Synthesis of New beta-lactam , 2-thioxoimidazolidin-4-one and Imidazole-5-one Derivatives from thiosemicarbazide and Their Biological Activity Study

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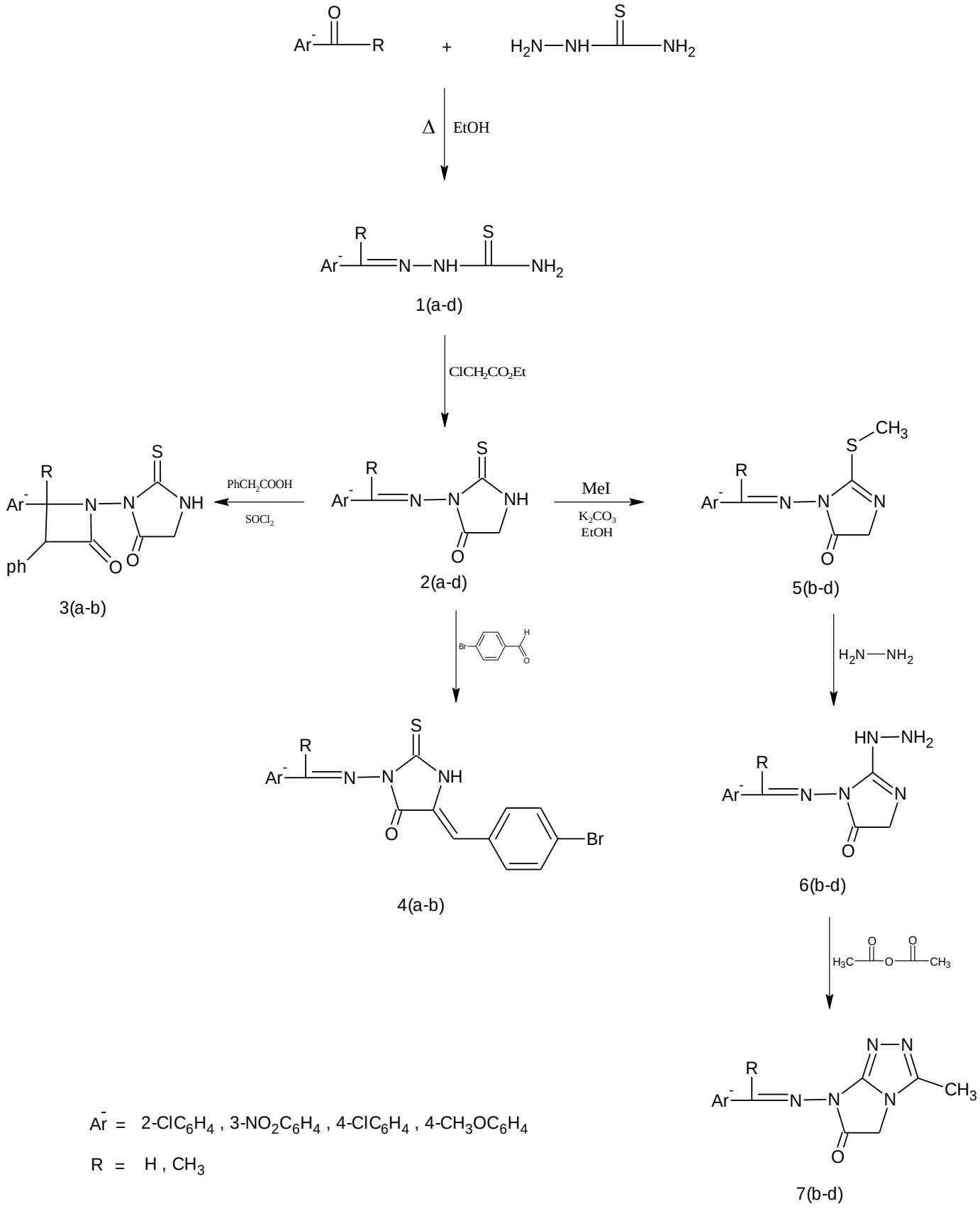
Abstract

New derivatives of thiosemicarbazide were synthesized by reaction of different aromatic aldehydes and ketones with thiosemicarbazide to give schiff-bases 1(a-d) . schiff-bases have been used for synthesized the thioimidazolidine 2(a-d) by reaction of schiff-bases with ethyl chloroacetatein in presence of anhydrous sodium acetate that transformed part of it in to Beta-lactam 3(a-b) compounds with phenyl acetic acid and thionyl chloride , The compounds 4(a-b) came from the reactor of 4-bromobenzaldehyde with compounds 2(a-b) , as well as reaction of compounds 2(b-d) with methyl iodide and anhydrous potassium carbonate to give 5 (b-d) , then added hydrazine hydrate formed 6(b-d) , then reaction with acetic anhydride to prepare 7(b-d) , The biological activity of the synthesized compounds was also studied . All newly compounds were characterized by using the proton nuclear magnetic resonance (^{1}H-NMR) ,mass spectra (Ms) , fourier transform infrared spectroscopy (FTIR) ,ultraviolet (UV) spectroscopy spectra , and studied their physical properties.

Keywords: thiosemicarbazide ,imidazole , imidazole-5-one , beta lactame

Introduction

Thiosemicarbazide is one of N-Aminothiourea compounds , as well it considers an effective control for bacterial leaf blight of rice also as a reagent for ketones , certain metals[1], of photography and as a rodenticide . In organic chemistry aldehyde or ketone condensation reaction with semicarbazide to form semicarbazone derivatives . such as Nitrofurazone used antibiotics[1] . when oxygen atom changes to sulfur atom in a semicarbazone we get thiosemicarbazone[1]. In past years thiosemicarbazone derivedes from related aldehydes and 2-formylpyridine have been of great interest because of their antineoplastic action [2] . Thiosemicarbazone derivatives have wide pharmaceutical interest and exhibit various biological activities such as anticancer , antifungal, rheumatism , antibacterial , coccidiodis, leprosy , antimalarial , antiviral and trypanosomiasis[2,3] . in organic synthesis Imidazol-thione derivatives are playing very important role and they have many applications as therapeutics and the methods for the synthesis of imidazole-2-thiones are classified according to reaction types including cyclization, reactions of halo- and oxoimidazole derivatives with sulfur-containing nucleophiles, and direct insertion of sulfur into position 2 of the imidazole ring [4-6] as well as herbicides and fungicides [7] .The 5-diphenylimidazolidin-2,4-dione and phenylimidazolone were used as anticonvulsants [8] . S-glucosylatedimidazolones[9] exhibit high activity against the human-immune deficiency virus[10] , the herpes simple virus[11] , The 1-aminoimidazolone used for the treatment of urinary tract infections as antimicrobial drug[12] , and as muscle relaxant drug for cardiac arrhythmia[13], Imidazolone-thione derivatives were reported as inhibitors of liver glycogen phosphorylases[14] . and serine protease[15] , Imidazole ring found in many drugs such as nitro imidazole which is used antifungal drugs[16,17], and the sedative midazolam[18] , more over some of these activities are antibacterial activites [19-22].



Ar = 2-ClC_6H_4 , 3-$NO_2C_6H_4$, 4-ClC_6H_4 , 4-$CH_3OC_6H_4$

R = H , CH_3

Synthesis of new compounds 1(a-d)- 7(b-d) from thiosemicarbazide

Experimental

Instruments

Melting point was determined in open capillary tube on gallenkamp melting point apparatus and are uncorrected .

The FT-IR spectra were recorded by using a perkin –Elmer 1600-series FT-IR spectrometer, mass spectra (Ms) .^{1}HNMR spc. were recorded onavariar –Mercury 200 µHZ spectrometer and solvents (DMSO-d_6) in Jordan University .

Chemicals

The chemical materials that were used (Fluka, BDH) brand, it is pure substances .

Synthesis of *N*'-Arylidenehydrazinecarbothioamide1(a-d)

To a stirring solution of thiosemicarbazide(0.01 mole) in absolute ethanol (20 ml), aromatic aldehyde or ketone (*o*-chlorobenzaldehyde , *m*-nitrobenzaldehyde , *p*-chloroacetophenon , *p*- methoxyacetophenon) (0.01 mole) were added. The mixture was refluxed for 4hrs., then cooled. The precipitate was filtered and recrystallized from appropriate solvent Tables (1) and (2).

Synthesis of *N*'-Arylideneamino-2- thioxoimidazolidin-4-one 2(a-d)

A mixture of 1(a-d) (0.01mol) and ethyl chloroacetate (0.01mol) in ethanol (50 ml) in presence of anhydrous sodium acetate (0.03mol) was heated under reflux for 4 hr. After cooling to room temperature, the reaction mixture was poured into ice water. The resulting solid was filtered off, washed with hot water, dried and recrystallized from appropriate solvent Tables (1) and (2).

Synthesis of 3-[2-(Arylidene)-4-oxo-3-phenylazetidin-1-yl]-2-thioxoimidazolidin-4-one(3a ,3 b)

To a stirring mixture of phenyl acetic acid (0.01mol) and triethylamin (2.02gm) in (40ml) chloroform with (0.01mol) compounds (2a or 2b) in ice bath was added drop wise of thionyl chloride (5ml) in 20ml chloroform then the reaction was stirred for (10 hrs) . After that the mixture was washed with (30ml,1NHCL) and three times with water, dried by Na_2SO_4(5g), recrystallized from appropriate solvent Tables (1) and (2).

Synthesis of 5-arylidene-3-substituted-2-thiohydantoins (4a,4b)

A mixture of (2a or 2b) (0.01mol) , appropriate aromatic aldehydes (4-bromobenzaldehyde) (0.01mol) and triethylamine (1 ml) was heated at 120-125 ^{o}C for 1hr without solvent. The reaction mixture was then left to cool at room temperature and acidified with dilute hydrochloric acid (2%). The crude product was filtered off, washed with water, dried and purified by recrystallization from the suitable solvent to give compounds (4a,4b), Tables (1) and (2).

Synthesis of 2-(methylsulfanyl)-3-[(Arylidene)amino]-3,5-dihydro-4*H*-imidazol-4-one 5(b-d)

A mixture of 2(b-d) (0.01mol) , methyl iodide (0.01mol) and anhydrous potassium carbonate (0.03 mol) in ethanol (50 ml) was heated under reflux for 4hrs. The reaction mixture was then cooled and poured in to water. The solid formed was filtered off, washed with water, dried and recrystallized from appropriate solvent Tables (1)and(2) [23].

Synthesis of 2-hydrazinyl-3-[(Arylidene)amino]-3,5-dihydro-4*H*-imidazol-4-one 6(b-d)

Hydrazine hydrate (99%)(10 ml) was added to a mixture of compound (5(b- d)) (0.001 mole) in abs. ethanol (30 ml). The reaction mixture was refluxed for 8 hrs. Then, the mixture was allowed to cool to room temperature .The solid formed was filtered off , washed with ethanol and recrystallized from appropriate solvent Tables (1)and(2) [23].

Synthesis of 3-methyl-7-[(Arylidene)amino]-5*H*-imidazo[2,1-*c*][1,2,4]triazol-6(7*H*)-one 7(b-d)

A solution of 6(b-d) (0.01mol) in acetic anhydride (25 ml) was heated under reflux for 4 hr, then cooled and poured into ice-water (50 mL) .The solid formed was filtered off , washed with water, dried and recrystallized from appropriate solvent Tables (1)and(2) [23] .

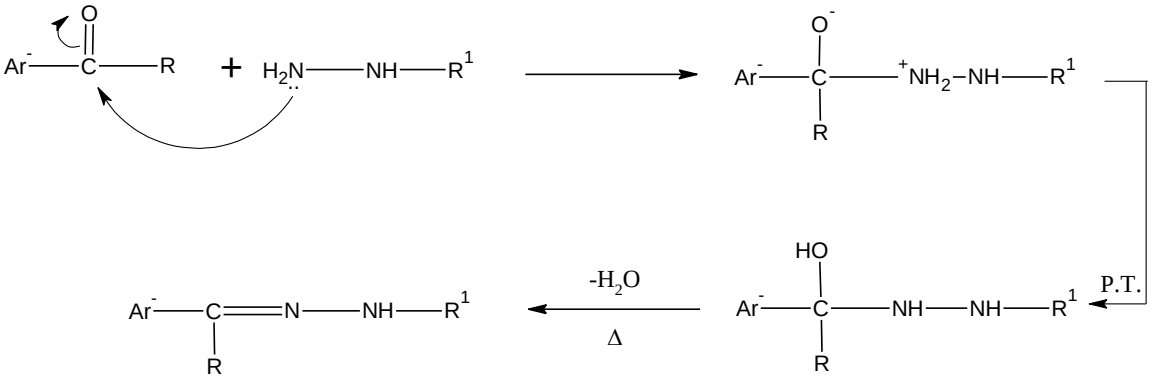
Antimicrobial evaluation

The newly synthesized heterocyclic compounds, as shown in Table 3 were tested for their antimicrobial activity against the following microorganisms :*Escherichia coli,klebsiella pneumonia* ,*staphylococcus aureus,Streptococcus lactis* , and *Candida albicans*. The preliminary screening of the investigated compounds was performed using the holes method. and the results are summarized in Table (3).

Results and discussion

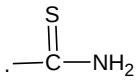
The research includes the preparation of *N*'-Arylidenehydrazinecarbothioamide 1(a-d) through aromatic aldehyde or ketone different interacts with thiosemicarbazide showed spectra FTIR(ν, cm^{-1}) frequency bands belonging to the (C=N) at (1608-1585) and (NH_2) at (3415 - 3232),λ_{max} (EtOH)(nm) at (220-248) responsible for (n→ π^*) transition of (N and O) atoms and at (298-320) due to ($\pi \rightarrow \pi^*$), and then added ethyl chloroacetate to synthesis of *N*'-Arylideneamino-2-thioxoimidazolidin-4-one 2(a-d) diagnosed by spectra of FTIR(ν, cm^{-1}) that gave the frequency bands characteristic belonging to a group $(C=O)_{amid}$ at (1720-1706) and the disappearance of the frequency (NH_2) group in Schiff-bases, λ_{max} (EtOH)(nm) at (221-242) responsible for (n → π^*) transition of (N and O) atoms and at (315-342) due to ($\pi \rightarrow \pi^*$),and diagnosed of 3-[2-(Arylidene)-4-oxo-3-phenylazetidin-1-yl]-2-thioxoimidazolidin-4-one (3a, 3b) that attended by the reactance of (2a,2b) with phenyl acetic acid and thionyl chloride has shown FTIR(ν, cm^{-1})(1761) return to the group (C=O) in the ring Beta-lactam and the disappearance of the shades (C = N) group .^{1}H-NMR(δ,ppm)showed 6.87-8.54(m,9H,ArH),4.12-4.31(s,1H,$CH)_{amid}$,7.00-7.12 (s,1H,$NH)_{amid}$,4.36-4.46(d,1H,$CH)_{Lactam}$,5.60-5.61(d,1H,$CH\text{-}N)_{Lactam}$, as shown in Figure (1) for 3a ,Synthesis of 5-arylidene-3-substituted-2-thiohydantoins(4a,4b) attended the interaction (2a,2b) with 4-bromobenzaldehyde has shown Spectra of FTIR(ν, cm^{-1}) have frequency peaks at $(C=O)_{amid}$ 1710- 1701, (C=C) 1649-1587,(C-Br) 810-806,and ^{1}HNMR (DMSO-d6)(δ,ppm),6.37-8.39(m,8H,ArH),8.49-8.79 (s,1H,CH=N), 6.50-6.96 (s,1H, CH=CH), 2.10-2.25 (s,1H, $NH)_{amid}$,as shown in Figure (2) for 4b , either synthesis of 2-(methylsulfanyl)-3-[(Arylidene)amino]-3,5-dihydro-4*H*-imidazol-4-one 5(b-d) came from reacting methyl iodide and anhydrous potassium carbonate to 2(b-d) where it showed FTIR(ν, cm^{-1}) $(C=O)_{amid}$ 1710-1718, (C=C) 1487-1597,(C=N) 1610-1674, MS (*m/z*) %: 278 (M^-, 98.50) for (5b), as shown in Figure (3) for 5d,then reaction with Hydrazine hydrate to synthesis of 2-hydrazinyl-3-[(Arylidene)amino]-3,5-dihydro-4*H*-imidazol-4-one 6(b-d) characterized by FTIR (ν, cm^{-1}) $(C=O)_{amid}$ 1712-1718,(NH_2) 3250-3493,(C=N)1602-1618 and the disappearance of the frequency (C-S) group and MS (*m/z*) %: 262(M^+,19.90)for (6d), as shown in Figure (4) for 6c then added acetic anhydride to prepare the derivatives 3-methyl-7-[(Arylidene)amino]-5*H*-imidazo[2,1-*c*][1,2,4]triazol-6(7*H*)-one7(b-d).The FTIR spectra for derivatives 7(b-d) showed stretching bands at (ν, cm^{-1})$(C=O)_{amid}$ 1714-1720,(C=N)1602-1684 and the disappearance of the frequency (NH_2),MS (*m/z*) %: 289 (M^-,98.60)for(7C), as shown in Figure (5) for 7b, Tables (2).The study of biological activity of all new prepared compounds were listed in the

Table (3) . All prepared compounds happened according to the following mechanisms:

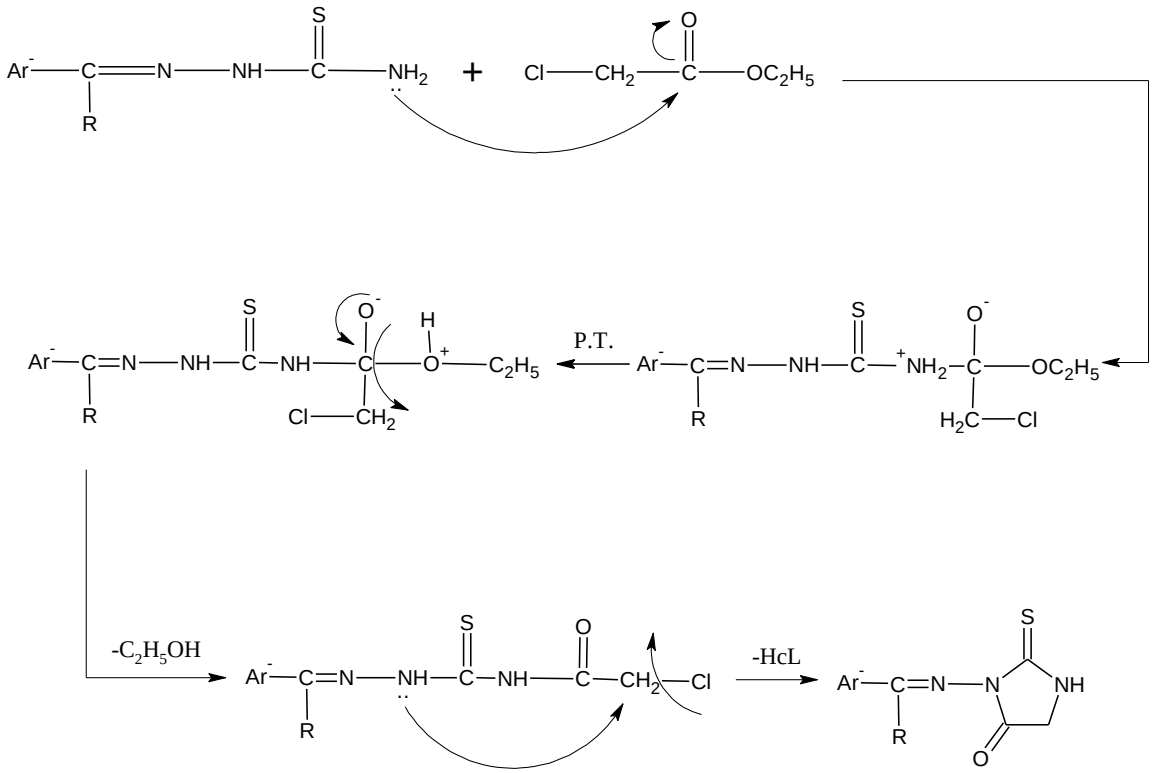


$\bar{Ar}$ = 2-ClC_6H_4 , 3-$NO_2C_6H_4$, 4-ClC_6H_4 , 4-$CH_3OC_6H_4$

R = H , CH_3

R^1 = 

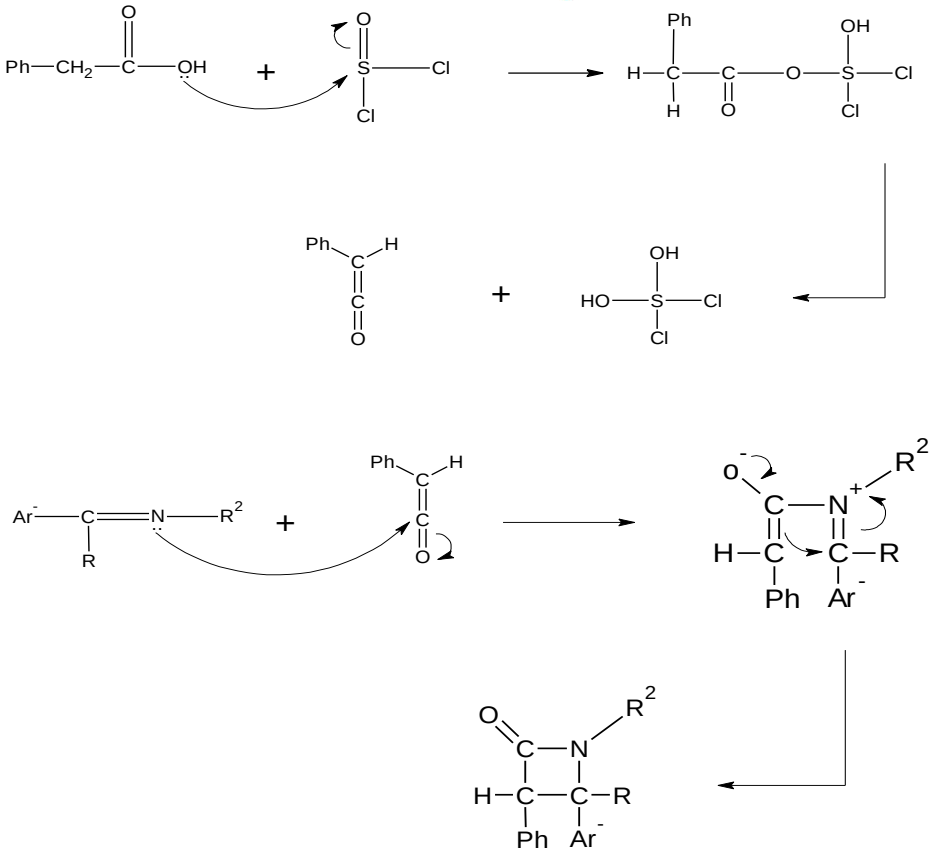
Mechanism synthesis of 1(a-d): (Nucleophilic addition reaction)



$\bar{Ar}$ = 2-ClC_6H_4 , 3-$NO_2C_6H_4$, 4-ClC_6H_4 , 4-$CH_3OC_6H_4$

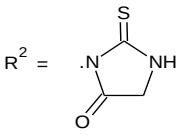
R = H , CH_3

Mechanism synthesis of 2(a-d): (cyclization mechanism)



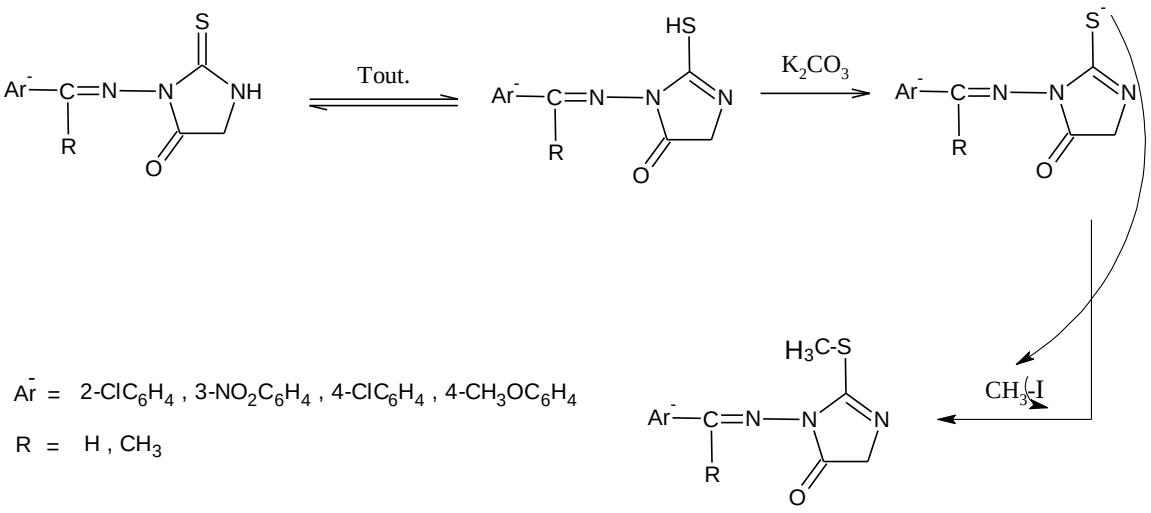
Ar = 2-ClC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-ClC$_6$H$_4$, 4-CH$_3$OC$_6$H$_4$

R = H , CH$_3$

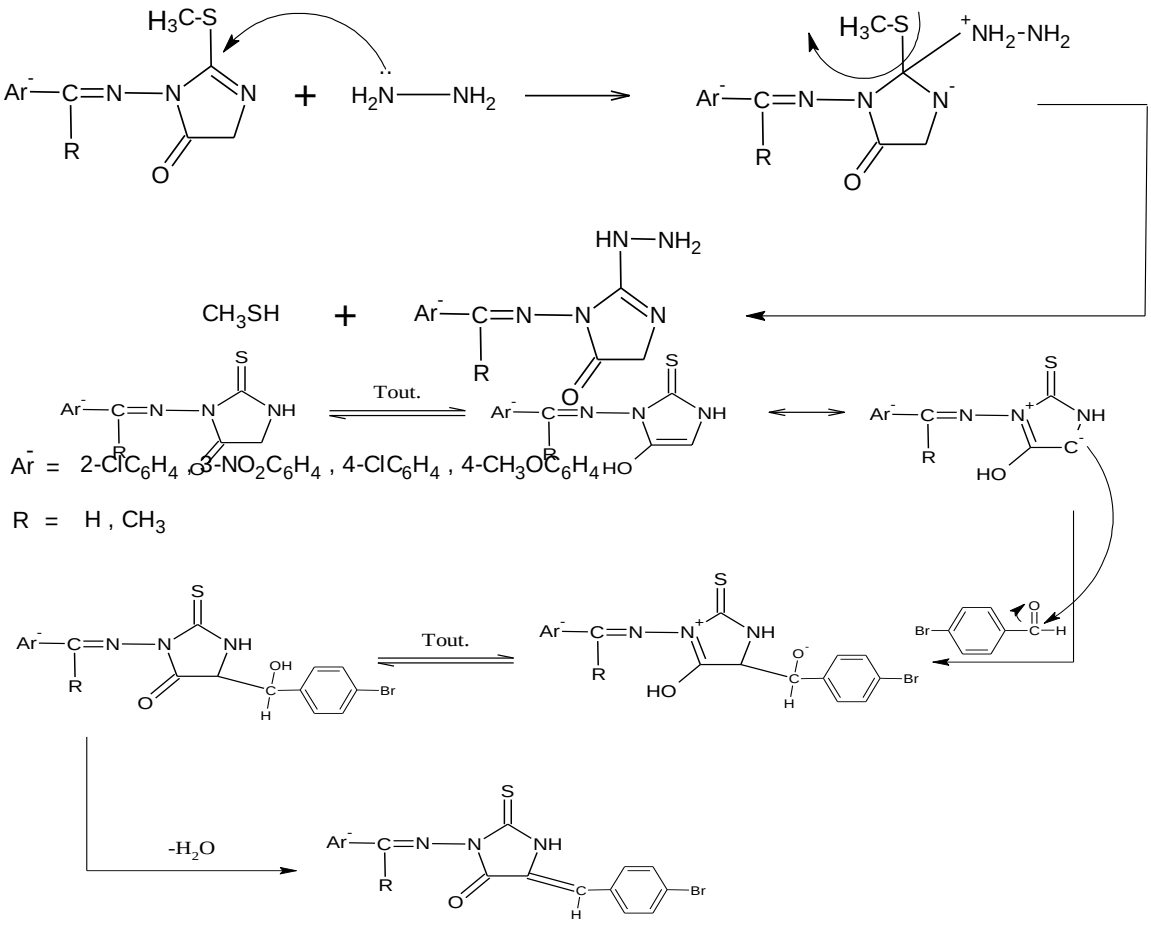


Mechanism synthesis of 3(a-d): (cyclization mechanism)

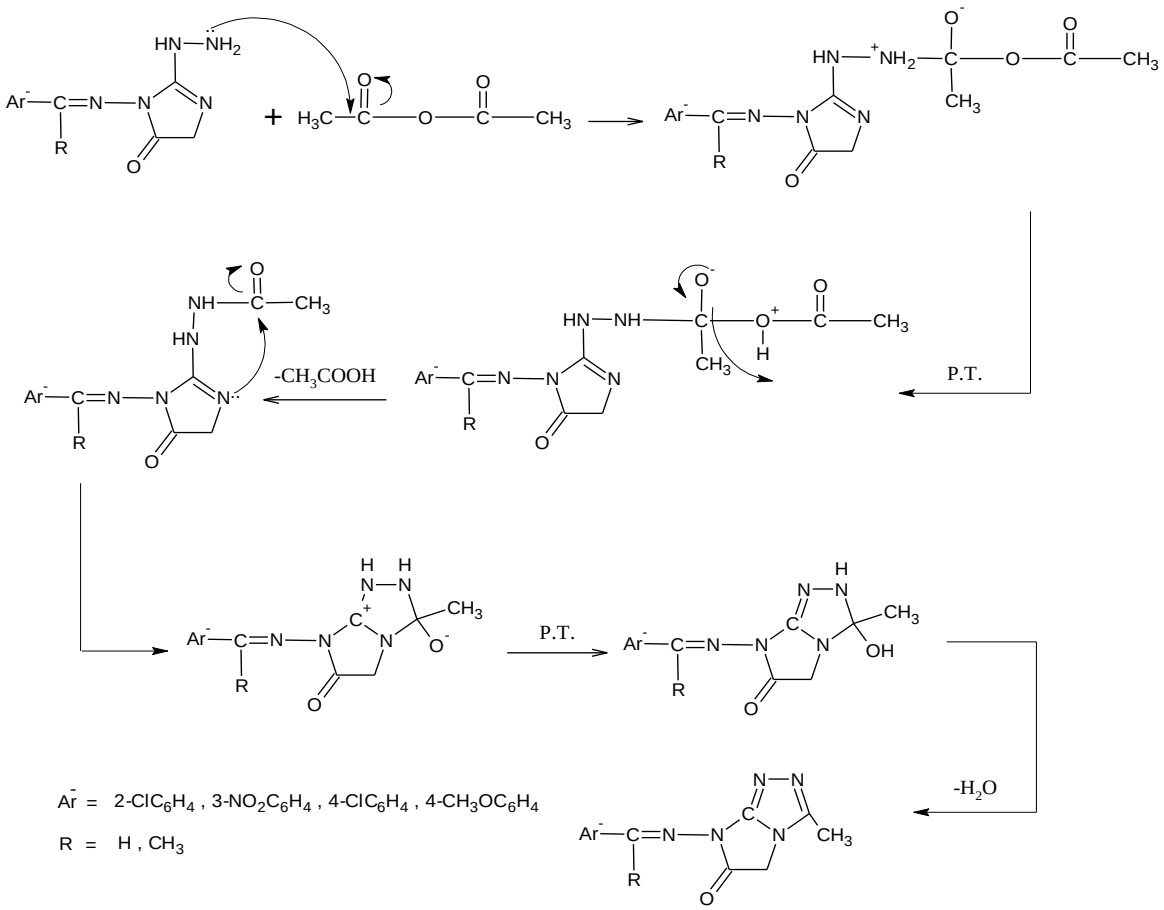
Mechanism synthesis of 4(a-d): (Nucleophilic substitution reaction)



Mechanism synthesis of 5(a-d):(SN2)



Mechanism synthesis of 6(a-d): (Nucleophilic substitution reaction)



Mechanism synthesis of 7(a-d): (Nucleophilic substitution reaction)

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Table (1):Physical properties of newly synthesized compounds

Comp. No.	M.P (C°) & State and colour	Recryst-solvent & Mol. formula(M. wt)	Yield %	chemical name of scientific
1a	216 Solid ,White	Ethanol:H_2o(2:1) $C_8H_8ClN_3S$ (213.68)	94	2-(2-chlorobenzylidene)hydrazinecarbothioamide
1b	244 Solid ,White	Ethanol:H_2o(2:1) $C_8H_8N_4O_2S$ (224.24)	90	2-(3-nitrobenzylidene)hydrazinecarbothioamide
1c	197 Solid ,White	Ethanol $C_9H_{10}ClN_3S$ (227.71)	89	2-[1-(4-chlorophenyl)ethylidene]hydrazinecarbothioamide
1d	176 Solid ,White	Ethanol:H_2o(1:1) $C_{10}H_{13}N_3OS$ (223.29)	91	2-[1-(4-methoxyphenyl)ethylidene]hydrazinecarbothioamide
2a	250 Solid ,White	Ethanol $C_{10}H_8ClN_3OS$(253.70)	83	3-[(2-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one
2b	216 Solid ,White	Ethanol:H_2o(2:1) $C_{10}H_8N_4O_3S$ (264.62)	80	3-[(3-nitrobenzylidene)amino]-2-thioxoimidazolidin-4-one
2c	267 Solid ,White	Ethanol:H_2o(1:1)$C_{11}H_{10}ClN_3OS$ (267.73)	82	3-{[1-(4-chlorophenyl)ethylidene]amino}-2-thioxoimidazolidin-4-one
2d	184 Solid ,White	Ethanol $C_{12}H_{13}N_3O_2S$ (263.31)	85	3-{[1-(4-methoxyphenyl)ethylidene]amino}-2-thioxoimidazolidin-4-one
3a	240 Solid ,yellow	Ethanol $C_{18}H_{14}ClN_3O_2S$ (371.84)	72	3-[2-(2-chlorophenyl)-4-oxo-3-phenylazetidin-1-yl]-2-thioxoimidazolidin-4-one
3b	Decompose Solid ,orange	Benzene $C_{18}H_{14}N_4O_4S$ (382.39)	77	3-[2-(3-nitrophenyl)-4-oxo-3-phenylazetidin-1-yl]-2-thioxoimidazolidin-4-one
4a	240 Solid ,orange	Ethanol:H_2o(1:1) $C_{17}H_{11}BrClN_3OS$ (420.71)	65	(5*Z*)-5-(4-bromobenzylidene)-3-[(2-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one
4b	230 Solid ,yellow	Ethanol $C_{17}H_{11}BrN_4O_3S$ (431.26)	72	(5*Z*)-5-(4-bromobenzylidene)-3-[(3-nitrobenzylidene)amino]-2-thioxoimidazolidin-4-one
5b	161 Solid ,orange	Ethanol:H_2o(1:1) $C_{11}H_{10}N_4O_3S$ (278.28)	52	2-(methylsulfanyl)-3-[(3-nitrobenzylidene)amino]-3,5-dihydro-4*H*-imidazol-4-one
5c	169 Solid ,orange	Ethanol $C_{12}H_{12}ClN_3OS$ (281.76)	62	3-{[1-(4-chlorophenyl)ethylidene]amino}-2-(methylsulfanyl)-3,5-dihydro-4*H*-imidazol-4-one
5d	138 Solid ,orange	Acetone $C_{13}H_{15}N_3O_2S$ (277.34)	70	3-{[1-(4-methoxyphenyl)ethylidene]amino}-2-(methylsulfanyl)-3,5-dihydro-4*H*-imidazol-4-one
6b	Oil,Brown	$C_{10}H_{10}N_6O_3$ (262.22)	63	2-hydrazinyl-3-[(3-nitrobenzylidene)amino]-3,5-dihydro-4*H*-imidazol-4-one
6c	171 Solid ,Pink	Ethanol $C_{11}H_{12}ClN_5O$ (265.69)	81	3-{[1-(4-chlorophenyl)ethylidene]amino}-2-hydrazinyl-3,5-dihydro-4*H*-imidazol-4-one
6d	165 Solid ,White	Ethanol $C_{12}H_{15}N_5O_2$ (261.27)	78	2-hydrazinyl-3-{[1-(4-methoxyphenyl)ethylidene]amino}-3,5-dihydro-4*H*-imidazol-4-one
7b	167 Solid ,orange	Ethanol $C_{12}H_{10}N_6O_3$ (286.24)	74	3-methyl-7-[(3-nitrobenzylidene)amino]-5*H*-imidazo[2,1-*c*][1,2,4]triazol-6(7*H*)-one
7c	160 Solid ,Brown	Ethanol $C_{13}H_{12}ClN_5O$ (289.72)	50	7-{[1-(4-chlorophenyl)ethylidene]amino}-3-methyl-5*H*-imidazo[2,1-*c*][1,2,4]triazol-6(7*H*)-one
7d	129 Solid ,orange	Ethanol $C_{14}H_{15}N_5O_2$ (285.30)	62	7-{[1-(4-methoxyphenyl)ethylidene]amino}-3-methyl-5*H*-imidazo[2,1-*c*][1,2,4]triazol-6(7*H*)-one

Table (2): Spectral data of the new synthesized compounds

Comp.No.	Spectral data	
	IR (ν, cm^{-1})	UV (EtOH)& ^{1}H NMR (DMSO-d)& MS(m/z , 100)
1a	(C = N) 1608 (NH_2) 3414-3244 (C-Cl) 750	UV (EtOH)(Wavelength(nm)/Abs): 320/1.689, 220/0.405
1b	(C = N) 1604 (NH_2) 3392-3232 (NO_2) 1523-1346	UV (EtOH)(Wavelength(nm)/Abs): 315/0.737, 222/0.410
1c	(C = N) 1585 (NH_2) 3400-3240 (C-Cl) 765	UV (EtOH)(Wavelength(nm)/Abs):320/0.523 , 245/1.216
1d	(C = N) 1604 (NH_2) 3400-3251 (C-O) 1245	UV (EtOH)(Wavelength(nm)/Abs):298/0.388 , 248/0.712
2a	$(C = O)_{amid}$ 1720 (C=C) 1637 (C=S) 1327	UV (EtOH)(Wavelength(nm)/Abs):315/3.296, 222/0.403
2b	$(C = O)_{amid}$ 1706 (C=C) 1639 (NO_2) 1517-1348	UV (EtOH)(Wavelength(nm)/Abs):320/2.643, 221/0.405
2c	$(C = O)_{amid}$ 1712 (C=C) 1610 (C=S) 1392	UV (EtOH)(Wavelength(nm)/Abs):324/0.425 , 223/1.226
2d	$(C = O)_{amid}$ 1720 (C=C) 1622,1602 (C=S) 1336	UV (EtOH)(Wavelength(nm)/Abs):342/0.013 , 242/0.394
3a	$(C = O)_{lactam}$ 1761 $(C = O)_{amid}$ 1728 (C=C) 1654,1602	UV (EtOH)(Wavelength(nm)/Abs):344/0.038 , 224/0.408 ^{1}HNMR (DMSO-d6) (δ) ,6.87-7.46ppm (m, 9H, ArH), 4.31ppm (S,1H,$CH)_{amid}$, 7.00ppm (S,1H, NH) $_{amid}$, 4.46ppm (d,1H,$CH)_{Lactam}$, 5.61ppm (d,1H, CH-N) $_{Lactam}$
3b	$(C = O)_{lactam}$ 1761 $(C = O)_{amid}$ 1712 (C=C) 1654,1585 (NO_2) 1529-1346	UV (EtOH)(Wavelength(nm)/Abs):364/0.040 , 224/0.224 ^{1}HNMR (DMSO-d6) (δ) ,7.44-8.54ppm (m, 9H, ArH), 4.12ppm (S,1H,$CH)_{amid}$, 7.12ppm (S,1H, NH) $_{amid}$, 4.36ppm (d,1H,$CH)_{Lactam}$, 5.60ppm (d,1H, CH-N) $_{Lactam}$
4a	$(C = O)_{amid}$ 1710 (C=C) 1649,1606 (C-Br) 810	UV (EtOH)(Wavelength(nm)/Abs):346/0.020 , 285/0.316 ^{1}HNMR (DMSO-d6) (δ) ,6.37-7.50ppm (m, 8H, ArH), 8.49ppm (S,1H,CH=N), 6.50ppm (S,1H, CH=CH), 2.10ppm (S,1H, NH) $_{amid}$
4b	$(C = O)_{amid}$ 1701 (C=C) 1639,1587 (NO_2) 1527-1348	UV (EtOH)(Wavelength(nm)/Abs):355/0.049 , 290/0.214 ^{1}HNMR (DMSO-d6) (δ) ,7.54-8.39ppm (m, 8H, ArH), 8.79ppm (S,1H,CH=N), 6.96ppm (S,1H, CH=CH), 2.25ppm (S,1H, NH) $_{amid}$
5b	$(C = O)_{amid}$ 1710 (C=C) 1579,1554 (C=N) 1622	UV (EtOH)(Wavelength(nm)/Abs):335/0.004 , 236/0.949 MS (*m/z*) %: 278 (M^-, 98.50)
5c	$(C = O)_{amid}$ 1718 (C=C) 1573,1487 (C=N) 1610	UV (EtOH)(Wavelength(nm)/Abs):303/0.723 , 238/1.237 MS (*m/z*) %: 281 (M^-, 97.50)

5d	$(C = O)_{amid}$ 1716 (C=C) 1597,1556 (C=N) 1674	UV (EtOH)(Wavelength(nm)/Abs):298/0.853 , 241/1.401 MS (*m/z*) %: 277 (M^+, 100)
6b	(C = O) 1712 (NH_2) 3493-3250 (C=N) 1618	UV (EtOH)(Wavelength(nm)/Abs):350/0.015 , 272/0.032 MS (*m/z*) %: 266 (M^-, 95.50)
6c	(C = O) 1718 (NH_2) 3404-3281 (C=N) 1612	UV (EtOH)(Wavelength(nm)/Abs):278/0.272 , 237/0.526 MS (*m/z*) %: 265 (M^-, 96.80)
6d	(C = O) 1714 (NH_2) 3412-3352 (C=N) 1602	UV (EtOH)(Wavelength(nm)/Abs):288/0.646 , 241/1.252 MS (*m/z*) %: 262 (M^+, 19.90)
7b	$(C = O)_{amid}$ 1720 (C=C) 1595,1556 (C=N) 1612	UV (EtOH)(Wavelength(nm)/Abs):336/0.008 , 276/0.016 MS (*m/z*) %: 286 (M^-, 97.60)
7c	$(C = O)_{amid}$ 1714 (C=C) 1597,1556 (C=N) 1684	UV (EtOH)(Wavelength(nm)/Abs):334/0.004 , 238/0.468 MS (*m/z*) %: 289 (M^-, 98.60)
7d	$(C = O)_{amid}$ 1718 (C=C) 1577,1510 (C=N) 1602	UV (EtOH)(Wavelength(nm)/Abs):311/0.156 , 242/0.347 MS (*m/z*) %: 285(M^+, 19.90)

Table (3): Biologicalactivities of newly synthesized compounds

Comp. NO.	Zone of Inhibition (mm)									
	Gram-negative				Gram-positive				Fungi	
	E.coli		Klebsiella P.		Steroptococcus SP.		Staphylococcus A.		Candida albicans	
	*1000	*500	1000	500	1000	500	1000	500	1000	500
1a	14	0	10	9	0	0	4	7	0	0
1b	19	11	19	19	12	20	5	0	0	0
1c	13	8	0	0	10	5	10	0	12	0
1d	10	12	18	15	12	10	9	8	0	0
2a	13	16	5	0	10	14	7	11	7	9
2b	12	6	0	0	17	22	10	8	0	0
2c	12	9	0	0	9	15	7	3	0	0
2d	14	12	19	21	10	12	0	0	0	0
3a	10	10	0	0	17	15	13	14	15	14
3b	11	12	0	0	8	12	13	9	0	0
4a	0	0	0	0	18	10	9	5	0	0
4b	12	10	0	0	10	6	9	2	0	0
5b	10	11	0	0	10	12	8	10	0	0
5c	11	9	0	6	12	4	7	3	0	10
5d	2	0	0	0	0	3	5	0	0	0
6b	16	10	0	5	9	5	0	4	0	0
6c	11	7	3	0	12	10	8	5	0	0
6d	3	0	0	0	5	0	0	4	0	0
7b	18	15	0	0	15	12	5	0	0	0
7c	4	9	0	0	10	8	2	5	0	0
7d	8	3	0	0	12	5	3	0	0	0
Flagyl	10	0	0	0	10	19	0	0	0	0

E.coli = Escherichia coli , Klebsiella P.= klebsiella pneumonia , Steroptococcus SP.=streptococcus species ,Staphylococcus A.= staphylococcus aureus
The sensitivity of microorganisms to the tested compounds is identified in the following manner:
Highly sensitive = Inhibition zone 3–22 mm
Not sensitive = Inhibition zone: 0 mm
*Concentration= 1000,500 ppm

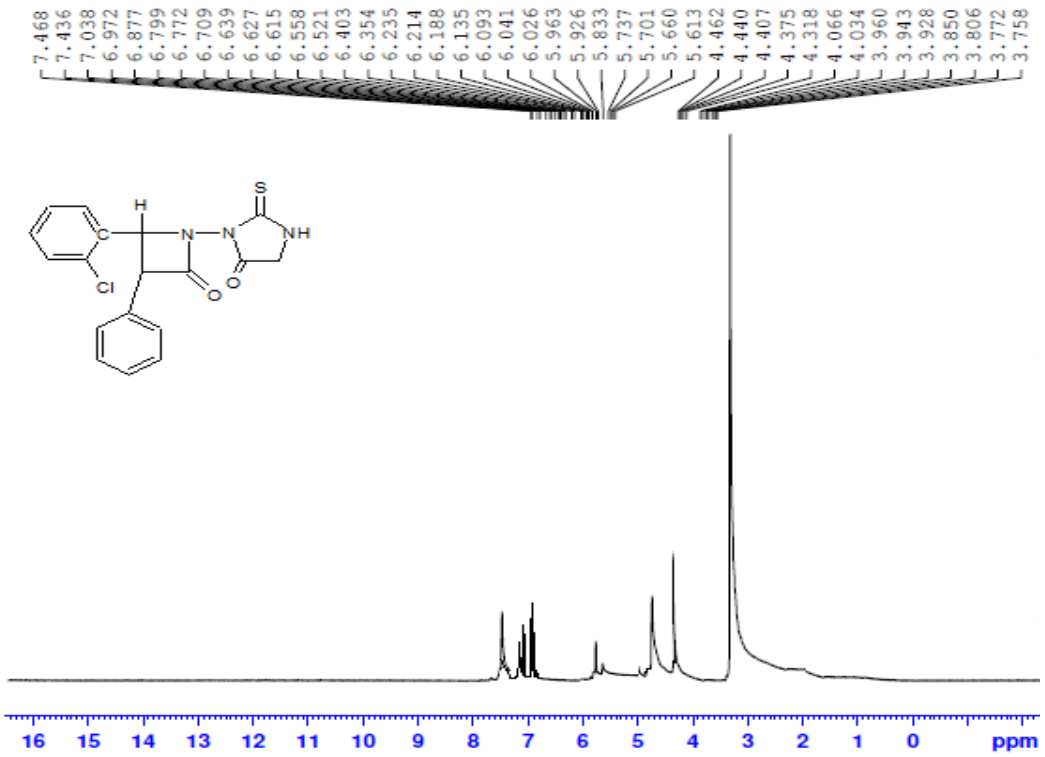

Figure (1): Proton nuclear magnetic resonance spectroscopy of 3a .

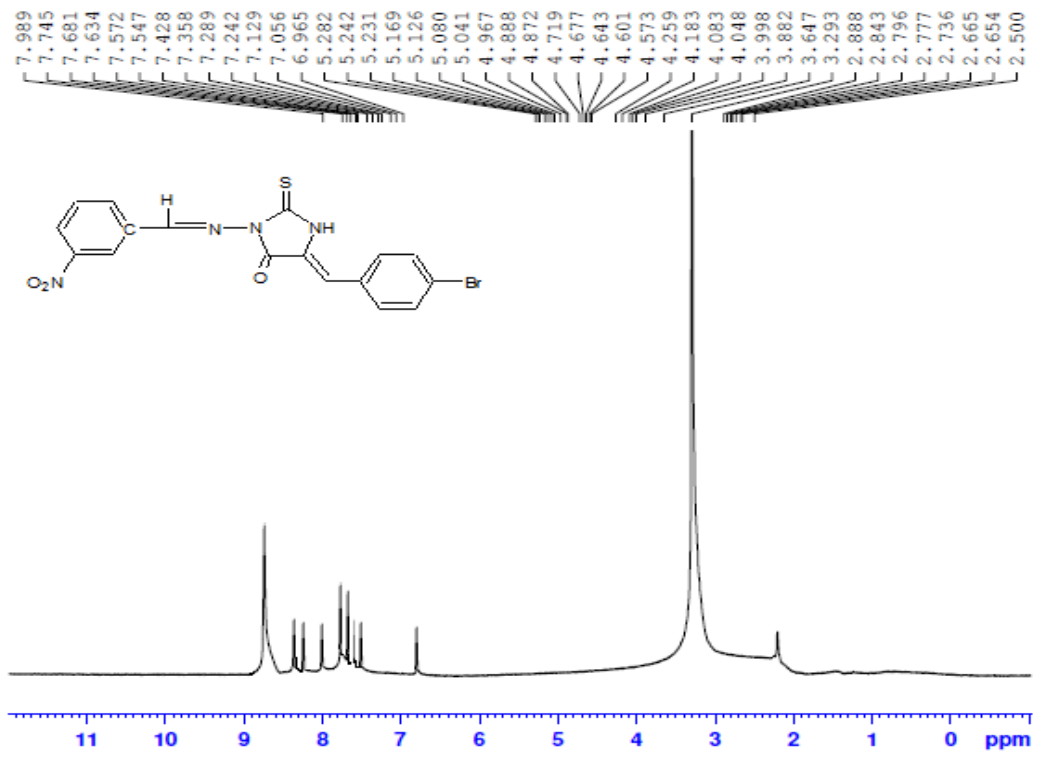

Figure (2): Proton nuclear magnetic resonance spectroscopy of 4b .

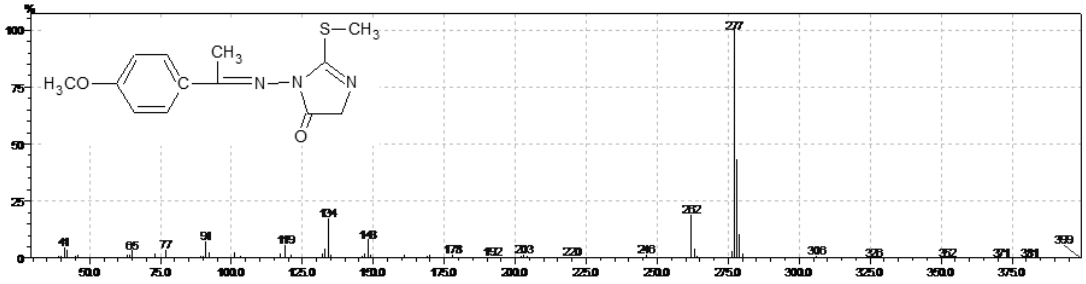

Figure (3): Mass spectra of 5d.

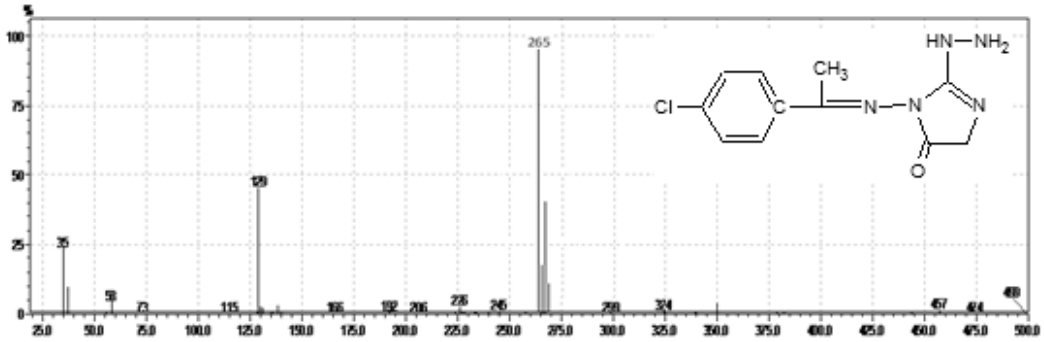

Figure (4): Mass spectra of 6c .

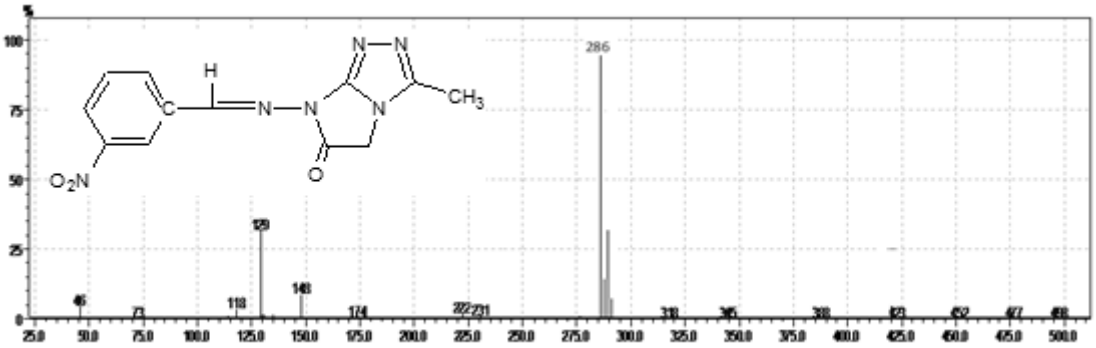

Figure (5): Mass spectra of 7b.