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Synthesis and study of biological activities of compounds derived from new Imidazole derivative

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Abstract

Background: Heterocyclic compounds are of great importance for the life, because many natural products such as hormones and antibiotics have structural subunits. Imidazole derivatives were used as a precursor for synthesis of many heterocyclic systems. The aim of current study was to use the easily available benzoyl thiourea for the synthesis of Imidazole derivative Ethyl 2-((1-benzoyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl) thio) acetate. Methods: the imidazole compounds of interest were synthesized using a range of precursors through addition, reflux and recrystallization reactions. Results: data obtained from current study revealed that the synthesized imidazole derivatives were characterised and their antibacterial activities were tested. These compounds exhibited powerful inhibition of growth anaist P. aerogenosa and S. aureus bacterial strains. Conclusions: Imidazole derivatives can be manufactured from available and cost-effective precursors to be employed as potent antibacterial agents.

Keyword: Benzoyl chloride, Thiourea, Imidazole, Chalcone, Schiff's base.

1. INTRODUCTION

The heterocyclic rings are of biological interest because of their potential chemical and physical properties [1]. heterocyclic compounds are of great importance to the life, because many natural products such as hormones and antibiotics have structural subunits [2,3]. The practical method of composition of these compounds used for synthesis of many organic compounds [4]. Nitrogen-containing heterogeneous compounds play an important role in medical chemistry by assisting in various biological processes [5]. In recent years imidazole derivatives containing nitrogen have attracted increased attention due to the broad spectrum of their biological activities [6]. Chalcone are still promising to conduct new drug analyzes. For this, new ways of synthesizing the alkalo derivatives which exhibited a range of pharmacological and biological effects [7]. Chalcone derivatives were reported to have a broad spectra of biological activities e.g. antimalarial [8,9], anticancer [10,11], antioxidant, anti-inflammatory [12-15], antimicrobial [16,17], antifilarial [18], antifungal [19, 20], larvicidal [21], and anticonvulsant activities [22]. Schiff"s bases were derived from some heterocyclic compounds which have broad spectra of biological activities e.g. antiviral, anti-glycation, anticonvulsant anti-inflammatory , antimicrobial, antidepressant, angiotensin-II receptor antagonist, and anticancer activity [23,24].

2. MATERIAL AND METHODS

2.1. Synthesis of 1-benzoyl-thiourea-[BT]

A solution of 2.28 g (0.03 mole) of thiourea in 25 ml 1,4-dioxane, was added drop-wise at room temperature to 1.40 g (0.01 mole) of benzoyl chloride, refluxed for 12 h, poured into ice-cold water, precipitated, filtered off and then solid recrystallized of suitable solvent to yield the wanted compound. Crude product was recrystallized from benzene.

(BT): White powder; yield 92%; m.p. 171-173 C°.

IR (ν/cm^{-1}): ν_{NH2} = 3308, ν_{NH} =3232, $\nu_{C=O}$ amide =1676, $\nu_{C=S}$ =1103.

^{1}H-NMR: δ (DMSO-d6):11.27(s,SH,1H), 9.88 (s,NH=CS,1H), 9.60 (s, CONH, 1H), 7.39- 8.01 (m, 5H, Aromatic).

MS, *m/z* $[M]^+$: 180 (180.3) found (calcu.).

2.2. Synthesis of ethyl 2-((1-benzoyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetate (1):

Benzoyl thioureas 1.8 g (0.01 mole) was dissolved in 30 ml of 1,4-dioxane. To this solution, anhydrous potassium carbonates 1.37g (0.01 mole), was added as a catalyst, after that ethyl chloroacetate (2.25 ml; 0.02mole) was added to above solution and stirred well. The mixture was refluxed for 7 hr. After that this solution was added to crush ice to get the solid. TLC indicates the presence of some impurities and recrystallized from water: ethanol (7:3) ml.

(1):- Red powder; yield=75%; m.p. 123-125 C°.

IR (ν/cm^{-1}): 3026 (C-Har), 2856-2933 (aliphatic C-H), $\nu_{C=O}$ ester = 1773, $\nu_{C=O}$ keton =1687, $\nu_{C=O}$ amide =1639, $\nu_{C=N}$=1599.

^{1}H-RMN: δH (DMSO-d6): 1.2 (t, CH_3-CH_2,3H), 4.6 (s, S-CH_2,2H), 4.4 (q, COO-CH_2,2H), 4.4 (s, CO-CH_2,2H), 7.2- 8.1 (m, 5H, Aromatic).

MS, *m/z* $[M]^+$: 306 (306.07) found (calcu.)

2.3. Synthesis of ethyl 2-((1-benzoyl (Arylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetate [2a-e]

To a solution of compound (1), 1g (0.0032 moles) in 30 ml ethanol aromatic aldehydes was added (o-bromobenzaldehyde, p-nitrobenzaldehyde, 4-dimethylamino benzaldehyde, benzaldehyde and anisaldehyde) (0.0032 mole) and 4 ml of 10% KOH solution and stirred for 24 hr at 25 C°. Then, ice-water was poured into precipitate with few drops of hydrochloric acid. The product was recrystallized from suitable solvent afford to get the compound of interest.

Ethyl2-((1-benzoyl-4-(2-bromobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetate(2a): Black powder; yield=68%; m.p. 150-153 C°.

IR (ν/cm^{-1}): 3068 (C-Har), 2872-2933 (C-H aliph), $\nu_{C=O}$ ester = 1739, $\nu_{C=O}$ keton =1718, $\nu_{C=O}$ amide =1647, $\nu_{C=N}$=1599, νC=CH=1579, ν_{C-Br}=759.

^{1}H-RMN: δH (DMSO-d6): 1.2 (t, CH_3-CH_2,3H), 4.2 (q, COO-CH_2,2H), 4.8 (s, S-CH_2,2H), 7.4- 8.0 (m, 9H, Aromatic), 8.2 (s, C=CH,1H).

MS, *m/z* $[M]^+$: 474 (473.34) found (calcu.).

Ethyl2-((1-benzoyl-4-(4-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetate(2b): Yellow powder; yield=70%; m.p. =192-194 C°.

IR (ν/cm^{-1}): 3086 (C-H ar), 2921-2983 (C-H aliph), $\nu_{C=O}$ ester = 1745, $\nu_{C=O}$ keton =1716, $\nu_{C=O}$ amide =1645, $\nu_{C=N}$=1597, νC=CH=1577, ν_{NO2}=1533-1342.

^{1}H-RMN: δH (DMSO-d6): 1.2 (t, CH_3-CH_2,3H), 4.4 (q, COO-CH_2,2H), 5.0 (s, S-CH_2,2H), 7.4- 8.0 (m, 9H, Aromatic), 8.6 (s, C=CH,1H).

MS, *m/z* $[M]^+$: 439 (439.08) found (calcu.).

Ethyl2-((1-benzoyl-4-(4-(dimethylamino)benzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetate(2c): Orang powder; yield=78%; m.p.160-163 C°.
IR (ν/cm^{-1}): 3063 (C-Har), 2810-2908 (C-H aliph), $\nu_{C=O}$ ester = 1743, $\nu_{C=O}$ keton =1705, $\nu_{C=O}$ amide =1637, $\nu_{C=N}$=1616, νC=CH=1527, $\nu_{p\text{-}N(CH3)2}$ = 804.
^{1}H-RMN: δH (DMSO-d6): 1.3 (t, CH_3-CH_2,3H), 4.2 (q, COO-CH_2,2H), 4.9 (s, S-CH_2,2H), 3.1 (s, N(CH_3)$_2$,6H), 7.62- 7.9 (m, 9H, Aromatic), 8.2 (s, C=CH,1H).
MS, *m/z* [*M*]$^+$: 437 (437.14) found (calcu.).

Ethyl2-((1-benzoyl-4-benzylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio) acetate(2d): White powder; yied=70%; m.p. =164-167 C°.
IR (ν/cm^{-1}): 3066 (aromatic C-H), 2872-2983 (aliphatic C-H), $\nu_{C=O}$ ester = 1737, $\nu_{C=O}$ keton =1707, $\nu_{C=O}$ amide =1647, $\nu_{C=N}$=1599 νC=CH=1577.
^{1}H-RMN: δH (DMSO-d6): 1.4 (t, CH_3-CH_2,3H), 4.1 (q, COO-CH_2,2H), 4.8 (s, S-CH_2,2H), 7.5- 7.7 (m, 10H, Aromatic), 8.2 (s, C=CH,1H).
MS, *m/z* [*M*]$^+$: 393 (393.10) found (calcu.).

Ethyl2-((1-benzoyl-4-(4-methoxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetate(2e): Yellow powder; yield=55%; m.p. 140-145 C°.
IR (ν/cm^{-1}): 3064 (C-Har), 2841-2983 (C-H aliph), $\nu_{C=O}$ ester = 1739, $\nu_{C=O}$ keton =1712, $\nu_{C=O}$ amide =1643, $\nu_{C=N}$=1593, νC=CH=1575, $\nu_{p\text{-}OH3}$ = 827.
^{1}H-RMN: δH (DMSO-d6): 1.2 (t, CH_3-CH_2,3H), 4.2 (q, COO-CH_2,2H), 4.8 (s, S-CH_2,2H), 3.8 (s, OCH_3,3H), 7.1- 7.9 (m, 9H, Aromatic), 8.2 (s, C=CH,1H).

2.4. Synthesis of 2-((1-benzoyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetohydrazide-3

To solution (1), 1g (0.0032 moles) in ethanol, hydrazine hydrate 80%, (0.32 g; 0.0065 moles) were added. Then refluxed for 10 hr and the obtained product was crystallized from ethanol.

2-((1-benzoyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio)acetohydrazide(3):
White powder; yied=60%; m.p. =245-250 C°.
IR (ν/cm^{-1}): 3039 (C-H ar), 2839-2953 (C-Haliph), ν_{NH2} = 3298, ν_{NH} =3186, $\nu_{C=O}$ keton =1662, $\nu_{C=O}$ amide =1639, $\nu_{C=N}$=1590.
^{1}H-RMN: δH (DMSO-d6): 3.8 (s, CO-CH_2,2H), 4.2 (s, S-CH_2,2H), 5.3 (s, NH2,2H), 7.1- 7.9 (m, 5H, Aromatic), 12.1 (s, NH,1H).
MS, *m/z* [*M*]$^+$: 294 (292.06) found (calcu.).

2.5. Synthesis of 2-((1-benzoyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)thio) (Arylidene)acetohydrazide- (4a-e)

To a solution of acid hyrazide (3), 2.92 g (0.01 mol) in methanol (30 ml with few drops of acetic acid, 0.01 mol of aromatic aldehydes (o-bromobenzaldehyde, p-nitrobenzaldehyde, 4-dimethylaminobenzaldehyde, benzaldehyde and anisaldehyde) were added, refluxed for 6 hr, then cooled and filtered. The obtained product was recrystallized from ethanol.

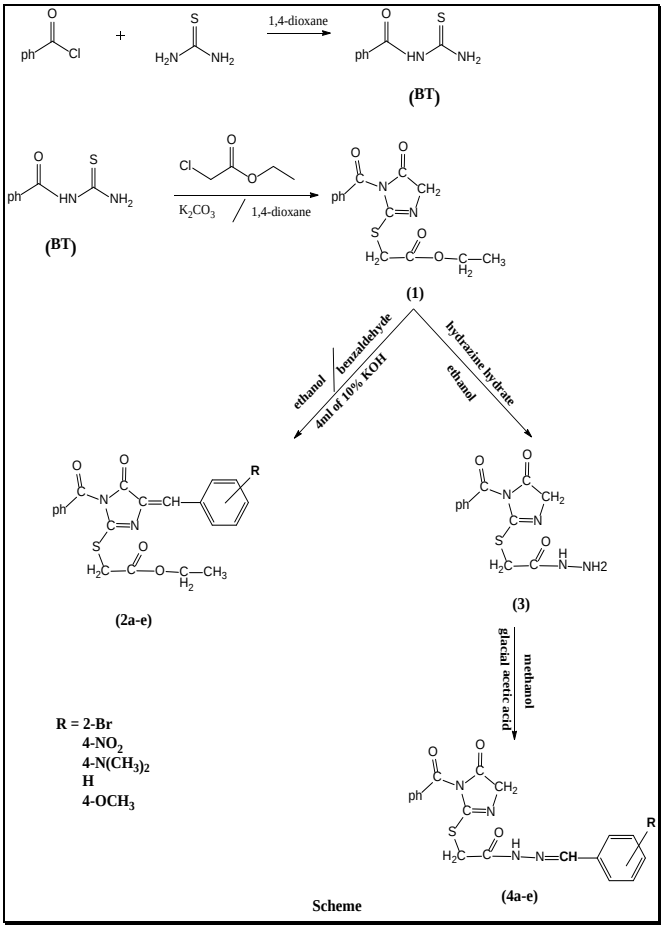
2-((1-benzoyl-5oxo-4,5-dihydro1H-imidazol-2-yl)thio)-N'-(2 bromobenzylidene) acetohydrazide(4a): white powder; yield=70%; m.p.187-190 C°.
IR (ν/cm^{-1}): 3082 (C-Har), 2854-2962 (C-H aliph), ν_{NH} =3207, $\nu_{C=O}$ keton =1683, $\nu_{C=O}$ amide =1645, $\nu_{C=N}$=1599, $\nu_{N=CH}$ = 1620.
^{1}H-RMN: δH (DMSO-d6): 4.6 (s, $COCH_2$,2H), 4.6 (s, S-CH_2,2H), 7.2-7.9 (m, 9H, Aromatic), 8.5 (s, N=CH,1H), 12.1 (s, NH,1H).

2-((1-benzoyl-5oxo-4,5-dihydro1H-imidazol-2-yl)thio)-N'-(4-nitrobenzylidene) acetohydrazide(4b): yellow powder; yield=75%; m.p. 278-280 C°.
IR (ν/cm^{-1}): 3061 (aromatic C-H), 2939 (aliphatic C-H), ν_{NH} =3207, $\nu_{C=O}$ keton =1678, $\nu_{C=O}$ amide =1639, $\nu_{C=N}$=1599, $\nu_{N=CH}$ = 1629, ν_{NO2}=1521-1344.
^{1}H-RMN: δH (DMSO-d6): 3.9 (s, $COCH_2$,2H), 4.3 (s, S-CH_2,2H), 7.5-7.9 (m, 9H, Aromatic), 8.8 (s, N=CH,1H), 12.1 (s, NH,1H).
MS, *m/z* [*M*]$^+$: 426 (425.08) found (calcu.).

2-((1-benzoyl-5oxo-4,5dihydro1H-imidazol-2-yl)thio)-N'-(4-(dimethylamino) benzylidene)acetohydrazide(4c): Orang powder; yied=65%; m.p. =268-270 C°.
IR (ν/cm^{-1}): 3068 (C-Har), 2866-3020 (C-H aliph), ν_{NH} =3213, $\nu_{C=O}$ keton =1674, $\nu_{C=O}$ amide =1641, $\nu_{C=N}$=1599, $\nu_{N=CH}$ = 1641, $\nu_{p\text{-}N(CH3)2}$ = 812.
^{1}H-RMN: δH (DMSO-d6): 2.9 (s, N(CH_3)$_2$,6H), 3.9 (s, $COCH_2$,2H), 4.3 (s, S-CH_2,2H), 7.3-7.9 (m, 9H, Aromatic), 8.1 (s, N=CH,1H), 11.2 (s, NH,1H), 12.2 (s, OH,1H).

2-((1-benzoyl-5oxo-4,5dihydro1H-imidazol-2-yl)thio)-N'-benzylidene acetohydrazide(4d): White powder; yield=60%; m.p. 200-203 C°.
IR (ν/cm^{-1}): 3078 (C-Har), 2810-3016 (C-Haliph), ν_{NH} =3213, $\nu_{C=O}$ keton =1680, $\nu_{C=O}$ amide =1641, $\nu_{C=N}$=1606, $\nu_{N=CH}$ = 1622.
^{1}H-RMN: δH (DMSO-d6): 4.50(s, $COCH_2$,2H), 4.50 (s, S-CH_2,2H), 7.30-7.90 (m, 10H, Aromatic), 8.22 (s, N=CH,1H), 11.41 (s, NH,1H).

2-((1-benzoyl-5oxo-4,5dihydro1H-imidazol-2-yl)thio)-N'-(4-methoxy benzylidene)acetohydrazide(4e): white powder; yied=65%; m.p. 185-190 C°.
IR (ν/cm^{-1}): 3088 (C-Har), 2847-3003 (C-Haliph), ν_{NH} =3211, $\nu_{C=O}$ keton =1678, $\nu_{C=O}$ amide =1633, $\nu_{C=N}$=1606, $\nu_{N=CH}$ = 1626, $\nu_{p\text{-}OH3}$ = 829.
^{1}H-RMN: δH (DMSO-d6): 3.82 (s, OCH3,3H), 3.91 (s, $COCH_2$,2H), 4.5 (s, S-CH_2,2H), 7.0-7.9 (m, 9H, Aromatic), 8.1 (s, N=CH,1H), 11.3 (s, NH,1H).



Scheme

3. RESULTS AND DISCUSSION

Our strategy was based on the use of easily available benzoyl thiourea which is synthesized from benzoyl chloride. The spectrum of IR of the benzoyl thiourea indicated a band at (C=O)1676 cm^{-1} for carbonyl of amide, a band at 3308 cm^{-1} for (NH2) and bands at 1103 cm^{-1} for (C=S). The spectrum of ^{1}H-NMR for benzoyl thiourea showed a singlet at 11.27 ppm due to (SH), singlet at 9.88 ppm due to NH=CS, singlet at 9.60 ppm due to (CONH), and many signals at 7.39-8.01 ppm due to aromatic protons. The reaction of benzoyl thiourea with ethyl 2-chloroacetate and 1,4-dioxane in the presence of K_2CO_3 for the synthesis of Imidazole derivative [ethyl 2-((1-benzoyl-5oxo-4,5dihydro1H-imidazol-2yl)thio)acetate] (compound 1). IR spectrum of compound (1) showed disappearance of absorption bands for NH_2, and a band of a (C=O) of ester appeared at 1773 cm^{-1} for ester, a band at 1687 cm^{-1} for carbonyl of ketone and bands at 1639 cm^{-1} for carbonyl of amide. The ^{1}H-NMR spectrum for compound (1) showed signal as triplet at 1.21 ppm for (CH_3-CH_2), singlet at 4.60 ppm due to (S-CH_2), and a quartet at 4.41 ppm for (COO-CH_2), singlet at 4.4 ppm due to (CO-CH_2), and many signals at 7.2-8.1 ppm due to aromatic protons. Chalcone of compound (1) in ethanol was treated with some aldehydes with 10% KOH gave ethyl 2-((1-benzoyl (Arylidene)-5-oxo4,5-dihydro1H-imidazol-2yl)thio)acetate (2a-e). Compounds (2a-e) were confirmed with IR spectral and ^{1}H-NMR data. IR spectrum showed a band of (C=CH) at 1575-1599 cm^{-1}. While ^{1}H-NMR spectra for derivatives (2a-e) showed good signals, singlet at 8.2-8.6 ppm due to (C=CH) and many signals at 7.1-8.0 ppm due to aromatic protons (5H s for phenyl ring ,4H dd for aryl ring). Ester, treated with hydrazine hydrate in ethanol, produced [2-((1-benzoyl-5oxo4,5-dihydro1H-imidazol-2yl)thio)acetohydrazide] (compound 3). The formation of compound (3) was confirmed by the disappearance of bands for ester and the presence of a band with 3298 cm^{-1} for (NH_2) and a band at 3186 cm^{-1} due to (NH). While 1H-NMR spectra showed singlet at 12.1 ppm due to (NH) and singlet at 5.3 ppm due to (NH_2), compound (3) reacted with some aldehydes and yielded [2-((1-benzoyl-5oxo-4,5dihydro-1H-imidazol-2yl)thio)(Arylidene)aceto hydrazide] (4a-e). The Schiff"s bases (4a-e) gave new IR absorption like CH=N at 1621-1641 cm^{-1} and showed absence of (NH_2) stretching vibrations. ^{1}H-NMR spectra of (4a-e) showed singlet in 8.11-8.80 ppm due to (N = CH) and many signals at 7.0-7.9 ppm due to aromatic protons (5H s for phenyl ring, 4H dd for aryl ring).

3.1. Antibacterial activity

The synthesized Imidazole derivatives were tested as antibacterial compounds using the agar disc-diffusion method against Pseudomonas aeroginosa and Staph. aureus bacteria. The control was DMSO which was used a solvent and the derivatives concentration was 10^{-3}M (Table 1). Results of current study showed that all the tested derivatives had antibacterial activities against Pseudomonas aeroginosa. In addition, all tested derivatives, except compounds (3, 4a, 4b, 4c, and 4e), had antibacterial activities against Staph. Aureus. Moreover, compound (4d) showed high inhibition against Pseudomonas aeroginosa and Staph. aureus bacteria. In addition, compounds 2c, 3, 4a, 4c, 4d and 3e showed good inhibition against Pseudomonas aeroginosa.

Therefore, imidazole derivatives can be manufactured from available and cost-effective precursors to be employed as potent antibacterial agents.

Table 1 shows antibacterial activities of compounds 1–4e at a concentration of 10^{-3} M

Comp. no.	Pseudomonas aeroginosa (Zone of bacterial growth inhibition/ mm)	Staphylococcus aureus (Zone of bacterial growth inhibition/ mm)
1	+ +	+ +
2 a	+ +	+ +
2 b	+ +	+ +
2 c	+ + +	+ +
2 d	+ +	+ +
2e	+ +	+ +
3	+ + +	-
4 a	+ + +	-
4 b	+ +	-
4 c	+ + +	-
4 d	+ + +	+ + +
4 e	+ + +	-

- : no inhibition, +: 3-6 mm, ++: 7-10 mm and +++: 11-15 mm. .

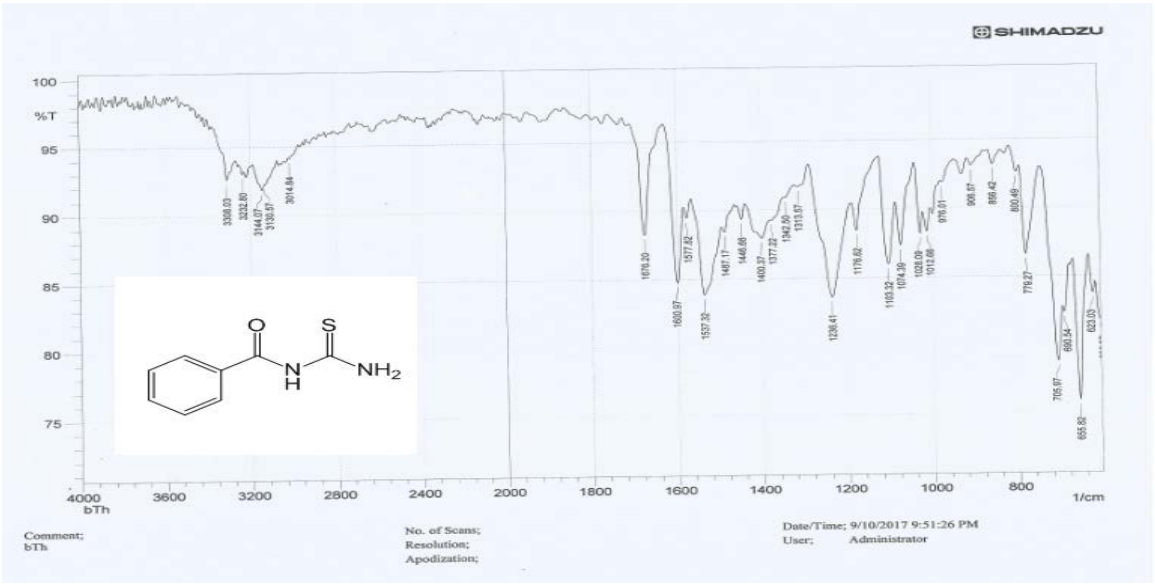


Figure 1 FTIR spectrum of (BT).

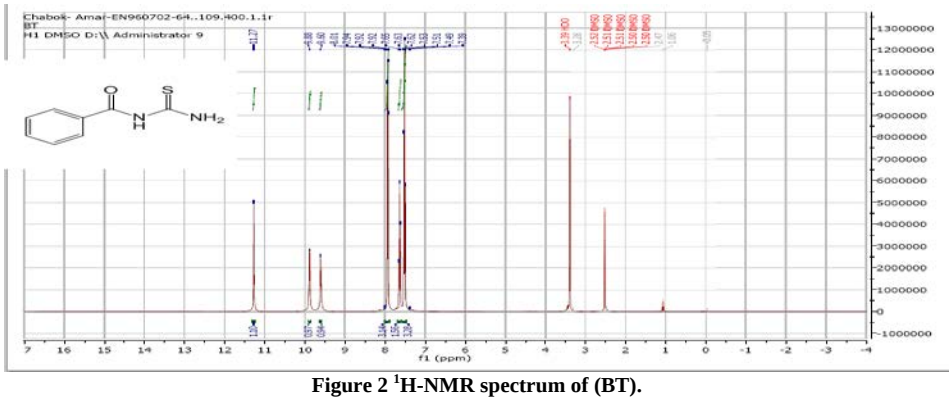


Figure 2 ^{1}H-NMR spectrum of (BT).

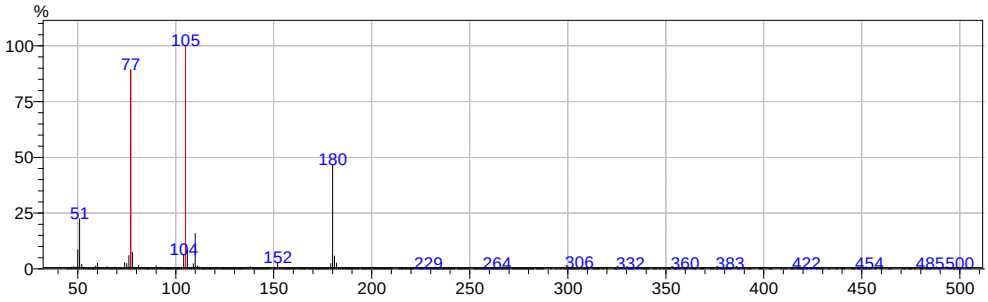


Figure 3 Mass spectrum of (BT).

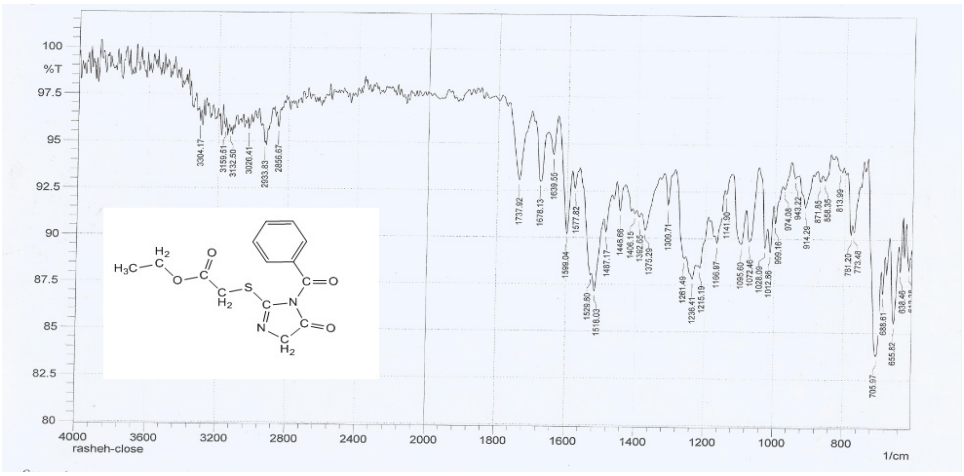


Figure 4 FTIR spectrum of compound 1.

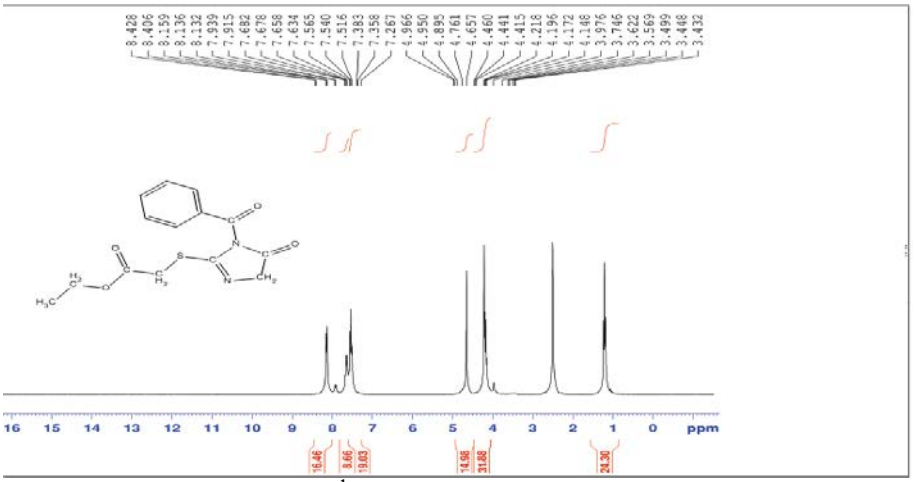


Figure 5 ^{1}H-NMR spectrum of compound 1.

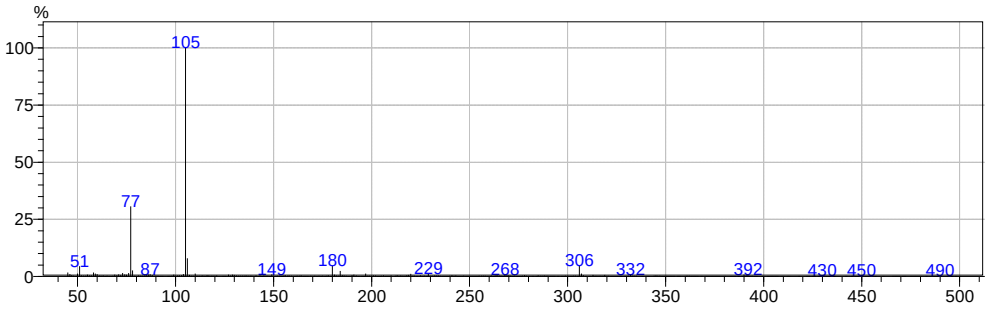


Figure 6 Mass spectrum of compound 1.

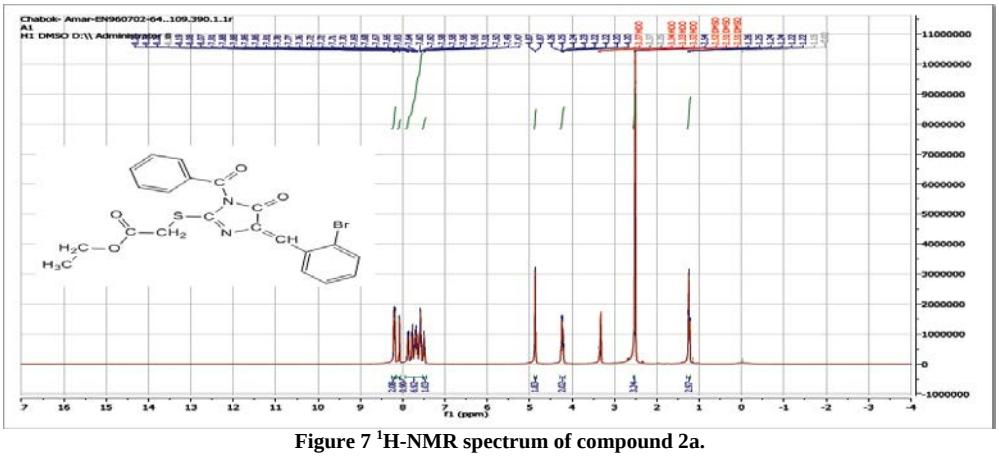


Figure 7 ^{1}H-NMR spectrum of compound 2a.

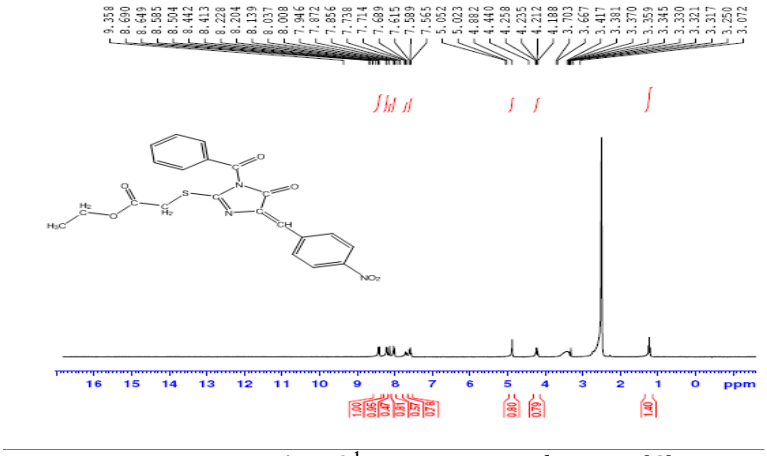


Figure 8 ^{1}H-NMR spectrum of compound 2b.

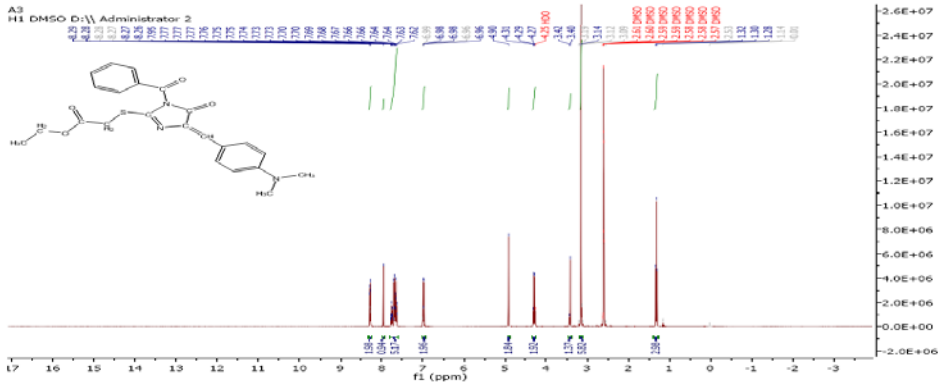


Figure 9 ^{1}H-NMR spectrum of compound 2c.

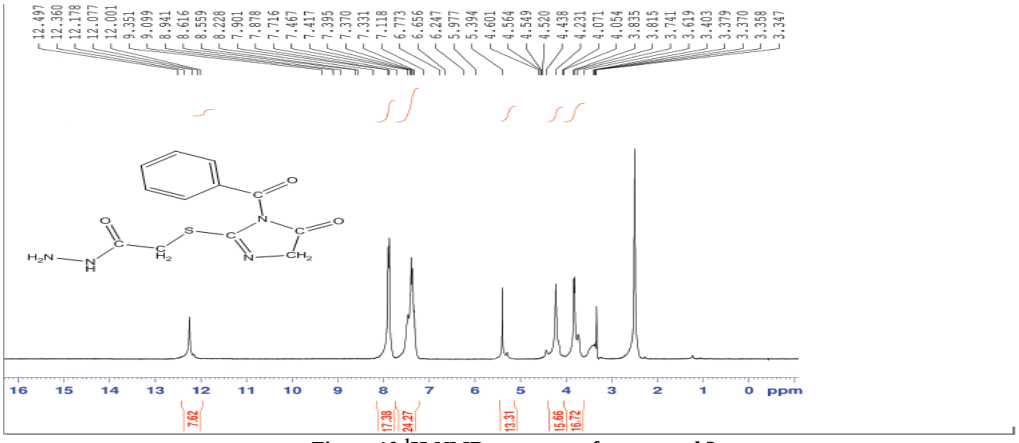


Figure 10 ^{1}H-NMR spectrum of compound 3.

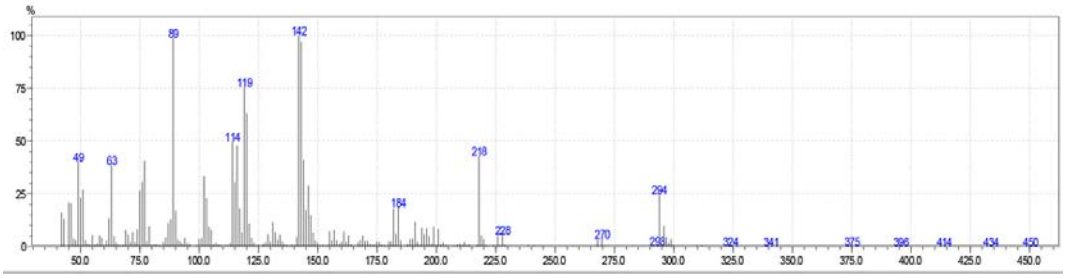


Figure 11 Mass spectrum of compound 3.

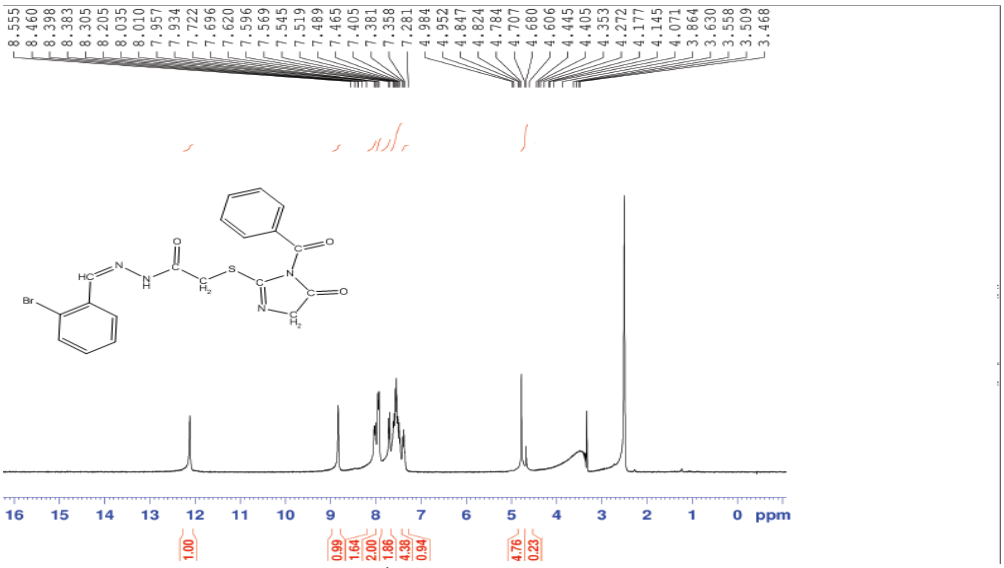


Figure 12 ^{1}H-NMR spectrum of compound 4a.

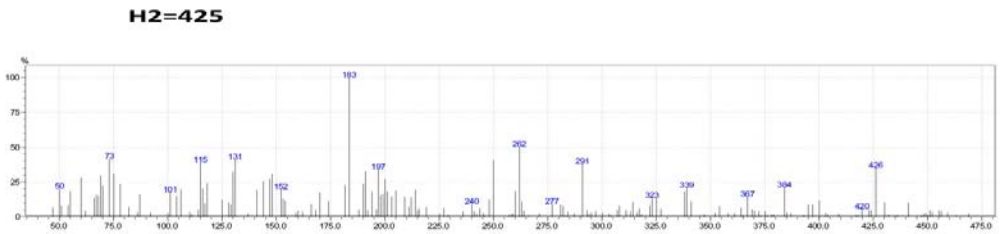


Figure 13 Mass spectrum of compound 4b.

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