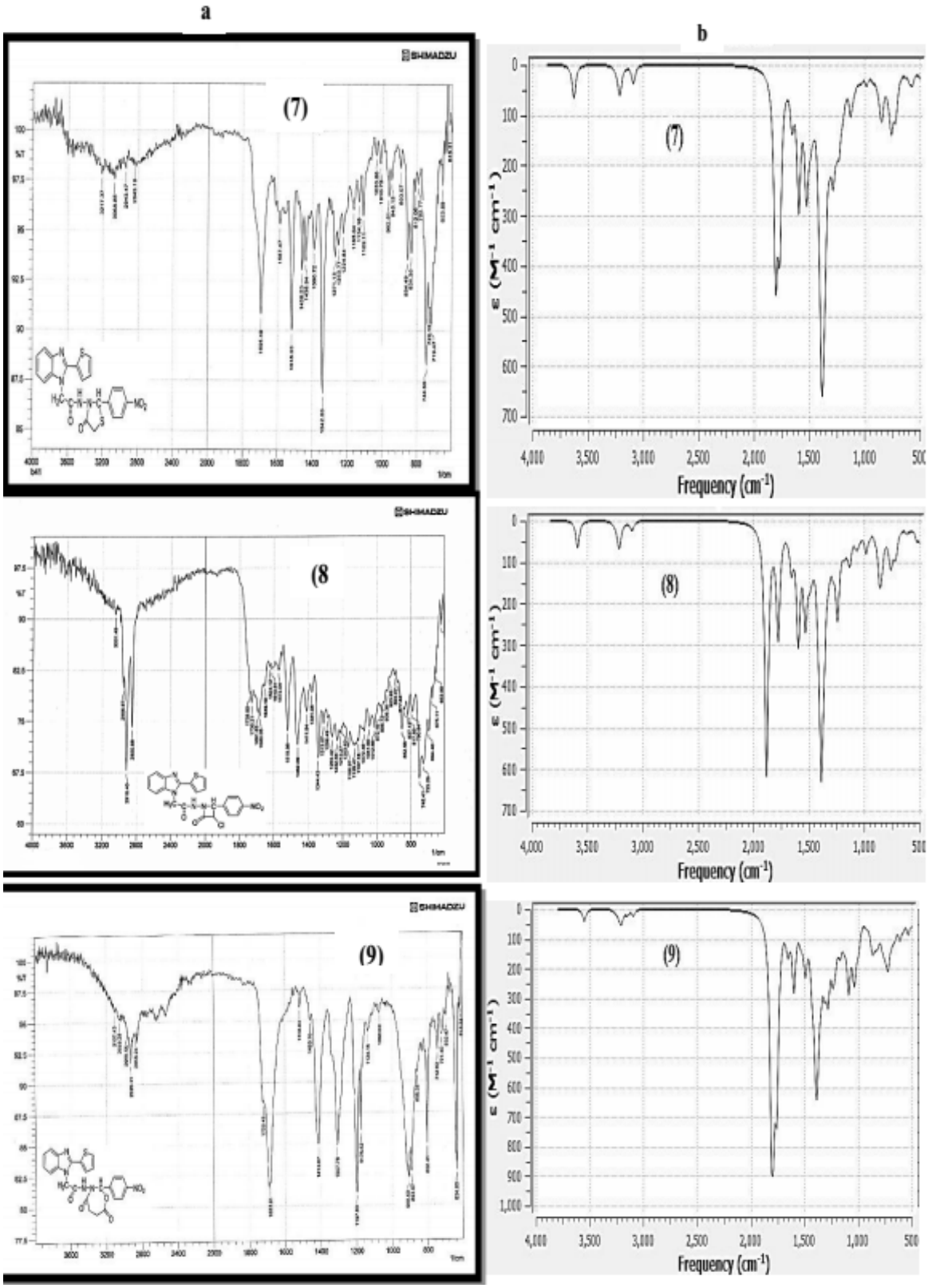


Figure 1. (a) Exparmintal, (b) Theoretical IR spectra of compounds under study

TABLE 3. Calculated and Experimental ^{1}H NMR chemical shifts of compound 8.

Atoms No.	Shift (ppm)	
	Calculated	Experimental
H-44	8.788	8.57
H-43	8.727	8.532
H-42	8.614	8.317
H-21	8.045	7.998
H-9	7.954	7.893
H-8,41,10,7	7.751	7.723
H-19,33,20	7.433	5.603
H-31	5.038	5.198
H-30	4.944	4.567
H-34	4.741	3.392

TABLE 4.Total energy, electronic states, energy gap,dipole moment (μ)and liner polarizability of the compounds under study.

Comp. .NO	Total Energy ((Hartrre	Electronic states (eV)		Eg (eV)	(μ (Debye
		HOMO	LUMO		
7	-2219.5581	-2.74	-5.96	3.22	4.263
8	-2280.9392	-2.71	-5.97	3.26	3.678
9	-2085.9608	-3.60	-5.91	2.31	5.823

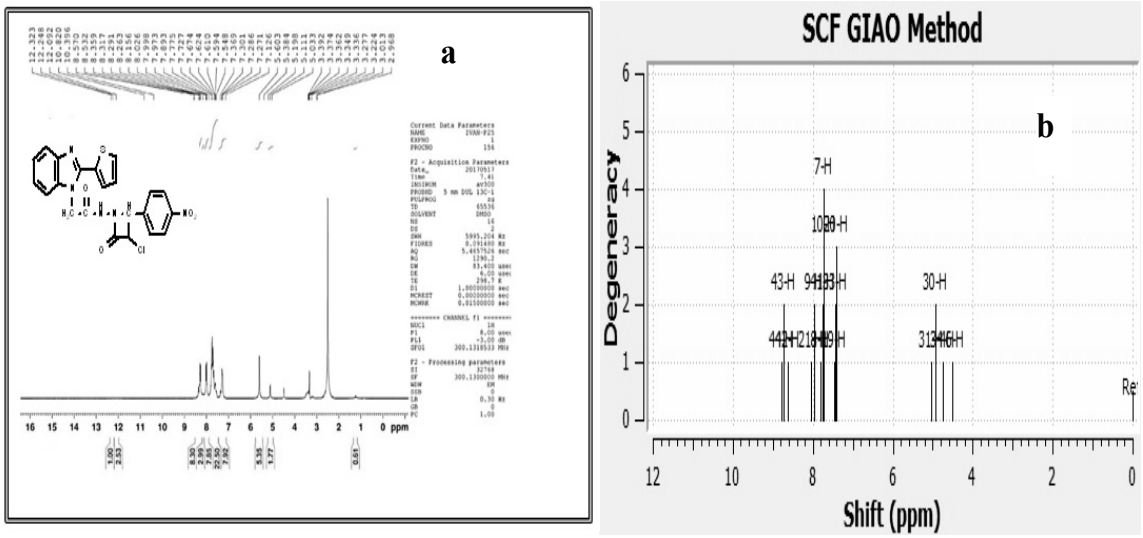


Figure 2. (a) Experimental (b) calculated ^{1}H NMR Spectra of compound 8

Frontier molecular orbitals analysis

In recent decades, it has been documented that frontier molecular orbitals (FMOs) are at their highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital. The frontier molecular orbital energy was obtained by using the B3LYP/6-31G (d, p) level of the optimized molecular structure. The 3D plots of the frontier orbitals are shown in Figure 4 where the computed HOMO is localized at the 2-(thiophen-2-yl)-1H-benzo[d]imidazole regions, and the LUMO is localized at the CH-(phenylnitro). It is noted that HOMOs have an overall π bonding character as well as non-bonding character, whereas LUMOs have an *anti*-bonding π character. The bioactivity of the molecule is attributed to the strong charge transfer interaction.

Indeed, Tabl 3 shows the values of the total energy and electronic states for the analyzed structure and the energy gap (, and dipole moment (μ) of the compounds under study. The eigen values of LUMO–HOMO energy gap reflect the chemical activity of the molecule. The drop of HOMO and LUMO energy gap ultimately indicates the charge transfer interaction occurring within the molecule, because of its strong electron-accepting ability of the electron acceptor group. In addition, the molecules dipole moment is a representative of a generalized measure of bond properties and charge densities in a molecule [27].

Antimicrobial activity

In this study it has been using the Amoxicillin drug as a standard antibacterial for comparison with the benzimidazole derivatives that is (Schiff base, 2-azetidinone, 4-thiazolidinone and 1,3oxazepan). It was observed that oxazepan (9) exhibits very considerable activity against (G+) and (G-) bacterial. All compounds were displaying reasonable activity for Candida (antifungal).

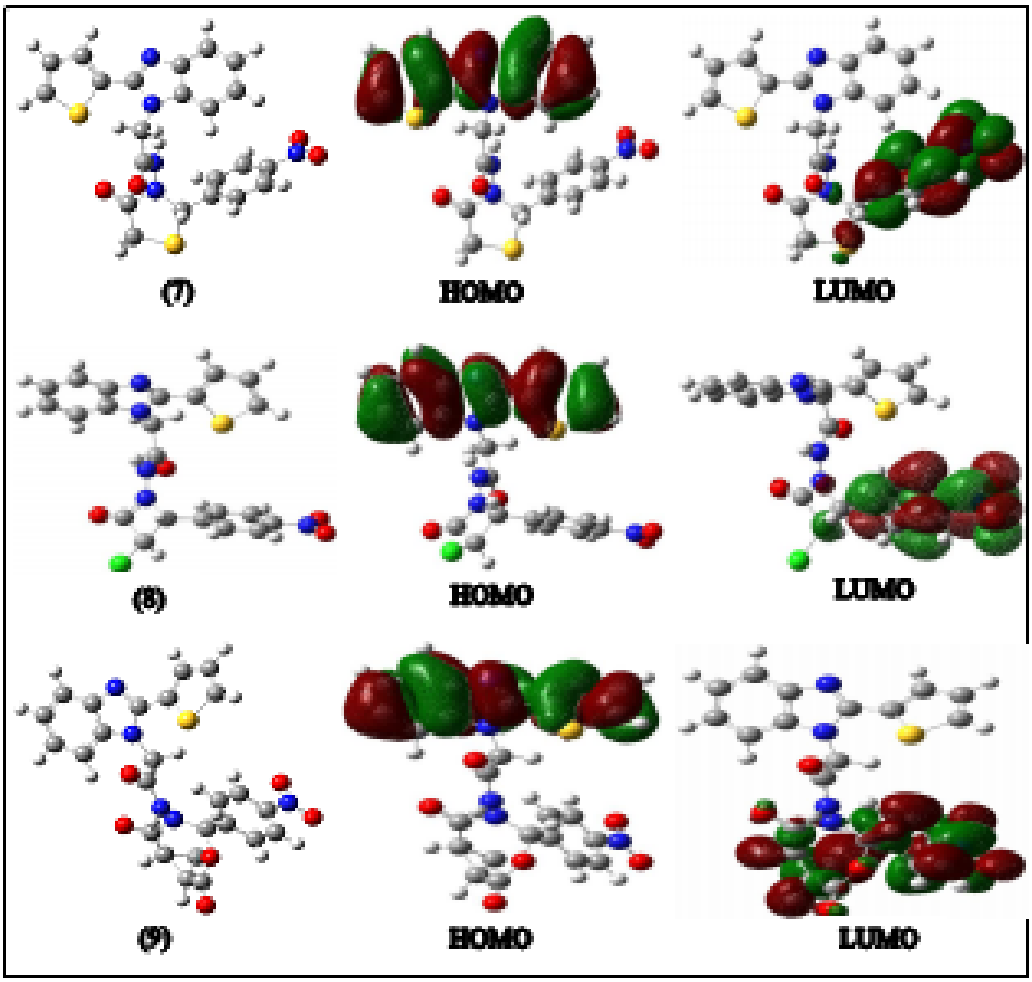


Fig. 3. Optimized geometries, HOMO and LUMOs of compound (7),(8) and (9) obtained with B3/LYB/6-31G(d,p).

Conclusion

In this work, the benzimidazole derivatives have been prepared and characterized by spectral and analytical data. These derivatives tested on fungi and four strains of bacteria, namely: S. epidermis is S. Areas as (G+), E. Cole and Klebsielllaspp as (G-), and it has been compared with Amoxicillin as caliber drug to reveal the potency of synthesized compounds. The fungi and bacteria found to be sensitive to compounds at high concentration (100 mg/ml) but no sensitivity at lesser concentration.

The next stage in the work scheme was to calculate the ^{1}H-NMR, vibrational frequencies and the calculated values were compared with experimental FT-NMR spectra. In addition, the electronic properties, such as HOMO and LUMO energies which have been performed by B3LYP/6-31G (d,p) showed both the chemical activity of the molecule and the bioactivity from the intermolecular charge transfer. Finally, the findings that were obtained by using the B3LYP/6-31G (d, p) functional have been consistent with the experimental and calculated values.

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