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ANTIMICROBIAL ACTIVITY AND MASS SPECTRA INVESTIGATION OF PREPARED NITROGEN HETEROCYCLES

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Abstract- The compounds (E)-5-(4-methoxyphenyl)-2-(2-(1-(4-methoxyphenyl)ethylidene)hydraz-ineyl)thiazole (2) and 3-((1-(4-methoxyphenyl)ethylidene)amino)-2-thioxoimid-azolidin-4-one (3) are prepared from cyclization of 2-(1-(4-methoxyphenyl)ethylid-ene) hydrazinecarbothioamide (1) with 2-bromo-1-(4-methoxyphenyl)ethanone and/or with ethyl chloroacetate in presence of fused sodium acetate. Treatment of (2) and (3) with acetic anhydride yielded the corresponding (E)-N'-(1-(4-methoxyphenyl)ethylidene)-N-(5-(4-methoxyphenyl)thiazol-2-yl)acetohydrazide (4) and 1-acetyl-3-((1-(4-methoxy-phenyl)ethylidene)amino)-2-thioxoimidazolidin-4-one (5), respectively. But when 4 reacts with aromatic aldehydes gives 5-(arylidene)-3-((1-(4-methoxyphenyl)ethylidene)amino)-2-thioxoimidazolidin -4-one ($6_{a,b}$), then the later react with acetic anhydride to give 1-acetyl-5-(arylidene)-3-((1-(4-methoxyphenyl)ethylid-ene)amino)-2-thioxoimidazolidin-4-one ($7_{a,b}$). The electron impact mass spectra of the above series of compounds have also been recorded and their fragmentation pattern is discussed. The prepared compounds also exhibited antimicrobial activity.

Keywords- Thiosemicarbazones, Thiazole, Thioxoimidazolidinone, Antimicrobial activity.

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Introduction

Hydantoins [imidazolidin-2,4–dione and 2-thioxoimidazolin-4-one] are belongs to heterocyclic compound, which has a wide range of biological and pharmacological properties such as antimicrobial activity (antifungal, antibacterial) [1], antitumor², antiinflammatry [2], anti HIV [3], anti-hypertensive [4], hydantoin exhibits diverse biological activities, such as anticonvulsant [5], antifungal activities [6], antithyroidal [7], antiviral [8], anti HIV [9], tuber culosis [10], anti arrhythmic [11] and anti convulsant [12]. Many imidazolidinones and thiazole derivatives are found possessing pharmacological activities like anaesthetic activity [14] and antimicrobial activity [15-20].

Keeping these in view, 5-(4-methoxyphenyl)-2-substituted-2-hydrazinylthiazole (3) and 3-substituted-2-thioxoimidazolidin-4-one (4) were prepared from the reaction of aromatic ketones and thiosemicarbazide to give aryl thiosemicarbazone followed by cyclization with ethyl chloroacetate or 2-bromo-1-(4-methoxyphenyl) ethanone in the presence of fused sodium acetate [13]. The chemical behavior of (3) and (4) towards acetic anhydride and aromatic aldehydes is described.

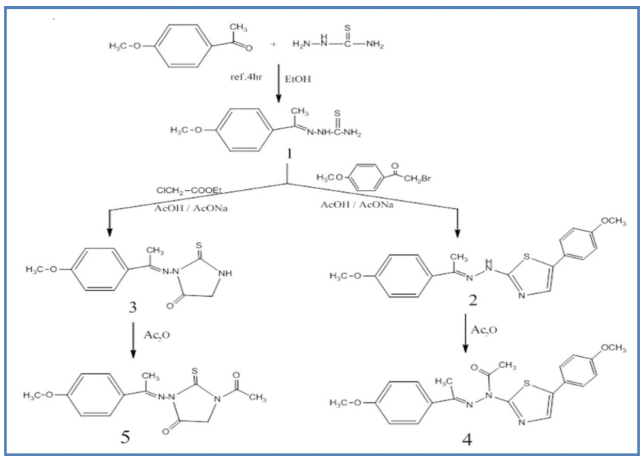
The electron impact (EI) ionization mass spectral fragmentations of some synthesized compounds were described.

Result and Discussion

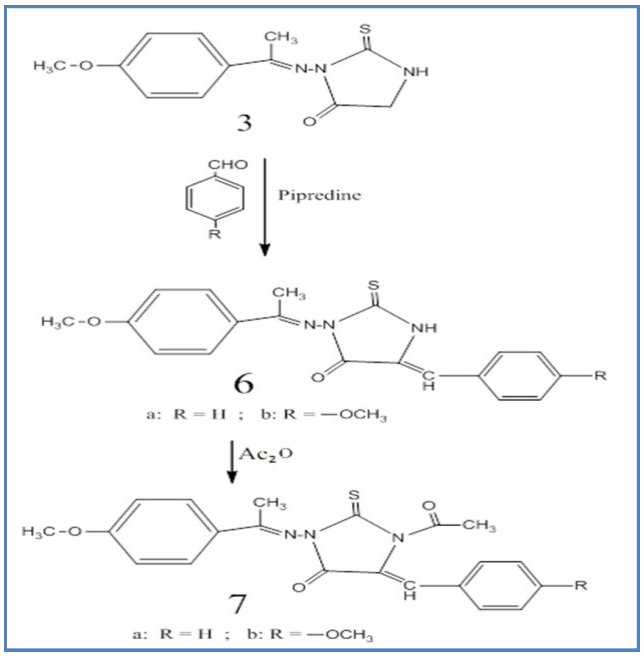
Chemistry

The reaction of 1-(4-methoxyphenyl)ethanone with thiosemicarbazide in ethanol under reflux gave the corresponding 2-(1-(4-methoxyphenyl) ethylidene)hydrazinecarb-othioamide (1). Treatment of compound (1) with 2-bromo-1-(4-methoxyphenyl) ethanone and/or with ethyl chloroacetate in presence of fused sodium acetate in ethanol under reflux yielded the corresponding (E)-5-(4-methoxy phenyl)-2-(2-(1-(4-methoxyphenyl) ethylidene)hydrazinyl) thiazole (2) and 3-((1-(4-methoxyphenyl)-ethylidene)amino)-2-thioxoimidazolidin-4-one (3) respectively. Acylation of compounds (2) and (3) with acetic anhydride under reflux led to the formation of (E)-N'-(1-(4-methoxyphenyl)ethylidene)-N-(5-(4-methoxyphenyl) thiazol-2-yl)acetohydrazide (4) and 1-acetyl-3-((1-(4-methoxy-phenyl)ethylidene)amino)-2-thioxoimidazolidin-4-one (5), respectively [Scheme-1].

Condensation of compound (3) with aromatic aldehydes (such as benzaldehyde and 4-methoxybenzaldehyde) in presence of piperdine under fusion gave 5-(arylidene)-3-((1-(4-methoxyphenyl) ethylidene)amino)-2-thioxoimidazolidin-4-one ($6_{a,b}$) that acylated with acetic anhydride under reflux led to the formation of 1-acetyl-5 -(arylidene)-3-((1-(4-methoxy phenyl)ethylidene) amino)-2-thioxoimidazolidin-4-one ($7_{a,b}$), respectively [Scheme-2].



Scheme 1-



Scheme 2-

Mass Spectrometry

All the spectra of synthesized compounds show relatively small molecular ions and peaks typical of a cleavage and rearrangement process type fragmentation [21-23]. The molecular ions of 1; [Fig-1], 3; [Fig-2] and [Fig-5] [Fig-3] fragmented further and involved pathway as illustrated in [Scheme-3], Where the molecular ion of 5 at m/z 305 fragmented to give the molecular ion of 3 at m/z 263 by losing CH_2CO that broken and lose C_2O to give the molecular ion of 1 at m/z 223 which fragmented to give the fragment of m/z 208 by losing NH. The fragment of m/z 208, which broken to give the fragment of m/z 163 by losing CHS radical. The fragment of m/z 163 was broken to give an ion of m/z 148 (the base peak of 1), which further broke to give an ion at m/z 134. It further underwent loss of H to give the fragment at m/z 133. The fragment of m/z 133 was broken in two pathway, in the first, it lose CH_2 gave the fragment of m/z 119 that was loss CO to give the fragment of m/z 91. In the second pathway, the fragment of m/z 133 broken to give an ion of m/z 107 that loss CH_2O to give an ion of m/z 77. The later loss CH_2=CH to form the fragment of m/z 50.

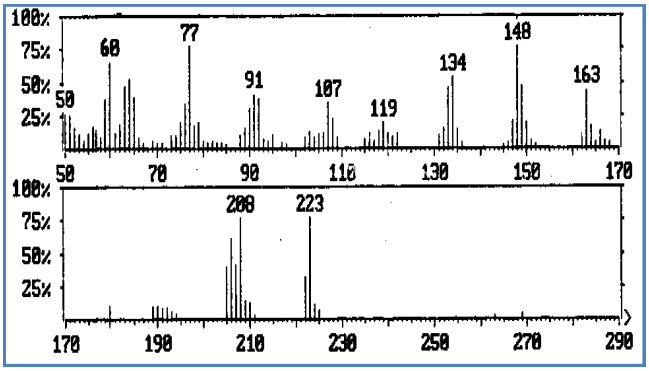


Fig. 1- 70 eV mass spectrum of compound 1

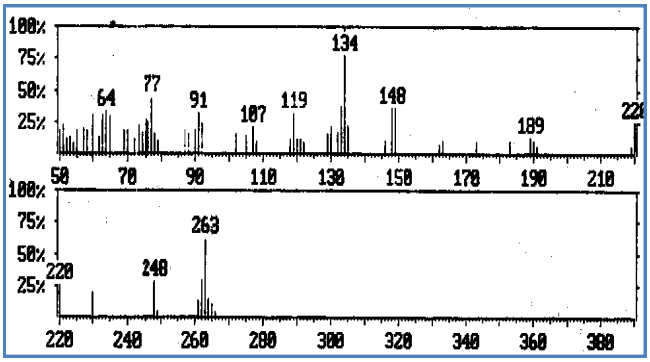


Fig. 2- 70 eV mass spectrum of compound 3

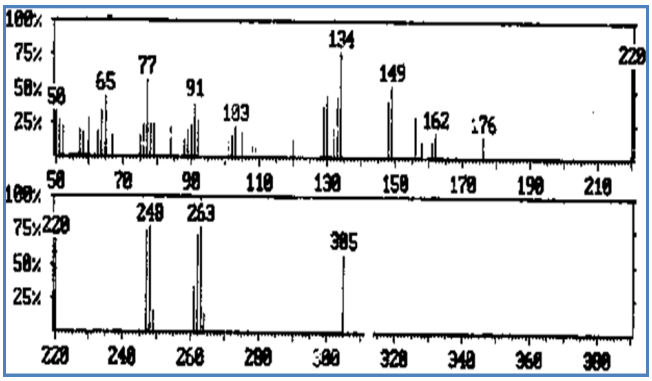


Fig. 3- 70 eV mass spectrum of compound 5

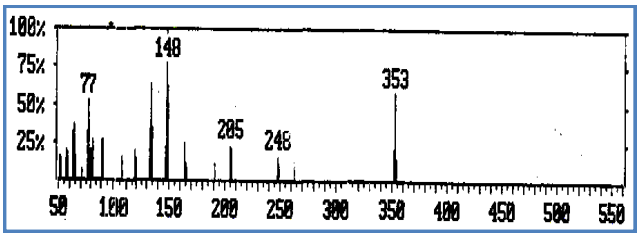


Fig. 4 -70 eV mass spectrum of compound 2

The molecular ion of compounds 4 (m/z 395) and 2 (m/z 353), [Fig-4] underwent fragmentations to produce peaks at m/z 205 and at m/z 248, the later can be loss ph-O-CH_2, then broken to give the fragment of m/z at 164 that further underwent loss of NH_2, CH_2, and H groups to give peaks at m/z 148 (the base peak), 134, and 133 respectively. The fragment of m/z 133 was broken in two pathways, in the first, it lose CH_2 gave the fragment of m/z 119 that was loss CO to give the fragment of m/z 91. In the second pathway, the

fragment of m/z 133 broken to give an ion of m/z 107 that loss CH_2O to give an ion of m/z 77. The later loss acetylene molecule to form the stable ion of m/z 51; [Scheme-4].

The molecular ion of compound 7a; (m/z 393), [Fig-6] fragmented by lose CH_2CO to give the molecular ion of 6a; (m/z 351) [Fig-5] which fragmented to give the molecular ion 3 (m/z 263) [Fig-2] underwent fragmentations to produce peaks at m/z 248,at m/z 263 and at m/z 163 the later further underwent loss of NH, CH_2, and H groups to give peaks at m/z 148, 134(the base peak), and 133 respectively. The fragment of m/z 133 was broken in two pathways as in [Scheme-5].

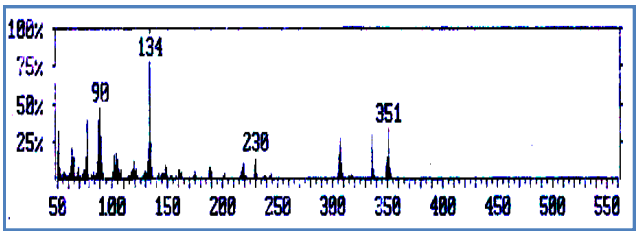


Fig. 5- 70 eV mass spectrum of compound 6a

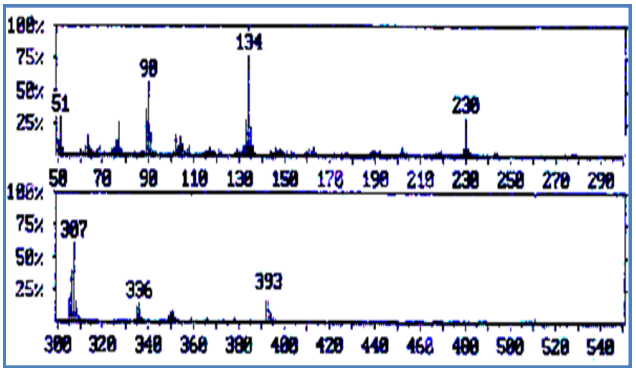
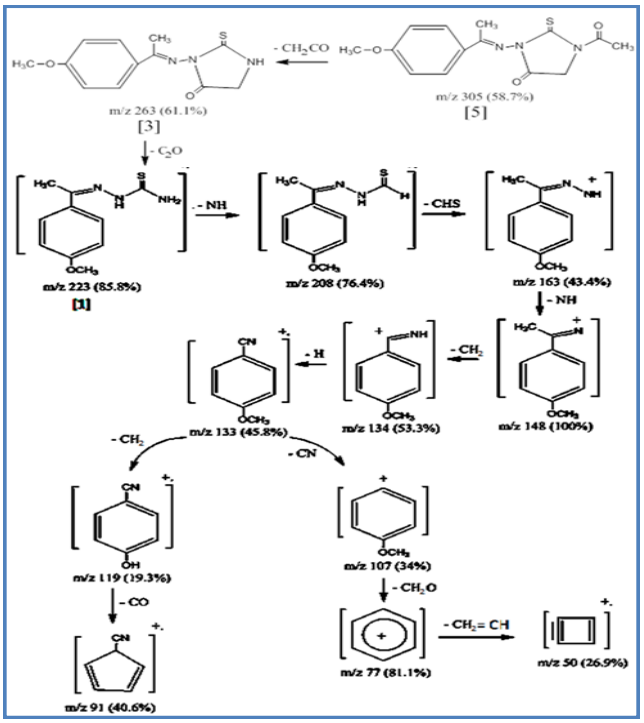
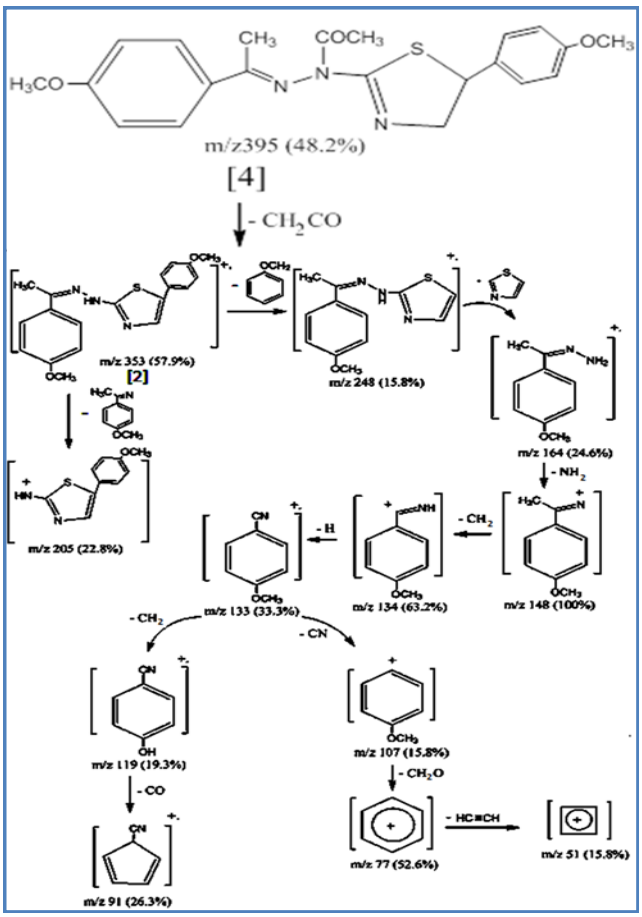


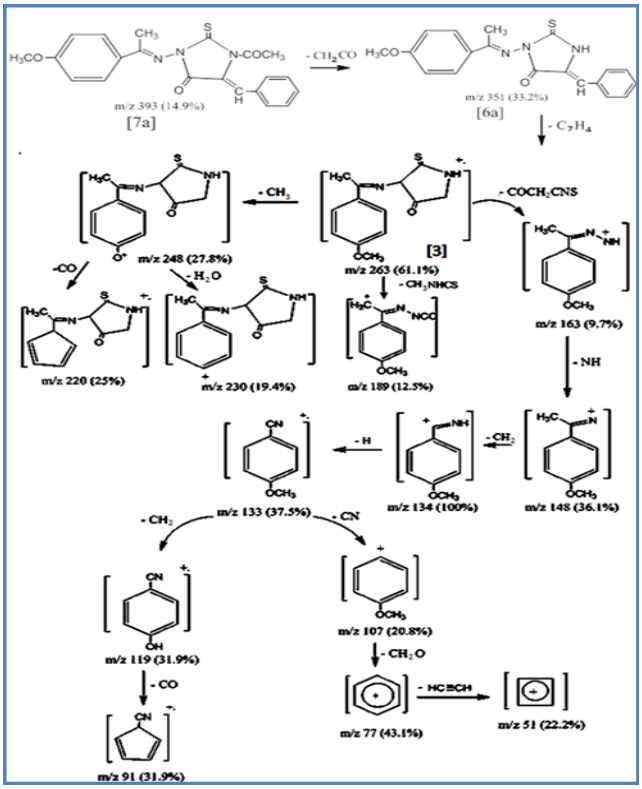
Fig. 6- 70 eV mass spectrum of compound 7a



Scheme 3- Main fragmentation pathway of compounds 1,3 and 5.



Scheme 4- Main fragmentation pathway of compounds 2 and 4.



Scheme 5- Main fragmentation pathway of compounds 3, 6a & 7a

Experimental Section

Melting points were determined in Capillaries with a Thomas Unimelt apparatus uncorrected. NMR spectra were recorded on a general electric QE300 instrument and chemical shifts are given with respect to TMS. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and a Biorad FTS7 (KBr). Mass spectra were obtained on a Jeol JMSD-300 spectrometer operating at 70 eV. Microanalyses were conducted using an elemental analyzer 1106.

2-(1-(4-methoxyphenyl)ethylidene)hydrazinecarbothioamide (1)

A mixture of 1-(4-methoxyphenyl)ethanone (0.01 mol), thiosemicarbazide (0.01 mol) in ethanol (20 ml) was heated under reflux for 4 hr, and then cooled. The solid formed was filtered off, dried and purified by recrystallization with ethanol to give 1 as colorless crystals, yield 85%, m.p: 155°C; IR (KBR): 3456, 3176(NH_2), 3240 (NH), 1630(C=N), 1605, 1592(C=C), 1422(C=S), 1138, 1086(C-O) cm^{-1}. ^{1}H-NMR (DMSO-d6): δ2.31(s, 3H, CH_3), δ3.78(s, 3H, CH_3-O),7(s, 1H, NH), 7.05-7.22(d, 2H,Ar-H), 7.91-8.08(d, 2H, Ar-H), 9.12(s, 2H, NH_2) ppm. MS (m/z,%): 223(M^+, 85.8), 208(76.4), 163 (43.4), 148(100), 134(53.3), 133(45.8), 119(19.3), 107(34), 91 (40.6), 77(81.1), 50(26.9). Anal. Calcd. For $C_{10}H_{13}N_3OS$: C, 53.81; H, 5.83; N, 18.83; O, 7.17; S, 14.35. Found: C, 53.46; H, 5.39; N, 18.81; S, 14.27.

5-(4-methoxy phenyl)-2-(2-(1-(4-methoxyphenyl) ethylidene) hydrazine-yl)thiazole (2)

3-(1-(4-methoxyphenyl)ethylideneamino)-2-thioxoimidazolidin-4-one (3)

A mixture of 1 (0.01 mol) , 2-bromo-1-(4-methoxyphenyl) ethanone and/or ethylchloroacetate (0.01 mol) in presence of sodium acetate (0.01 mol) and acetic acid was heated under reflux for 2 hr. the reaction mixture was cooled and acidified with dilute acetic acid . The crude product was filtered off, washed with water, dried and purified by ethanol to give compounds 2 and 3.

Compound 2 as pale yellow crystals yield 82 %,m.p: 170°C ; IR (KBr): 3296(NH), 1630(C=N), 1605, 1592(C=C), 1150(C-S), 1138, 1086(C-O)cm^{-1}.

^{1}H-NMR (DMSO-d6): δ2.19(s, 3H, CH_3), δ3.55(s, 6H, CH_3-O),8.11 (s, 1H, NH), 7.11-7.43(d, 4H,Ar-H), 7.71-7.89(d, 4H, Ar-H) ppm. MS (m/z, %): 353(M^+, 57.9), 248(15.8), 205(22.8), 164(24.6), 148 (100), 134(63.2), 133(33.3), 119(19.3), 107(15.8), 91(26.3), 77 (52.6), 51(15.8). Anal.Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.59; H, 5.38; N, 11.89; S, 9.06. Found: C, 64.22; H, 5.18; N, 11.64; S, 8.92.

Compound 3 as pale yellow crystals yield 75%, m.p: 178°C; IR (KBr): 3229(NH), 1685(C=O), 1630(C=N), 1585(C=C), 1448(C=S), 1120, 1075(C-O) cm^{-1}. ^{1}H-NMR (DMSO-d6): δ2.01(s, 3H, CH_3), δ3.65(s, 3H, CH_3), 4.42(s, 2H, $NHCH_2CO$), 7.09-7.27(d, 2H, Ar-H), 7.51-7.78 (d, 2H, Ar-H), 8.20(s, 1H, NH) ppm. MS (m/z,%): 263 (M+, 61.1), 248(27.8), 230(19.4), 220(25), 189(12.5), 163(9.7), 148 (36.1), 134(100), 133(37.5), 119(31.9), 107(20.8), 91(31.9), 77 (43.1), 51(22.2) . Anal.Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.75; H, 4.94; N, 15.96; S, 12.16. Found: C, 54.55; H, 4.63; N, 15.74; S, 11.88.

N'-(1-(4-methoxyphenyl)ethylidene)-N-(5-(4-methoxyphenyl) thiazol-2-yl)acetohydrazide [4]

1-acetyl-3-((1-(4-methoxyphenyl)ethylidene)amino)-2-thioxoimidazolid-in-4-one [5]

A solution of 2 and/or 3 (0.01 mol), in acetic anhydride (25 ml) was heated under reflux for 4 hrs, then cooled and poured onto ice-water. The resulting product was filtered off, washed with water, dried and purified by benzene to give 4 and/or 5 respectively.

Compound 4, as red crystals, yield 63%, m.p: 80°C; IR (KBr): 1682 (C=O), 1630(C=N), 1602(C=C), 1139(C-S), 1120, 1075(C-O) cm^{-1}. ^{1}NMR (DMSO-d6): δ 1.98(s, 3H, $COCH_3$), δ 2.38(s, 3H, CH_3-C=N), δ 3.74(s, 6H, CH_3-O), 7.05-7.21(d, 4H, Ar-H), 7.3(s, 1H, N-CH=), 7.5-7.88(d, 4H, Ar-H) ppm. Anal. Calcd. for $C_{21}H_{21}N_3O_3S$: C, 63.79; H, 5.31; N, 10.63; S, 8.10. Found: C, 63.51; H, 4.97; N, 10.38; S, 7.89.

Compound 5, as pale yellow crystals, yield 70%, m.p: 140°C; IR (KBr): 1675(C=O), 1631(C=N), 1603(C=C), 1412(C=S), 1108, 1028 (C-O) cm^{-1}. ^{1}NMR (DMSO-d6): δ 2.02(s, 3H, $COCH_3$), δ 2.41(s, 3H, CH_3-C=N), δ 3.82(s, 3H, CH_3-O), 4.35(s, 2H, N-CH_2-CO), 7.13-7.28 (d, 2H, Ar-H), 7.71-7.95(d, 2H, Ar-H) ppm. MS(m/z,%): 305(M^+, 58.7), 263(100), 248(91.3), 220(67.4), 176(15.2), 162(17.4), 149 (52.2), 134(80), 120(13), 91(39.1), 77(56.5), 50(32.6). Anal. Calcd. For $C_{14}H_{15}N_3O_3S$: C, 55.08; H, 4.91; N, 13.77; S, 10.49. Found: C, 54.89; H, 4.55; N, 13.54; S, 10.21.

5-(arylidene)-3-((1-(4-methoxyphenyl)ethylidene)amino)-2-thioxoimida-zolidin-4-one ($6_{a,b}$)

A mixture of 3; (0.01 mol) and aromatic aldehydes (such as benzaldehyde and 4-methoxybenzaldehyde); (0.01 mol) in presence of piperdine (2ml) was fused on a hot plate at 120-125°C for 1hr. the reaction mixture was cooled and acidified with dilute hydrochloric acid (2 %). The crude product was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 6.

5-(benzylidene)-3-((1-(4-methoxyphenyl)ethylidene)amino)-2-thioxoimida-zolidin-4-one (6_a) as yellow crystals, yield 68%, m.p: 230°C. IR (KBr): 3239(NH), 1704(C=O), 1620(C=N), 1605(C=C), 1432(C=S), 1120, 1033(C-O) cm^{-1}. ^{1}HNMR (DMSO-d6): δ 2.36(s, 3H, CH_3-C=N), δ 3.65(s, 3H, CH_3-O), 6.28(s, 1H, =CH-), 7.10-7.23 (d, 2H, Ar_1-H),7.5-7.73(m, 5H, Ar_2-H), 7.85-7.99(d, 2H, Ar_1-H),8.12 (s, 1H, NH) ppm. MS (m/z, %): 351(M^+, 33.2), 336(29.3), 306(15.5), 230(12.9), 134(100), 90(46.7), 77(38), 51(31.1). Anal. Calcd. For $C_{19}H_{17}N_3O_2S$: C, 64.95; H, 4.84; N, 11.96; S, 9.11. Found: C, 64.87; H, 4.52; N, 11.82; S, 8.79.

5-(4-methoxybenzylidene)-3-((1-(4-methoxyphenyl)ethylidene) amino)-2-thioxoimidazoli-din-4-one (6_b) as pale yellow crystals, yield 75 %, m.p: 210°C. IR (KBr): 3221(NH), 1700(C=O), 1629 (C=N), 1603, 1590(C=C), 1408(C=S), 1185, 1067(C-O) cm^{-1}. ^{1}HNMR (DMSO-d6): δ 2.25(s, 3H, CH_3-C=N), δ 3.72(s, 6H, CH_3-O), 6.44(s, 1H, =CH-), 7.08-7.20(d, 2H, Ar_1-H),7.3-7.41(d, 2H, Ar_2-H), 7.71-7.82(d, 2H, Ar_1-H), 7.87-7.93(d, 2H, Ar_2-H), 8.36(s, 1H, NH) ppm. MS (m/z, %): 381(M^+,51.3), 366(48.7), 274(9.6), 248 (8.7), 191(17.4), 164(100), 149(67.8), 134(46.1), 121(33), 91 (37.4),77(45.2), 51(27.8). Anal Calcd. For $C_{20}H_{19}N_3O_3S$: C, 62.99; H, 4.98; N, 11.02; S, 8.39. Found: C, 62.87; H, 4.63; N, 10.88; S, 8.11.

1-acetyl-5-(arylidene)-3-((1-(4-methoxy phenyl)ethylidene) amino)-2-thioxoimida-zolidin-4-one ($7_{a,b}$)

A solution of ($6_{a,b}$) (0.01 mol), in acetic anhydride (25 ml) was heated under reflux for 4 hrs, then cooled and poured onto ice-water. The resulting product was filtered off, washed with water, dried and purified by benzene to give 7.

1-acetyl-5-(benzylidene)-3-((1-(4-methoxy phenyl)ethylidene) amino)-2-thioxoimid-azolidin-4-one (7_a) as yellow crystals, yield 65%, m.p: 270°C. IR (KBr): 1728(C=O), 1611(C=N), 1598(C=C), 1473(C=S), 1110, 1025(C-O) cm^{-1}. ^{1}HNMR (DMSO-d6): δ2.11(s, 3H, CH_3-CO), 2.45(s, 3H, CH_3-C=N), δ 3.88(s, 3H, CH_3-O), 6.48(s, 1H, =CH-), 7.15-7.29(d, 2H, Ar_1-H),7.6-7.83(m, 5H, Ar_2-H), 7.89-8.03(d, 2H, Ar_1-H) ppm. MS (m/z, %): 393(M^+, 4.9), 350(6.5), 336 (13.6), 307(60.7), 230(29.3), 134(100), 121(4.4), 90(56.1), 77 (26.5), 51(25). Anal. Calcd. For $C_{21}H_{19}N_3O_3S$: C, 64.12; H, 4.83; N, 10.68; S, 8.14. Found: C, 64.08; H, 4.55; N, 10.31; S, 7.93.

1-acetyl-5-(4-mehoxy benzylidene)-3-((1-(4-methoxy phenyl)ethylidene)amino)-2-thiox-oimidazolidin-4-one (7_b) as pale yellow crystals, yield 63 %, m.p: 230°C. IR (KBr): 1718(C=O), 1648(C=N), 1612, 1583(C=C), 1419(C=S), 1194, 1081(C-O) cm^{-1}. ^{1}HNMR (DMSO-d6): δ2.22(s, 3H, CH_3-CO), 2.52(s, 3H, CH_3-C=N), δ 3.79 (s, 6H, CH_3-O), 6.42(s, 1H, =CH-), 7.02-7.23(d, 2H, Ar_1-H),7.35-7.44(d, 2H, Ar_2-H), 7.64-7.79(d, 2H, Ar_1-H), 7.83-7.97(d, 2H, Ar_2-H) ppm. Anal Calcd. For $C_{20}H_{19}N_3O_3S$: C, 62.41; H, 4.96; N, 9.92; S, 7.56. Found: C, 62.11; H, 4.73; N, 9.58; S, 7.12

Antimicrobial Activity

***In vitro* Antibacterial Screening**

Applying the agar plate diffusion technique [24, 25] all of the compounds were screened in Vitro for antibacterial activity against *Bacillus subtilis, Streptococcus penumonia, Staphylococcus aureas, E.coli* and *Pseudomonas solanarium*. The compounds were tested at (10mg, 50mg and 100mg) concentrations and the activity was determined by measuring the zone of inhibition. The screening results given in [Table-1] where, the activities of compounds were compared with *streptomycin* as antibacterial standard. The compound (7b) showed maximum antibacterial potency. Compounds 6 and 7 have more activity, Compound (4) has nearly activity and compounds 1, 2, 3 and 5 have less activity compared with *streptomycin* against all bacterial organisms.

Table 1-Antibacterial Activity

Comp.	Gram Positive Bacteria									Gram Negative Bacteria					
	Bacillus subtilis			*Streptococcus*			*Staphylococcus aureas*			*E. coli*			*Pseudomonas sp.*		
	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg
1		3	6	1	5	9			7			6		2	8
2	2	6	11		7	13		2	9		1	7		1	10
3		7	13	1	10	15	4	11	14	1	5	10	5	9	14
4	6	18	23	3	15	18	6	16	21	7	12	18	6	13	16
5		5	15		14	16	1	15	17		5	11	5	10	14
6a	5	13	21	4	18	27	7	16	20	5	13	19	7	14	19
6b	12	28	31	19	27	35	14	20	32	9	16	27	10	19	29
7a	10	21	27	9	19	25	8	19	24	11	19	25	11	18	28
7b	15	24	36	18	28	33	13	20	28	9	18	29	12	22	31
streptomycin	3	7	18	2	11	17	4	16	20	8	17	22	6	12	27

***In vitro* Antifungal Screening**

The compounds (1-7) were evaluated for their in vitro antifungal activity against *Aspergillus nigaer, Candia albicans*, and *Penicillium sp*. using an agar dilution method [26]. The screening results given in [Table-2] where, the activities of compounds were compared with *Ketoconazole* as antifungal standard. Compounds 6b and 7b have more activity, Compounds (4, 6a and 7a) have nearly activity and compounds 1, 2, 3 and 5 have less activity compared with *Ketoconazole* against all Fungal organisms.

Table 2- Antifungal Activity

Comp.	*Aspergillus niger*			*Penicillium sp.*			*Candia albicans*		
	10 mg	50mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg
1			3	1	5	8			5
2		2	6	1	9	11			8
3	1	5	9		11	13		7	11
4	5	11	18	3	9	15	3	12	17
5		6	10		12	14	1	9	13
6a	9	14	19	4	16	18	6	13	19
6b	15	23	32	15	22	35	15	21	39
7a	11	16	21	7	18	23	8	15	22
7b	17	24	33	17	29	38	17	26	40
ketoconazole	8	13	18	7	17	21	6	17	21

Conclusion

The antimicrobial data revealed that with slight modifications in the structure one can plan for the drug design.

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