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Research Article

# Synthesis and identification of novel 2-thioxo-imidazolidin-4-one derivatives containing azo and ester groups

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**ABSTRACT**

The compounds 3-[4-(4-methoxybenzoyloxy) benzylideneamino]-2-thioxo-imidazolidine-4-one(3)aand 4-(1-(5-oxo-2-thioxoimidazolidin-1-ylimino)ethyl)phenyl acetate(3)b were prepared from the reaction of aromatic aldehyde or ketone(1)a,bwith thiosemicarbazide to give aryl thiosemicarbazones(2)a,b ,followed by cyclization with ethylchloroacetate in the presence of fused sodium acetate. Treatment the compounds(3)a,bwith 4-hydroxybenzenediazoniumchloride yielded the correspondings4-((4-((4-hydroxyphenyl)diazenyl)-5-oxo-2-thioxoimidazolidin-1-ylimino)methyl)phenyl 4-methoxybenzoate(4)aand4-(1-(4-((4-hydroxyphenyl)diazenyl)-5-oxo-2-thioxoimidazolidin-1-ylimino)ethyl)phenyl acetate(4)b.The new 2-thioxo-imidazolidin-4-one with esters (5-7)a,b synthesized by reacting (4)a,b with different acid chlorides. The synthesized compounds were characterized by IRand$^{1}$HNMR spectra (of some of them) in order to elucidatetheir structures.

**Key words**:thiosemicarbazones, 2-thioxo-imidazolidin-4-one, azo compounds, esters.

## INTRODUCTION

2-Thioxo-imidazolidin-4-onesan important class of cyclic amides due to their use in medicinal chemistry as antimicrobial [1-3], antioxidant[4], antischistosomal [5],and in prodrug design [6] also some of these used as fungicides and herbicides in agrochemical research [7]. Additionally,they are very useful as organocatalysts for enantioselectiveFriedel–Crafts alkylations [8] or as building blocks for the synthesis of anyheterocycles;such as 3-substituted derivatives of 2-thioxo-imidazolidin-4-one [9], imidazoline-4-one,imidazothiazine, diazinone, and diazepinone [10].Azo compounds are continuously receiving attention in scientific research on account of using them in the industry.Nowadays,many synthetic azo compounds,especially heterocyclic ones,have a wide rangeof uses in the industry[11,12]. It was found tohave biological applications in medicine as antimicrobial [13] anti-inflammatory, anthelmintic and antibacterial compounds[14].Heterocycles containing ester moiety attracted interest since their presence in a lot of drugs such asNifidipine,Loratadine and Plavix, other heterocyclic esters exhibit divers pharmacological activity such as antimicrobial [15] and anticancer [16] while 2-thioxo-imidazolidin-4-one esters showed good herbicidal activity [17].These observations were prompted tothe synthesis of 2-thioxo-imidazolidin-4-one derivatives bearing azo and ester groups in this study.

## EXPERIMENTAL

### Materials

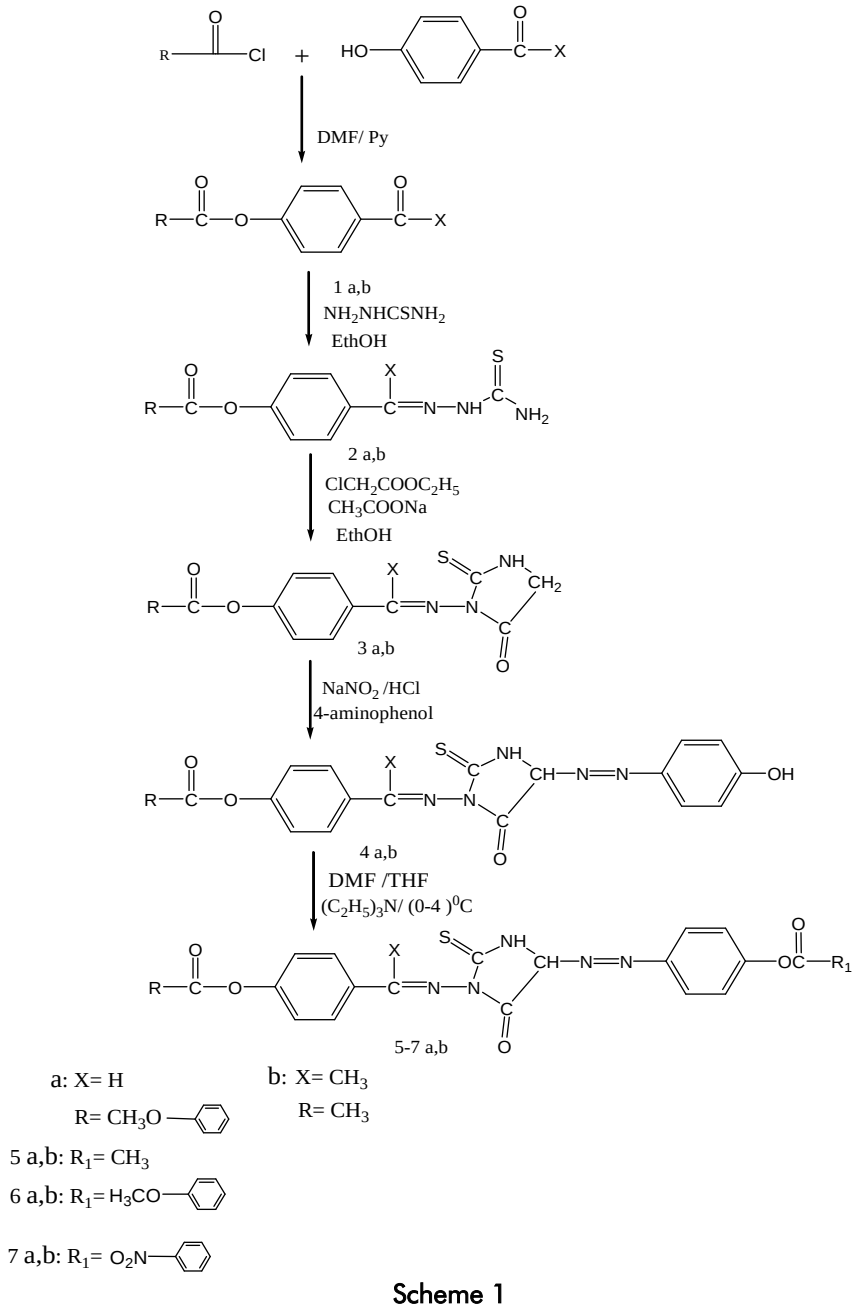
All chemicals and solvents were obtained from BHD Company and Fluka Company Ltd and were used without further purification. The compounds throughout this work were named according to the IUPAC system using Chem. Draw Ultra Computer Program.

### Instruments

All melting points are uncorrected and were determined in open capillary tubes in Gallenkamp MF-600 melting point apparatus. IR spectra were recorded by using Shimadzu Fourier Transform Infrared Spectrophotometer (using KBr disc).The H$^{1}$NMR spectra were recorded onBruker, model: ultra-shield 300 MHz using DMSO as a solvent and TMS as an internal standard and chemical shifts (δ) are given in ppm.

### Methods

The compoundswere accomplished as given in Scheme 1




Scheme 1

Preparation of compounds(1)a,b and(2)a,b:The desired compounds were synthesized using the reported methods [18,19].

Preparation of compounds(3)a,b:

A mixture of thiosemicarbazones(2)a,b (0.01mol) ,etylchloroacetate (0.03mol) and fused sodium acetate (0.03mol) was dissolved in absolute ethanol(10 mL) then heated for 8 hrs. The mixture of reaction was poured over cold water and the separated solid was filtered, washed with water and recrystallized from ethanol.

**4-((5-oxo-2-thioxoimidazolidin-1-ylimino) methyl) phenyl 4-methoxy benzoate(3)a** as pale yellow crystals ; yield (77%) ; mp:238-240 ◦C ; FT-IR(υ $cm^{-1}$): 3429$cm^{-1}$υ(NH), 1726$cm^{-1}$υ(C=O),1635$cm^{-1}$υ(C=N), 1228$cm^{-1}$υ(C=S).

**4-(1-(5-oxo-2-thioxoi midazolidin-1-ylimino)ethyl) phenyl acetate (3)b** as pink powder ; yield (74%) ; mp:174-176 ◦C ; FT-IR(υ $cm^{-1}$): 3420$cm^{-1}$υ( NH); 1716$cm^{-1}$υ(C=O);1622$cm^{-1}$υ(C=N), 1223$cm^{-1}$υ(C=S).$^1$HNMR (DMSO-$d_6$),(δ ppm):11.99(s,1H,NH), 7.20,7.92(d,4H,Ar-H),3.89(s,2H,$CH_2$), 2.4(s,3H,$COCH_3$),2.3(s,3H,-$C(CH_3)$=N).

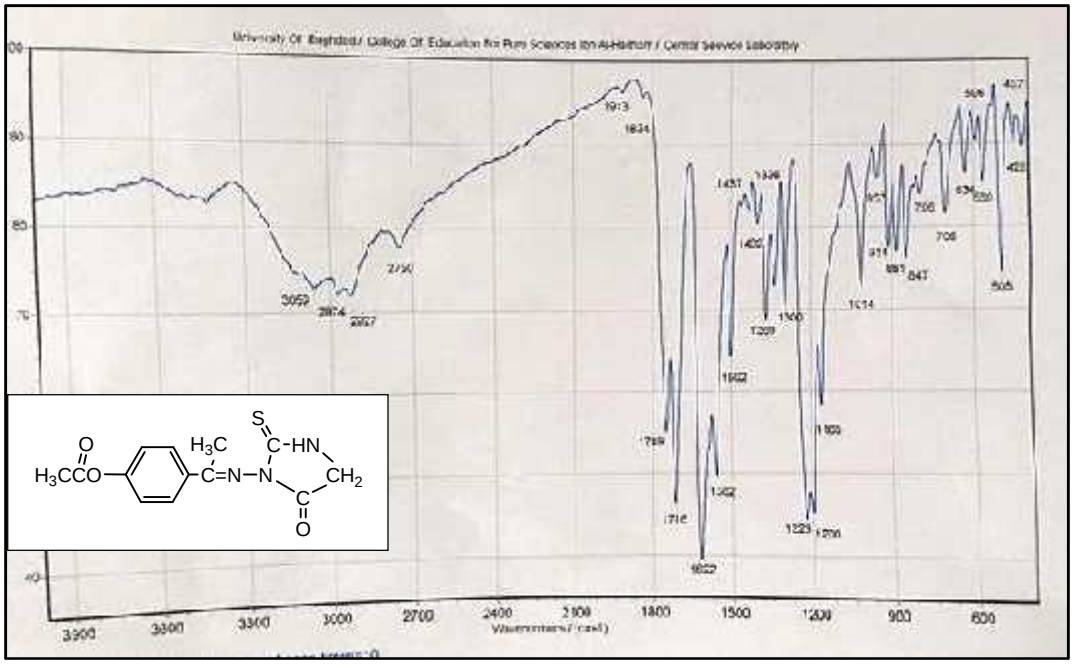


**Figure (1):FTIR Spectrum of compound (3)b**

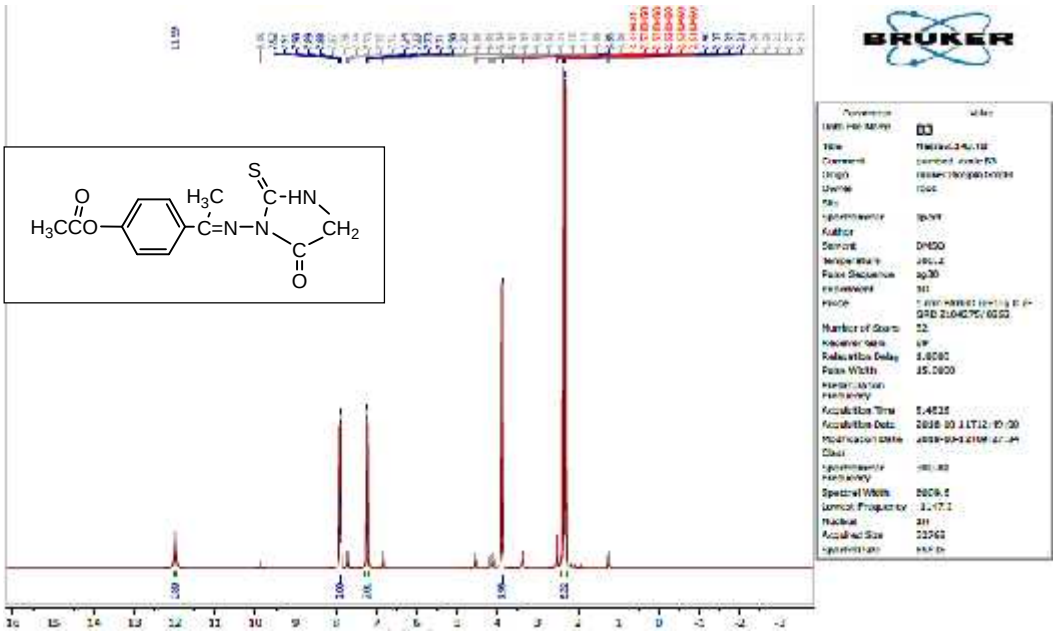


**Figure (2):$^1$HNMR Spectrum of compound (3)b**

Synthesis of 4-((4-((4-hydroxyphenyl)diazenyl)-5-oxo-2-thioxoimidazolidin-1-ylimino)methyl)phenyl 4-methoxybenzoateof (4)a and 4-(1-(4-((4-hydroxyphenyl)diazenyl)-5-oxo-2-thioxoimidazolidin-1-ylimino)ethyl)phenyl acetate(4)b: These compounds were synthesized by two steps:

**Diazotization**: 4-hydroxy aniline (0.02mole) was dissolved in a 12mL of concentrated hydrochloric acid (50%) and the mixture wascooled to (0-5)$^0$C, then(8mL) of a solution contains sodium nitrite (20%) was added dropwise to form diazonium salt.

**Coupling**: To a cold solutionat (0-5)$^0$C of 3a or 3b (0.01 mole) in aqueous NaOH (50mL ,10%) the cold diazonium solution from step A was added portionwise with stirring during 45 min. After complete addition, the reaction mixture was stirred for a further 2 hr in an ice bath.The solid that separated was filtered off, washed with water, and finally recrystallized from ethanol.

**4-((4-((4-hydroxy phenyl)diazenyl)-5-oxo-2-thioxo imidazolidin-1-ylimino)methyl) phenyl4-methoxy benzoate(4)a** as pale yellow crystals ; yield (73%) ; mp:215-218 ◦C ; FT-IR(υ cm$^{-1}$): 3439cm$^{-1}$υ(OH),3240cm$^{-1}$υ(NH),1724cm$^{-1}$υ(C=O),1629cm$^{-1}$υ(C=N),1481cm$^{-1}$υ(N=N azo),1251cm$^{-1}$(C=S);$^1$HNMR (DMSO-d$_6$),(δ ppm ) :10.03

(s,1H,OH), 4.54(s,2H,at C4 of heteroring), 8.3(m,12H, Ar-H). 3.86(s,3H,$OCH_3$), 2.59(s,3H,CH3-C=N), 6.82-

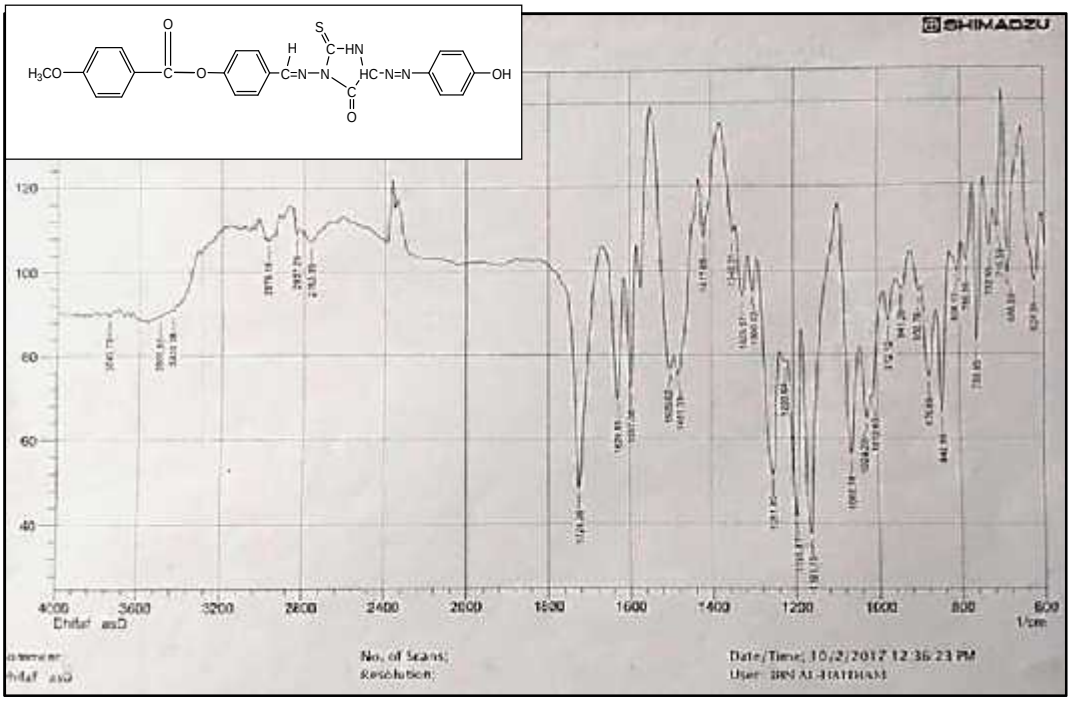



**Figure (3):FTIR Spectrum of compound (4)a**

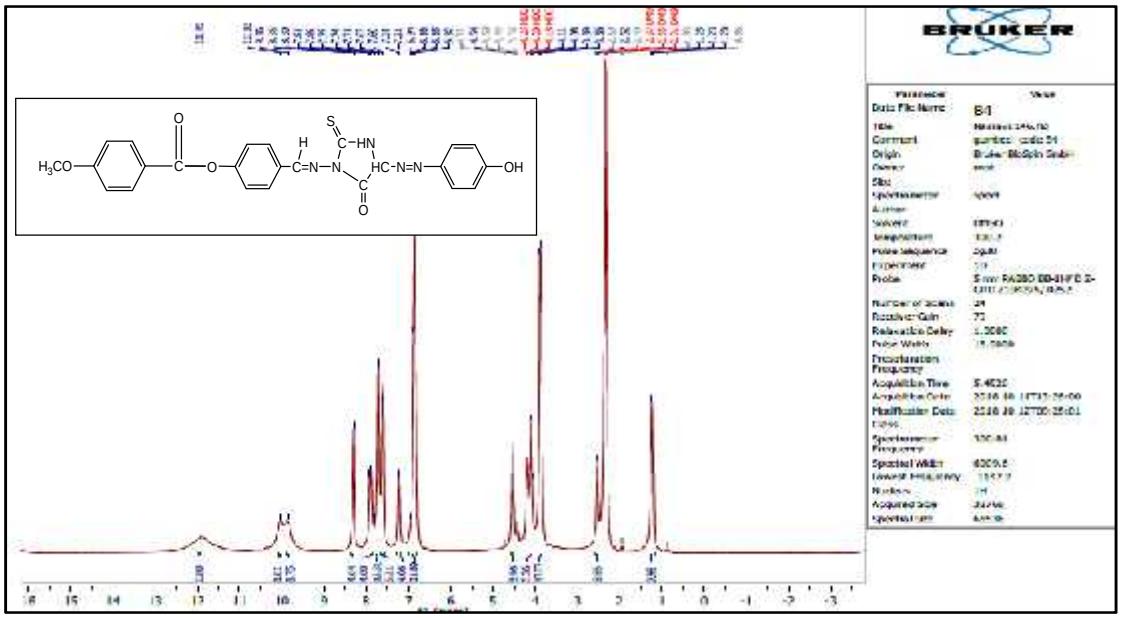



**Figure (4):$^1$HNMR Spectrum of compound (4)a**

**4-(1-(4-((4-hydroxyphenyl)diazenyl)-5-oxo-2-thioxo imidazolidin-1-ylimino)ethyl) phenyl acetate (4)b** as off white crystals ; yield (85%) ; mp:230-235 ◦C ; FT-IR(υ $cm^{-1}$): 3300$cm^{-1}$υ( OH),3242$cm^{-1}$ υ(NH),1745$cm^{-1}$,1691$cm^{-1}$υ(C=O),1627$cm^{-1}$υ(C=N),1429$cm^{-1}$υ(N=N),1203$cm^{-1}$υ(C=S).

General procedure for the synthesis of (5-7)a,b:

To a stirred solution of compounds4a or 4b (0.001mol) and triethylamine (3 drops)in dried mixture of (5ml DMF:10 ml THF), acid chloride was added dropwise at(0-4) $^0$C.The reaction mixture was stirred continuously for 3hr to allow the corresponding esters to form,then the precipitate of triethylamine hydrochloride salt was filtered and the filtrate mixture poured into ice cold water and the resulting solid was filtered and washed with water.

**4-((4-((4-acetoxyphenyl)diazenyl)-5-oxo-2-thioxo imidazolidin-1-ylimino)methyl) phenyl4-methoxy benzoate (5)a**as off white crystals ; yield (66%) ; mp:146-158 ◦C ; FT-IR(υ $cm^{-1}$):3275$cm^{-1}$υ(NH ),

1722cm$^{-1}$υ(C=O),1627cm$^{-1}$υ(C=N),1508cm$^{-1}$υ(N=N),1193cm$^{-1}$υ(C=S).

**4-(1-(4-((4-acetoxyphenyl)diazenyl)-5-oxo-2-thioxo imidazolidin-1-ylimino)ethyl) phenyl acetate (5)b** as white crystals; yield (49%) ; mp:190-192 ◦C ; FT-IR(υ cm$^{-1}$): 3240cm$^{-1}$υ(NH ), 1732,1680cm$^{-1}$ υ(C=O),1640cm$^{-1}$υ(C=N),1508cm$^{-1}$υ(N=N),1199cm$^{-1}$υ(C=S).

**4-((1-(4-(4-methoxybenzoyloxy)benzylideneamino)-5-oxo-2-thioxoimidazolidin-4-yl)diazenyl) phenyl 4-methoxy benzoate (6)a** as brown crystals; yield (73%) ; mp:119-121 ◦C ; FT-IR(υ cm$^{-1}$): 3259cm$^{-1}$υ(NH),1751,1699cm$^{-1}$ υ(C=O),1643cm$^{-1}$υ(C=N),1516cm$^{-1}$υ(N=N),1207cm$^{-1}$υ (C=S);$^{1}$HNMR (DMSO-$d_6$),(δ ppm ) :12.19 (s,1H,NH),8.5 (s,1H,CH=N),7.35-7.76(2d,4H,4-substituted benzene ring),4.04(s,2H,at C4from imidazolidinone), 2.42(s,3H,$CH_3$-C=O), 2.37(s,3H,$CH_3$-C =N).

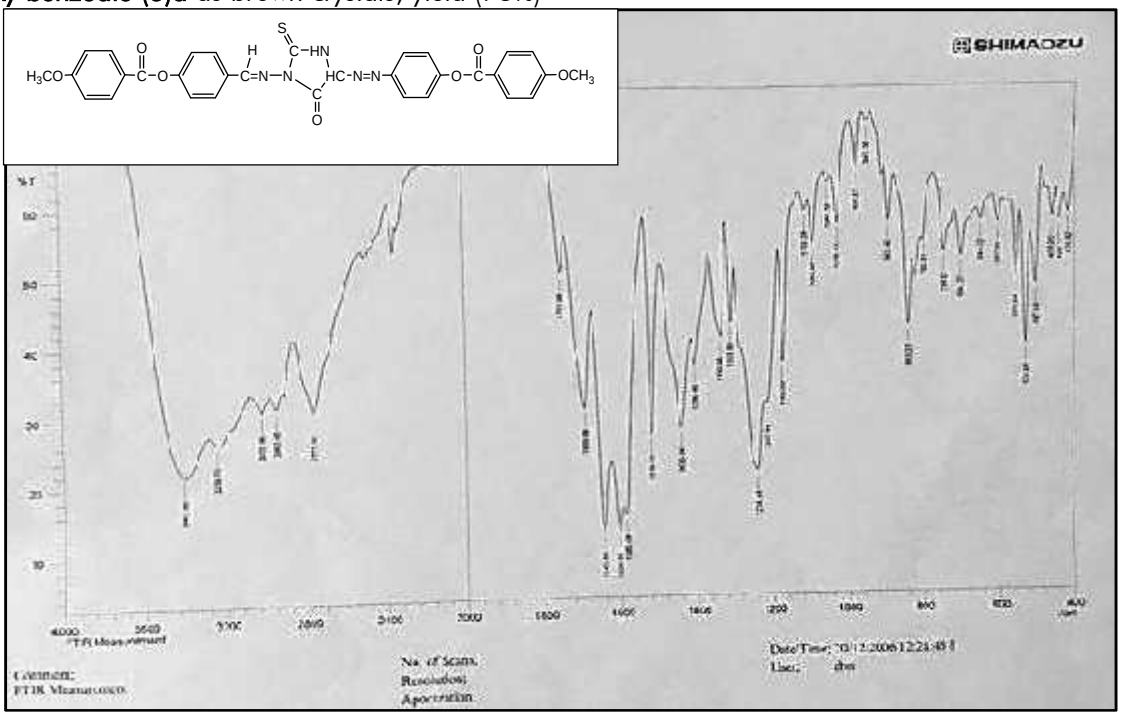



**Figure (5): IR Spectrum of compound (6)a**

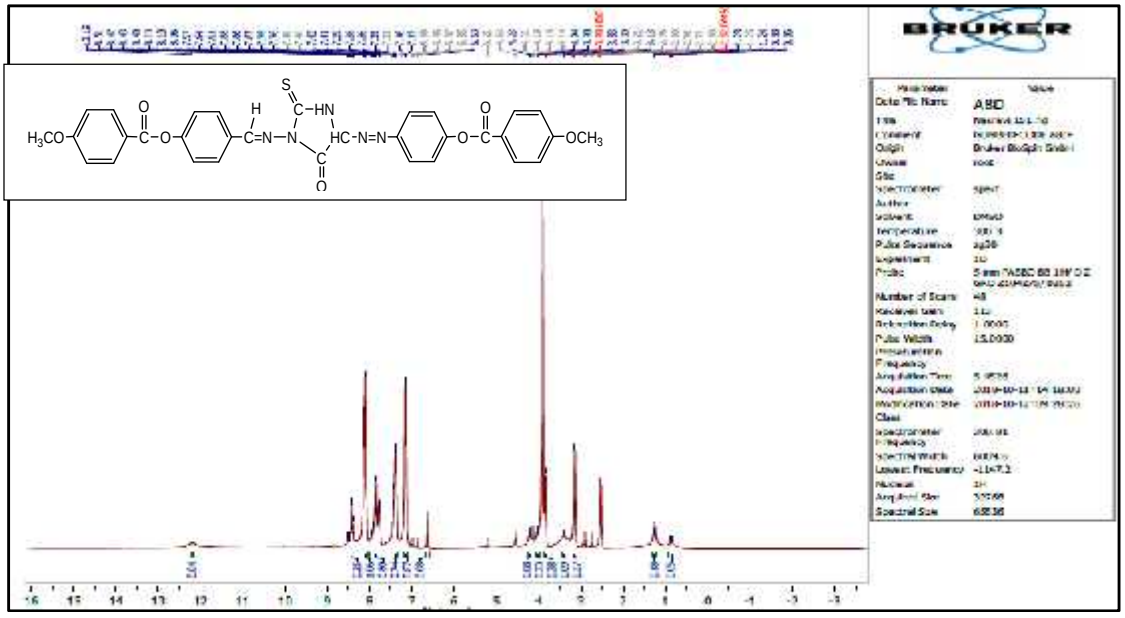



**Figure (6):$^{1}$HNMR Spectrum of compound (6)a**

**4-((1-(1-(4-acetoxyphenyl)ethylideneamino)-5-oxo-2-thioxoimidazolidin-4-yl)diazenyl)phenyl-4-methoxybenzoate (6)b** as white powder ; yield (86%) ; mp:109-111 ◦C ; FT-IR(υ cm$^{-1}$): 3290cm$^{-1}$υ(NH),

1710,1680$cm^{-1}$ υ(C=O) ,1627$cm^{-1}$υ(C=N), 1508$cm^{-1}$υ(N=N),1222$cm^{-1}$υ(C=S).

**4-((1-(4-(4-methoxybenzoyloxy)benzylideneamino)-5-oxo-2-thioxoimidazolidin-4-yl)diazenyl)phenyl 4-nitrobenzoate (7)a**as white crystals; yield (87%) ; mp:162-164 ◦C ; FT-IR(υ $cm^{-1}$): 3300$cm^{-1}$υ(NH ),1720$cm^{-1}$(C=O),1629$cm^{-1}$ υ(C=N) ,1506$cm^{-1}$υ(N=N),1300$cm^{-1}$υ($NO_2$),1195$cm^{-1}$υ(C=S).

**4-((1-(1-(4-acetoxyphenyl)ethylideneamino)-5-oxo-2-thioxoimidazolidin-4-yl)diazenyl)phenyl 4-nitrobenzoate (7)b** as pale yellow crystals; yield (87%) ; mp:162-164 ◦C ; FT-IR(υ $cm^{-1}$): 3195$cm^{-1}$υ(NH),1741$cm^{-1}$,1683$cm^{-1}$(C=O),1645$cm^{-1}$υ(C=N),1498$cm^{-1}$υ(N=N),1517$cm^{-1}$asym.υ($NO_2$), 1309$cm^{-1}$ sym.υ($NO_2$).

## RESULTS AND DISCUSSION

4-(4`-methoxybenzoyloxy) benzaldehyde(1)a and 4-(4`-methoxybenzoyloxy) acetophenone(1)b was prepared from reaction of 4-alkoxybenzoylchloride with 4-hydroxy benzaldehyde or 4-hydroxyacetophenone in dry pyridine and DMF.The two compounds were used as starting materials for the preparation of thiosemicarbazones(2)a,b.The FTIR spectrum of (2)b manifested many peaks in the region 3437-3074$cm^{-1}$ which assigned to symmetric and asymmetric stretching vibration of NH and $NH_2$ groups in addition to characteristic absorption bands at 1741$cm^{-1}$ C=O,1615$cm^{-1}$ C=N and1220$cm^{-1}$for C=S .Treatment of compounds (2)a,b with ethylchloro acetate in the presence of fused sodium acetate gave the corresponding's imidazolidin-4-ones (3)a,b.The FTIR spectrum of (3)b exhibited the disappearance of absorption bands of NH and $NH_2$ groups in the thiosemicarbazone and appearance of anew stretching band at 3420$cm^{-1}$,1716$cm^{-1}$, 1223$cm^{-1}$due to NH, C=Oand C=S of imidazolidenonerespectively confirming ring formation.The$^1$HNMR spectrum of compound (3)b showed the following features: one sharp singlet at δ(11.99) ppm that could be attributed to one proton of NH and four aromatic protons appeared as pear of doublet at δ(7.20) and δ (7.92)ppm,.The spectrum also showed one singlet at δ (3.89) ppm due to two protons of $CH_2$ groups and two sharp singlates at δ (2.4)ppm and at δ(2.3) ppm due to the three protons of $COCH_3$ and -$C(CH_3)$=N respectively.Treatment of(3)a,bwith 4-hydroxybenzendiazonium chloride yielded azocompounds (4)a,b which were identified by FTIR and $^1$HNMR.The FTIR spectrum of (4)adisplayedthe appearance of a newbroadbandat 3439$cm^{-1}$due to stretching vibration of phenolic hydroxyl and another band at 1481$cm^{-1}$ due to the N = N group. $^1$HNMR spectrum of compound (4)arevealedthe following chemical shifts: a singlet signal at δ (10.03) ppm for one proton of OH group.A singlet signal at δ (4.54)ppm for two protons at C4 of hetero ring, singlet signal at δ (3.86)ppm for three protons of $OCH_3$ group.Finally a singlet signal at δ (2.59)ppm assigned to three protons of $CH_3$-C=Ngroup, besides to multiple signal appeared in the region at δ (6.82-8.3)ppm for twelve aromatic protons.Azo compounds (4)a,bwere converted to ester compounds through treating them with different acid chlorides. The esters' FTIR spectra exhibited the disappearance of the phenolic hydroxyl band and the appearance of characteristic absorption bands at (1720-1770) $cm^{-1}$ of the new formed ester groups. The$^1$HNMR spectrum of (6)a (for example) exposed one singlet signal at δ (12.19) ppm of NH proton , one singlet signal at δ (8.5) ppm of CH=N proton, one singlet signal at δ (4.04) ppm of two protons at C4 from imidazolidinone ring besides two singlet signals for $CH_3CO$ and $CH_3$-C=N at δ (2.42) ppm and δ (2.37) ppm, respectively[20]. The four aromatic protons of 4-substituted benzene ring appeared as two doublets in the region δ (7.35-7.76) ppm.

## REFERENCES


1. Arora K., Verma S., Joshi R., Pardasani P. and Pardansani R. T. 2011. Synthesis, configurational analysis and antimicrobial activity of imidazolidinone ,thiazolidinone and isoxazolone derivatives of 9,10-phenantherenequinone. *Indian Journal of Chemistry*, 50B: 83-88.
2. Jamal Abdul Nasser A., Idhayadhulla A., Surendra Kumar R. and Selvin J.2010. Synthesis of Some 2-Thioxo-imidazolidin-4-one Derivatives and its Antimicrobial Activity. *E-Journal of Chemistry*, 7(4): 1320-1325.
3. Abd El Fattah, M.E.,Soliman A.H.andAbd Allah H. H. 2010.Synthesis and study of the biological activity of some new Thiohydantoin Derivatives.14th International Electronic Conference on Synthetic Organic Chemistry. 1-30 November.
4. Beena K. P., Rajasekaran A., Manna P. K. and Suresh R. 2017.Design, Synthesis, Characterization and Invetro Antioxidant Evaluation of Some Substituted Dihydropyrmidinone Derivatives.*World Journal of Pharmaceutical Research*,6(5):984-993.
5. Pitta M.G.R., Silva A.C.A., AL NevesJ. K., Silva P.G., IrmaoJ. I., MalagueñoE., Santana J. V., Lima M.C.A., GaldinoS. L., Pitta I. R. and Albuquerque M.C.2006.New imidazolidinicbioisosters: potential candidates for antischistosomal drugs.*MemInstOswaldo Cruz, Rio De Janeiro*,101 (Suppl. I):313-316.
6. Deepa Padmaja, Manikandan Palanivelu, Babu Ganesan, Seena, Arunraj Natarajan. "Formulation, Evaluation and Validation of Newly Formulated Laportea Arishta." International Journal of Pharmacy Research & Technology 4.2 (2014), 10-17.
7. Han J., Dong H., Xu Z., Wang J. and Wang M. 2013. Synthesis and Activity of Novel Acylthiourea with Hydantoin. Int. J. Mol. Sci.,14: 19526-19539.
8. Pecchioli T., Muthyala M. K., Haag R. and Christmann M. 2015. Multivalent polyglycerol supported imidazolidin-4-one organocatalysts for

enantioselectiveFriedel–Crafts alkylations.*Beilstein J. Org. Chem*.,11:730–738.

9. Muhsen T. R. , Tomma J. H. and MukhlusA. J. A. 2012.Synthesis and Characterization of Novel Compounds Containing of Imidazolidinone and Oxazepine Rings.*Ibn Al-Haitham Journal for Pure and Applied Science*-University of Baghdad,25(3):276-283.
10. Kononowicz K. K. , Karolak-Wojciechowska J., Muller C. E., Schumacher B., PekalaE.andSzymanska E.2001.Imidazo-thiazine, -diazinone and -diazepinone derivatives. Synthesis, structure and benzodiazepine receptor binding.*Eur. J. Med. Chem*.,36:407–419.
11. PawarA. B., More S. P. andAdivarekarR.V.2018.Dyeing of Polyester and Nylon with Semi-synthetic Azo Dye by Chemical Modification of Natural Source Areca Nut.*Natural Products and Bioprospecting*,8:23–29.
12. Sener N.,Erskin S., Sahin C., Yilmez M. and Sener I.2017.Synthesis, Characterization, and Fluorescence Studies of Novel Heterocyclic Azo Dyes Derived from Benzothiazole.*Journal of Heterocyclic Chemistry*,54(6):3510-3518.
13. Ali H. M., Majeed H. A., Al-Asadi I. A., Abdulredha A. S., HussainA. A.2018.Structures effects of two azo dyes associated with their antimicrobial activities.*Journal of Chemical, Biological and Physical Sciences*,8(2):171-185.
14. Shaikh A. and Meshram J. S. 2015.Design, Synthesis and Pharmacological Assay of Novel AzoDerivatives of Dihydropyrimidinones.*Cogent Chemistry*,1:1019809.
15. Nikalje G., GhodkeS.andMirza Sultan B. N.2014.2-Azetidinone-A Brief Review.*World Journal of Pharmaceutical Research*,3(2):2589-2625.
16. Martins P., Jesus J., Santos S., Raposo L. R., Roma-Rodrigues C., Baptista P. V. and Fernandes A. R.2015.Heterocyclic Anticancer Compounds: Recent Advances and the Paradigm Shift towards the Use of Nanomedicine's Tool Box.*Molecules*,20,16852-16891.
17. Han J., Wang J., Dong H., Lei J., Wang M. and Fang J. 2011. Synthesis and Herbicidal Activity of 5-(4-Hydroxybenzyl) -2-Thioxoimidazolidin-4-one Esters.*Molecules*,16:2833-2845.
18. Jamel N. M., Baker R. K. and Tomma J. H.2017. Synthesis, Characterization andInvestigation the Antibacterial Activity of New Heterocyclic Compounds Derived From 4-(4`-methoxy benzoyloxy)benzaldehydethiosemicarbazone.*Ibn Al-Haitham Journal for Pure and Applied Science*,University of Baghdad ,30(1),155-168.
19. Tomma J. H., Ayyash A. N. and Jaffer H. J.2018.Synthesis And Characterization Of Some New Quinolin-2(1H)-Ones And Imidazoles Containing 1, 3, 4-Thiadiazoline Ring Derived From Thiosemicarbazone.*Research Journal of Pharmaceutical, Biological and Chemical Sciences*,9(6):177-185.
20. Tomma J. H., Baqir R. K. and Al-Dujaili A. H.2018. Synthesis, Characterization and Biological Activity of New Ester Containing Azo Group Derived From 2-Amino-1, 3, 4-Thiadiazoline Derivatives.*Journal of Global Pharma Technology*,10(05):490-497.