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SECTION 9. Chemistry and chemical technology.

ANTIFUNGAL ACTIVITY OF SOME NEW β -LACTAM AND IMIDAZOLE DERIVATIVES

Abstract: *Trichophyton mentagrophytes* causes a variety of infections in both animals and humans. It is a zoophilic fungus and most human diseases are contacted from animals. It is of worldwide distribution and has a very wide range of hosts. The aim of this study was to evaluate the antifungal activity of compounds of derivatives (C4) and (C7) in vivo and in vitro. The antifungal activity was determined by the agar method against *T. mentagrophytes*. Derivatives were synthesized by the reaction of cinnamic acid with thionyl chloride to give the corresponding acid chloride (C1). Carbohydrazide (C2) was obtained by the reaction of (C1) with hydrazine hydrate. Compound (C2) undergoes the character condensation reaction with aromatic aldehyde (4-bromobenzaldehyde) in absolute ethanol gave the Schiff's base (C3). Treating a phenyl acetic acid in triethyl amine with (C3) in the presence of SOCl_2 to form the appropriate β -lactams (C4). Reaction of compound (C1) with glycine in sodium hydroxide solution gave acid (C5). Oxazole derivative (C6) was synthesized by the reaction of (C5) with aromatic aldehydes (2-chlorobenzaldehyde) in acetic acid and acetic anhydride. Imidazole derivatives (C7) was synthesized by the reaction of Hydrazine hydrate with (C6) in dry benzene. The product compounds were characterized by FT-IR, U.V and ^1H NMR spectra. The results showed that cyclic compound had highly effect against *T. mentagrophytes* (in vitro) and in treatment skin infection (in vivo) when the healing was occur after 10 days compare with control.

Key words: *Trichophyton mentagrophytes*, β -lactams, Imidazole.

Language: English

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1.Introduction

Trichophyton is a genus of fungi, which includes the parasitic varieties that cause tinea, including athlete's foot, ringworm, jock itch, and similar infections of the nail, beard, skin and scalp. *Trichophyton* fungi are molds characterized by the development of both smooth-walled macro- and microconidia (Lorch et al.,2015). *Trichophyton mentagrophytes* is a member of a homogenous group of fungi called dermatophytes. Dermatophytes form a group of pathogenic fungi which have a marked affinity for keratin, attacking skin, hair and nails. *T. mentagrophytes* like other dermatophytes has the ability to break down or digest keratinized areas in humans, birds and other mammals [2]. Hydrolysis of keratin by keratinases is an important aspect of fungal pathogenesis. For dermatophytes to induce active infection, the arthroconidia lodging on the skin surface must be able to penetrate the stratum corneum [3]. Five different keratinolytic enzymes

from ten strains of *T. mentagrophytes* have been isolated. These enzymes are known to play a role in pathogenesis of infections caused by these organisms in both humans and animals. In Nigeria, *T. mentagrophytes* has been isolated from cases of foot infections in coal miners [4] and from school children [5]. In Amsterdam, Nieboer *et al.* [6] isolated *T. mentagrophytes* twice as often as *T. rubrum* from industrial workers using common shower rooms. In a study of ringworm in coal miners in Britain, Gentles and Homes [7] recovered *T. mentagrophytes* alone from 224 of 346 clinical specimens, and *T. rubrum* and *T. mentagrophytes* from 13 specimens. Heterocyclic compounds had been receiving considerable attention due to their pharmacological and pesticidal importance [8-16]. Imidazole is an organic compound with the formula $\text{C}_3\text{H}_4\text{N}_2$ [17]. Imidazole is a monoacidic base having the ability to form crystalline salts with acids [18]. Imidazole is a 5-membered planar ring, which is



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soluble in water and other polar solvents. The compound is classified as aromatic due to the presence of a sextet of π -electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring [19]. A β -lactam ring is a four-membered ring. A lactam is a cyclic amide. It is named as such because the nitrogen atom is attached to the β -carbon relative to the carbonyl. The simplest β -lactam possible is azetidin-2-one [20]. Up to 1970, most β -lactam research was concerned with the penicillin and cephalosporin groups, but since then, a wide variety of structures have been described [21]. This work was carried out to determine Antifungal activity of some New β -lactam and Imidazole derivatives.

2. Material and Methods

2.1. Synthesis

Infrared spectra were recorded on (FTIR-8400s Fouriero Trans Form Infrared Spectrophotometer Shimadzu). UV Spectra were recorded on UV-Visible spectrophotometer (VARIAN) UV-1650PC. $^1\text{H-NMR}$ spectra (Burker DMX -500 NMR spectrophotometer) were recorded on ultra shield 300 MHZ in Jordan, with tetra methyl silane as internal standard and DMSO as a solvent. Melting points were determined in a (Gallen kamp MFB-600-Melting point apparatus) melting point apparatus with sample contained in open capillary glass tube in an electrically heated metal block apparatus, and were uncorrected. All chemicals were supplied from BDH, Merck, Fluka and used without further purification.

2.1.1. Synthesis of chloro-1-benzothiophene-2-carbonyl chloride(C1)

Cinnamic acid (29.63g, 0.20 mol), chlorobenzene (150 ml), and SOCl_2 (119g, 1 mol) was stirred at room temperature for 30 min. then, pyridine (1.58 g, 0.02 mol) was carefully added and

the reaction mixture was refluxed for 72 h. The resulting residue was suspended in hot cyclohexane (400 ml) and immediately filtered. Upon staying at room temperature overnight, the title compound (C1) crystallized as yellow needles.

2.1.2. Synthesis of 3-chlorobenzothio[phenene]-2-carbohydrazide(C2)

A mixture of compound (C1) (2.29g ,0.01 mol) and hydrazine hydrate (99%, 0.32 g, 0.01 mole) in benzene (25 mL) was refluxed for 4 h. Upon cooling the solution, a solid appeared. This was recrystallized from ethanol to afford the desired compound(C2).

2.1.3. Synthesis of 3-chloro-N'-(Arylidene)benzo [b] thiophene-2 carbohydrazide(C3)

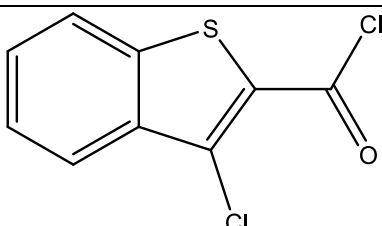
Aryl aldehyde (0.01 mol) was added to a stirred solution of compound (C2) (2.27g ,0.01 mol) in absolute ethanol (30 ml) and the mixture was refluxed for 8 h. After cooling, the mixture was filtered and the solid recrystallized from ethanol to afford the desired compound(C3).

2.1.4. Synthesis of N-(2-(Aryl)-4-oxo-3-phenylazetididin-1-yl)-3-chlorobenzothio[phenene]-2-carboxamide(C4)

To a mixture of phenylacetic acid (1.35 g, 0.01mol), imine (C3) (0.01mol) and triethylamine (4.04 g, 0.01mol) in dry dichloromethane (40 ml) at 0°C , a solution of SOCl_2 (15 ml) in dry dichloromethane(20 ml) was added as drop wise . The mixture was stirred 24 h at room temperature. Then the mixture was washed successively with 1N HCl (30ml), water ($3 \times 30\text{ml}$), and 5% NaHCO_3 (30ml). The organic layer was separated and dried over anhydrous sodium sulphate (Na_2SO_4), and then filtered solvent was removed under reduce pressure. The solid recrystallized from DMSO: H_2O to afford the desired compound. The physical properties are listed in Table (1).

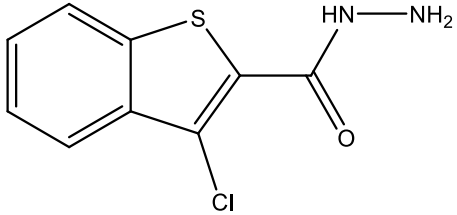
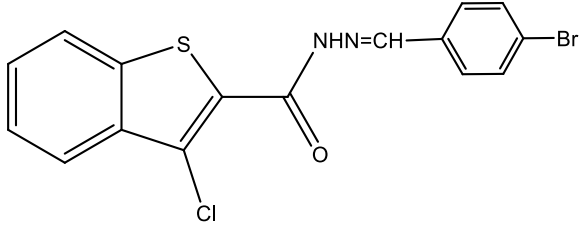
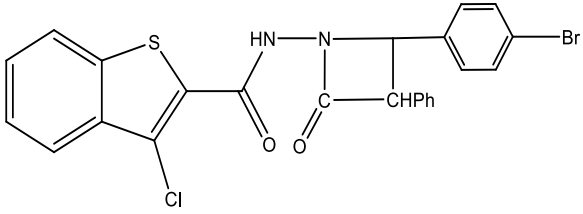
Table (1)

Physical properties of compounds (C1 – C4).

Comp. No	Compound structure	Colour	Yield %	M.P
C1		Yellow	73	111-113

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C2		orange	92	182-184
C3		Dark orange	81	132-134
C4		Dark green	71	161-163

Synthesis of 2-(3-chlorobenzothien-2-yl)acetamide (C2)

Compound (C1) (2.29 g, 0.01 mol) was added to a stirring solution of L-glycine (0.75 g, 0.01 mol) and sodium hydroxide (50 ml, 10% solution). Then, the reaction mixture was shaken vigorously for 1 h, and a few grams of crushed ice were added with stirring. After that, the solution was acidified with conc. HCl and the product was collected and recrystallized from ethanol.

2.1.6. Synthesis of 2-(3-chlorobenzothien-2-yl)-N-(4-bromophenyl)acetamide (C3)

Aromatic aldehyde (0.01 mol) was added to a stirring mixture of compound (C5) (2.69 g, 0.01

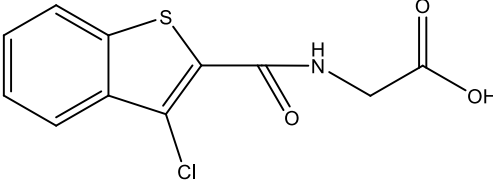
mol), acetic acid (5 ml) and acetic anhydride (20 ml). The temperature of reaction was increased to 70 °C for 10 min., then the mixture was poured into crushed ice and stirred for 30 min. the product was collected and recrystallized from ethanol to afforded the desired compound.

2.1.7. Synthesis of 1-amino-2-(3-chlorobenzothien-2-yl)-4-(Arylidene)-1H-imidazol-5(4H)-one (C7)

Hydrazine hydrate (99%, 10 ml) was added to a mixture of compound (C6) (0.01 mol) in dry benzene (5 ml). The reaction mixture was refluxed for 20 h after cooling the solid product was obtaining and recrystallized from ethanol. The physical properties are listed in Table (2).

Table (2)

Physical properties of compounds (C5 – C7).

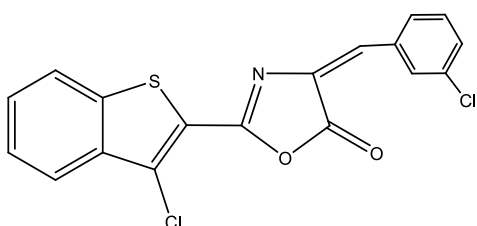
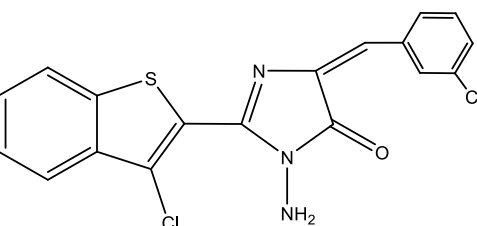
Comp. No	Compound structure	Colour	Yield %	M.P
C5		brown	89	124-126

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C6		orange	60	136-138
C7		bronze	67	127-129

2.2. Determination of antifungal activity *In Vitro*:

These compounds of derivatives (C4, C7) was assayed for antifungal activity against *T. mentagrophytes* by using Potato Dextrose Agar (PDA) plate. A fungal plug (5 mm diameter) was removed from the 5 day old culture. The plug was transferred onto the center of the PDA plate, which had been loaded with different concentration of compound (C4, C7) derivatives compounds (1000, 10000) $\mu\text{g/ml}$. The plate was incubated for 5-7 days at 30°C and was monitored for a colony diameter in mm, and compare with control [22].

2.3. Measurement LD50 for compound (C4)

Five groups of 6 mice (4weeks old), weighting approximately 20 gm ,from National Center For Drug Control and Research (NCDCR), were injected intra peritoneal with 0.5ml of (C4) and from each concentration from the stock (500,1000, 5000,10000) $\mu\text{g/ml}$, two mice were injected with 0.5ml normal saline and two mice were injected with 0.5ml DMSO as a control .After 24 hr, all mices(which injected) were examined ,and

determined the concentration which was killed half of animals and consider LD_{50} [23].

2.4. Determination of antifungal activity *in vivo*:

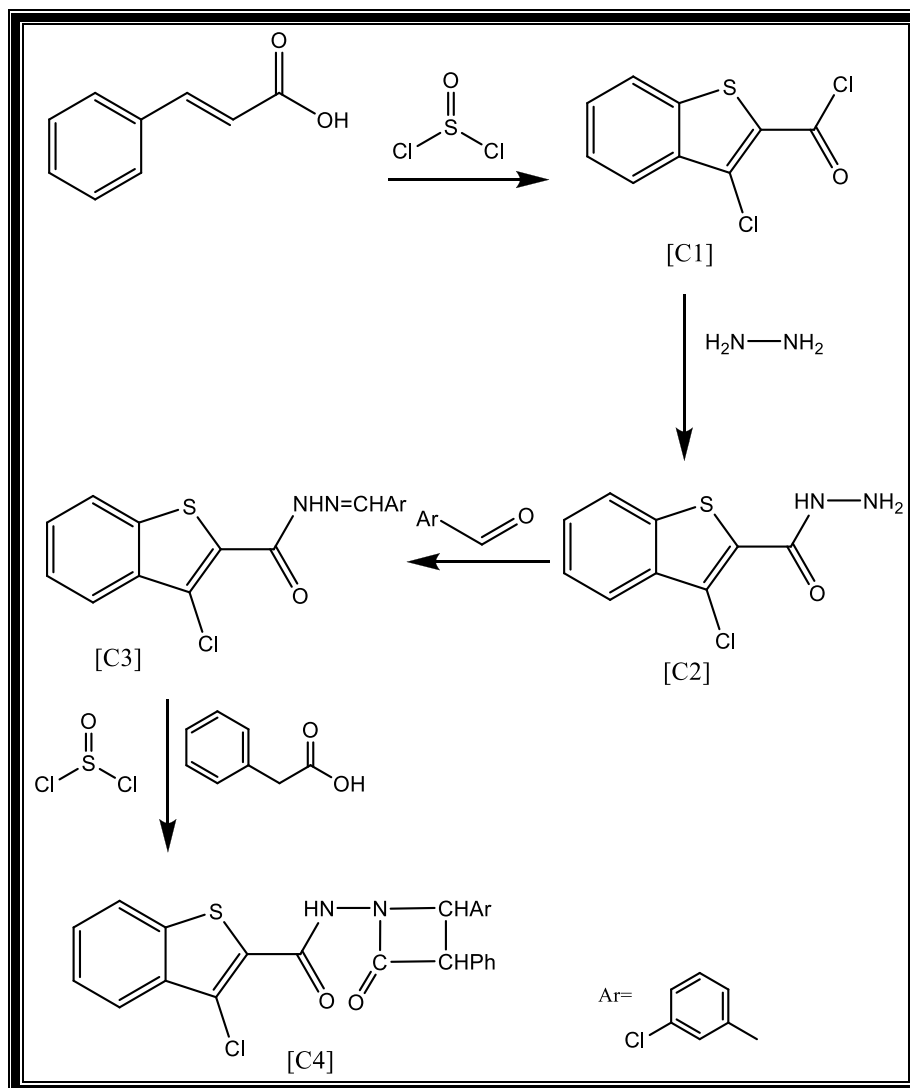
Skin infection in Rabbit with *Trichophyton mentagrophytes* fungus was done by contaminated the skin by fungus suspension and the infection was monitoring and show the scale in skin and hair. compounds (C4) was assayed for antifungal activity against *Trichophyton mentagrophytes in vivo* for treatment the skin infection in Rabbit with 500 $\mu\text{g/ml}$ /3 time daily for one week, Vaseline was used as ointment in the control group.

3. Results and Discussion

3.1. Synthesis

T. mentagrophytes, representing the complex, is a highly keratinolytic fungus. It secretes a variety of proteases which enable it to attack different karatinous substrates. It is a non-fastidious fungus.

For the synthesis of the targeted compounds (C1- C4), the reaction sequences are outlined in scheme (1):

Scheme (1): Synthesis β -lactam derivatives.

Synthesis of 3-Chlorobenzothiophene-2-carbonyl chloride (C1)

For synthesis of the target compounds (C1) which was prepared by the reaction of cinnamic acid and thionyl chloride. The structure of compound was confirmed by FT-IR and U.V spectrum. The FT-IR spectrum of compound (C1) (Fig. 1) shows disappearing of stretching vibration of (OH) group of carboxylic acid at (2500-3300) cm^{-1} and increasing

frequency of (C=O) to (1763) cm^{-1} , also spectrum shows another bands, (3059) cm^{-1} for aromatic (C-H), band at (1597,1479) cm^{-1} due to aromatic (C=C), bands at (700) cm^{-1} for stretching vibration of (C-S-C) group and bands at (758) cm^{-1} for stretching vibration of (C-Cl) group. U.V. spectrum showed two absorption λ_{max} at 232 nm (π - π^*) and 344nm (n - π^*) electronic transition.

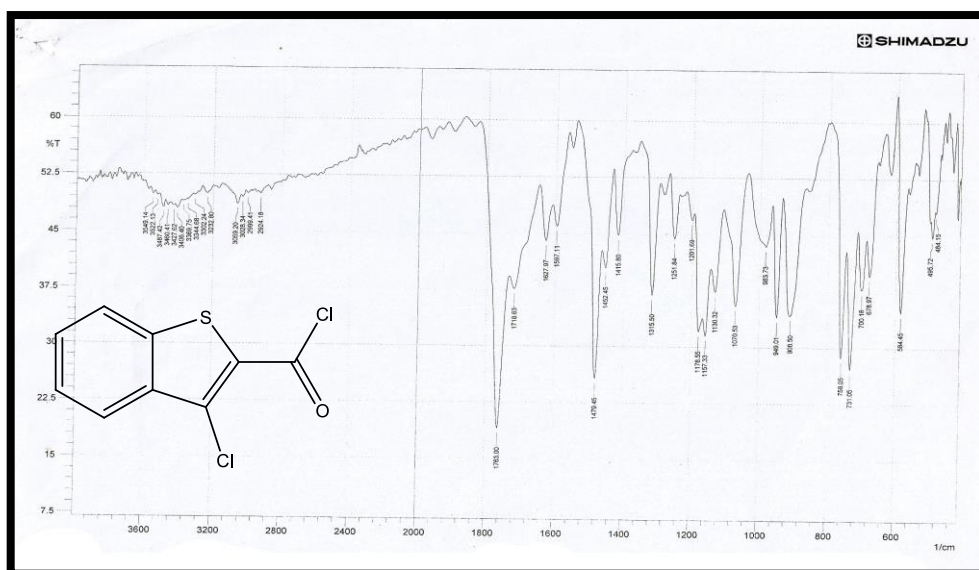


Fig. 1: The FT-IR spectrum of compound (C1).

Synthesis of 3-chlorobenzobenzothiazole-2-carbohydrazide(C2)

This compound was obtained by the reaction of 3-Chlorobenzobenzothiazole-2-carbonyl chloride(C1) with hydrazine hydrate. The structure of compound (C2) was confirmed by FT-IR, U.V and ¹H-NMR spectrum. FT-IR spectrum of compound (C2) (fig.2) shows the following bands, two bands at (3317-3286) cm⁻¹ due to stretching vibration (asymmetric and symmetric) for (NH₂) group, band at (3200) cm⁻¹ due to stretching vibration of (NH), decrease stretching vibration of carbonyl group to (1653) cm⁻¹.

UV spectrum of compound (C2) shows intense maxima at (268 nm) and (328 nm) due to π→π* and n→π* electronic transition, respectively. The ¹H-NMR of compound (C2) (Fig. 3), shows the following signals:

- Singlet at (12.40) ppm due to one (NH) group proton.
- Multiplet at (7.60-8.10) ppm due to four aromatic protons.
- Singlet at (4.72) ppm due to two (NH₂) group protons.

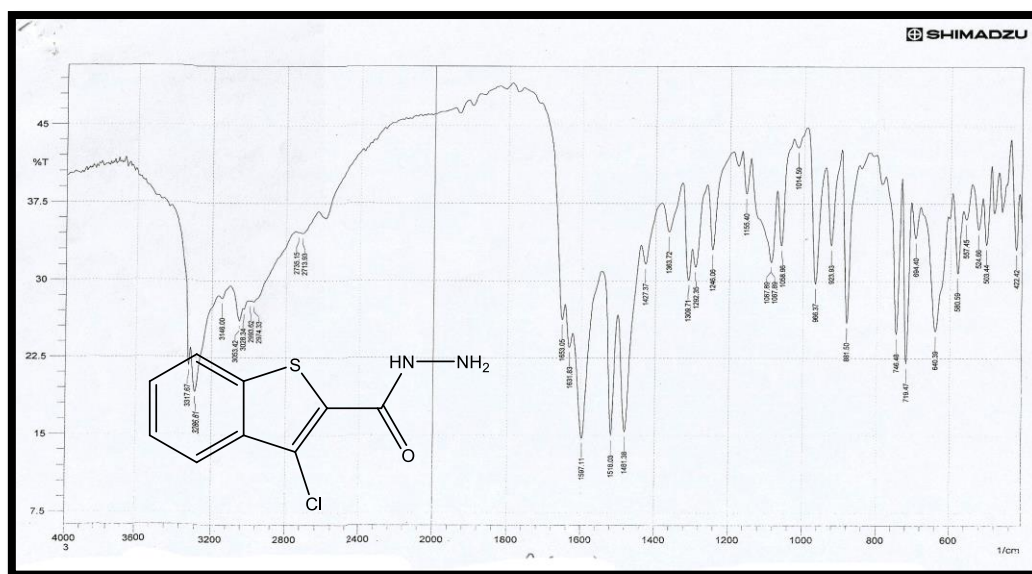


Fig. 2: The FT-IR spectrum of compound (C2).

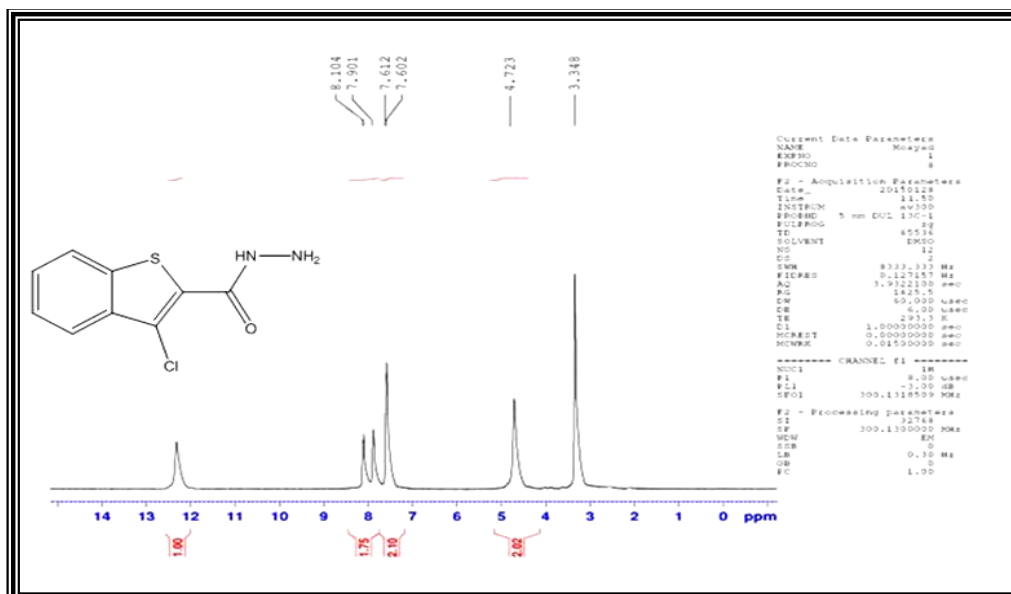


Fig. 3: The $^1\text{H-NMR}$ spectrum of compound (C2).

Synthesis of 3-chloro-N'-(Arylidene)benzo[b]thiophene-2-carbohydrazide (C3)

Compound (C2) undergoes the character condensation reaction with aromatic aldehyde in absolute ethanol to give the Schiff- base (C3). The formation of these Schiff's base was indicated by the disappearance of the NH_2 stretching vibration band. The structure of compound (C3) was confirmed by

FT-IR and U.V spectrum. FT-IR spectrum (fig 4) of compound (C3), shows the following bands, band at $(3215) \text{ cm}^{-1}$ due to stretching vibration of (NH) group, and band at $(1620) \text{ cm}^{-1}$ for stretching vibration of (C=N) group. UV spectrum of compound (C3) shows intense maxima at (248 nm) and (335 nm) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition, respectively.

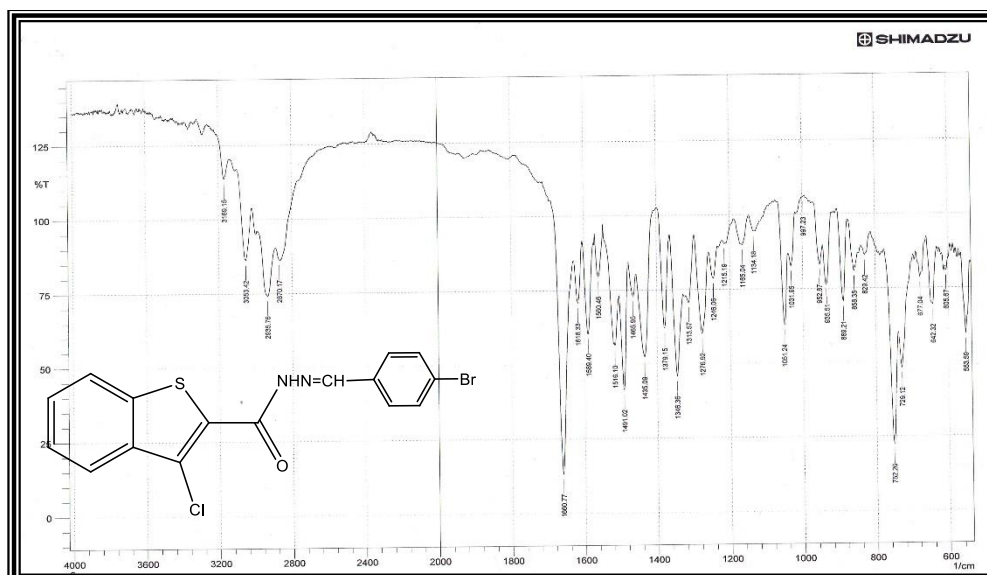


Fig. 4: The FT-IR spectrum of compound (C3).

Synthesis of N-(Aryl)-4-oxo-3-phenylazetidin-1-yl)-3-chlorobenzo[b]thiophene-2-carboxamide (C4)

Synthesis of β -lactam was done by treating a phenylacetic acid with triethylamine to form anion which then producing cycloaddition reaction with

(C3) in the presence of SOCl_2 to form the appropriate β -lactam (C4). The formation of these β -lactams was indicated by the appearance of the two stretching vibration bands $(1722, 1701) \text{ cm}^{-1}$ to carbonyl group. The structure (C4) was confirmed by FT-IR, U.V and $^1\text{HNMR}$ spectrum. FT-IR spectra

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(fig 5) , Table (3) shows the stretching vibration bands at $(3201) \text{ cm}^{-1}$ due to (NH) group , band at $(3061) \text{ cm}^{-1}$ due to aromatic (C-H) ,band at $(2982,2890) \text{ cm}^{-1}$ aliphatic (CH),band at $(1722,1701) \text{ cm}^{-1}$ for(C=O) group and band at $(1591,1512) \text{ cm}^{-1}$ for aromatic (C=C). UV spectrum of compound (C4) shows intense maxima at (276 nm) and (358 nm) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition, respectively.

The $^1\text{H-NMR}$ of compound (C4) (Fig. 6), shows the following signals:

- Singlet at (12.5) ppm due to (NH) group proton.
- Doublet,

Doublet at (8.01-8.16) ppm due to two aromatic proton.

- Multiplet at (7.87-7.94) ppm due to four proton of aromatic ring of benzothiophen.

- Multiplet at (7.47-7.72) ppm due to five proton of phenyl ring .

Doublet at (7.38-7.40) ppm due to two aromatic proton.

- Doublet at (5.60-5.62) ppm due to (CHCO) group proton.

- Doublet at (4.46-4.47)ppm due to (CH-N) group proton.

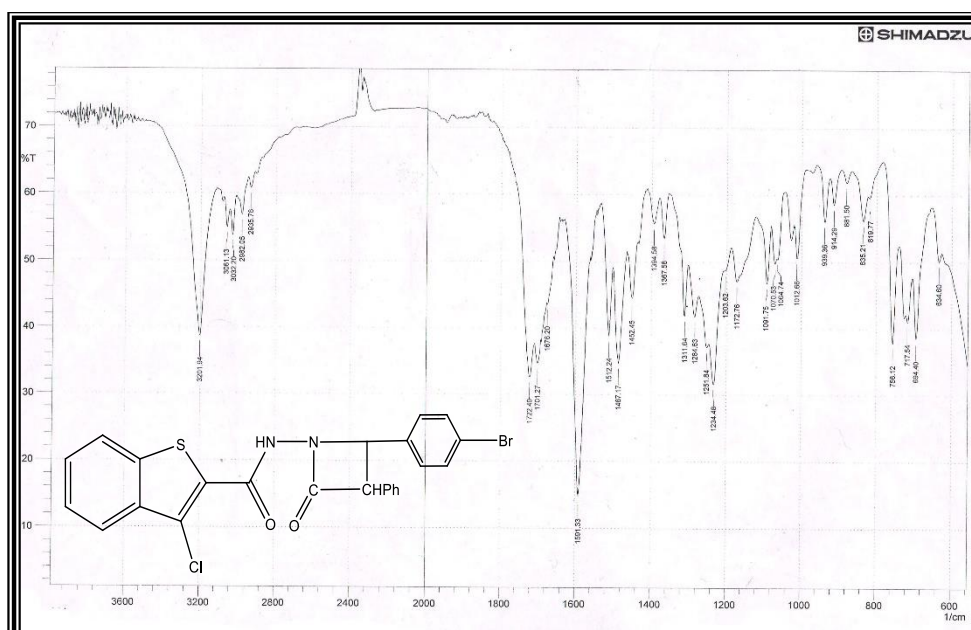


Fig. 5: The FT-IR spectrum of compound (C4)

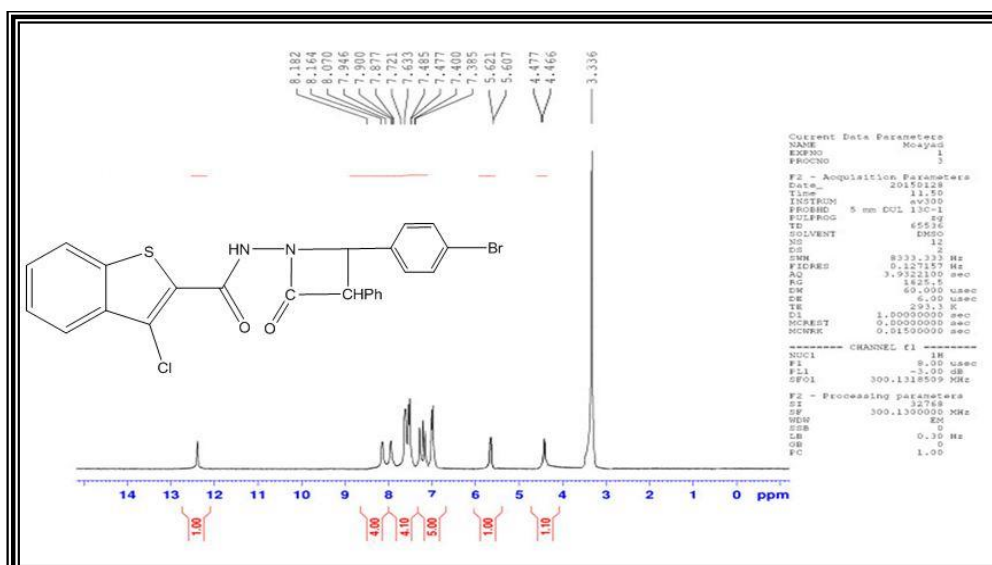


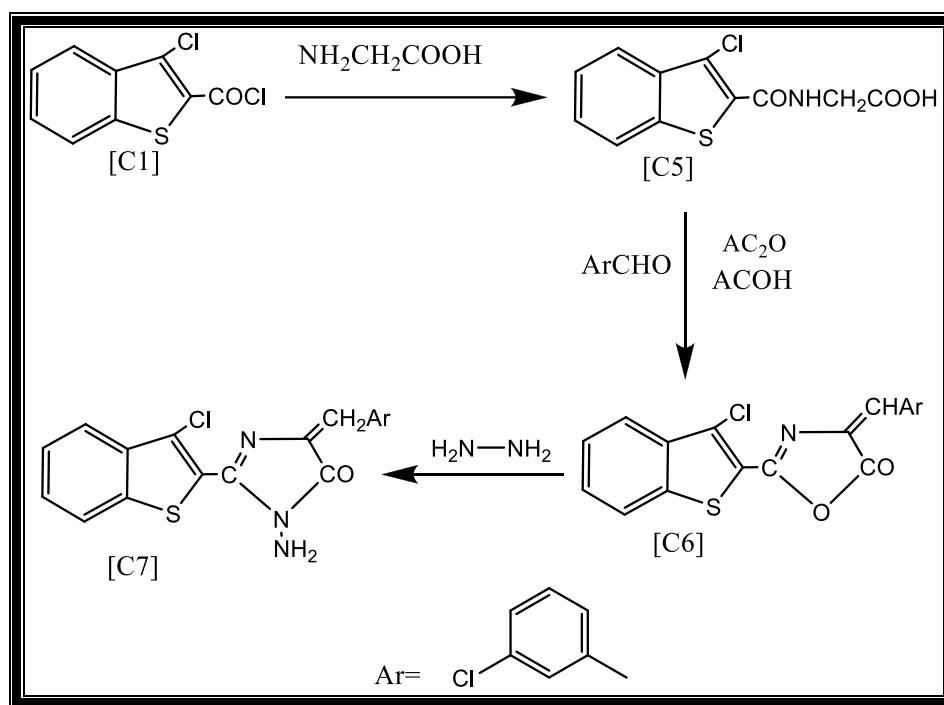
Fig. 6: The $^1\text{H-NMR}$ spectrum of compound (C4)

Table (3)

IR spectral data for compounds (C1 – C4).

Comp. No	Characteristic IR bands $\nu(\text{cm}^{-1})$					
	NH	CH aromatic	C=O	C=N	C=C aromatic	other
C1		3059	1763		1597,1452	
C2	3200	3053	1653		1597,1479	3317,3286 (NH ₂)
C3	3215	3051	1643	1620	1589,1546	3191(N=CH), 637(C-Br)
C4	3201	3061	1722,1701		1591,1512	628(C-Br)

For the synthesis of the targeted compounds (C5- C7), the reaction sequences are outlined in scheme (2):



Scheme (2) : Synthesis Imidazole derivatives.

Synthesis of 2-(3-chlorobenzothiophen-2-carboxamido)acetic acid (C5)

This compound was synthesized by the reaction of compound (C1) with glycine in sodium hydroxide solution. The formation of (C5) was indicated by the appearance of the two stretching vibration bands to carbonyl group and the appearance of the two stretching vibration bands to NH, OH group. The

structure (C5) was confirmed by FT-IR, U.V and ¹HNMR spectrum. FT-IR spectrum (fig. 7) shows the stretching vibration bands at (3390) cm⁻¹ due to (NH) group, (3200-2500) cm⁻¹ broad band for (OH) group, band at (3061) cm⁻¹ due to aromatic (C-H), band at (2983,2939) cm⁻¹ due to aliphatic (CH), band at (1726,1685) cm⁻¹ due to two(C=O) and band at (1597,1533) cm⁻¹ due to for aromatic (C=C). UV spectrum of compound (C5) shows intense maxima

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at (257nm) and (317 nm) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition, respectively. The $^1\text{H-NMR}$ of compound (C5) (Fig. 8), shows the following signals:

- Singlet at (12.70) ppm due to (OH) group proton.

- Singlet at (9.65) ppm due to (NH) group proton.

- Multiplet at (7.47-8.11) ppm due to four aromatic protons.

- Singlet at (4.11) ppm due to two (CH_2) proton.

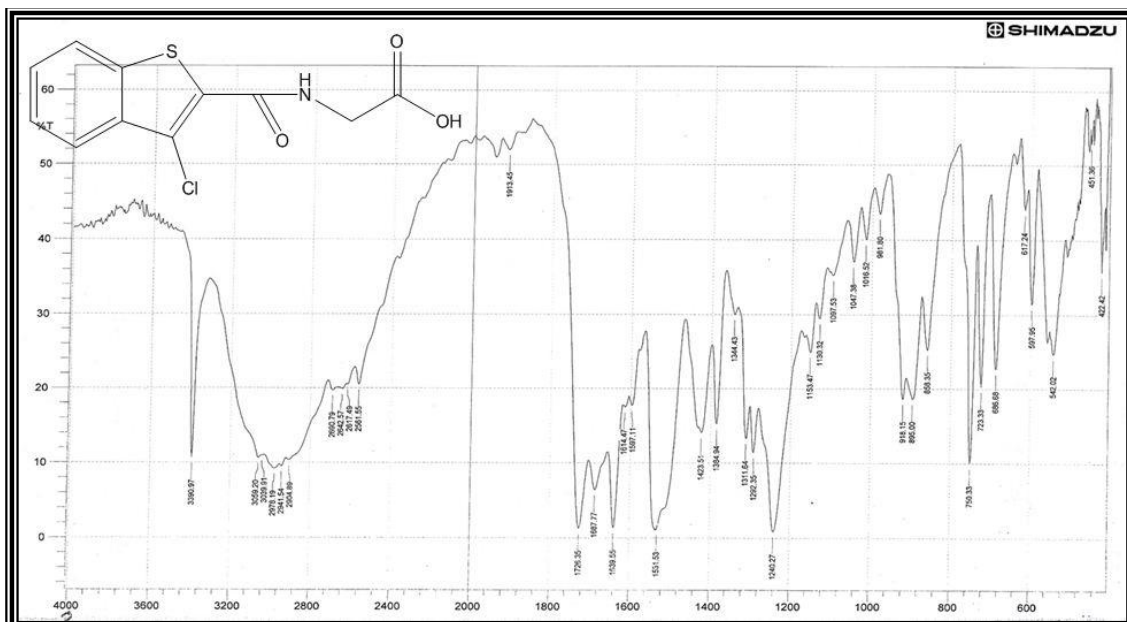


Fig. 7: The FT-IR spectrum of compound (C5).

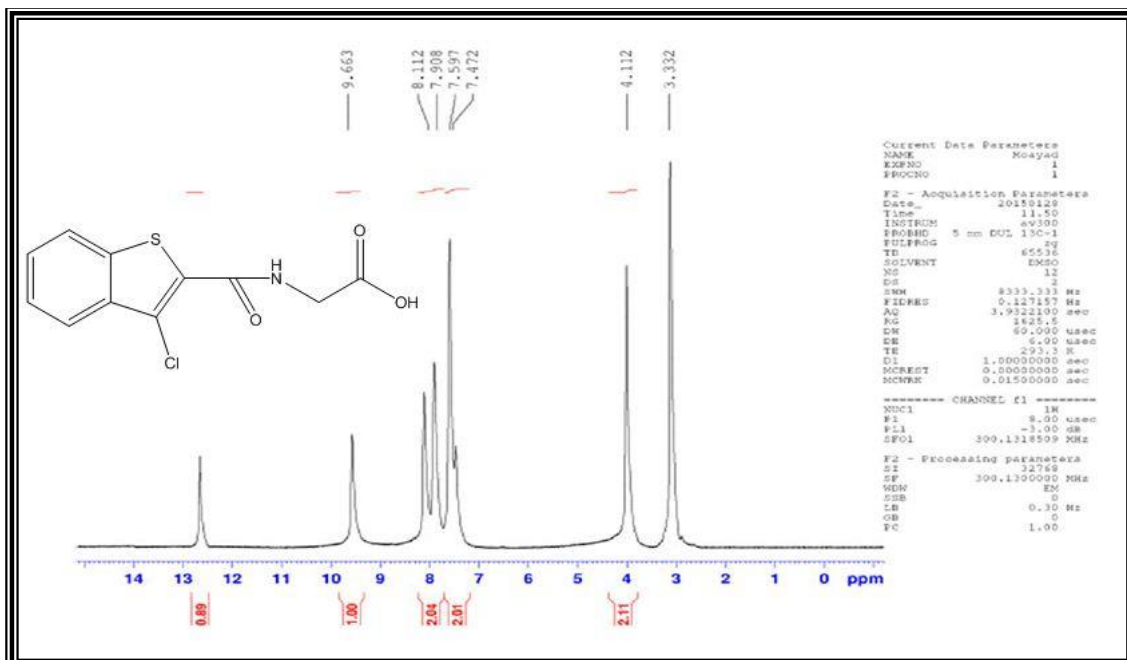


Fig. 8: The $^1\text{H-NMR}$ spectrum of compound (C5).

Synthesis of 2-(3-chlorobenzo[b]thiophen-2-yl)-4-(Arylidene)oxazol-5(4H)-one (C6)

This title compounds were synthesized according to the reaction of acid (C5) with aromatic

aldehyde in acetic acid and acetic anhydride to give (C6). The formation of title compounds was indicated by the disappearance of the two stretching vibration bands to NH, OH groups and appearance of

the one stretching vibration bands to carbonyl group (1766) cm^{-1} . The structure (C6) was confirmed by FT-IR and U.V spectrum . FT-IR spectrum (fig .9), shows the stretching vibration bands at (3060) cm^{-1} due to (=CH) group, band at(3028) cm^{-1} due to aromatic (C-H), band at (1766) cm^{-1} due to

(C=O), band at(1643) cm^{-1} due to (C=N) and band at (1591,1558) cm^{-1} due to aromatic (C=C) . UV spectrum of compound (C6) shows intense maxima at (274 nm) and (325 nm) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition, respectively.

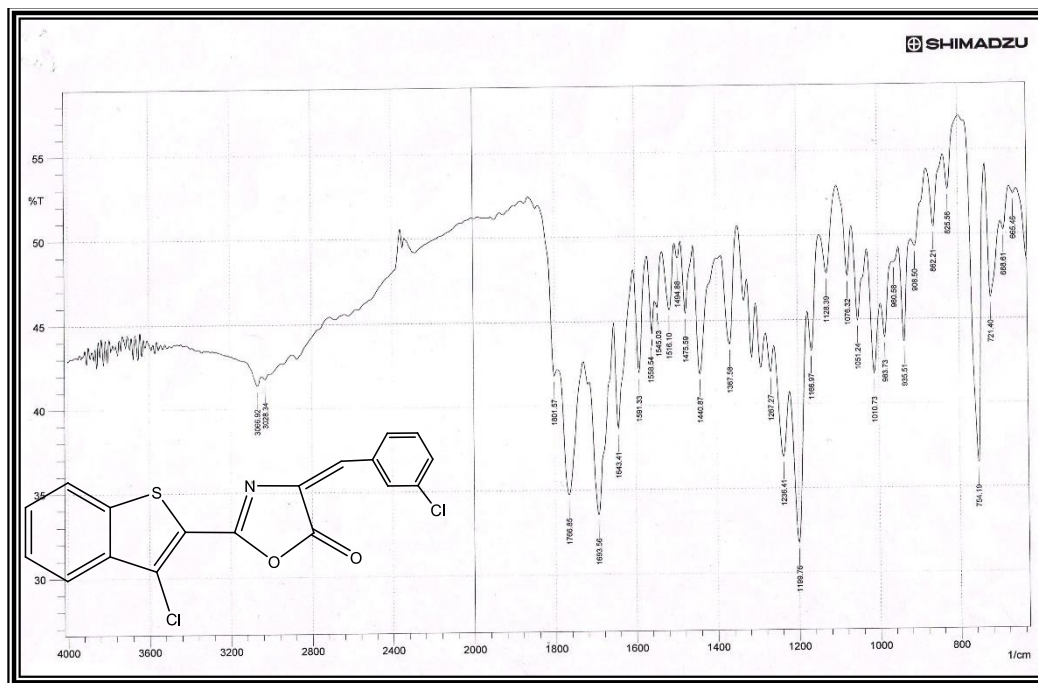


Fig. 9: The FT-IR spectrum of compound (C6).

Synthesis of 1-amino-2-(3-chlorobenzo[b]thiophen-2-yl)-4-(Arylidene)-1H-imidazol-5(4H)-one(C7)

These compounds were synthesized when Hydrazine hydrate in dry benzene was refluxed with oxazole(C6) to give (C7). Title compound was indicated by the appearance of the stretching vibration bands (3335,3279) cm^{-1} to NH_2 groups and decreasing of stretching vibration bands (1641) cm^{-1} to carbonyl groups. The product (C7) was confirmed by FT-IR and U.V. spectrum. FT-IR

spectrum(Fig.10), Table (4) shows the stretching vibration bands at (3335,3279) cm^{-1} due to stretching vibration (asymmetric and symmetric) for (NH_2) group, band at (3057) cm^{-1} due to for (=CH) group, band at (3030) cm^{-1} due to aromatic (C-H), band at (1641) cm^{-1} due to(C=O) group, band at (1606) cm^{-1} due to (C=N) group and band at (1564,1514) cm^{-1} due to for aromatic (C=C). UV spectrum of compound (C7) shows intense maxima at (281 nm) and (318 nm) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition, respectively.

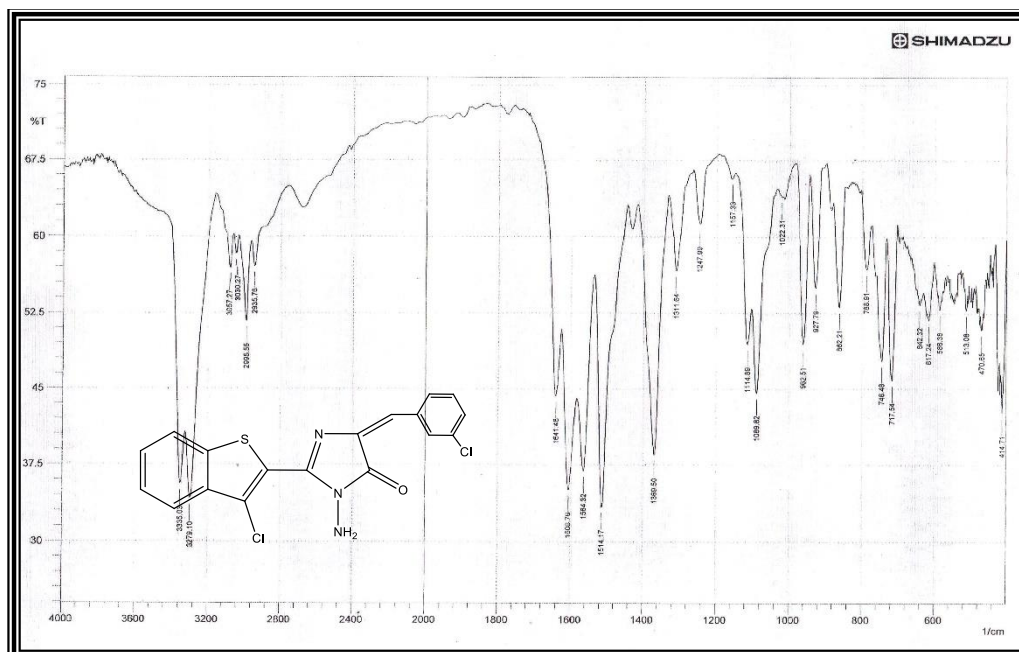


Fig. 10: The FT-IR spectrum of compound (C7).

Table (4)

IR spectral data for compounds (C5 – C7).

Comp. No	Characteristic IR bands $\nu(\text{cm}^{-1})$					
	=CH	CH aromatic	C=O	C=N	C=C aromatic	other
C5		3061	1726 acid, 1685 amide		1597,1533	3390(NH),3200-2400(OH),2983
C6	3060	3028	1766	1643	1591,1558	754(C-Cl)
C7	3057	3030	1641	1606	1564,1514	788(C-Cl)

3.2. Determination of antifungal activity *In Vitro*:

Compounds were evaluated for inhibitory activity against *Trichophyton mentagrophytes*, (C4 and C7) exhibited potent antifungal activity. *T. mentagrophytes* with a world-wide distribution and a wide range of animal hosts including mice, guinea-pigs, kangaroos, cats, horses, sheep and rabbits. Produces inflammatory skin or scalp lesions in humans, particularly in rural workers. Kerion of the scalp and beard may occur. Invaded hairs show an ectothrix infection but do not fluoresce under Wood's ultra-violet light [13]. Evidence of derivatives possessing antifungal properties has been shown previously for compound (C4).

3.3. Determination of antifungal activity *In vivo*:

The effect of compound (C4) in treatment of skin infection in Rabbit with *T. mentagrophytes* fungus *in vivo* was study by using the compound as lotion as concentration (1000 $\mu\text{g/ml}$) subLD50. The results showed that cyclic compound had highly effect in treatment skin infection when the healing was occur after 10 days compare with control.

The disease process in dermatophytosis is unique for two reasons: Firstly, no living tissue is invaded the keratinised stratum corneum is simply colonised. However, the presence of the fungus and its metabolic products usually induces an allergic and inflammatory eczematous response in the host. The

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type and severity of the host response is often related to the species and strain of dermatophyte causing the infection. Secondly, the dermatophytes are the only fungi that have evolved a dependency on human or animal infection for the survival and dissemination of their species [13].

4. Conclusions

New derivatives of imidazole were synthesized and characterized using IR,

¹HNMR and GC MS spectroscopy method. The antifungal study of these derivatives against *T. mentagrophytes* was studied. The novel derivatives were identified as promising antifungal agents.

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