

Synthesis of new 1,3-thiazole and 1,3 oxazole from 3-chlorobenzo[b]thiophene and evaluation of anti-bacterial activity

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Abstract

1,3- thiazole ,1,3 oxazole have been synthesized and evaluated anti-bacterial activity for some them. all derivatives were synthesized from acid chloride(Z_1) . Carbohydrazide (Z_2) was obtained by the reaction of 3-Chlorobenzo [b]thiophene-2-carbonyl chloride (Z_1) with hydrazine hydrate or ethylene di amine to get(Z_3) .and then react with chloro acetyl chloride to yield (Z_4,Z_5) , thiourea or thiosemicarbazide in absolute ethanol was reacted with (Z_4,Z_5) to get 1,3- thiazole. urea was reacted with (Z_1) to yield (Z_{10}). then (Z_{11}) have been synthesized from reaction ethyl chloroacetate with (Z_{10}), potassium carbonate was added as catalyst to yield 1,3 oxazole. 1,3-thiazole were synthesized by using the same steps given in synthesis of 1,3 oxazole . The product compounds were characterized by FTIR and 1H NMR spectra

Keyword benzo [b]thiophene , 1,3- thiazole,1,3 oxazole

INTRODUCTION

1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen separated by one carbon(1) Heterocycles having heteroatom N, S shows profound biological activities(2) 1,3 - thiazole is one of the most important compounds in heterocyclic chemistry and drug designing and detection (3) such as anti-microbial [4-6], antitumor(7) ,antiangiogenic (8), analgesic (9), Antioxidant activity(10)

1,3Oxazole is a five membered ring consisting of three carbon atoms, one nitrogen atom, and one oxygen atom separated by one carbon(11) . Oxazoles play a fundamental role in the synthesis of numerous biologically active drugs such as anticancer(12), antimicrobial(13)Antihelmenthic(14)Antipathogenic(15),analgesics(16), antiinflammatory,(17), Antifungal(18).

EXPERIMENTAL

Synthesis of 3-Chloro-1-benzothiophene- [Z_1]:

$SOCl_2$ (59.5g , 0.5mole) was added to mixture of Cinnamic acid (14.81g , 0.10 mole) and chloro benzene (75ml) , was stirred at room temperature for 40 min . then , pyridine (0.79 g , 0.01mol) was neatly added and the reaction mixture was refluxed for 72 h. The resulting was suspended in hot cyclohexane (200 ml) and promptly filtered. Upon staying at room temperature overnight, the title compound [Z_1] crystallized as yellow needles

Z_1 :yield (85%),p.m (112-113),color (yellow) , FT-IR cm^{-1} ,C=C aromatic (1595,1577),C=O(1763),CH aromatic(3061), other(C-Cl) (754) 1H - NMR(PPM)(DMSO d) , m(7.3-8) benzo [b]thiophene aromatic proton

Synthesis of chlorobenzo[b]thiophene-2-carbohydrazide [Z_2,Z_3]:

A mixture of compound (Z_1) (1.14g ,0.005mol) and ethylene diamine (0.3gm,0.005mole) or hydrazine hydrate (99%, 0.16 g, 0.005mole) in benzene (15ml) was refluxed for 4 h. onto cooling the solution a solid showed and recrystallized from ethanol and water to award the desired compound [Z_2,Z_3] . Recy.solvent ethanol

Z_2 :yield, (90%) m.p (154-155),color (orange), FT-IR cm^{-1} ,NH (3165) ,NH₂(3244) ,(C=C)

aromatic(1591,1568),(C=O)(1645),(CH) aromatic (3051), 1H -NMR(PPM)(DMSO d), (4.72)(s,NH₂), (7.60-8.10) (m ,aromatic proton) ,(12.4)(s, NH)), Recy.solvent ethanol

Z_3 :yield, (85%) ,m.p (178-180),color (Bright yellow) , FT-IR cm^{-1} ,NH (3250) ,NH₂ (3277,3294) ,(C=C) aromatic(1533,1475),C=O(1627),(CH) aromatic(3072), (CH) aliphatic(2926,2945), 1H -NMR(PPM)(DMSO d), (4.93) (s,NH₂),

(3.2-3.36) (t,CH₂) aliphatic proton near(NH₂) group, (3.65-3.8) (t,CH₂) aliphatic proton near(NH) group),(8.6) (NH) group , (7.77-8) (m,benzo[b]thiophene aromatic proton)

Synthesis 3-chloro-N'-(2-Synthesis chloroacetyl)benzo[b] thiophene-2-carbohydrazide(Z_4-Z_5)

chloroacetyl chloride (0.72ml,0.006 mole) was added drop wise to a solution of compound (Z_2) or (Z_3) (0.006mole) in benzene (40ml) and refluxed for 4h. then a reaction mixture was cooled to room temperature , and recrystallized the product from solvent appropriate

Synthesis N'-(5-aminothiazol-2-yl)-3-chlorobenzo[b]t thiophene-2-carbohydrazide(Z_6-Z_9)

(0.03mole) of compounds (Z_4 or Z_5) were refluxed for 12 h with (0.03 mole,2.28 gm) thiourea or(2.73gm,0.03mole) thiosemicarbazide in ethanol (25ml) excess solvent was removed and the mixture after cooling were poured in to ice bath. was obtained solid product that filtered, washed with 2% NaHCO₃ solution followed by water. and recrystallized from appropriate solvent.

Synthesis N-substituted) benzoyl thioureas($Z_{10}-Z_{11}$)

A mixture of compound (Z_1) (0.01 mole) and thiourea (1.52gm, 0.02 mole) or urea (1.2gm, 0.02 mole) in dioxane (25 ml) was refluxed for 4h The reaction mixture was cooled and poured in to water (100 ml). solid product has formed and filtered , washed with water, and recrystallized from appropriate solvent to give ($Z_{10}-Z_{11}$).

Synthesis Ethyl 2-amino-5-(3-chlorobenzo[b]thiophen-2-yl)thiazole-4-carboxylate($Z_{12}-Z_{13}$)

($Z_{10}-Z_{11}$) (0.01mole) was dissolved in (30ml dioxane). anhydrous potassium carbonate was added to this a solution as catalyst, then ethyl chloro acetate (1.22gm,0.01 mole) was added drop wise to solution and stirred well, this reaction mixture was refluxed for about 3h .that reaction was cooled to room temperature , reaction mixtrure was poured in the ice bath . and recrystallized from appropriate solvent

Synthesis 2-amino-5-(3-chlorobenzo[b]thiophen-2-yl)thiazole-4-carboxylic acid($Z_{14}-Z_{15}$)

1,3-thiazole -5-carboxylate (0.005 mole) was dissolved in about (30 ml) of ethanol. potassium hydroxide solution (1N) was added. This reaction mixture was refluxed for about (2 h). after that the reaction mixture was cooled to room temperature. Then solution

dil HCl was added drop wise. was precipitated formed solid was filtered off, washed with water, dried and recrystallized from appropriate solvent to give (Z₁₄-Z₁₅)

Z₄:yield, (71%) ,m.p(112-113),color (brown) , FT-IR cm⁻¹ ,NH (3209) , ,C=C aromatic(1585,1465),C=O(1693,1645),(CH) aromatic(3059) , (CH) aliphatic (2983) ,other(C-Cl)(856) ,¹H-NMR(PPM)(DMSO d) , (7.88) for (s,NH) near (COCH₂) , (8.1)(s,NH)near C=O , (3.9) (s,COCH₂) aliphatic proton , (7.32-7.4) (m,aromatic proton)

Z₅:yield, (80%) ,m.p (182-184),color (orange) , FT-IR cm⁻¹ ,NH (3165) , ,C=C aromatic(1595,1514),C=O(1681,1672),(CH) aromatic(3012) , (CH) aliphatic (2812,2987) ,other(C-Cl)(752) ,¹H-NMR(PPM)(DMSO d) (8.77) (s,s tow NH) , (4.2) (sCOCH₂) , (3.4-3.56) (m,CH₂CH₂),m(7.1-7.43)(m,aromatic proton)

Z₆:yield, (84%) ,m.p (118-120),color (bronze) , FT-IR cm⁻¹ ,NH (3288) , ,C=C aromatic(1583,1527),C=O(1657),(CH) aromatic(3024) , (N=C) (1626) , (NH₂)(3367) ,¹H-NMR(PPM)(DMSO d) ,s(3.91) for (NH) , m(7.2-7.75) aromatic proton , s(7.78) for(C=CH) aliphatic proton of thiazole ring , ,s(8.12) for (NH)near C=O

Z₇:yield, (92%) ,m.p (197-198),color (brown) FT-IR cm⁻¹ ,NH (3196) , (C=C) aromatic(1541,1500),C=O(1639),(CH) aromatic(3066) , (N=C) (1583) ,(NH₂) (3236)

Z₈:yield, (74%) ,M.P (208-210),color (Deep yellow) , FT-IR cm⁻¹ ,NH (3250) , ,C=C aromatic(1579,1500),C=O(1695),(CH) aromatic(3039) , (N=C) (1645) ,(NH₂) (3354) (CH) aliphatic(2845, 2922) ,¹H-NMR (PPM)(DMSO d) , m(3.85-4) for (CH₂andCH₂) aliphatic proton ,s(4.8) for (NH)near CH₂s(6.95) for (NH₂) , m(7.3-7.86) aromatic proton ,s(7.9) for(C=CH) aliphatic proton of thiazole ring , ,s(8.65) for (NH)near C=O

Z₉:yield, (74%) ,m.p (208-210),color (yellow), FT-IR cm⁻¹ ,NH (3142) ,(C=C) aromatic(1573,1492),C=O (1656),(CH) aromatic(3030) , (N=C) (1622) ,(NH₂) (3384) ¹H-NMR(PPM)(DMSO d) , s(2) for (NH₂) , m(3.55-3.67) for (CH₂andCH₂) aliphatic proton ,s(4.1) for (NH)near CH₂ ,s(6,87)for(C=CH) aliphatic proton of thiazole ring , m(7.23-7.65) aromatic proton ,s(8.4) for (NH) near thiazole ring , (8.5) for (NH)near C=O

Z₁₀:yield, (90%) ,m.p (143-144),color (orange), FT-IR cm⁻¹ ,NH (3250) ,(C=C) aromatic(1512,1498),C=O (1656,1622),(CH) aromatic(3060) , (NH₂) (3227) ¹H-NMR(PPM)(DMSO d) , (7.8-8) (s,NH₂) group , (7.72) (s,NH) , (7.60)(m, aromatic proton).

Z₁₁:yield, (87%) ,m.p (112-123),color (yellow), FT-IR cm⁻¹ ,NH (3228) ,(C=C) aromatic(1593,1543),C=O (1699,1664),(CH) aromatic(3063),(NH₂) (3338,3377) .

Z₁₂:yield, (83%) ,m.p (163-165),color (yellow), FT-IR cm⁻¹ ,NH (3228) , (C=C) aromatic(1595,1514),C=O (1724),(CH) aromatic(3049) , (NH₂) (3259,3317) (N=C)(1656) , (C=C) (1639) ¹H-NMR(PPM)(DMSO d) , (12.4)(s, NH) , (4.72)(s,NH₂) , (7.60-8.10) (m, aromatic proton).

Z₁₃:yield, (80%) ,m.p (182-184),color (orange), FT-IR cm⁻¹ ,NH (3228) , (C=C) aromatic(1577,1514),C=O (1708),(CH) aromatic(3066) , (NH₂) (3333,3367) (N=C)(1662) , (C=C) (1612)

Z₁₄:yield, (75%) ,M.P (187-188),color (white), FT-IR cm⁻¹ ,NH (3117) , (C=C) aromatic(1599,1502),C=O (1710),(CH) aromatic(3049) , (NH₂) (3308,3365) (N=C)(1656) , (C=C) (1639) (OH)(2500-3402) ¹H-NMR(PPM)(DMSO d) , (10.45)for (s,COOH) group , s(6.8)NH₂ m(7.2-7.8) benzo[b]thiophe aromatic proton

Z₁₅:yield, (84%) ,M.P (118-120),color (bronze), FT-IR cm⁻¹ ,NH (3213),C=O (1708,1662),(CH) aromatic(3066) , (NH₂) (3333,3363) (N=C) (1612) , (C=C) (1639) (OH)(2500-3454) ¹H-NMR(PPM)(DMSO d) , (10.45)for (s,COOH) group (6.8)(sNH₂) ,(7.2-7.8)(m,aromatic proton)

RESULT AND DISCUSSION

All compounds were shown in scheme (1,2)

For synthesis of the target compound [Z₁] which was prepared by the reaction of cinnamic acid and thionyl chloride. The FT-IR spectrum of compound [Z₁] (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 ,

The ¹H-NMR of compound [Z₁] shows the following signals:

- Multiplate at (7.33-8.) ppm due to four aromatic protons.

This compound was obtained by the reaction of 3-Chlorobenzo [b]thiophene-2-carbonyl chloride [Z₁] with hydrazine hydrate or ethylene diamine. The structure of compound [Z₂,Z₃] were confirmed by FT-IR and 1HNMR spectrum. FT-IR spectrum of compound [Z₃] shows the, band at (3250) cm-1 due to stretching vibration of (NH) , two bands at (3277-3294) cm⁻¹ due to stretching vibration (asymmetric and symmetric)for (NH₂)group ,decrease stretching vibration of carbonyl group to(1627) cm⁻¹.Spectrum

The ¹H-NMR of compound [Z₃] shows the following signals:

- Singlet at (8.6) ppm due to one (NH) group proton.

- Multiplate at (7.77-8.) ppm due to four aromatic protons.

- Singlet at (4.93) ppm due to tow (NH₂) group proton

- Triplate at (3.2-3.36) for (CH₂) aliphatic proton near (NH₂)

-Triplate at (3.65-3.8) for (CH₂) aliphatic proton far (NH₂)

These compounds were synthesized when (Z₂ or Z₃) in dry benzene was refluxed with chloro acetyl chloride to give [Z₄-Z₅]. The

Title compound was indicated by the disappearance of the stretching vibration bands dure to NH₂ and the appearance of the two carbonyl stretching vibration bands groups .The product[Z₄] was confirmed by FT-IR . spectrum FT-IR spectrum(Fig.1) , band at (3059) cm-1 due to aromatic (C-H) , tow band at (1693,1645) cm-1 due to(C=O) group , band at(1585,1565) cm⁻¹ due to aromatic (C=C) and band at(756) cm⁻¹ due to for (C-Cl) group . Spectrum also shows other characteristic The ¹H-NMR of compound [Z₄] (Fig.10), shows the following signals:

- Singlet at (3.9) ppm due to (COCH₂) group aliphatic proton

- Singlet at (7.88) ppm due to (NH) group near (COCH₂).

- Multiplate at (7.2-7.32) ppm due benzo[b]thiophene aromatic proton

- Singlet at (8.1) ppm due to (NH) group near (C=O)

- Multiplate at (7.32-7.4) ppm due to benzo[b]thiophene aromatic proton

These compounds were synthesized by the reaction of [Z₄,Z₅] with thiourea or thiosemicarbazide in absolute ethanol .

The formation of 1,3-thiazole was indicated by the appearance vibration (asymmetric and symmetric) for (NH₂)group and disappearance of the carbonyl stretching vibration bands .the structure [Z₉] was confirmed by FT-IR and ¹H-NMR

The ¹H-NMR of compound [Z₉] (Fig.11), shows the following signals:

- Singlet at (2) ppm due to for (NH₂) group

- Multiplate at (3.55-3.67) ppm due (CH₂andCH₂) aliphatic proton

- Singlet at (4.1) ppm due to (NH) near CH₂

- Singlet at (6.87) ppm due C=CH) aliphatic proton of thiazole ring

-Multiplate at(7.23-7.65) ppm due aromatic proton

- Singlet at (8.4) ppm due to (NH) near thiazole ring

- Singlet at (8.5) ppm due to (NH) near C=O

to yield compounds [Z₁₀, Z₁₁] by treating 3-Chlorobenzo [b]thiophene-2-carbonyl chloride [Z₁] with thiourea or urea in 1,4 dioxane .

The structure of compounds [Z₁₀,Z₁₁] were confirmed by the appearance stretching vibration bands to (NH₂) and the decrease stretching vibration of the carbonyl group.] shows The structure [Z₁₀] was confirmed by FT-IR and 1H-NMR. FT-IR spectrum(fig5) , shows the stretching vibration band at (3142) cm-1 due to (NH) groups , band at (3060) cm-1 due to aromatic (C-H) ,bands at(1656,1622) due to (C=O) , band at (3284) due to (NH2) group and band at (1515,1498) cm-1 due to aromatic (C=C) group (fig5) of compound [Z₁₀]
The ¹H-NMR of compound [Z₁₀] (Fig12) shows the following signals:

Multiplate at (7.60-7.32) ppm due benzo[b]thiophene aromatic proton

- Singlet at (7.72) ppm due to (NH) group .
- Singlet at (7.8-8) ppm due to (NH) group.

Have been synthesis Compounds [Z₁₂, Z₁₃] from reaction ethyl chloroacetate with compounds (Z₁₀-Z₁₁) in 1,4 dioxane, potassium carbonate was added as catalyst .

The formation (Z₁₂-Z₁₃) were indicated by the disappearance (asymmetric and symmetric) for stretching vibration of (NH₂) group the increase stretching vibration of carbonyl group . FT-IR cm-1(fig 6) , shows the stretching vibration band at ,NH (3228) ,(C=C) aromatic(1577,1514),C=O (1708),(CH) aromatic(3066), (NH₂) (3333,3367) (N=C) (1662), (C=C) (1612) the structure of compound [Z₁₃] was confirmed by FT-IR and 1HNMR spectrum fig (13)

- Singlet at (6.4) ppm due to (NH₂) group
- Singlet at (8.2) ppm due to (NH) group.
- Multiplate at (7.3-7.52) ppm due aromatic proton
- Singlet at (8.1) ppm due to (NH)
- Multiplate at (7.32-7.4) ppm due aromatic proton
- Quartet at (4.1) ppm due to(CH₂) aliphatic

- Triplet(1.3-1.4) ppm due to(CH₃) aliphatic for Prepare compounds (Z₁₄,Z₁₅) from hydrolysis in Sodium hydroxide of compounds (Z₁₂,Z₁₃) of then processed the product in a dilHCl

The formation (Z₁₄-Z₁₅) were indicated by decrease stretching vibration of carbonyl group and the appearance of vibration (OH) group of carboxylic acid at(2500-3300) cm-1

The structure of compound [Z₁₄,Z₁₅] were confirmed by FT-IR and 1HNMR spectrum. FT-IR spectrum for (Z₁₅) shows the stretching vibration band at , NH (3213),C=O (1708,1662),(CH) aromatic(3066), (NH₂) (3333,3363) ,(N=C)(1612), (C=C) (1639) (OH)(2500-3454)

- and 1HNMR spectrum fig (14) shows the
- Singlet at (6.08) ppm due to (NH₂) group.
- Multiplate at (7.36-7.78) ppm due aromatic proton
- Singlet at (10.66) ppm due for (COOH) .

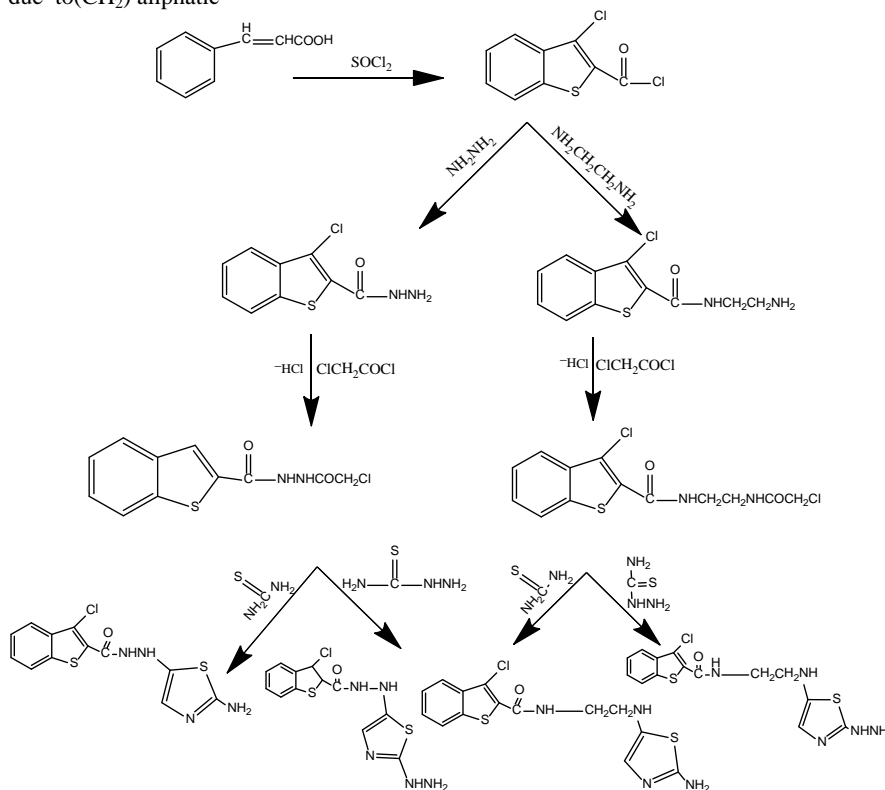
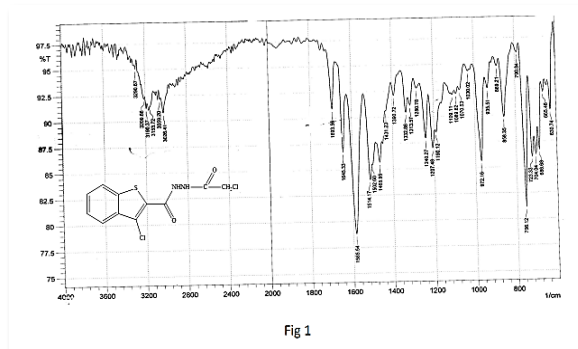


Figure 2- Scheme(1) synthesized compounds (Z₁-Z₉)

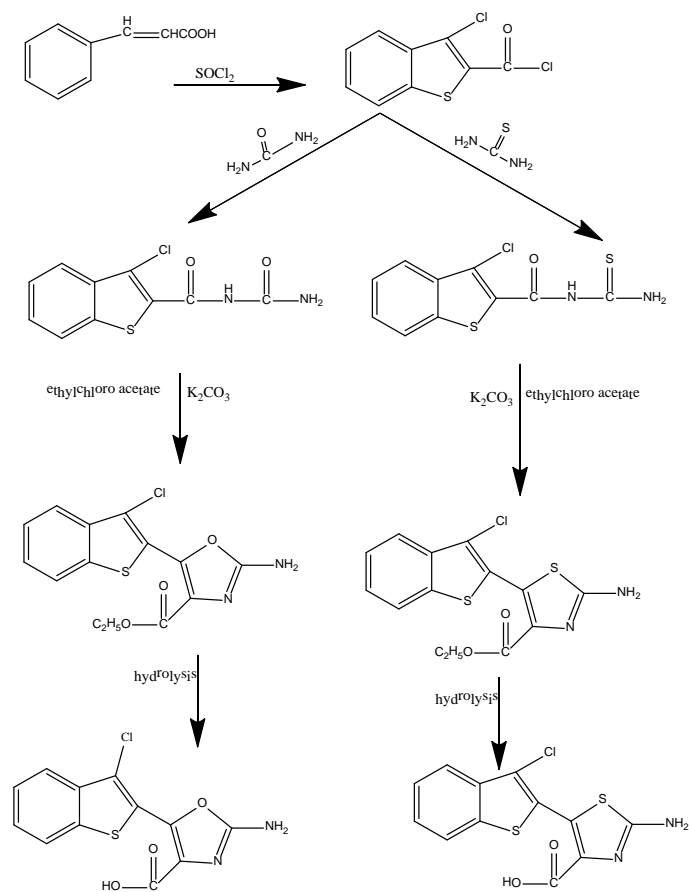


Figure 3 - Scheme(2) synthesized compounds (Z₁₀₋₁₅)

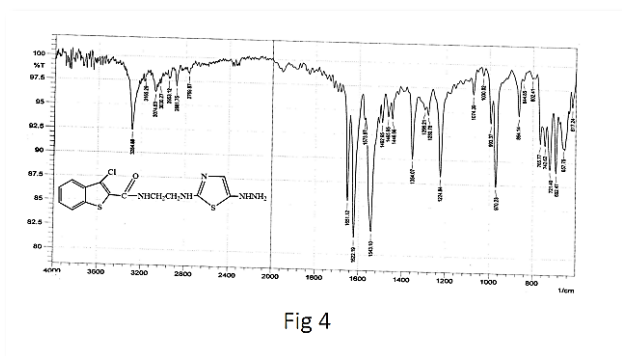


Fig 4

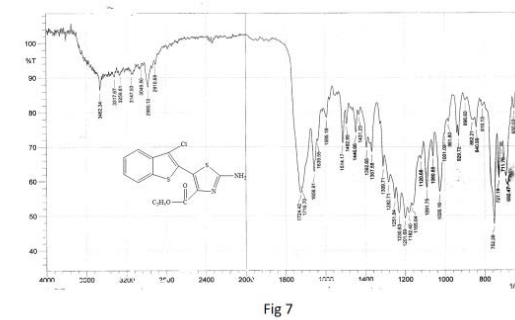


Fig 7

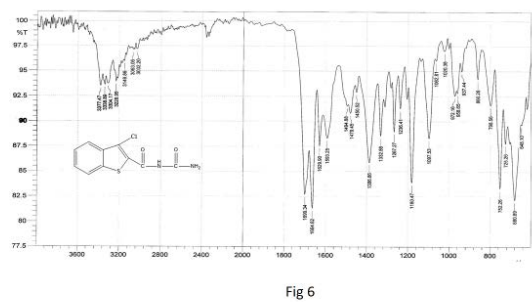


Fig 6

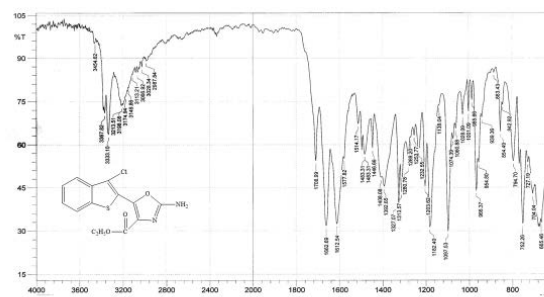


Fig 8 •

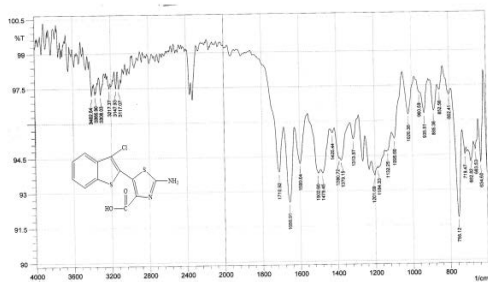


Fig 9

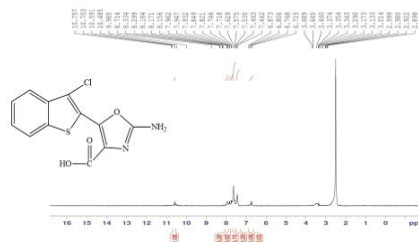


Fig 14

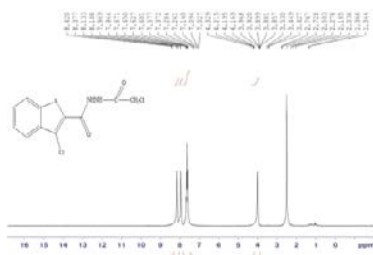


Fig 10

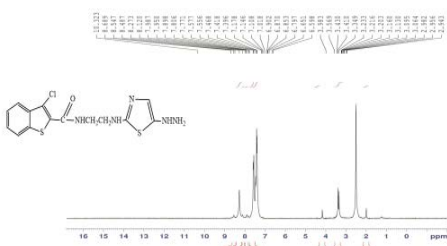


Fig 11

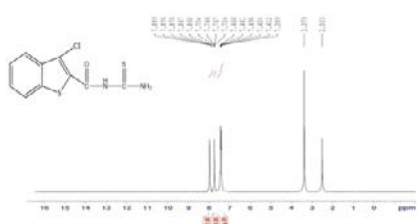


Fig 12

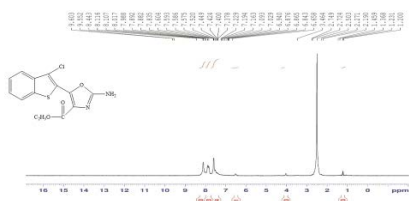


Fig 13

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