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Synthesis and biological evaluation of some Benzimidazole derivatives

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ArticleInfo

Received
11/Jun./2017

Accepted
17/Oct./2017

Abstract
Group of benzimidazole derivatives are considered as an important class of compounds; they are present in a major of products with broad spectrum in industrial and biological activities. Several of derivatives that have been efficiently synthesized for -1H-benzo[d]imidazole as starting material to Synthesis of some new Schiff bases ,2-azetidinone and 4-thiazolidinone derivatives .The structures were characterized by FTIR and ^{1}H-NMR spectra. All The synthesized compounds were screened for their antimicrobial activities against two (gram +ve) and (gram -ve) kind of bacteria s well as fungi using the micro dilution procedure and compared with amoxicillin activity.

Keywords: benzimidazole, 2-Azetidinone, 4-thiazolidinone, antimicrobial activity

الخلاصة
مجموعة من مشتقات البنزيميدازول تعتبر فئة هامة من المركبات. فهي موجودة على نطاق واسع من المركبات الرئيسية التي تدخل في الانشطة البيولوجية والصناعية . عديد من المشتقات تم تحضيرها بكفاءة من -1H-benzo[d]imidazole كمادة اساس لتحضير بعض مشتقات قواعد شف, 2-2-أزيتيدينون و 4-ثيازوليدينون الجديده. وتم تشخيص المركبات بواسطة طيف الاشعة التحت الحمراء و مطياف النووي المغناطيسي للبروتون فحص جميع المركبات المحضرة لأنشطتها المضادة للميكروبات ضد نوعين من البكتيريا (الكرام الموجب) و (الكرام السالب) وكذلك الفطريات باستخدام إجراء التخفيف الجزئي ومقارنتها مع النشاط أموكسيسيلين.

Introduction

Benzimidazole is the most common and important among heterocyclic compounds. They are very important in many medicinal formulations found in a wide range of drugs, most vitamins and other natural products. In addition to the biological activity these compounds, are used as anti-inflammatory [1], antimicrobial [2][4] antiviral [5] anti-cancer [6][7], Antioxidants [8] and cytotoxic activity [9]. Schiff base derivatives have been attracted researchers interest in bioorganic and medicinal chemistry fields to their significance for antibacterial, antifungal activities and insecticidal properties [10][11]. The 2-Azetidinones (nitrogen containing four-membered heterocyclics) have the most significant range of research in medicinal chemistry field and were considered as a substantial contribution of science to humanity [12][13] Recently several studies have shown that PPAR γ / thiazolidinedione decrease IGF-1 levels and, thus, reduce cancer growth in carcinomas such as the pancreas, colon, liver, and prostate [14]. In this study, we aimed to synthesize new heterocyclic derivative from o-phenylendiamine containing, benzimidazole, 2-azetidinones,4-thiazolidinone moieties with predictable biological activities.

Experimental Materials and Physical Measurements

All the chemicals that applied in our study are obtainable from [Fluka co. and Sigma Aldrich]; The Melting points (m.p) have been specified by Electro thermal capillary 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 ethyl acetate. Infrared spectra were obtained using ATR technique Shimadzu 8400S, Fourier Transforms Infrared spectroscopy SHIMADZU in the range (500-4000) cm-1, made in japan, at chemistry department, College of Science, Mustansiriyah University. The 1H-NMR spectra were obtained on a Bruker, model ultra-shield 300MHz in Ahl-Al-Bayt University, Amman, Jordan. Using tetramethylsilane (TMS) as internal reference and DMSO-d6, CDCl3 as solvents.

2-(4-bromophenyl)-1H-benzo[d] imidazole (1).

a mixture of 4-bromobenzaldehyde (0.05mole, 9.25g), o-phenylendiamine (0.05mole, 5.4g), (0.05mol, 5.20g NaHSO3) and (50ml)N,N-dimethyl formamide (DMF) as solvent. The mixture was refluxed for 20 hrs, the completion of the reaction was observed by (TLC) using ethylacetate:hexane system (3:7). The mixture was poured in (50 ml) cold water, The result product was filtered, washed with cold water, dried and recrystallized from ethanol to obtain (78%) yield of compound (1) with grey color , melting point (276-278 °C) .(15)

Ethyl 2-(2-(4-bromophenyl)-1H-benzo [d]imidazol-1-yl) acetate(2).

A mixture of compound (1) (0.03mol, 8.1g), K2CO3 (0.07mole, 10g ethylchloro acetate (0.035mol, 6g) in (50mL) dry acetone as solvent. The mixture was refluxed for 6 hrs. The solvent was removed under reduced pressure, the products were collected by filtration and washed with water and recrystallization from 95% ethanol to give Yield: 87%; m.p: 139-141°C; F-TIR (ATR. Cm-1), νmax : (3064, arom. C-H), (2926-2966, C–H aliph.), 1743 (C= O, aceter); ¹H-NMR (DMSO-d6), δ, ppm. 7.28-7.79 (m, 8H, ArH), 5.3 (s, 2H, CH2), 4.08-4.15 (q, 2H, CH2), 1.11-1.15 (t, 3H, CH3).

2-(2-(4-bromophenyl)-1H-benzo [d]imidazol-1yl)acetohydrazide(3).

Compound (2) (0.093 mol, 8g) and hydrazine hydrate 80% (16mL) were mixed and refluxed for 10 hrs. with (20ml) of absolute ethanol as solvent, the precipitate was formed in the mixture filtered and washed with cold water, dried and purification from ethanol 95% . Yield: 78%; m.p: 298-302°C;F-TIR(ATR, cm−1), νmax: 3342,3294(NH2),3167(NH) ,1689(C=O ,amide),1600 (C = N); ¹H-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).

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

Compound (3) (0.0043mol, 1.48g), (0.0042mole) of the various aldehyde and 0.1 mL of glacial acetic acid in (50ml) methanol was refluxed for 8 hrs. The formed precipitate was filtered, dried and purification from ethanol.

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

Yield: 69%; m.p: 171-173°C; F-TIR (ATR, cm−1), νmax : 3192(NH),1683 (C= O amid), 1610 (C=N), 1H-NMR (DMSO-d6), ppm δ : 8.23 (s,1H, NH) 8.03-7.31 (m, 13H, Ar-H, CH=N), 5.10(s, 2H, CH2).

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

Yield: 78%; M. p: 247-249°C; F-TIR (ATR, cm−1), ν max: 3203(NH), 1672 (C= O), 1599(C=N); 1H-NMR. (DMSO-d6,) δ, ppm: 8.24 (s, 1H, NH) 8.04-7.26 (m, 13H, Ar-H, CH=N,), 5.06(s, 2H, CH2).

2-(2-(4-bromophenyl)-1H-benzo[d] imidazol-1-yl)-N'-(4-N,N-dimethylbenzylidene)acetohydrazide (6).

Yield: 51%; m. p: 241-243°C; F-TIR(ATR, cm−1), ν max : 3161 (NH), 1672 (C= O), 1614 (C= N); 1H-NMR (DMSO-d6,) δ, ppm:8.09 (s, 1H, NH), 7.91 - 6.65 (m, 13H, Ar-H,CH=N), 5.01 (s, 2H, CH2) ,2.96 (s, 6H, (-CH3)2).

General procedure for the synthesis of 2-azetidinones (7-9):

Compounds (4-6) (0.001mol), triethyl amine (0.025 mol) in dry 1,4-dioxane (10mL) was stirred in ice water bath (0-5°C). chloroacetyl-chloride (0.01mol) was added drop wise to mixture, then stirred for 3 hrs. The mixture was refluxed for 6 hrs. mixture was filtrated and the solvent was removed under reduced pressure, the product was collected by filtration

and washed with water, dried and recrystallization from chloroform.

2-(2-(4-bromophenyl)-1H-benzo[d] imidazol-1-yl)-N-(3-chloro-2-(4-N,N-bromophenyl)-4-oxoazetidin-1-yl)acetamide(7).

Yield: 42%; m .p: 77-80°C; F-TIR(ATR, cm−1), ν max : 3181 (NH),1728 (C=O, B- Lactam), 1678 (C=O, amide); ¹H-NMR (300 MHz, DMSO-d6, δ, ppm):8.35(s, 1H, NH), 8.31 -7.27 (m, 12H, Ar-H), 5.6 (d, 1H, CH-Cl) , 5.11(s, 2H, CH2), 4.5 (d, 1H, N-CH).

2-(2-(4-bromophenyl)-1H-benzo[d]imidazol-1-yl)-N-(3-chloro-2-(4-N,N-chlorophenyl)-4-oxoazetidin-1-yl)acetamide(8).

Yield: 57%; m. p: 104-106°C; F-TIR(ATR, cm−1), ν max :3171(NH),1730 (C=O ,B- Lactam), 1687 (C=O amide); ¹H-NMR (DMSO-d6) δ, ppm: 8.43 (s, 1H, NH), 8.36 - 7.24 (m, 12H, Ar-H),4.9(s, 2H, CH2),5.57 (d, 1H, CH-Cl) ,5.03 (d, 1H, N-CH) .

2-(2-(4-bromophenyl)-1H-benzo[d] imidazol-1-yl)-N-(3-chloro-2-(4-N, N-dimethylphenyl)-4-oxoazetidin-1-yl) acetamide(9).

Yield: 57%; m. p: 144-145°C; F-TIR(ATR, cm−1), ν max :3172(NH), 1733(C= O, B- Lactam), 1684 (C=O ;amide); ¹H-NMR (300 MHz, DMSO-d6, δ, ppm): 8.74 (s, 1H, NH), 8.01 -7.13 (m, 12 H, Ar-H),5.21(s, 2H, CH2),5.38 (d, 1H, CH-Cl) ,5.11 (d, 1H, N-CH) .

General procedure for the synthesis of4-thiazolidinone(10-12):

A mixture of Compounds (4-6) (0.001mol) was solved in 25mL chloroform with ZnCl2 (0.01g) and (0.005mol) of thioglycolic acid was added to the mixture, the mixture was refluxed for 10hrs. The reaction completion was monitored by thin layer chromatography (TLC) using ethylacetate:hexane system (3:7). The solvent was removed under reduced pressure, residue treated by 10% NaHCO3 solution to remove excess of mercaptoacetic acid, washed with water, dried and recrystallization from suitable solvent.

2-(2-(4-bromophenyl)-1H-benzo[d] imidazol-1-yl)-N-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)acetamide(10).

Yield: 54%; M. p: 257-258°C; F-TIR(ATR, cm−1), ν max : 3167 (NH), 1726(C=O thiazolidinon), 1683 (C=O of amide); ¹H-NMR (DMSO-d6) δ, ppm:8.02(s, 1H, NH), 7.76-7.25 (m, 12H, Ar-H), 5.54(s, 1H, N-CH), 4.89 (s, 2H, CH2), 3.37-3.95 (d-d, 2H, S-CH2 C=O thiazolidin, geminal proton).

2-(2-(4-bromophenyl)-1H-benzo[d]imidazol-1-yl)-N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)acetamide(11)

Yield: 69%; m. p: 272-274°C; F-TIR(ATR, cm−1), ν max : 3209(NH),1726 (C=O), 1683 (C=O of amide); 1H-NMR (300 MHz, DMSO-d6, δ, ppm): 8.04 (s, 1H, NH), 7.77-7.27 (m,12 H, Ar-H), 5.8 (s, 1H, N-CH), 4.87 (s, 2H, CH2), 3.95-3.8 (d-d, 2H, S-CH2 C=O thiazolidin, geminal proton).

2-(2-(4-bromophenyl)-1H-benzo[d] imidazol-1-yl)-N-(2-(4-N,N-dimethylphenyl)-4-oxothiazolidin-3-yl)acetamide(12).

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).

Biological activities

Antimicrobial activities

In vitro antimicrobial testing effects of benzimidazole derivatives were estimated against four bacterial strains namely .The antimicrobial activity was determined using the agar well diffusion method (16). Dimethyl sulfoxide worked as a control and the test was outright at 100mg/mL concentration using (DMSO) as solvent. The fungi and 4 bacteria was sub cultured in agar. The plates were incubated at 37

°C and checking after 24 hrs. for bacteria and 48 hrs. for fungi Table 1.

Table 1. Antimicrobial evaluation of compounds.

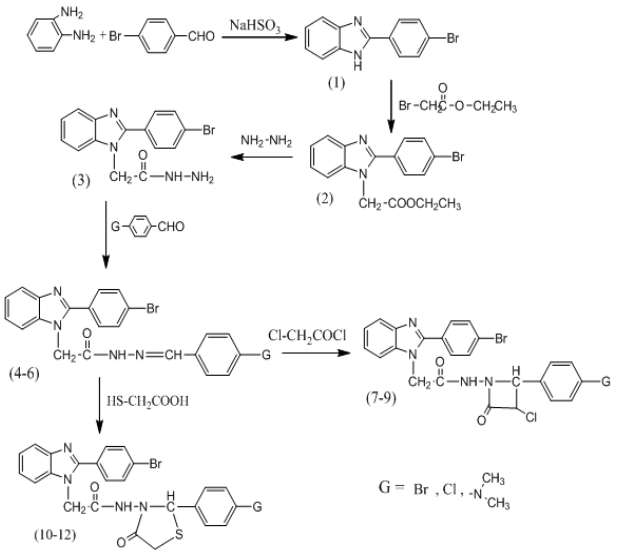
Hetero-cyclic deriva-tives	inhibition zone (mm) at 100 mg/mL				
	Gram positive		Gram negative		Fungi
	S. au-reus	*S.epidermi dis*	*E.co li*	*Klebsiel lla spp*	*C.albica ns*
3	5	6	3	11	5
4	6	3	10	-	-
5	10	-	10	12	-
6	6	8	9	6	8
7	14	14	16	14	14
8	12	14	15	16	15
9	18	12	11	10	15
10	25	20	-	20	19
11	19	17	12	-	17
12	15	-	13	20	20
Amoxi-cillin	10	17	16	17	21

Results and Discussion

Synthesis

Benzimidazole derivatives were synthesized following outlined in scheme 1.

2-(4-chlorophenyl)-1H-benzo[d]imidazole (1) was prepared via the condensation of p-bromobenzaldehyde with o-phenylenediamine in DMF and NaHSO3 as ring closing agent all the structures of compounds have been characterized on the base of their (TLC) thin layer chromatography, and spectral data. The F-TIR spectrum of compound (2) displayed the appearance of new absorption band at1743 cm-1 which belonged to (C=O ester). While the 1H-NMR showed triplet signal at 1.15 ppm related to (-CH3) and quartet at 4.08-4.15 ppm belonged to CH2,while a multiple signal at 7.28-7.79 ppm due to eight aromatic protons Figure(1).The Reaction between ester compound and hydrazine hydrate (80%) afforded the acid hydrazide derivatives (3) in typical yield. The spectrum showed the appearance of the NH2 stretching absorption near 3342, 3294 cm-1 and C=O amide at 1689cm-1with disappearance the carbonyl of ester Figure 2. Spectrum of 1H-NMR for compound (3) showed singlet signals 4.37 ppm due to (NH_2) and 4.85 ppm was attributed protons of CH2 and 9.58ppm belonged to NH, aromatic protons were appeared at 7.81-7.28 ppm figure 3. [17]. Schiff base (4-6) was obtained by the Reaction of compound (3) with various benzaldehyde in methanol. The formation of Schiff base has been indicated by the presence in their FT-IR spectra of imine (N=CH) stretching band at 1614-1599 cm^{-1} combined with the disappearance of (NH2) stretching band of amine of compounds (3) and carbonyl of benzaldeyde Figure (4). The 1H-NMR spectrum of compound (4) showed singlet signals 5.10 ppm was assigned to (-CH2), 8.23ppm that related to (NH) proton and aromatic protons(Ar-H, C=N) were appeared at 8.03-7.31 ppm. Figure 5. Treatment of compounds (4-6) with Et3N and chloroacetyl chloride (C2H2OCl2) obtained azetidinyl derivatives (7-9) The F-TIR spectrum indicated the appearance of 1733-1728 cm^{-1} band due to (C=O) β-lactam with disappearance of imine (N=CH) in the region 1614-1599 cm^{-1} figure (6) .In the 1H-NMR doublet signals at 4.5 -5.6 ppm integrating for protons ring of azetidinyl, protons of aromatic resonate at 8.3 -7.13 ppm Figure 7.



Scheme 1

Scheme 1: Benzimidazole derivatives were synthesized following outlined in scheme

Moreover, cyclization of Schiff bases (4-6) with mercaptoacticacid in chloroforme afforded thiazolidenone (10-12), the structures of these compounds were confirmed by the presence of carbonyl stretching band at 1728-1726 cm-1 due to thiazolidinone ring was the characteristic evidence for success of cyclization step

Figure 8. 1H-NMR spectrum of compound (10) showed doublet of doublet signals at 3.37-3.95 ppm and 4.89 ppm assigned to Protons of thiazolidinone ring Figure 9.

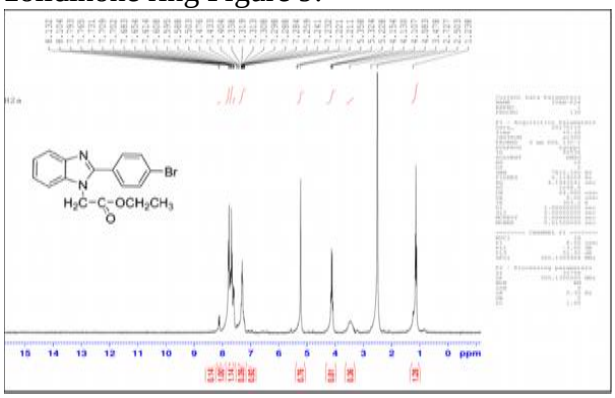


Figure 1: The ¹H-NMR spectrum of compound 2.

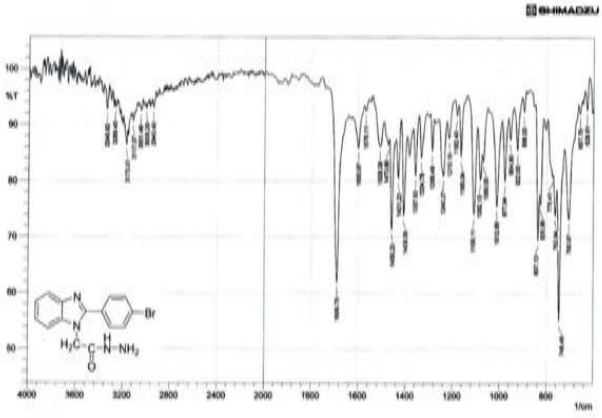


Figure 2: The FT-IR spectrum of compound 3.

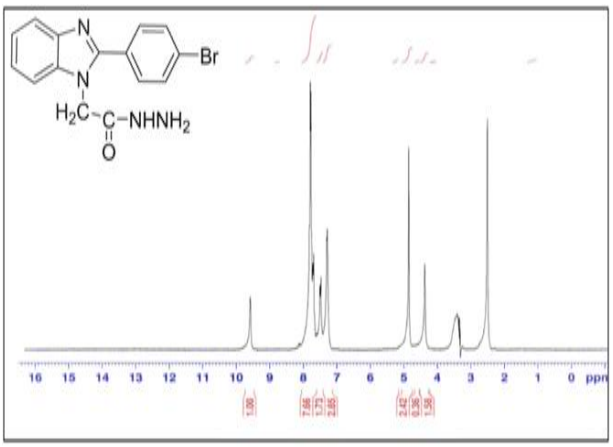


Figure 3: The ¹H- NMR spectrum of compound 3.

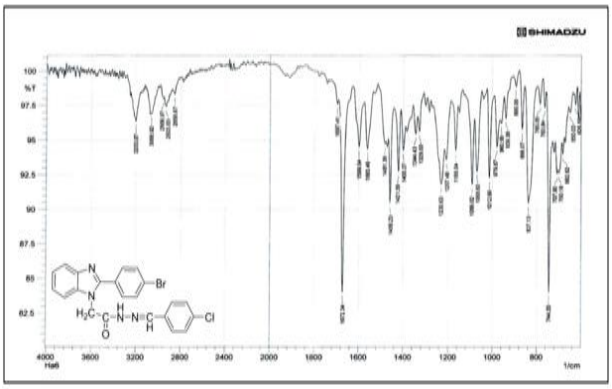


Figure 4: The FT-IR spectrum of compound 5.

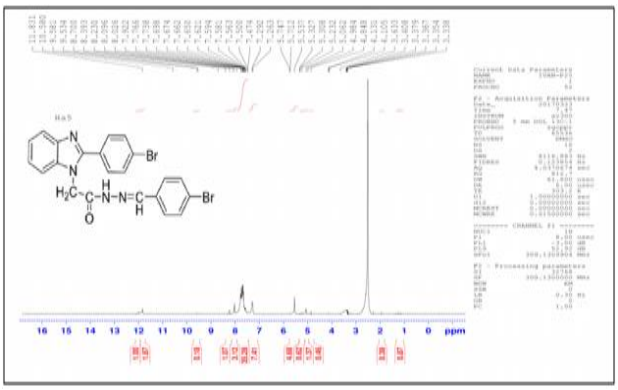


Figure 5: The ¹H- NMR spectrum of compound 4.

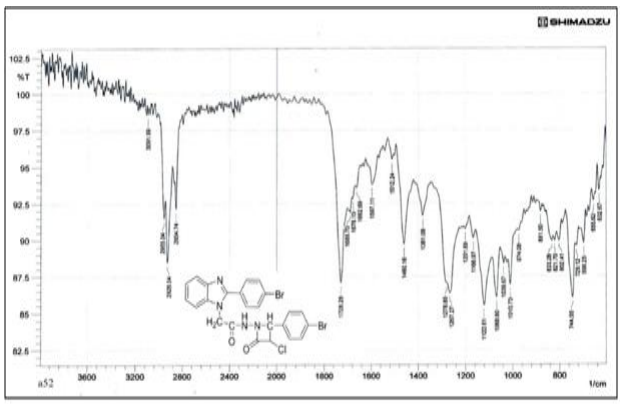


Figure 6: The FT-IR spectrum of compound 7.

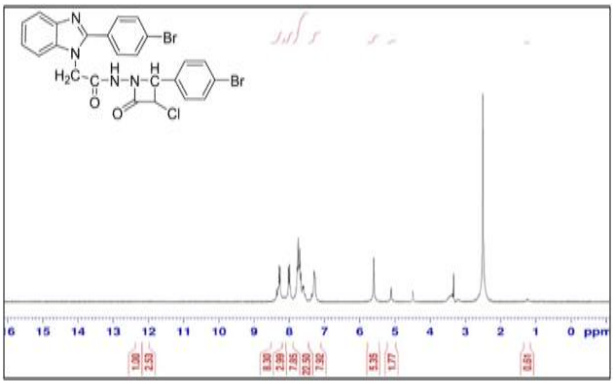


Figure 7: The ¹H- NMR spectrum of compound 7.

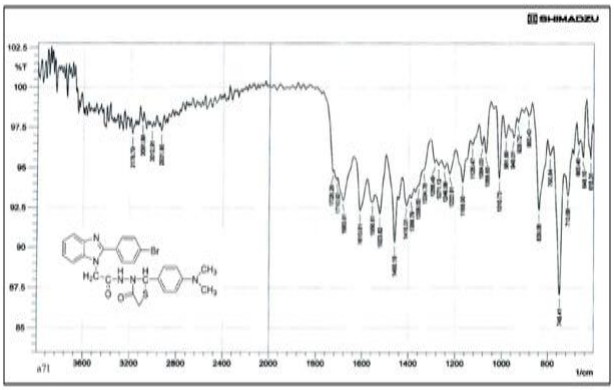


Figure 8: The FT-IR spectrum of compound 12.

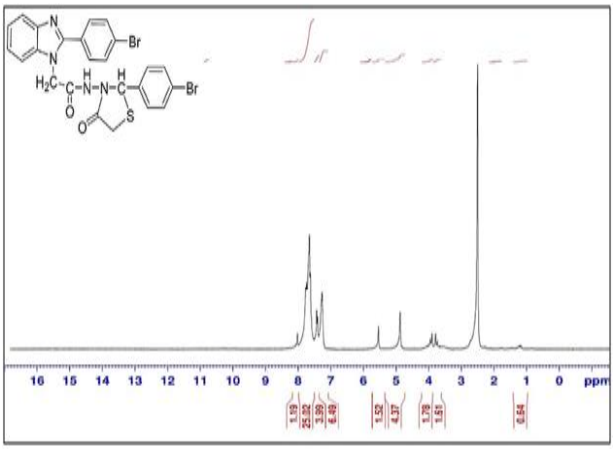


Figure 9: The ¹H- NMR spectrum of compound 10.

Antimicrobial activity

The synthesized of benzimidazole, schiff base, 2-azetidinone and 4-thiazolidinone moieties which in charge of antimicrobial activity. Its seems compounds (10, 11) show excellent inhibition against all bacterial species as well as candida. All the compounds were found to exhibit moderate to good antifungal. Standard antibacterial drug Amoxicillin was used for comparision. The experiments were performed in triplicate in order to minimize errors.

Conclusions

The benzimidazole derivatives were prepared and characterized by spectral and analytical data. Antifungal and Antibacterial activity of Benzimidazole derivatives was concluded in differentiation with Amoxicillin as caliber drug to reveal the potency of synthesized derivatives. The selected fungi and all the four strains of bacteria namely: C.Albicans, S.epidermidis. S. Aureus as (G+) , E. Coli and Klebsiellla spp as (G-) ,were found to be sensitive to all derivatives at concentration (100 mg/ mL) but no sensitivity at lower concentration.

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