Iraqi National Journal of Chemistry

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Synthesis, Characterization and Biological Evaluation of Some 6-Methoxy-2-mercaptobenzimidazole Derivatives

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Abstract

N-(4-methoxy phenyl) acetamide was prepared from acylation of para methoxy aniline which on further processes such as nitration followed by hydrolysis reduction finally cyclization with 4-methoxyphenylenediamine and carbon disulfide in presence of potassium hydroxide in ethanol to afford compound (5)which was treated with hydrazine hydrate in presence of potassium hydroxide in ethanol to obtain 6-methoxy-2-hydrazino benzimidazole MBI (6)was then treated with substituted aromatic aldehydes in presence of ethanol to obtained Schiff bases(6a-d).The new 6-methoxy-2-mercaptobenzimidazole derivatives (8a-b) are synthesized by Mannich reaction from 6-methoxy -2-mercapto benzimidazole by reaction between secondary amine and formaldehyde. 2-(2-ethyl-1-methyl-5-nitro-1H-imidazol-4-ylthio)-6-methoxy-benzimidazole (9) was synthesized from the reaction of compound MBI with 1-methyl-2-ethyl-4-chloro-5-nitroimidazole. Some the synthesized compounds are confirmed by Melting points, FT-IR, ^{1}H-NMR spectral and are evaluated for Anti-bacterial activity against Escherichia coli, *Pseudonas aeruginosa* , Staphylococcus aureus, *Staphylococcus pyogenes*

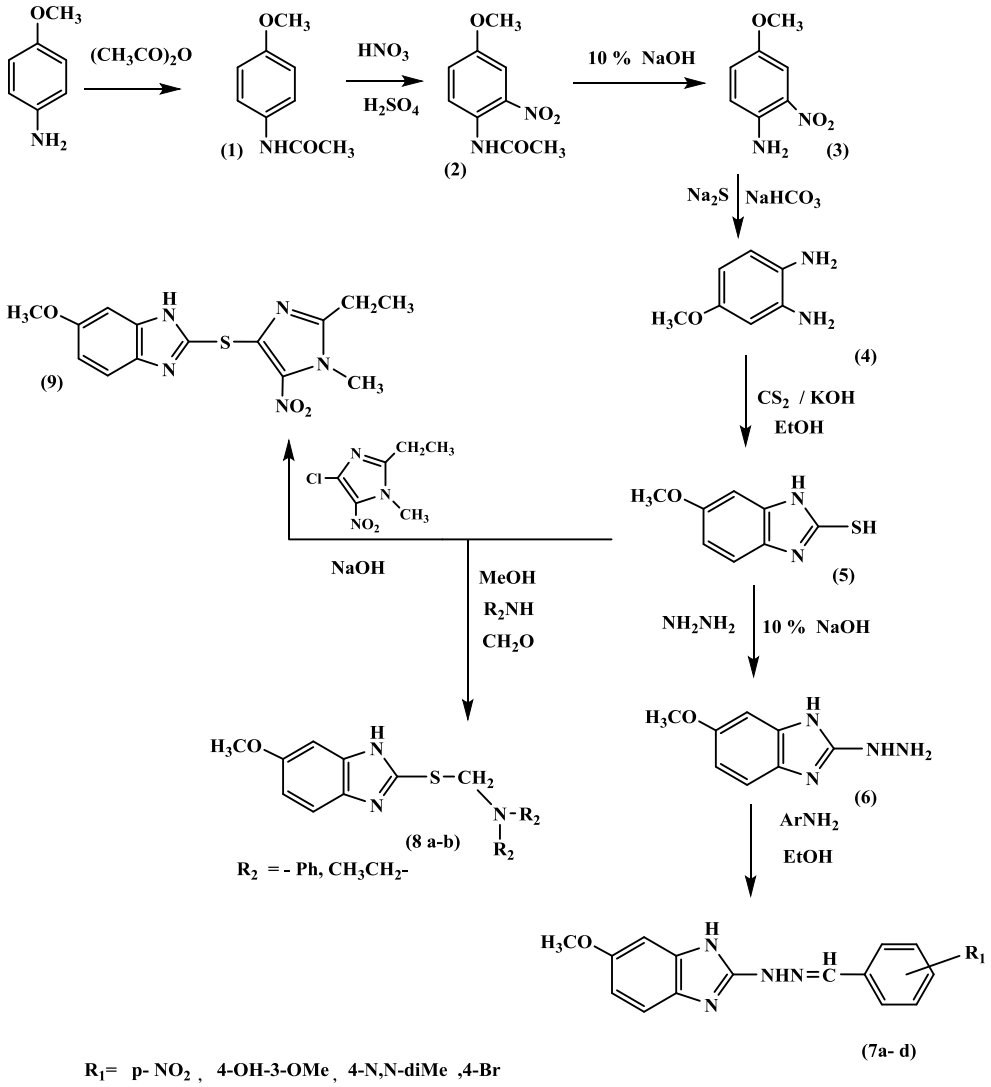
and Anti-fungal activity against.*Candida albicans* .*Microsporum canis*, *Aspergillus fumigates*.

Keywords: 4-methoxy aniline, benzimidazole ,Antifungal activity**,** heterocycle ,antimicrobial,

Introduction

A number of 2-mercaptobenzimidazoles have been synthesized by Vanallan and Deacon methods[1], 2-mercapt benzimidazole derivatives, one of the most important derivatives of Benzimidazole, for the reason that of their broad range of biological activities such as antimicrobial, anticancer, anthelminthic, antiarrhythmic, anticonvulsant, antioxidant, ant mycobacterial, antiulcer, androgen receptor antagonist, antiprotozoal, antiviral, antitumor,

anti-hypertensives, cysticidal, antihistaminics, antifungal, antifolate, antiseroton in, nematicidal , radioprotective [3],Also, some of them are known to possess properties antitubercular,[4] antagonist[5] and antifungal,[6]Further, substituted 2-mercapto benzimidazoles have been used as metal corrosion inhibitor[7], heavy metal ions adsorbents[8] and rubber products antioxidant,[9] They also how a large variety of biological activities including inhibitors of HIV, herpes (HSV-1), influenza, and anti-hepatitis C virus (HCV) [10], Epstein-Barr[11], Further, substituted 2-mercapto benzimidazoles have been utilized as metal corrosion inhibitor[12] heavy metal ions adsorbents[13]. and rubber products antioxidant [14], In present study 6-methoxyhydrazinobenzothiazole (6) combined with substituted benzaldehyde to form new series of derivatives, which were synthesized and evaluated for antimicrobial activity.



Scheme(1): The reactions sequence for the synthesis of some new 6-methoxy-2-mercaptobenzimidazole derivatives. (5), (7a-d) to (8a-b) .

Materials and Methods

Melting points were determined by open capillary using Sturat Melting point apparatus and are uncorrected. IR spectra were recorded as KBr on Shimadzu FT-IR-8300 spectrophotometer in Tikrit university ,1H NMR spectra were recorded on 500 MHz in Yildiz Teknik University Bruker using $CDCl_3$/DMSO and Elemental analysis was performed on Perkin-Elmer Series 2400. The synthetic method is described in Scheme (1) readjustment.

General procedures

Synthesis of N-(4-methoxyphenyl) acetamide (1) [15]

To well a stirred ice cold solution of (2.46 gm, 0.02mole) of 4-methoxy aniline in 25ml acetic acid and (9.34gm,0.11mole) acetic anhydride. The mixture was then was refluxed on steam bath for 3 hours .After standing at room temperature for 1h.it was added into the crushed ice with continuous stirring. The resulting solid was filtered, washed with water and recrystallized from %75, ethanol with activated charcoal. Melting point was 130–132^{o}C and the yield was 89%.

Synthesis of 4-methoxy -2-nitro acetanilide (2)

In a round bottom and under perfect ice-cold condition stirred was placed of *N*-(4-methoxyphenyl) acetamide(1)(5g ,0.02mol) was added to it mixture of (15 ml) sulphuric acid and (11ml ,0.02mole) concentrated nitric acid in an ice bath with constant stirring for 1hs .After the addition, the reaction mixture changed to yellow solution, the resulted mixture was poured into crushed ice ,The precipitate yellow solid was formed were collected by filtration ,washed with water and dried to recrystallized from ethanol, as crystalline white solid. Yield 90 %, m p = 116- 118 ^{0}C.

Synthesis of (4-methoxy-2-nitrophenyl) amine (3)

To a solution of 4-methoxy -2-nitro acetanilide (2) (1.89gm, 0.009mole) in methanol (60 mL), and After completion of reaction, the reaction mixture changed to yellow was stirred at room temperature for1h,and basified to a pH of 7-8 by using (2.16gm, 0.027 mole) 10% sodium hydroxide solution, the mixture was refluxed for 2 hrs. and then allowed to cool to room temperature for another 3hrs.and the formed precipitate was filtered, washed with ice cold water and then dried and purified by recrystallized from methanol .Yield: 91 %, m.p.122 -123 $^{\circ}$C.

Synthesis of 4-methoxy phenylene-1,2-diamine (4)

To A stirred solution of N-(4-methoxy -2-nitrophenyl)amine (3) (1.34gm, 0.008mole) and (3.84gm, 0.016mole) of $Na_2S.9H_2O$ in10 ml of water was added 1.18gm, 0.014mole $NaHCO_3$ in10 ml of water .The reaction mixture was stirred for 5 h at 90°C on hot plate. After then the solid product was collected by filtration and washed with cooled distilled water, dried and recrystallized with ethanol. Yield: 96 %, m.p.46 - 48°C.

Synthesis of 6-methoxy-2-mercuptobenzimidazole MBI: (5) [16]

A mixture of (21.8gm,0.2 mole) (1.0gm, 0.0072mole) of ortho hydroxyl aniline in absolute ethanol (150ml), potassium hydroxide (11.3 gm ,0.2 mole) was added then carbon

disulphide (15.34 gm 0.2 mole,12.38 ml) was added gradually with stirring. The mixture was refluxed for 6hours.till H_2S gas ceased, then 1.5gm of charcoal was added and the reaction mixture was heated on a water bath at (60-70°C) for15 minutes the charcoal is separated by filtration. The filtrate at a temperature between (65-75°C), 150ml of warm water (60-70°C) was added followed by 25ml of acetic acid with good stirring and the reaction mixture was acidified by dropwise addition of (6ml,1N) acetic acid. After completion of reaction the reaction mixture was filtered and the precipitated as white crystals. The solution was kept in the freezer till the solution completely froze and then allowed to melt; the precipitated is collected, filtered, then washed with cooled distilled water, dried and recrystallized from ethanol, yield 7٥% and m.p. 261- 264℃.

Synthesis of 6-methoxy (benzimidazole-2-yl) hydrazine (6) [17]

To a warm hydrazine hydrate solution of (0.02mol) 6-methoxy-2-mercapto benzimidazole (0.01mol), ethanol (10 ml) was added (10%) aq. NaOH and after the completion of addition, the mixture was refluxed for 6 h. The solid separated was filtered, washed with cooled distilled water, dried and recrystallized from absolute ethanol. Yield: 64 %, m.p. 225-223°C.

Synthesis of (2-acetamide benzothiazole-2-yl)-6- aryl hydrazone(7_{a-d})

6-methoxyhydrazinobenzothiazole (6) (0.01mole, 1.93g) was mixed with substituted benzaldehyde (0.01mol) in ethanol (30ml), the reaction mixture was refluxed for 4hrs after the addition of 4 drops of glacial acetic acid. The resultant solution was poured onto crushed ice and solid product was filtered, washed with methanol, and then dried and crystallized from the appropriate solvent. The physical properties of the synthesized are given in tables (1,2).

Table (1) Physical Properties for compounds (7a-d)

Comp. No.	R_1	m.p. °C	Molecular formula	Yield%	colour	Rec. Sol
a	NO_2	196-198	$C_{14}H_{12}N_5O_3$ 298.3	٧٨	yellow	ACOH
b	4-OH-3-OMe	160-163	$C_{15}H_{16}N_5O_3$ 314.3	٨٤	milky	EtOH
c	4-Br	60-61	$C_{14}H_{12}N_5OB_r$ 346.2	٨٠	White	Acetone
d	N,N-dimethyl	90-93	$C_{16}H_{18}N_5O$ 296.3	٨٧	Brown	٥٠% EtOH

6-methoxy(1-ethyl-2-methyl-4-nitroimidazolyl-5-mercapto)benzimidazole(9)[18]

A mixture of 18.88 g (0.10 mole) of nitrochlorimidazole,18.04 g (0.10 mole) of 6-methoxy -2-mercapto benzimidazole (5) and 10 g (0.10 mole) of 40% NaOH aq. The mixture was stirred for 3hrs. at 70°C. Acetic acid (4-5 ml) was added to the boiling reaction mixture

until the aqueous layer gave an acidic reaction, the reaction was cooled, poured into ice cold water. the precipitate was filtered, washed with water, dried and recrystallized from water (with charcoal). Yield 39.6g (82%), m.p. 225- 226°C

Synthesis of Mannich base of 6-methoxy- 2-mercaptobenzimidazole derivatives (8a-b)

In a 250 ml round bottomed flask equipped with a magnetic bar stirrer and condenser, a mixture of 6-methoxy-2-mercaptobenzimidazole (1mmol) and secondary amine (1.2mmol) in methanol with continuous stirring. To this solution, of 1ml of 37% formaldehyde under ice-cold condition. The reaction mixture was then allowed to stir for further 1 hr. in ice-bath. The solid product was kept in refrigeration for 24hrs. and the formed precipitate was isolated by filtered, washed with water, dried and crystallized from the appropriate solvent [19]. The physical properties of the synthesized compound are given in Table (2).

Table (2) Physical Properties for compounds (7a-b)

Comp. No.	R1	m.p.°C	Molecular formula	Yield %	colour	Rec. Sol
a	Ph	162- 164	$C_{21}H_{19}N_3OS$ 361.5	80	White	MeOH
b	CH_3CH_2	153-155	$C1_3H_{19}N_3OS$ 265.4	٨٣	milky	50%EtOH

Results and Discussion

In resent work we synthesize some 2-mercapto-6-methoxy-benzimidazole derivatives (5) as starting materials for preparing 2-mercapto-6-methoxy-benzimidazole (5) MBI derivatives initially we conducted reaction between 6-methoxy-2-phenylenediamine (1mmol) and CS_2 (1mmol) in ethanol (10 mL) under basic condition, we use potassium hydroxide as base which produced MBI with high yield and purity. Compound MBI was characterized by ^{1}H NMR, IR, ^{13}C-NMR and mass spectroscopy. The FT-IR spectra of compound [5] shows disappearance of absorption band at 2520- 2565 cm^{-1} due to *ν*(S-H) and appearance of strong absorption bands at 3286 cm^{-1} *ν*(N-H) and the appearance of clear strong absorption band at (1625-1610) cm^{-1} due to *ν*(C=N) imidazole. while C-S-C bands are noticed at the range 650-656cm^{-1}. ^{1}H-NMR spectrum of compound (5) showed clear singlet signal at δ= 12.41ppm due to (NH) group proton, while signal at δ=12.50 ppm due to (S-H) signal at δ= 3.72ppm due to (OCH_3) while, multiplet signals at δ= (6.5 - 7.14) ppm for aromatic protons. 2-Hydrazinobenzothiazole (6) is prepared from the reaction of 2-mercapto benzothiazole (5) with hydrazine hydrate in presence of sodium hydroxide in which the spectral data confirms formation of this compound. as shown in table (3).

The IR spectrum compound (6) shows absorption bands at 3359 and 3265 cm^{-1}due to stretching (-NH-NH_2) group in hydrazine with disappearance the bond of (SH) at (2520-2665), while absorption of C-H stretching at 2827-2860 $cm^{-1}$and 2916-2920 cm^{-1} and absorption of C=N at 1596-1648cm^{-1}. Also two bands of absorption of aromatic C=C are noticed at 1494-1523 cm^{-1} and 1439-1450cm^{-1}. ^{1}H-NMR spectra of compound (6) showed clear singlet signal at δ=2.08 ppm due to (CH_3) group protons, signals at δ= (3.5 and 3.8) ppm

due to (NH_2) and (NH) of hydrazine moiety while, multiplet signals at δ= (7.27-8.12) ppm for aromatic protons and singlet signal at δ= 8.61 ppm for imine proton (-N=CH-).

The 2-benzylidene-6-methoxy-2-hydrazide-substituted benzothiazole (7a-d) are synthesized from the reaction of compound (6) with substituted benzaldehyde. The IR spectra of the compounds (7a-d) shows strong band in the region (1605-1630) cm^{-1} as due to (C=N) stretching vibration imine, and disappeared two characteristic absorption bands at 3359 and 3265 cm^{-1} due to of a symmetric and symmetric (-NH-NH_2) group stretching.^{1}H-NMR spectra of compounds (7a-d) showed clear singlet signal at δ=2.08 ppm due to (CH_3) group protons, while, multiplet signals at δ=(7.27-8.12) ppm for aromatic protons and singlet signal at δ= 8.61 ppm for imine proton (-N=CH-).

2-mercupto-6-methoxyBenzimidazole-2-thiol MBI (5) can be alkylated at thiol group by halo compound of chloroimidazole in dry acetone which is used as alkylating agent to SH group triethyl amine act as a base nucleophilic attack to the thiol group (-SH) of the compound MBI (5) then deprotonate and then nucleophilic attack to the haloimidazole having chloride group which is a good leaving group to get thioimidazole.This compound(9) shows disappearance the bond of (SH) at (2520-2665), while absorption of C-H stretching at 2827-2860cm^{-1} and 2916-2920cm^{-1} while absorption of C=N at 1596-1648cm^{-1}. There were also two bands related to the absorption of aromatic C=C absorbed at 1494-1523cm^{-1} and 1439-1450cm^{-1} there is also appearance of characteristics bands at (1560,1350cm^{-1}) which represent asymmetric and symmetric NO_2 stretching.

6-methoxy-2-mercaptobenzimidazole (5) was allowed to undergo the Mannich reaction with secondary amines namely diphenyl amine, diethyl amine using 37% formaldehyde in absolute methanol to give Mannich base derivatives (8a-b). The IR spectrum of the synthesized compound (8a-b) shows disappearance of the band of (SH) at (2520-2665), while C-S-C bands are noticed at the range 750-756cm^{-1}, appearance the band of NH at (3275-3350 cm^{-1}) and the band of CH_2 stretching at (1448 -1463 cm^{-1}). shown in table (4). The ^{1}HNMR spectrum of the compounds (8a-b) shows the proton signals due to NH groups which were recorded between (4.88 – 5.75 ppm) integrating for one proton, and CH_2 proton signal at (3.70 – 5.78 ppm).

Both IR and ^{1}H-NMR spectrum respectively together with the absence of SH proton of 6-methoxy-2-mercaptobenzimidazole confirmed the formation of compounds (8a-b) as shown in table (4).

Table (3) infrared spectrum data for compounds (7a-d)) cm^{-1}

Comp. No	R_1	IR (ucm^{-1},KBr)				
		v N-H imidazole	v Ar-H	v C-H aliph	v C=N	v C-O (OCH3)
7a	4-NO_2	3150	3046	2976	1577	1137
7b	4-OH-3-OMe	3165	3038	2987	1595	1025
7c	4-Br	3134	3065	2954	1597	1145
7d	N,N-dimethyl	3167	3054	2967	1605	1036

Table (4) infrared spectrum data for compounds (8a-b) cm^{-1}

Comp. No. 8b	R_1	IR (ucm^{-1},KBr)					
		v N-H imidazole	v Ar-H	v C=N	v C-H aliph	v C-S	v C-O (OCH3)
8a	CH_3CH_2	3150	3050	1589	2976	1141	1126
8b	Ph	3165	3073	1597	2987	1260	1035

In our research of new antimicrobial agents, some of synthesized compounds (7a-d) were evaluated for antimicrobial activity by estimating the minimum inhibitory concentration (Ampicillin) by adopting serial dilution technique and the results were summarized in Table (5).

The data recorded in table (5) indicated that compounds (7a-d) showed moderate antibacterial activity against the Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*).while among these two compounds, $A7_a$ contains (nitro) group and $A7_b$ contains Br at the 4th position of cyclic benzene. These results indicate that larger groups at 4th position of cyclic benzene have no significant contribution to the antibacterial activity of these compounds. All these compounds are compared with the standard reference (Streptomycin) for their antibacterial activities. Only $A7_a$ with *nitro* group and $A7_b$ with bromo group at the 4th position of cyclic benzene as cyclic benzene showed moderate antifungal activity. So again the results evidence that larger groups at 4th position of cyclic benzene have no significant contribution to the antifungal activity of these compounds.All these compounds are compared with the standard reference (fluconazole) for their antifungal activities.

Table5: Antimicrobial and Antifungal evaluation of compounds (7a-d)

Comp.No.	***Antibacterial Activity***				***Antifungal activity***		
	inhibition percentage %						
	Gram Nagative		***Gram Positive***		***fungi***		
	Escherichia coli	*Pseudonas aeruginosa*	*Staphylococcus aureus*	*Staphylococcus pyogenes*	*Candida albicans*	*Microsporum*	Aspergillus fumigates
7a	**81**	**67**	**63**	**66**	76	84	70
7b	54	50	61	55	**50**	**56**	**54**
7c	**73**	**76**	**70**	**80**	78	77	80
7d	50	55	55	63	66	54	60
Ampicillin	100	100	100	100	---	---	---
fluconazole	---	---	---	---	100	100	100

Anti-bacterial Activity

The antibacterial activity was performed by cup-plate method. All the synthesized compounds were dissolved in 10 ml DMF at a concentration of 50 mcg/ml.The respective

bacterial culture was spread (swabbed) into the nutrient agar plates for uniform distribution of colonies. Using a sterile cork borer, 8 mm wide well was made on each agar plates. All the synthesized compounds (50 mcg/mL) were poured into each wells using a sterile micropipette and Ampicillin (50 mcg/mL) were used as standard. The plates were incubated for 24 hr at 37^{o}C. After incubation, the zone of inhibition was measured.

Antifungal Activity

The antifungal activity was tested against *Candida albicans*by cup plate method. All the synthesized compounds were dissolved in DMF solution at a concentration of 250 mcg/mL. The fungal culture was spread (swabbed) into the sabouraud dextrose agar plates for uniform distribution of colonies.using a sterile cork borer, 8 mm wide well was made on each agar plates. All the synthesized compounds (250 mcg/mL) were poured into each wells using a sterile micropipette and Ketoconazole (250 mcg/mL) were used as standard. The plates were incubated for 48 h at 270C. After incubation, the zone of inhibition was measured.

تحضير وتشخيص وتقييم الفعالية البايولوجية لبعض مشتقات

٦-ميثوكسي-٢-مركبتوبنزواميدازول

أحمود خلف جبر

قسم الكيمياء – كلية العلوم- جامعة تكريت

المستخلص

حضرN-(4-ميثوكسي فنيل) اسيتامايد من اسيلة بارا ميثوكسي انيلين والذي اجريت عليه عمليات مثل النيترة ثم تحلل مائي واختزال واخيرا تمت عملية الحولقة بوساطة التفاعل بين ٤- ميثوكسي فنيل ثنائي امين انيلين وثنائي كبريتيد الكاربون بوجود هيدروكسيد البوتاسيوم في الايثانول لينتج المركب (٥) والذي عومل مع الهيدرازين المائي بوجود هيدروكسيد الصوديوم في الايثانول لينتج ٦-ميثوكسي -٢- مركبتو بنزاميدزول (٦) بعدها يعامل مع الديهايدات اروماتية مختلفة في الايثانول لينتج قواعد شف .(6a-d) .حضرت المشتقات الجديدة ٦-ميثوكسي-٢- مركبتو بنزاميدزول (8a-b) بوساطة تفاعل مانخ من الفورمالديهايد.المركب ٢(٢-اثيل -١-مثيل -٥-نايترو -١-اميدازول ثايول) ٦- ميثوكسي بنزواميدازول (٩) والذي حضر من تفاعل المركب (٥) مع ١- مثيل -٢-اثيل -٤-كلورو-٥-نايتروميدازول .بعض المركبات المحضرة تم تاكيدها بواسطة درجة الانصهار وطيف الاشعه تحت الحمراء والرنين النووي المغناطيسي البروتوني وتحليل العناصر CHNS وتم تقييم الفعالية البايولوجية لانواع مختلفة من البكتيريا وللفطريات .

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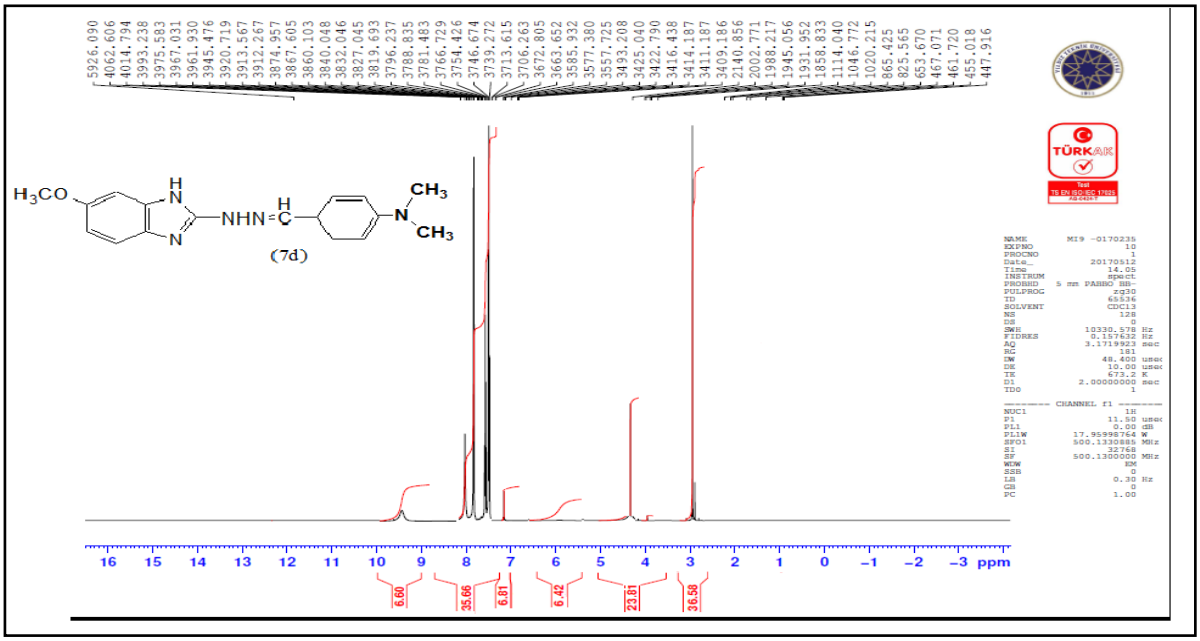

Fig (1) ^{1}H-NMR spectrum of compound (7d)

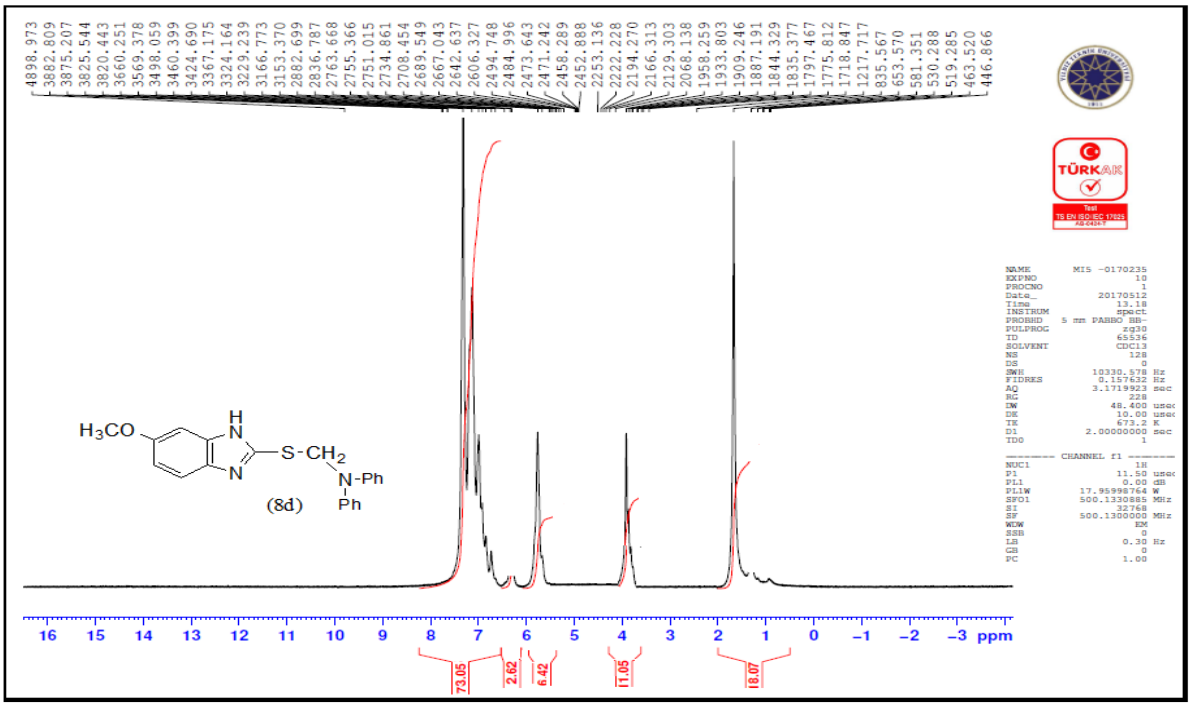

Fig (2) ^{1}H-NMR spectrum of compound (8d)

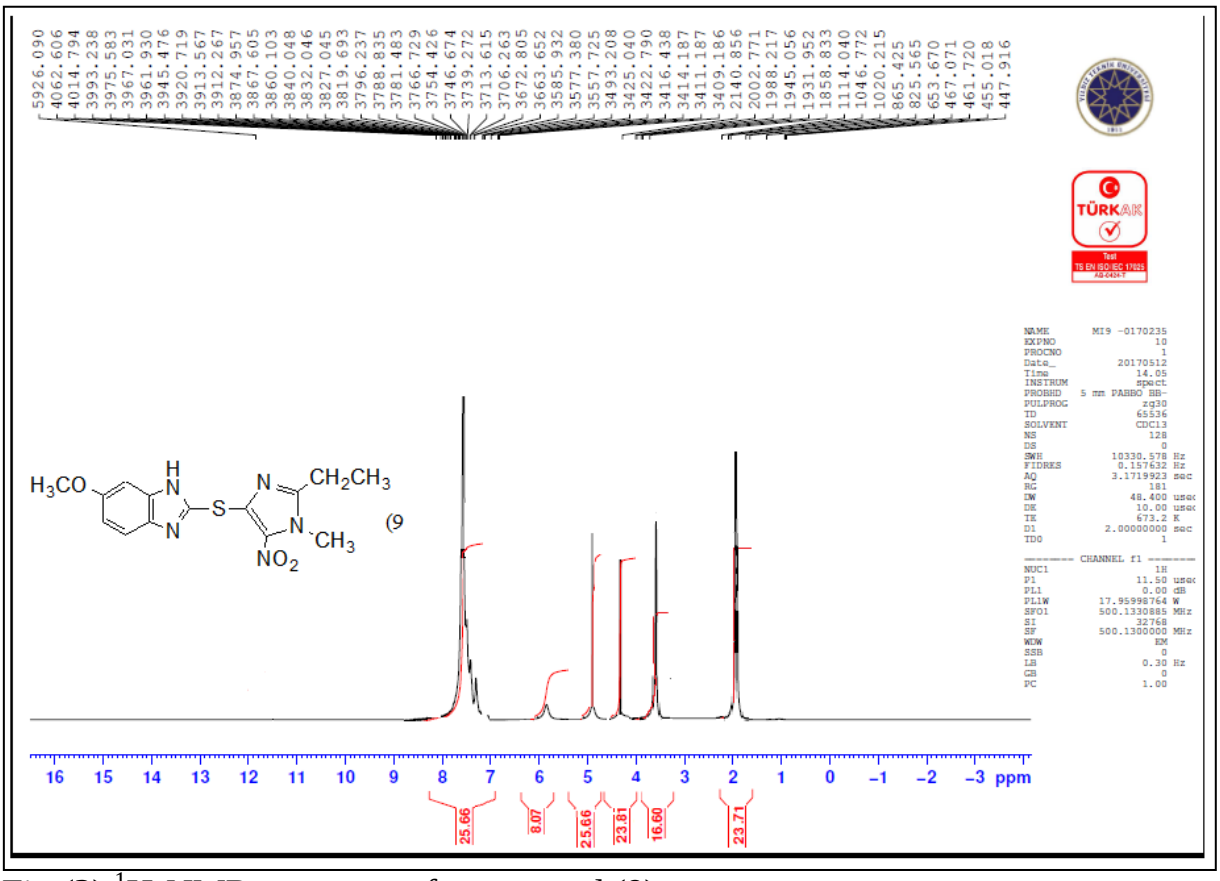

Fig (3) ^{1}H-NMR spectrum of compound (9)

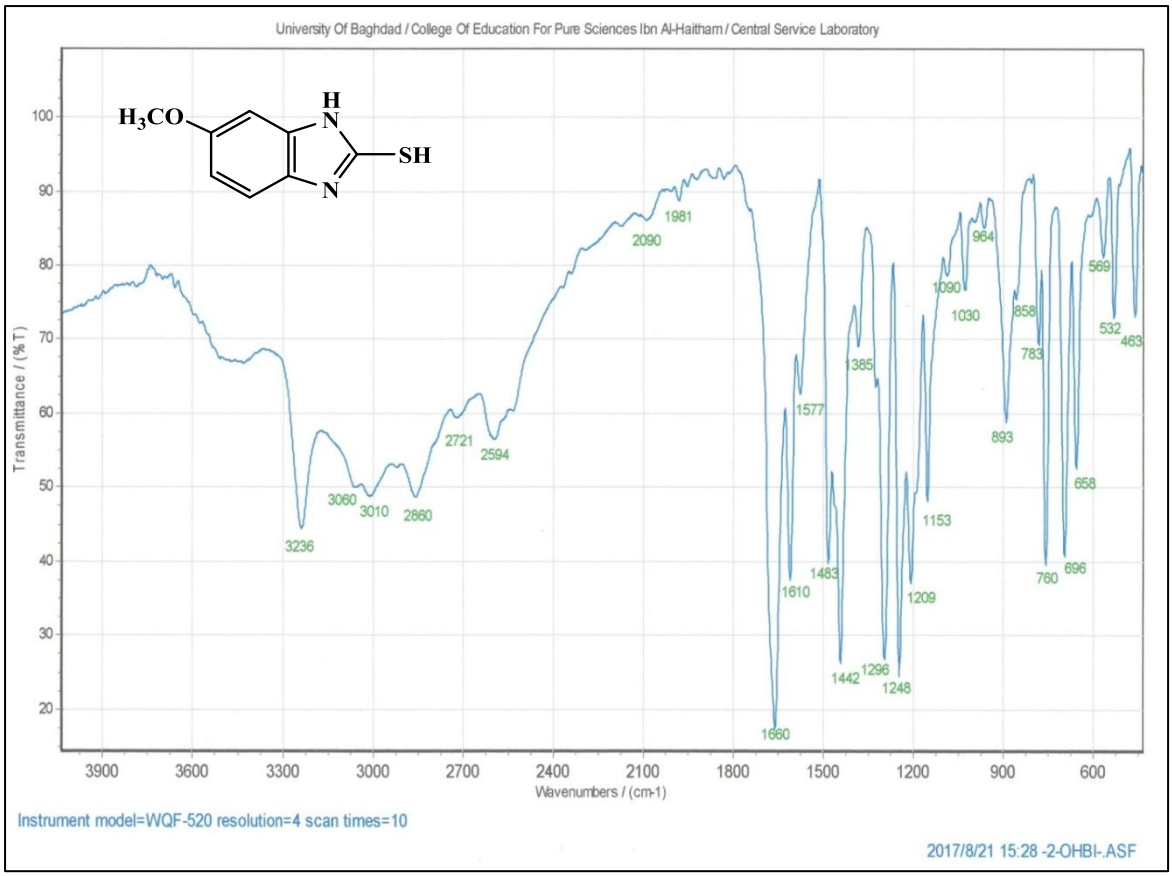

Fig (4) FT-I.R. spectrum of compound (5)

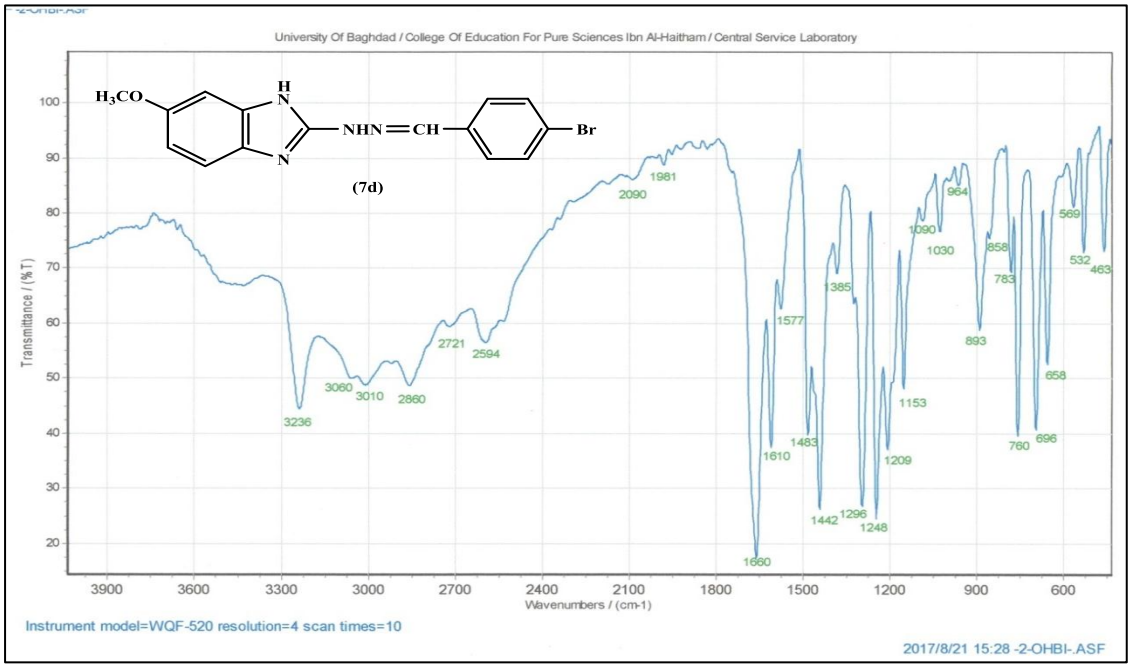

Fig (5) FT-I.R. spectrum of compound (7d)

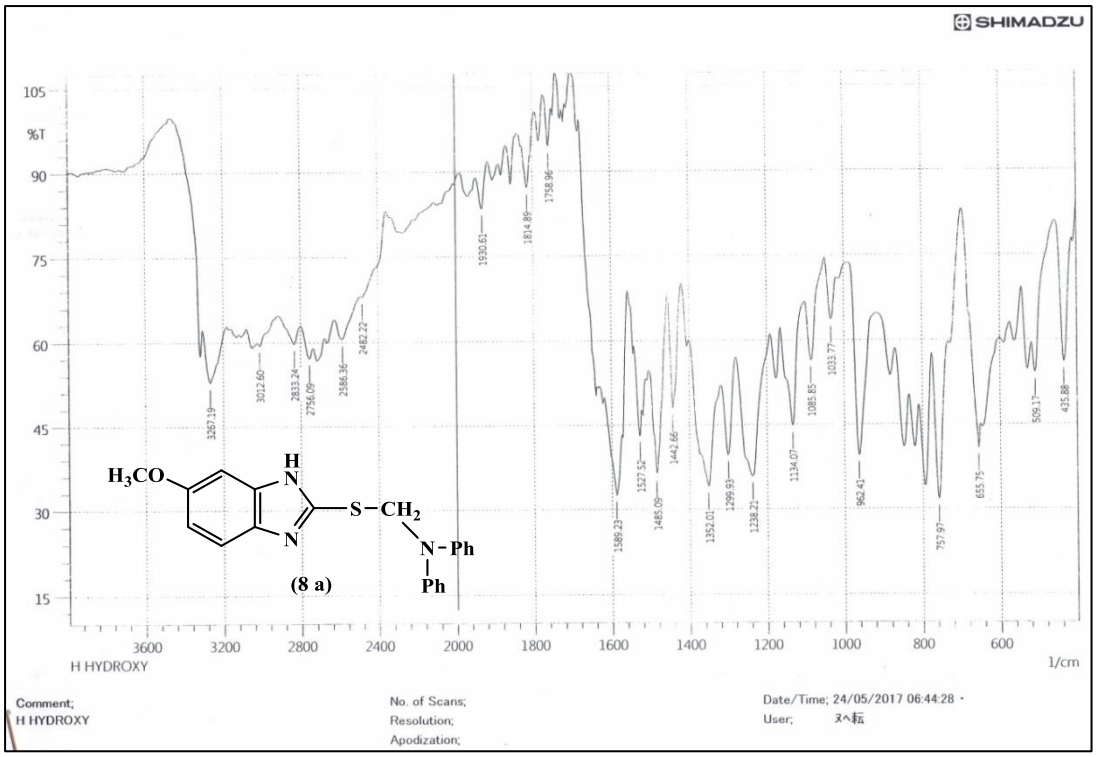

Fig (6) FT-I.R. spectrum of compound (8a)

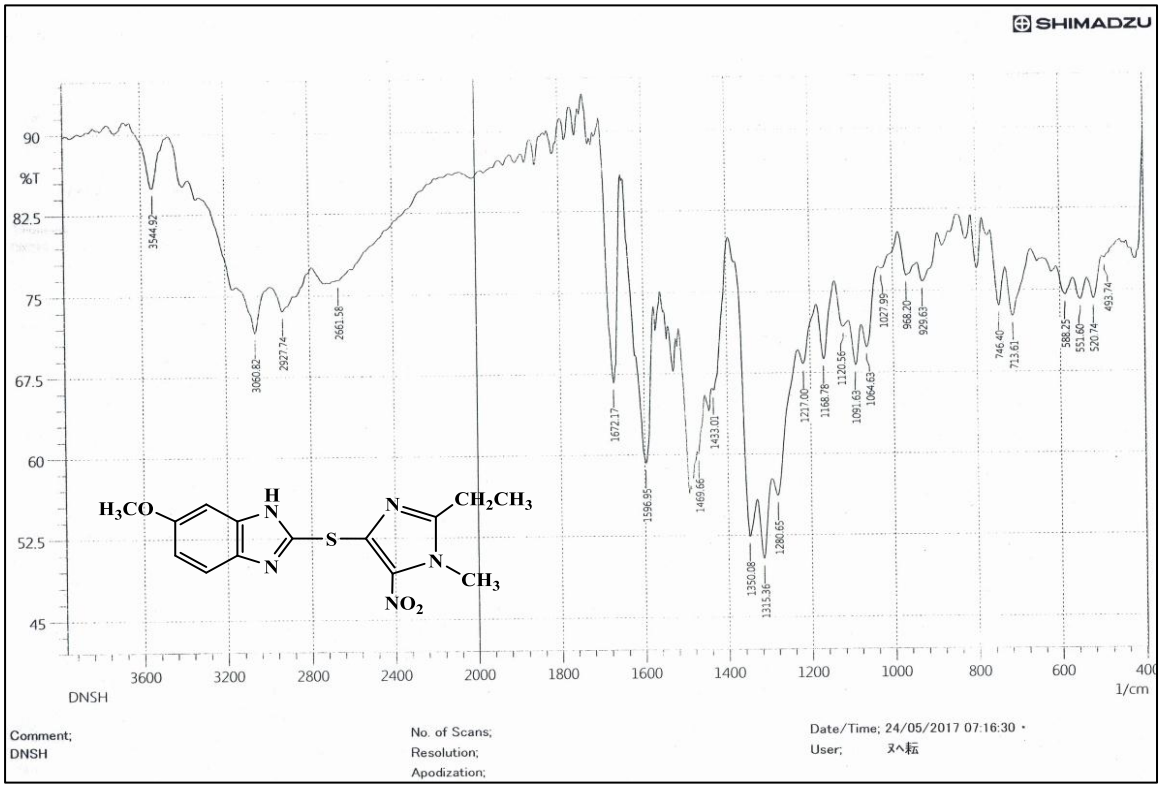

Fig (7) FT-I.R. spectrum of compound (9)