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Synthesis and characterization of thiazole and 2-thioxoimidazolidinone derivative; their antibacterial and anticancer properties

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Abstract 5-Aryl-2-[(5-substituted-3-methoxy-2-hydroxybenzylidene)-hydrazine]-thiazoles (**3a,b**) and 3-[(5-substituted-3-methoxy-2-hydroxybenzylidene)amino]-4-oxo-imidazolidin-2-thiones (**4a,b**) were prepared via cyclization of 5-substituted-3-methoxy-2-hydroxy-benzaldehyde thiosemicarbazones (**2a,b**) with $\acute{\omega}$-bromomethyl aryl ketones and ethyl chloroacetate in fused sodium acetate. Acetylation of thiazoles and imidazolidinone derivatives with acetic anhydride yielded the diacetyl derivatives (**5a,b** and **6a,b**). Acetylation of **4** with acetic anhydride in fused sodium acetate gave the corresponding triacetyl derivatives (**7a,b**). Synthesized compounds were characterized by EI-MS and NMR spectroscopy. The biological activity studies of thiazoles and imidazolidinone were carried out against antimicrobial and anticancer activities.

Keywords Imidazolidine · Thiosemicarbazide · Antimicrobial and anticancer activities

Introduction

Sulpha drugs are well recognized for various physiological activities [1, 2], and antibacterial, fungicidal, and pesticidal properties [3], while imidazolidines and thiazoles have been associated with various biological activities [4–8]. In a previous work, El-Deen and coworkers [9–11] reported the synthesis of thiazoles and imidazolidinone with $\acute{\omega}$-bromomethyl aryl ketones and ethyl chloroacetate. This

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paper describes the synthesis of thiazoles (**3**) and imidazolidinone (**4**) from condensation of 5-substituted-3-methoxy-2-hydroxybenzaldehydes (**1a,b**) with thiosemicarbazide which gave 5-substituted-3-methoxy-2-hydroxybenzaldehyde thiosemicarbazones (**2a,b**), followed by cyclization of **2** with with $\acute{\omega}$-bromomethyl aryl ketones and ethyl chloroacetate in fused sodium acetate. The EIMS fragmentation pattern and NMR data of the synthesized compounds is also discussed.

Chemistry

Synthesis

The synthetic pathways leading to the new thiazole and imidazolidinone derivatives are illustrated in Scheme 1. Condensation of 5-substituted-3-methoxy-2-hydroxybenzaldehydes (**1a,b**) with thiosemicarbazide and gave 5-substituted-3-methoxy-2-hydroxybenzaldehyde thiosemicarbazones (**2a,b**). Treatment of compound **2** with $\acute{\omega}$-bromomethyl aryl ketones, such as (4-methylphenacyl bromide and 4-methoxy phenacyl bromide) and ethyl chloroacetate in sodium acetate in methanol under reflux, yielded the corresponding 5-aryl-2-[(5-substituted-3-methoxy-2-hydroxy-benzylidene)-hydrazineo]-thiazoles (**3a,b**) and 3-[(5-substituted-3-methoxy-2-hydroxybenzylidene) amino]-4-oxo-imidazolidin-2-thiones (**4a,b**).

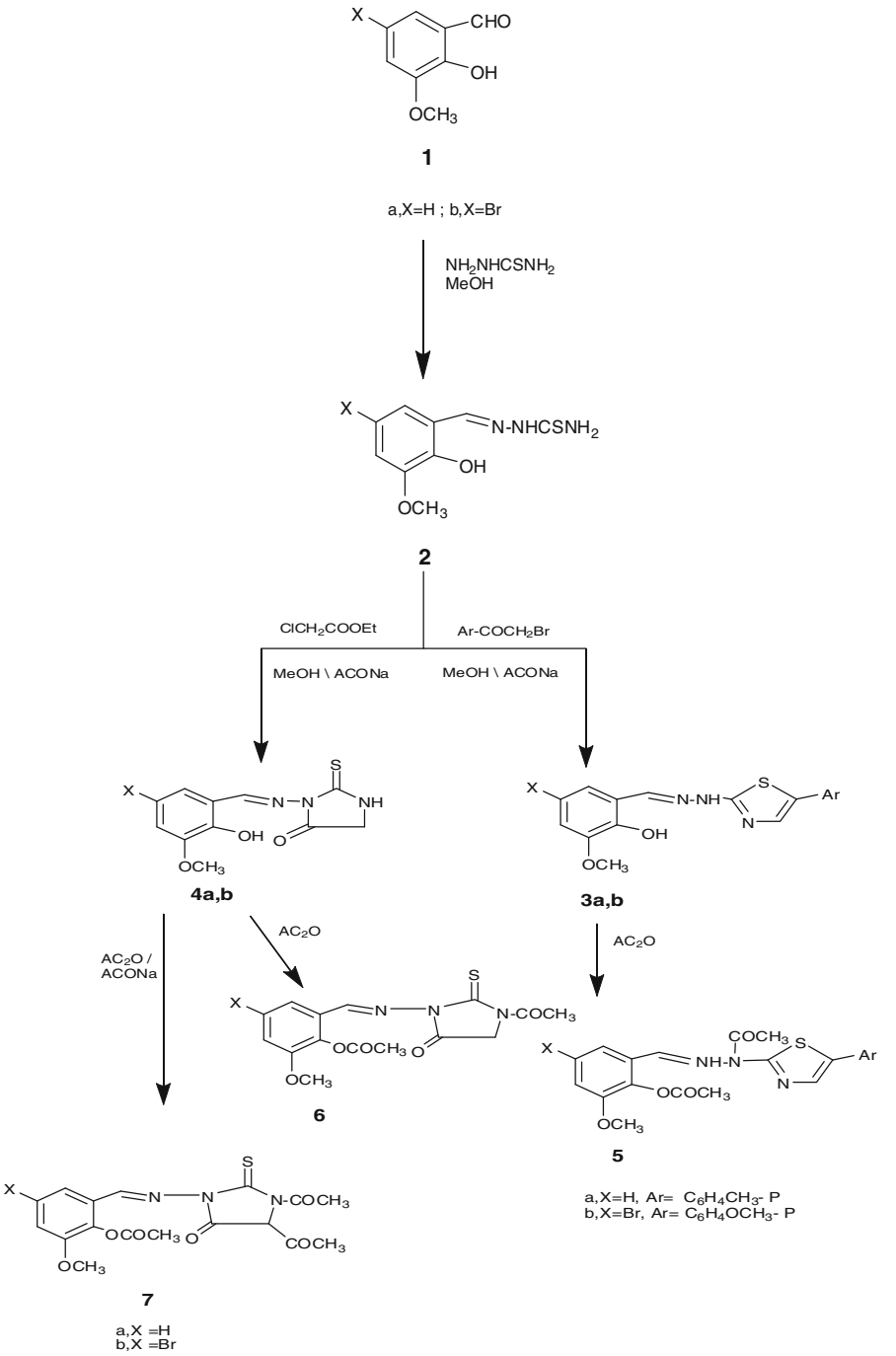
Acetylation of compounds **3** and **4** with acetic anhydride under reflux led to the formation 5-aryl-2-[(5-substituted-3-methoxy-2-acetoxybenzylidene)-acetyl-hydrazino]-thiazoles (**5a,b**) and 1-acetyl-3-[(5-substituted-3-methoxy-2-acetoxy-benzylidene) amino]-4-oxo-imidazolidin-2-thione (**6a,b**). 1,5-Diacetyl-3-[(5-substituted-3-methoxy-2-acetoxy-benzylidene) amino]-4-oxo-imidazolidin-2-thiones (**7a,b**) were prepared via acetylation [12] of compound **4** with acetic anhydride in the presence of fused sodium acetate under reflux.

Mass spectrometry

After studying the MS fragmentation pattern, different fragmentation pathways were suggested which are discussed in the following paragraphs [13, 14].

Compounds **3** and **5**

The mass spectra of synthesized compounds **3(a,b)** (Fig. 1), **5a** (Fig. 3) and 5b showed intense molecular ion peaks at *m/z* 339, 433/435, 423, and 517/519 consistent with the molecular formulae $C_{18}H_{17}N_3O_2S$, $C_{18}H_{16}N_3BrO_3S$, $C_{22}H_{21}O_4S$, and $C_{22}H_{20}N_3BrO_5S$, respectively. The molecular ion of compounds **3(a,b)** fragmented to produce stable ions at *m/z* 322 and *m/z* 416 after losing the hydroxyl group (OH). The fragment ions at *m/z* 322 and *m/z* 416 fragmented via the suggested pathways **A** to a fragment of ions at *m/z* 190 and *m/z* 206, corresponding to the molecular ion of 5-(4-alkylphenyl)-2-aminothiazole. It underwent further loss of NH_2CN, S, and acetylene C_2H_2 and gave peaks at *m/z* 148, 164, *m/z* 116, 132, and



Scheme 1 Heterocyclization of arylsemicarbazone

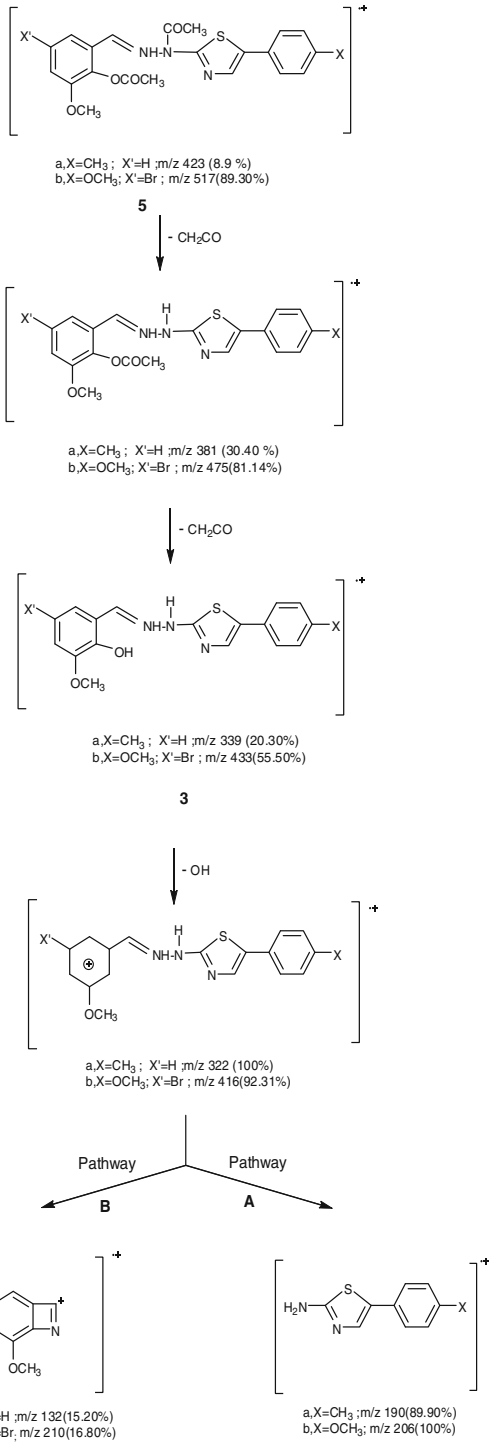
m/z 91, 107, respectively. The fragment ions at *m/z* 322 and 416 were also found to undergo fragmentation via pathway **B** to produce the ions of *m/z* 132 and 210, which further fragmented and gave a fragment of ions at *m/z* 106 and *m/z* 184 by losing the cyano group (CN). The ions of *m/z* 106 and *m/z* 184 were broken and gave the ions of *m/z* 76 and 154 by losing the formaldehyde molecule. The diacetyl derivatives **5(a,b)** were broken and gave fragment ions at *m/z* 381 and 475 by losing the ketene molecule (CH_2CO). The loss of the ketene molecule from the fragment ions at *m/z* 381 and 475 gave a fragment of ions at *m/z* 339 and *m/z* 433, corresponding to the molecular ion of compounds **3(a,b)**, respectively. The fragment ions at *m/z* 339 and *m/z* 433 broke further via a pathway similar to compounds **3(a,b)** (Scheme 2).

Compounds **4, 6** and **7**

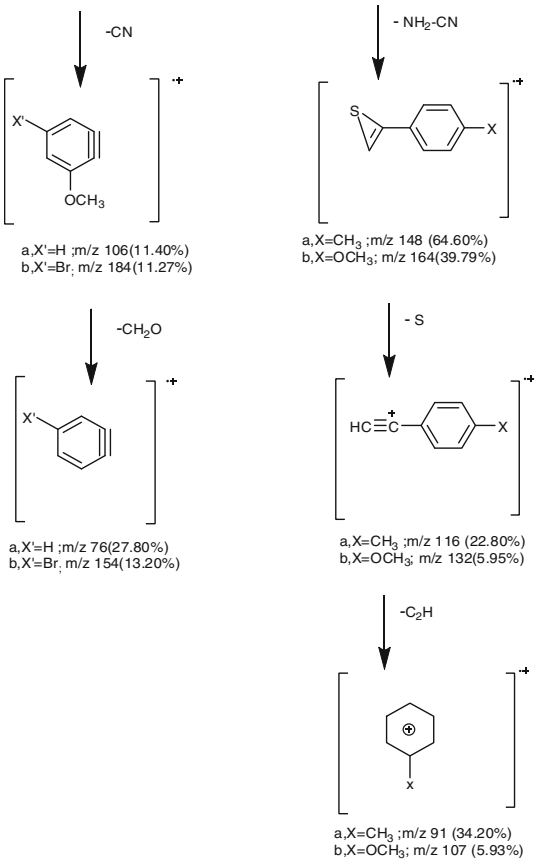
The mass spectra of compounds **4(a,b)** were fully consistent with the assigned structures. In most cases, intense molecular ion peaks were observed. Thus, compounds **4(a,b)** showed intense molecular ion peaks at *m/z* 265 and *m/z* 343/345, corresponding to the molecular formulae $C_{11}H_{11}N_3O_3S$ and $C_{11}H_{10}N_3BrO_3S$, respectively. The molecular ion of *m/z* 265 and 343 fragmented via the pathway **A** and gave the stable ion of *m/z* 248 and ion of *m/z* 326 by losing the hydroxyl group (OH). The fragment ions of *m/z* 248 and *m/z* 326 were broken to give fragment ions of *m/z* 219 and *m/z* 297 which lost the formyl group (CHO). The fragmentation led to ions of *m/z* 177, 255; *m/z* 162, 240; *m/z* 117, 195, and *m/z* 89, 167, respectively. Accordingly, the same molecular ion of *m/z* 265 and 343 fragmented via the pathway **B** to give a fragmentation of *m/z* 150 and *m/z* 228, and it underwent further loss of NH and the two-formyl group (CHO) and gave peaks at *m/z* 135, 213; *m/z* 106, 184, and *m/z* 77, 155, respectively. Also, the same molecular ion of *m/z* 265 and *m/z* 343 fragmented with rearrangement via pathway **C** and gave the ion of *m/z* 116, corresponding to 2-thioxo-imidazolidin-2-thione. The molecular ion peaks of compounds **6(a, b)** were observed at *m/z* 349 and 427/429, corresponding to molecular formulae $C_{15}H_{15}N_3O_5N$ and $C_{15}H_{14}N_3BrO_5S$, respectively. The loss of the ketene molecule (CH_2CO) from the molecular ion peaks at *m/z* 349 and *m/z* 427 gave peaks at *m/z* 307 and *m/z* 385. The fragment ions of *m/z* 307 and 385 fragmented to give a peak at *m/z* 265, 343, corresponding to the molecular ion of compounds **4(a,b)** by losing the ketene molecule. The molecular ion triacetyl derivatives **7(a,b)** were observed at *m/z* 391 and 469/471, corresponding to the molecular formulae $C_{17}H_{17}N_3O_6N$ and $C_{17}H_{16}N_3BrO_6S$, respectively (Schemes 3 and 4).

The loss of the ketene molecule from the molecular ion peaks at *m/z* 391 and 469 gave peaks at *m/z* 349 and 427, corresponding to molecular ion peaks of compound **6(a,b)**, respectively. The EIMS of compounds **4a**, **6a** showed a base peak of *m/z* 279. The mass spectra of compounds **4b**, **6b** and **7b** showed a base peak at *m/z* 76, 325 and *m/z* 63 (Figs. 1, 2, 3, 4, 5).

Scheme 2 Fragmentation pattern of thiazole **3** and **5**



Scheme 2 continued



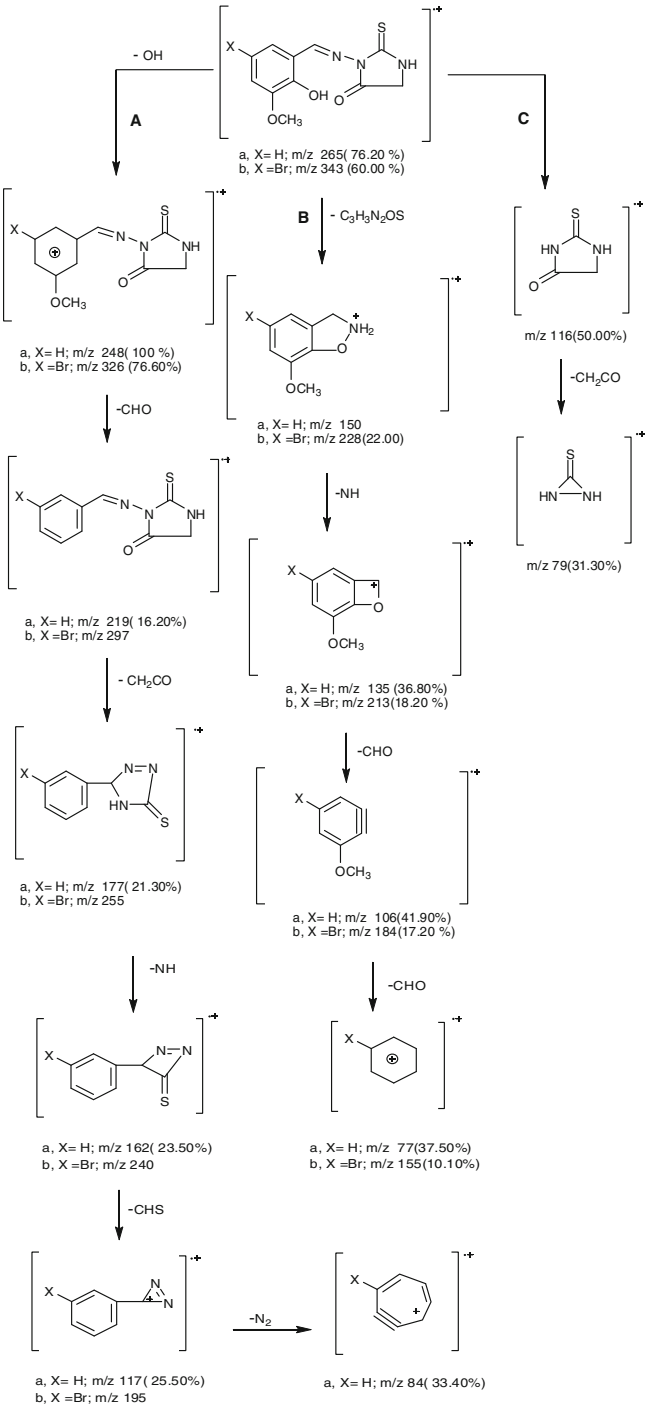
Biological assay

Antimicrobial activity

All the compounds **3–6** were in vitro screened for their antibacterial activity against Gram-positive [*Bacillus subtilis* (RCMBOOO107), *Streptococcus pneumonia* (RCMBOOO105), *Staphylococcus aureus* (RCMBOOO106)] and Gram-negative [*Escherichia coli* (RCMBOOO103) and *Pseudomonas* sp. ATCC 9027] bacteria by the drug diffusion method [15]. The zone of inhibition was measured in mm and was compared with standard drugs. DMSO was used as a blank and streptomycin was used as antibacterial standard. All the compounds were tested at 50, 100, and 150 mg concentrations. The data are summarized in Table 1, and show that all compounds display certain antibacterial activity.

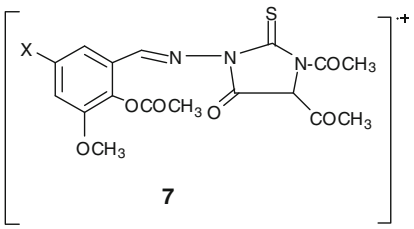
Anticancer activity

The cytotoxic and antitumor activities of prepared compounds **3–7** were tested against the MCF-7 and HePG2 cell lines according to the method of Masmann [16] and



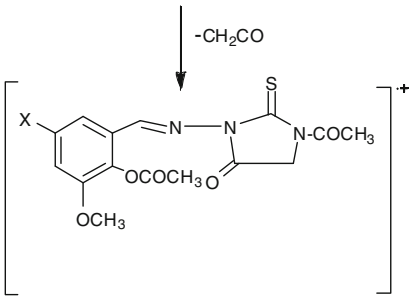
Scheme 3 Fragmentation pattern of compound **4**

Scheme 4 Fragmentation pattern of compounds **6** and **7**

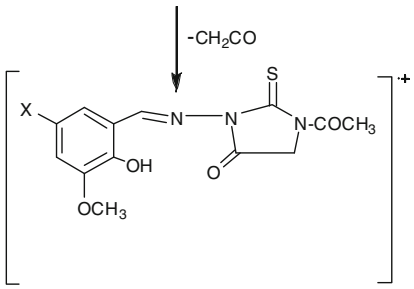


7

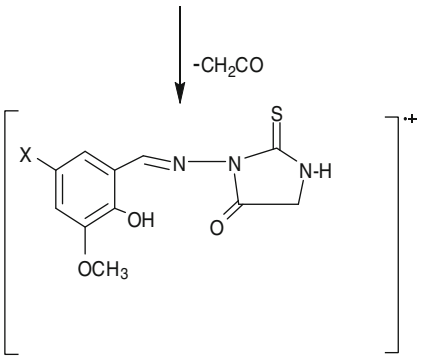
a,X =H, m/z 391(21.30%)
b,X =Br, m/z 469



a,X =H, m/z 349 (7.90%)
b,X =Br, m/z 427(12.10%)



a,X =H, m/z 307 (22.71%)
b,X =Br, m/z 385(56.10%)



a,X =H, m/z 265 (76.20%)
b,X =Br, m/z 343(60.00%)

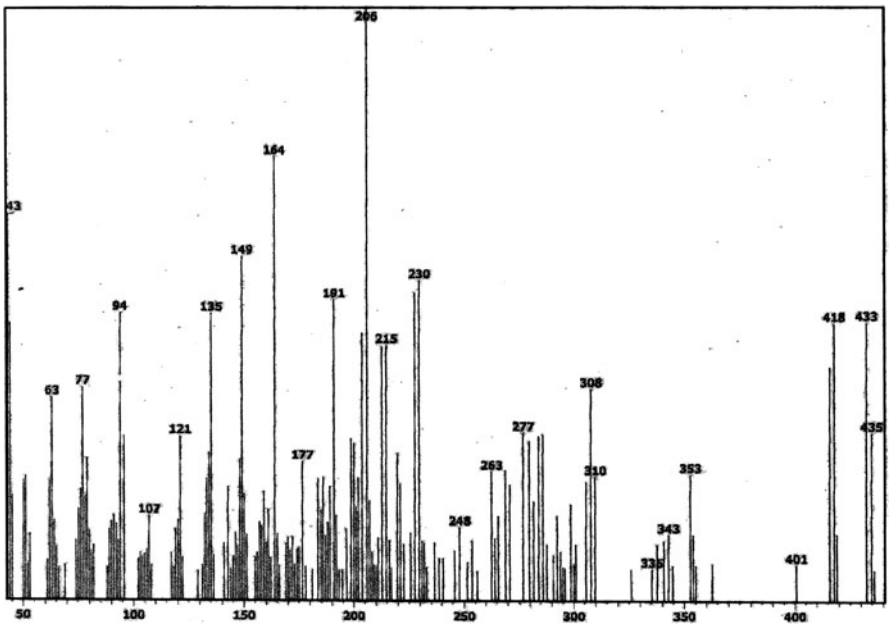


Fig. 1 EIMS spectrum of compound **3b**

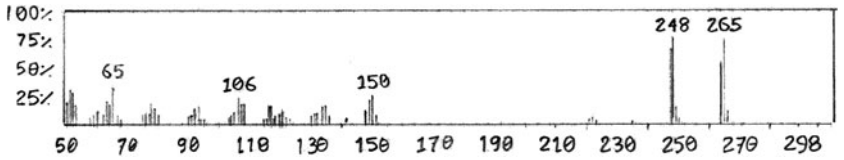


Fig. 2 EIMS spectrum of compound **4a**

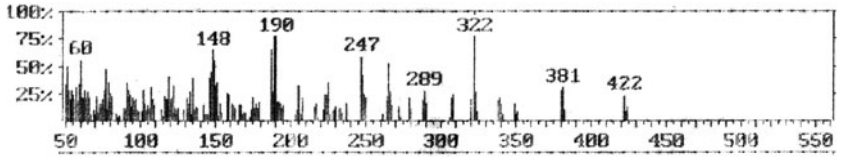


Fig. 3 EIMS spectrum of compound **5a**

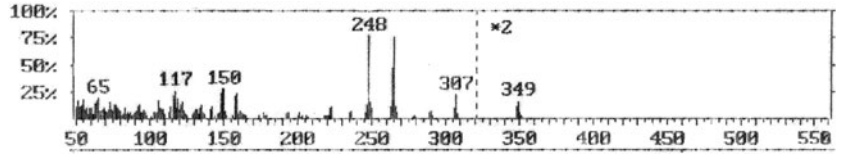


Fig. 4 EIMS spectrum of compound **6a**

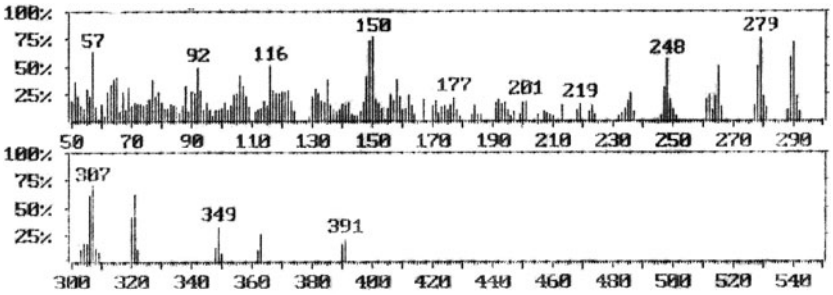


Fig. 5 EIMS spectrum of compound **7a**

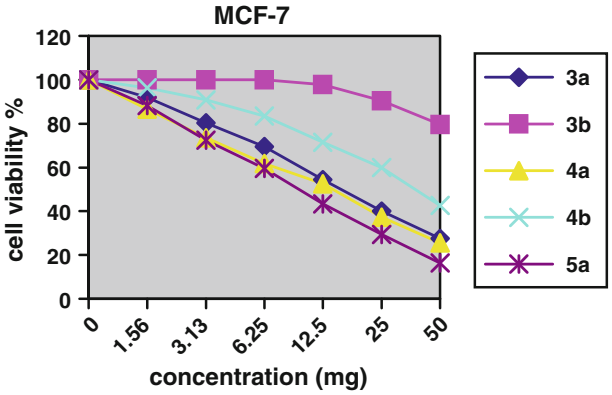


Fig. 6 The inhibitory activities against breast carcinoma cells

Vijayan et al. [17]. The inhibitory activities against breast carcinoma cells (MCF-7 cell line) and hepatocellular carcinoma cells (HePG2 cell line) were detected by using different concentrations of the tested compounds (50, 25, 12.5, 6.25, 3.125, and 1.56 mg), and the viability cells (%) were determined by the colorimetric method. Also, the (IC_{50}) was calculated from Tables 2, 3 and Figs. 6, 7, 8, and 9.

Table 4 summarizes the results of cytotoxicity testing against human breast carcinoma cells lines and heptocellular carcinoma cells lines (IC50).

The results revealed that all tested compounds have cytotoxic and antitumor activity against the breast carcinoma cell line and the hepatocellular carcinoma cell line except compounds **3b**, **5b** and **7a**. Compound **4a** (IC_{50} 14.50 mg, IC_{50} 6.90 mg) and compound **5a** (IC_{50} 12.00 mg, IC_{50} 9.90 mg) are the best.

Conclusion

In this work, the synthesis and antimicrobial and the anticancer activities of new thiazole and 2-thioxoimidazolidine derivatives **3–7** are described. The compounds showed in vitro growth inhibitory activities against the tested organisms including higher than streptomycin. Compounds **4a** and **5a** are more potent than the other

Table 1 Antibacterial activity of all prepared compounds **3–6**

Compound	Gram-positive bacteria									Gram-negative bacteria					
	Bacillus subtilis			*Streptococcus pneumonia*			*Staphylococcus aureus*			*E. coli*			*Pseudomonas* sp.		
	50 mg	100 mg	150 mg	50 mg	100 mg	150 mg	50 mg	100 mg	150 mg	50 mg	100 mg	150 mg	50 mg	100 mg	150 mg
3a	+++	+++	+++	+++	+++	+++	+	++	+++	+	+	+	−	+	+
3b	−	−	−	−	+	+	−	−	−	+	++	+++	+++	+++	+++
4a	−	−	+	−	++	++	+	+	++	−	−	+	−	−	−
4b	−	+	+	+	+	++	+	++	++	−	−	+	−	+	+
5a	+	+	+	++	+++	+++	+++	+++	+++	+	++	++	++	++	+++
5b	−	+	+	+	+	++	+	+	+	−	−	−	−	−	−
6a	+	+	+	++	+++	+++	+	++	+++	−	−	−	−	−	−
6b	+++	+++	+++	+	++	+++	++	++	++	+	++	++	+++	+++	+++
Streptomycin	+++	+++	+++	++	+++	+++	+	++	+++	+	+++	+++	+	+	++

+++ High activity, ++ moderate activity, + low activity, − no activity

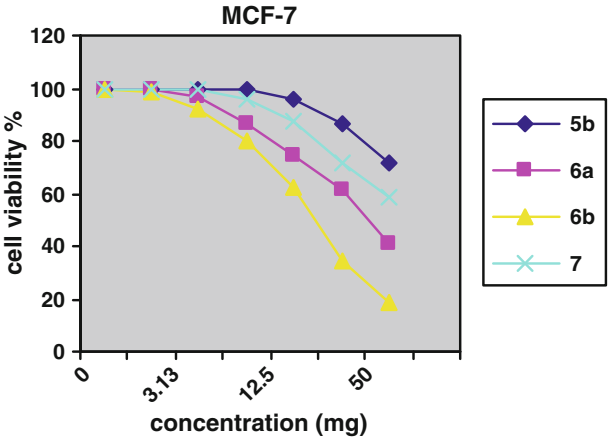


Fig. 7 The inhibitory activities against breast carcinoma cells

Table 2 Evaluation of cytotoxicity against MCF-7 cell line

Sample conc. (mg)	Viability (%)								
	3a	**3b**	**4a**	**4b**	**5a**	**5b**	**5a**	**6b**	**7**
50	27.56	79.62	25.62	42.70	16.28	71.24	40.82	18.76	58.94
25	39.98	90.44	37.36	59.86	29.46	86.48	61.44	34.28	71.28
12.5	54.32	97.76	52.48	71.52	43.32	95.86	74.56	62.53	87.36
6.25	69.47	100.00	61.73	83.38	59.60	100	86.93	80.42	96.12
3.125	80.26	100.00	73.44	90.84	72.43	100	96.75	91.55	100
1.56	91.84	100.00	86.62	96.35	88.12	100	100	98.14	100
0	100	100.00	100.00	100	100	100	100	100	100

Table 3 Evaluation of cytotoxicity against HePG2 cell line

Sample conc. (mg)	Viability (%)								
	3a	**3b**	**4a**	**4b**	**5a**	**5b**	**6a**	**6b**	**7**
50	33.82	68.74	13.98	39.44	21.18	62.48	30.58	31.94	59.13
25	45.70	80.18	22.86	58.68	32.92	80.52	48.72	41.53	68.74
12.5	62.38	91.50	38.12	69.40	48.64	89.36	63.40	70.48	80.36
6.25	79.45	98.63	51.38	78.42	63.58	98.92	76.94	82.13	89.97
3.125	90.10	100	67.29	89.23	79.14	100	85.58	91.86	96.59
1.56	98.32	100	81.56	96.14	92.53	100	93.79	97.98	100
0	100	100	100	100	100	100	100	100	100

compounds against human breast carcinoma cell line and hepatocellular carcinoma cell line. The biological data revealed that, with slight modifications in the structure, one can plan for the drug design.

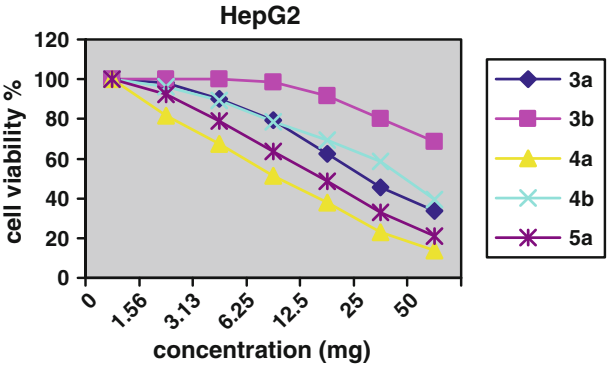


Fig. 8 The inhibitory activities against hepatocellular carcinoma cells

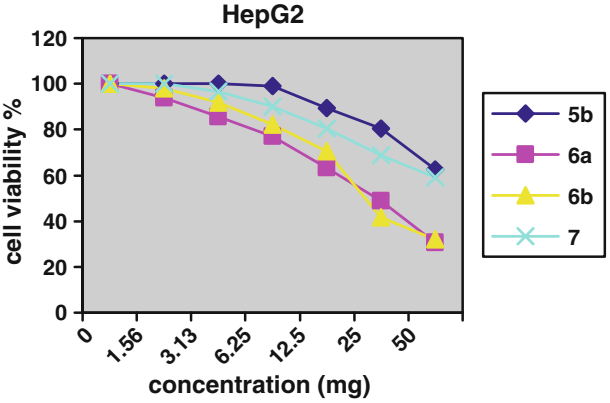


Fig. 9 The inhibitory activities against hepatocellular carcinoma cells

Experimental

NMR spectra were recorded on a General Electric QE 300 instrument and chemical shifts are given in δ (ppm) with TMS as internal references. IR spectra were recorded on Perkin-Elmer 1420 and Biorad FTS 7 spectrometers in KBr pellets. Mass spectra were obtained on a Jeol JMS D-300 spectrometer operating at 70 eV. Microanalyses were conducted using a 1106 elemental analyzer. Melting points were uncorrected and were determined on Gallenkamp electric melting point apparatus.

5-Substituted-3-methoxy-2-hydroxy-benzaldehyde thiosemicarbazones (**2a,b**)

A mixture of **1** (0.01 mol) and thiosemicarbazide (0.01 mol) in methanol (30 ml) was heated under reflux for 4 h, then cooled. The solid formed was filtered off, dried and purified by recrystallization from ethanol to give 2.3-methoxy-2-hydroxybenzaldehyde thiosemi-carbazone **2a** as pale yellow crystals, yield 78 %, m.p. 250 °C.

IR (KBr): 3,500–2,842 (br-OH), 3,456, 3,163 (NH_2), 3,344 (NH), 1,615 (C=N), 1,326 (C=S), 1,211, 1,056 (C–O)cm^{-1}. ^{1}H-NMR ($CDCL_3$): δ 3.94 (s,3H,OCH_3), 6.89 (s,2H,NH_2), 7.12–7.51 (m,3H,Ar–H), 7.81 (s,1H,CH=N), 9.92 (s,1H,NH), 11.14 (s,1H,OH) ppm. MS: (*m/z*, %): 226 (M^++1, 12.5), 255 (M^+, 100), 223 (7.60), 209 (2.70), 208 (7.6), 194 (3.90), 193 (2.50), 180 (2.40), 179 (1.50), 166 (2.00),165 (5.50), 164 (4.70),152 (6.90),151 (5.90), 150 (33.90), 149 (25.30), 148 (18.80), 137 (9.90), 135 (22.20), 134 (9.90), 133 (8.50), 132 (6.80), 131 (9.70), 130 (5.90), 121 (9.90), 120 (8.60),119 (8.60), 109 (5.40), 108 (12.90), 107 (12.20), 106 (20.00), 105 (16.60), 102 (11.80), 94 (6.80), 93 (12.80), 92 (8.80), 91 (7.30), 79 (16.20), 78 (18.00), 77 (61.70), 76 (33.50), 75 (24.00), 66 (10.80), 65 (28.00), 64 (12.30), 63 (16.20), 60 (49.50), 59 (14.80), 53 (22.20), 52 (29.90), 51 (35.20), 50 (19.50). Anal. Found: C, 47.89; H, 4.68; N, 18.52; S, 14.02. $C_9H_{11}N_3O_2S$ requires: C, 48.00; H, 4.89; N, 18.67; S, 14.22.

5-Bromo-3-methoxy-2-hydroxybenzaldehyde thiosemicarbazone **2b** as pale yellow crystals, yield 73 %, m.p. 220 °C. IR (KBr): 3,550–2,980 (br.OH), 3,452, 3,106 (NH_2), 3,325 (NH), 1,616 (C=N), 1,535 (C=C), 1,365 (C=S), 1,249, 1,064 (C–O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.97 (s,3H,OCH_3), 6.74 (s,2H,NH_2),7.26 (s,1H,Ar–H),7.73 (s,1H,Ar–H), 8.37 (s,1H,CH=N), 9.83 (s,1H,NH), 11.01 (s,1H,OH) ppm. MS: (*m/z*, %): 305 (M^++2,21.90), 304 (M^++1,10.40), 303 (M+,10.40), 296 (6.30), 295 (8.30), 293 (11.50), 292 (10.40), 291 (8.30), 290 (12.50), 289 (11.50), 288 (11.50), 266 (19.80), 264 (15.60), 263 (13.50), 261 (10.40), 245 (6.30), 244 (17.70), 243 (11.50), 230 (18.70), 229 (29.20), 228 (28.10), 227 (31.30), 217 (14.60), 215 (18.80), 214 (14.60), 213 (10.40), 211 (11.50), 200 (11.50), 199 (13.50), 197 (7.30), 186 (28.10), 185 (18.80), 184 (14.60), 183 (12.50), 181 (13.50), 171 (11.50), 164 (12.10), 158 (14.60), 157 (16.70), 156 (11.50), 145 (10.40), 144 (12.50), 143 (10.40), 141 (16.70), 134 (11.50), 133 (16.70), 131 (10.40), 130 (10.40), 122 (19.80), 121 (11.50), 120 (13.50), 119 (18.80), 118 (15.60), 117 (12.10), 107 (16.70), 106 (12.50), 105 (25.00), 104 (26.00), 103 (14.60), 102 (28.10), 94 (16.70), 93 (22.90), 92 (13.50), 91 (20.80), 81 (41.70), 79 (50.00), 78 (52.10), 77 (74.60), 76 (79.20), 75 (60.40), 66 (16.70), 65 (33.30), 64 (49.00), 63 (51.00), 62 (41.70), 60 (77.90), 59 (100.00), 58 (25.00), 53 (46.90), 51 (41.70), 50 (61.50). Anal. Found: C, 35.38; H, 3.19; N, 13.66; S, 10.45. $C_9H_{10}N_3BrO_2S$ requires: C, 35.64; H, 3.30; N, 13.86; S, 10.56.

5-Aryl-2-[(5-substituted-3-methoxy-2 hydroxy-benzylidene)-hydrazino]-thiazoles (**3a,b**)

*3-[(5-Substituted-3-methoxy-2-hydroxy benzy-lidene)amino]-4-oxo-imidazolidin-2-thiones (**4a,b**)*

A mixture of **2a,b** (0.01 mol) with $\acute{\omega}$-bromomethyl aryl ketones such as (4-methylphenacyl bromide and 4-methoxy phenacyl bromide) and ethylchloroacetate in presence of fused sodium acetate in methanol under reflux for 4 h, then cooled and poured into water. The solid formed was filtered off, dried and purified by recrystallization from suitable solvent to give **3** and **4**.

Table 4 IC_{50} (mg) values of tumor cell lines after 72 h continuous exposure to test compounds

Compound	Tuinor type/cell line	
	MCF-7	HePG2
3a	16.20	21.70
3b	Weak	Weak
4a	14.50	6.90
4b	39.40	36.30
5a	12.00	9.90
5b	Weak	Weak
6a	38.90	23.90
6b	34.90	21.50
7a	Weak	Weak

IC_{50} is the concentration that induces 50 % growth inhibition compared with untreated control cells

MCF-7 human breast carcinoma cell line, *HePG2* human hepatocellular carcinoma cell line

5-(*p*-Tolyl)-2-[(3-methoxy-2-hydroxybenzylidene)-hydrazino]-thiazoles (**3a**) as yellow crystals, yield 69 % m.p. 190 °C. IR(KBr): 3,490–2,970 (br.OH), 3,289 (NH), 1,616 (C=N), 1,605, 1,583 (C=C), 1,215, 1,125, 1,093 (C–O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.46 (s,3H,CH_3), 3.89 (s,3H,OCH_3), 6.97–7.75 (m,8H,Ar-HandH-thiazole), 8.21 (s,1H,CH=N), 9.81 (s,1H,NH), 11.20 (s,1H,OH)ppm. MS: (*m*/*z*, %):340 M^++1, 5.70), 339 (M^+,21.90), 338 (M^+−1,3.00), 323 (8.30), 322 (28.60), 321 (14.90), 226 (14.40), 225 (100), 224 (9.50), 204 (2.80), 208 (10.50), 207 (6.30), 191 (7.00), 190 (41.90), 189 (8.90), 188 (6.70), 176 (6.40), 175 (3.20), 174 (4.10), 166 (3.40), 165 (5.40), 164 (3.70),162 (3.90), 152 (8.60), 151 (10.80), 150 (42.20), 149 (36.60), 148 (36.90), 147 (22.90), 137 (13.20), 136 (10.70), 135 (27.60), 134 (24.90), 133 (12.60),131 (12.20), 122 (13.70),121 (16.40), 119 (11.70), 118 (9.70), 108 (19.80), 107 (15.10), 106 (25.20), 105 (19.20), 104 (11.10), 102 (13.90), 101 (11.20), 94 (10.30), 93 (16.50), 91 (16.00), 90 (10.00), 80 (13.20), 79 (17.20), 78 (21.30), 77 (69.80), 76 (36.90), 75 (12.10), 66 (14.30), 65 (36.30), 64 (14.30), 63 (25.10), 60 (47.50), 59 (18.90), 53 (20.70), 52 (40.90), 51 (40.30), 50 (22.00). Anal. Found: C, 63.66; H, 4.97; N, 12.23; S, 9.35. $C_{18}H_{17}N_3O_2S$ requires: C, 63.72; H, 5.01; N, 12.39; S, 9.44.

5-(*p*-Methoxyphenyl)-2-[(5-bromo-3-methoxy-2-hydroxybenzylidene)-hydrazino]-thiazoles (**3b**) as yellow crystals, yield 69 % m.p. 140 °C. IR (KBr): 3,480–2,951 (br.OH), 3,225, (NH), 1,618 (C=N), 1,605, 1,591 (C=C), 1,225, 1,093 (C–O)cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 3.91–3.97 (s,6H,2×OCH_3), 6.91–7.68 (m,7H, Ar-HandH-thiazole), 8.31 (s,1H,CH=N), 9.88 (s,1H,NH), 11.21 (s,1H,OH) ppm. MS: (*m*/*z*, %): 435 (M^++2,28.35),433 (M^+,46.74), 418 (46.60), 416 (39.39), 354 (11.110), 353 (21.30), 343 (11.12), 341 (10.02), 310 (20.89), 308 (35.70), 306 20.05), 300 (6.31), 299 (16.29), 294 (8.27), 292 (14.26), 286 (28.00), 284 (27.74), 282 (16.77), 280 (26.98), 277 (28.35), 271 (19.60), 269 (53.92), 228 (51.85), 226 (11.80), 224 (19.87), 220 (24.84), 215 (43.07), 213 (42.81), 207 (16.93), 206 (100), 204 (45.12), 199 (27.28), 197 (12.17), 191 (50.60), 184 (20.60), 177 (23.44), 172 (10.72), 170 (10.72), 164 (74.75), 161 (15.41), 159 (18.40), 150 (18.07), 149 (57.91), 148 (23.81), 143 (19.22), 135 (48.25), 134 (24.99), 133 (20.56), 121

(27.69), 120 (13.65), 119 (12.08), 107 (12.024), 96 (27.75), 94 (48.38), 91 (14.34), 90 (13.37), 89 (12.07), 79 (24.00), 78 (17.64), 77 (35.87), 76 (18.73), 65 (9.13), 64 (13.53), 63 (34.12), 62 (20.14), 53 (11.21), 51 (20.92), 50 (20.22). Anal. Found: C, 49.66; H, 3.59; N, 9.62; S, 7.22. $C_{18}H_{16}N_3BrO_3S$ requires: C, 49.88; H, 3.69; N, 9.70; S, 7.39.

3-[3-Methoxy-2-hydroxybenzylidene)amino]-4-oxo-imidazolidin-2-thione (**4a**) as pale yellow crystals, yield 73 % m.p. 320 °C. IR (KBr): 3,520–2,947 (br.OH), 3,417 (NH), 1,708 (C=O), 1,635 (C=N), 1,249, 1,087 (C–O)cm^{-1}. ^{1}H-NMR(DMSO-d_3): δ 3.20 (s,2H,$NHCH_2CO$), 3.95 (s,3H,OCH_3), 7.12–7.60 (m,3H,Ar–H), 8.21 (s,1H,CH0=N), 10.20 (s,1H,NH), 11.32 (s,1H,OH)ppm. MS: (*m/z*, %): 266 (M^++1,10.5), 265 (M^+,76.20), 264 (M^+−1, 55.30), 249 (15.80), 248 (100), 247 (67.60), 235 (2.5), 234 (2.00), 222 (8.30), 221 (6.10), 218 (2.60), 205 (1.60), 194 (1.80), 193 (1.70), 192 (2.00), 176 (2.50), 175 (1.80), 174 (4.90), 165 (2.20), 163 (1.70), 162 (2.60), 151 (5.60), 150 (26.30), 149 (21.50), 148 (12.00), 136 (6.90), 135 (16.80), 134 (18.20), 132 (9.20), 130 (6.90), 122 (10.20), 121 (14.10), 120 (10.00), 119 (9.60), 117 (18.90), 116 (16.40), 108 (18.10), 107 (16.00), 106 (23.30), 105 (10.70), 93 (15.50), 92 (14.20), 91 (7.30), 89 (5.20), 79 (14.10), 78 (18.30), 77 (16.10),76 (12.80), 66 (8.30), 65 (34.90), 64 (18.20), 63 (21.00), 53 (16.70), 52 (28.30), 51 (31.30), 50 (17.40), 90 (13.37), 89 (12.07), 79 (24.00), 78 (17.64), 77 (35.87), 76 (18.73). Anal. Found: C, 49.62; H, 4.03; N, 15.58; S, 11.97. $C_{11}H_{11}N_3O_3S$ requires: C, 49.81; H, 4.15; N, 15.85; S, 12.07.

3-[(5-Bromo-3-methoxy-2-hydroxybenzylidene)-amino]-4-oxo-imidazolidin-2-thione (**4b**) as yellow crystals, yield 71 % m.p. 310 °C. IR (KBr): 3,520–2,950 (br.OH), 3,429 (NH), 1,716 (C=O), 1,635 (C=N), 1 605, 1,589 (C=C), 1,319 (C=S), 1,211, 1,110 (C–O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.21 (s,2H,$NHCH_2CO$), 3.93 (s,3H,OCH_3), 7.23 (s,1H,Ar–H), 7.52 (s,1H,Ar–H), 8.61 (s,1H,CH=N), 9.90 (s,1H,NH), 12.05 (s,1H,OH)ppm. MS: (*m/z*, %): 345 (M^++2,43.30), 344 (M^++1,60.90), 343 (M^+,60.00), 342 (M^+−1,50.00), 339(16.70), 328 (66.70), 327 (30.00), 326 (76.70), 264 (23.30), 172 (16.70), 154 (6.70), 148 (6.70), 135 (6.70), 123 (20.00), 120 (40.00), 119 (36.70), 118 (26.70), 117 (53.30), 116 (33.30), 105 (3.30), 104 (33.30), 103 (6.70), 102 (33.30), 96 (26.70), 89 (46.70), 88 (16.70), 84 (26.70), 82 (40.00), 81 (20.00), 80 (10.00), 78 (10.00), 76 (100), 68 (43.30), 64 (33.30), 60 (26.70), 59 (20.00), 58 (63.30), 53 (6.70), 50 (20.00). Anal. Found: C, 38.26; H, 2.78; N, 12.09; S, 9.13. $C_{11}H_{10}N_3BrO_3S$ requires: C, 38.48; H, 2.91; N, 12.24; S, 9.33.

5-Aryl-2-[(5-substituted-3-methoxy-2-acetoxy-benylidene)-acetylhydrazino]thiazoles (**5a,b**)

*3-[(5-Substituted-3-methoxy-2-acetoxybenzylidene) amino]-4-oxo-1-acetylimidazolidin-2-thiones (**6a,b**)*

A solution of **3** and **4** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 2 h, then cooled and poured into ice-water. The solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to give **5** and **6**.

5-(*p*-Tolyl)-2-[(3-methoxy-2-acetoxybenzylidine)-acetylhydrazine]thiazole (**5a**) as pale yellow crystals, yield 68 %, m.p. 80 °C. I.R(KBr): 1,758 (C=O), 1,715 (C=O), 1,630 (C=N), 1,605, 1,585 (C=C), 1,215, 1,085 (C–O)cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.30 (s,3H,CH_3), 2.43 (s,3H,$COCH_3$), 2.60 (s,3H,$OCOCH_3$), 3.87 (s,3H,OCH_3), 7.03–7.76 (m,8H,Ar-HandH-thiazole), 9.21 (s,1H,CH=N) ppm. MS: (*m*/*z*, %): 424 (M^++1,12.70), 423 (M^+,8.90), 422 (M^+−1,22.80), 382 (10.10), 381 (30.40), 380 (27.80), 350 (6.30), 349 (15.20), 340 (15.20), 340 (15.20), 339 (20.30), 338 (17.70), 323 (26.60), 322 (100), 320 (19.00), 308 (24.00), 307 (20.30), 290 (15.20), 289 (26.60), 288 (17.70), 280 (11.40), 279 (20.30), 276 (13.90), 266 (26.60), 265 (51.90), 264 (21.50), 250 (20.80), 249 (24.10), 248 (41.80), 247 (58.20), 233 (11.10), 232 (11.40), 230 (12.70), 217 (15.60), 216 (12.70), 208 (20.30), 205 (31.60), 204 (10.10), 195 (13.90), 194 (11.40), 193 (15.20), 192 (17.70), 191 (16.50), 190 (89.90), 189 (88.6), 188 (26.60), 187 (64.60), 179 (16.50), 178 (11.40), 177 (15.50), 175 (20.30), 167 (13.90), 166 (13.90), 162 (13.90), 161 (15.20), 159 (24.10), 151 (34.20), 150 (31.60), 149 (54.40), 148 (64.40), 147 (44.30), 146 (38.00), 132 (15.20), 131 (20.30), 123 (11.40), 122 (31.60), 121 (20.30), 120 (19.00), 119 (40.50), 118 (19.00), 116 (22.80), 108 (19.00), 107 (30.40), 105 (13.90), 103 (15.20), 102 (27.80), 97 (19.00), 96 (17.70), 95 (20.30), 93 (24.10), 92 (27.80), 91 (34.20), 90 (11.40), 80 (25.30), 79 (34.20), 77 (46.80), 76 (27.80), 66 (20.30), 65 (26.60), 64 (20.30), 63 (27.80), 61 (20.30), 60 (55.70), 59 (32.90), 57 (30.40), 52 (27.80), 51 (49.40), 50 (32.90). Anal. Found: C, 62.26; H, 4.83; N, 9.78; S, 7.49. $C_{22}H_{21}N_3O_4S$ requires: C, 62.41; H, 4.96; N, 9.93; S, 7.56.

5-(*p*-Methoxyphenyl)-2-[(5-bromo-3-methoxy-2-acetoxybenzylidine)-acetylhydrazino]thiazole (**5b**) as pale yellow crystals, yield 67 %, m.p. 85 °C. I.R (KBr): 1,753 (C=O), 1,716 (C=O), 1,631 (C=N), 1,606, 1,589 (C=C), 1,212, 1,175, 1,083 (C–O)cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 2.35 (s,3H,$COCH_3$), 2.55 (s,3H,$OCOCH_3$), 3.95–3.97 (s,6H,2O×CH_3), 7.03–7.61 (m,7H,Ar-HandH-thiazole),8.36 (s,1H,CH = N) ppm. MS:(*m*/*z*, %): 519 (M^++2,100), 518 (M^++1,30.20), 517 (M^+,76.20), 512 (25.11), 498 (43.12), 496 (34.52), 478 (13.28), 476 (89.14), 443 (25.29), 434 (55.50), 418 (82.55), 416 (92.31), 384 (14.80), 361 (14.58), 353 (32.79), 343 (16.91), 341 (12.25), 336 (20.17), 328 (23.27), 326 (18.14), 310 (15.42), 309 (56.61), 307 (67.71), 305 (36.97), 294 (10.23), 291 (17.00), 288 (28.91), 286 (35.46), 284 (36.27), 264 (11.84), 263 (35.07), 251 (10.87), 249 (15.98), 248 (57.12), 232 (14.94), 231 (13.50), 230 (34.69), 229 (96.76), 227 (71.12), 220 (24.12), 215 (25.71), 213 (23.55), 206 (87.98), 204 (40.63), 202 (11.62), 200 (16.22), 194 (14.06), 191 (30.44), 189 (16.34), 186 (10.93), 184 (11.27), 164 (39.79), 161 (7.84), 150 (7.16), 149 (21.92), 135 (22.79), 134 (9.17), 119 (6.34), 104 (5.82), 91 (7.25), 90 (7.28), 77 (12.78), 76 (12.43), 75 (13.09), 63 (9.51), 62 (5.65), 50 (4.61), 43 (76.85). Anal. Found: C, 51.03; H, 3.68; N, 8.07; S, 6.13. $C_{22}H_{20}N_3BrO_5S$ requires: C, 51.06; H, 3.87; N, 8.12; S, 6.19.

1-Acetyl-3-[(3-methoxy-2-acetoxybenzylidene) amino]-4-oxo-imidazolidin-2-thione (**6a**) as pale yellow crystals, yield 65 %, m.p. 260 °C. IR(KBr): 1,762, 1,724, 1,695 (C=O), 1,625 (C=N), 1,608, 1,585 (C=C), 1,328 (C=S), 1,215, 1,095 (C–O)cm^{-1}. ^{1}HNMR(DMSO-d_6): δ 2.34 (s,3H,$COCH_3$), 2.56 (s,3H,$OCOCH_3$), 3.25 (s,2H,NCH_2CO), 3.91 (s, 3H, OCH_3),7.12–7.58(m,3H,Ar–H), 8.35 (s,1H,CH=N) ppm. MS: (*m*/*z*, %): 350 (M^++1,2.50), 3 49 (M^+,7.90), 348 (M^+−

1,5.40), 307 (22.10), 306 (9 0.30), 290 (6.80), 289 (6.20), 267 (5.70), 266 (11. 3 0), 265 (75.40), 264 (46.50), 263 (11.00), 249 (15. 30), 248 (100), 247 (11.90), 236 (7.60), 235 (6.20), 223 (11.80), 222 (9.60), 194 (5.70), 193 (5.40), 192 (4.20), 177 (5.10), 165 (2.30), 159 (23.5 0), 158 (20.70), 151 (7.40), 150 (27.80), 149 (27.50), 148 (24.10), 135 (12.50), 134 (10.20), 132 (9.10), 131 (7.90), 122 (15.00), 121 (12.70), 119 (17.60), 118 (10.50), 117 (25.50), 116 (20.10), 107 (9.90), 106 (17.00), 104 (5.70), 93 (12.20), 92 (10. 80), 91 (6 0.5 0), 78 (8.60), 77 (12.70), 76 (11. 90), 73 (14.70), 6 5 (19.50), 64 (16.70), 63 (14.40), 59 (10.20), 53 (1 0.80), 52 (11.30), 51 (16.40), 50 (11.60). Anal. Found: C, 51.48; H, 4.13; N, 11.96; S, 9.02. $C_{15}H_{15}N_3O_5S$ requires: C, 51.57; H, 4.30; N, 12.03; S, 9.17.

1-Acetyl-[(5-bromo-3-methoxy-2-acetoxybenzylidene) amino]-4-oxo-imidazolidin-2-thione (**6b**) as pale yellow crystals, yield 63 %, m.p. 230 °C. IR(KBr): 1,766, 1,732, 1,699 (C=O), 1,651 (C=N), 1,608, 1,583 (C=C), 1,319 (C=S), 1,180, 1,010 (C–O)cm^{-1}. ^{1}HNMR(DMSO-d_6): δ2.35 (s,3H,$COCH_3$), 2.49 (s,3H,$OCOCH_3$), 3.23 (s,2H,NCH2CO), 3.95 (s,3H, OCH3), 7.33 (s,1H,Ar–H), 7.63 (s,1H,Ar–H), 8.33 (s,1H,CH=N) ppm. MS:(*m/z*, %): 429 (M^++2, 1.30), 427 (M^+,1.70), 388 (22.00), 387 (58.50), 386 (34.10), 385 (56.10), 384 (51.20), 345 (31.70), 344 (63.40), 343 (65.90), 342 (75.60), 328 (65.90), 327 (61.00), 326 (70.70), 325 (100), 314 (22.00), 308 (22.00), 307 (26.80), 306 (29.30), 275 (9.80), 274 (17.10), 265 (29.30), 264 (31.70), 246 (12.20), 245 (22.00), 227 (36.60), 219 (14.60), 218 (17.10), 214 (17.10), 213 (22.00), 203 (14.60), 202 (29.30), 201 (29.30), 199 (29.30), 198 (29.30), 190 (22.00), 189 (11.50), 188 (14.60), 187 (14.60), 185 (19.50), 173 (12.60), 159 (43.90), 158 (9.80), 150 (7.30), 147 (2 4.40), 146 (19.50), 142 (63.40), 135 (36.60), 133 (24.40), 122 (17.10), 120 (29.30), 119 (22.00), 118 (17.10), 117 (58.60), 116 (29.30), 114 (43.90), 113 (43.90), 112 (17.10), 107 (24.40), 106 (19.50), 102 (31.70), 95 (24.40), 93 (41.50), 92 (9.50), 91 (26.8 0), 89 (14.60), 88 (19.50), 87 (26.80), 82 (36.60), 8 1 (24.40), 79 (41.50), 77 (12.20), 75 (12.20), 74 (22.00), 72 (22.00), 71 (22.00), 65 (26.80), 64 (31.70), 63 (63.40), 62 (41.50), 61 (26.80), 59 (73.20), 54 (41.50), 53 (39.00), 51 (22.00), 50 (19.50). Anal. Found: C, 42.01; H, 3.05; N, 9.63; S, 7.22. C_{15} H_{14} N_3BrO_5S requires: C, 42.15; H, 3.28; N, 9.84; S, 7. 49.

1,5-Dicetyl-3-[(5-substituted-3-methoxy-2-acetoxy-benzylidene)-amino]-4-oxo-imidazolidin-2-thione (**7a,b**)

A mixture of **4** (0.01 mol) and fused sodium acetate (0.03 mol) in acetic anhydride (25 ml) was heated under reflux for 3 h, then cooled and poured into ice-diluted hydrochloric acid. The solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to **7**.

1,5-Dicetyl-3-[(3-methoxy-2-acetoxybenzylidene)amino]-4-oxo-imidazolidin-2-thione (**7a**) as pale yellow crystals, yield 62 %, m.p. 180 °C. IR (KBr): 1,763, 1,725, 1,698 (C=O), 1,625 (C=N), 1,603, 1,588 (C=C), 1,325 (C=S), 1,225, 1,125, 1,089(C–O) cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 2.21 (s,3H,$COCH_3$), 2. 43 (s,3H,$OCOCH_3$), 2.51 (s,3H,OCH_3), 5.67 (s, 1H,NCH$(CO)_2$), 7.31 (s,1H,Ar–H), 7.61(s,1H,Ar–H), 8.46 (s,1H,CH=N), 3.93 (s,3H,OCH_3) ppm. MS: (*m/z*, %): 391 (M^+,21.30), 390 (M^+−1,15.40), 363 (24.30), 362 (10.30), 349 (32.40), 348(12.50), 322 (11.80), 321

(61.80), 320 (41.20), 308 (12.50), 307 (96.90), 306 (61.00), 305 (61.20), 304 (16.90), 291 (22.80), 290 (71.30), 289 (57.40), 288 (10.30), 280 (22.10), 279 (100), 278 (50.00), 277 (14.00), 265 (49.30), 264 (22.40), 250 (10.30), 249 (19.10), 248 (56.60), 247 (30.90), 236 (24.30), 235 (18.40), 223 (14.00), 219 (16.20), 218 (10.30), 213 (13.20), 201 (18.40), 200 (16.90), 195 (10.30), 194 (16.20), 193 (14.70), 192 (19.40), 191 (16.20), 177 (21.30), 176 (14.00), 175 (10.30), 170 (14.00), 164 (19.10), 163 (13.20), 162 (23.50), 161 (11.80), 152 (15.40), 151 (19.10), 150 (81.60), 149 (73.50), 148 (39.70), 136 (13.20), 135 (36.60), 134 (16.20), 133 (17.60), 132 (25.00), 131 (28.70), 130 (22.10), 122 (27.20), 121 (25.70), 120 (26.50), 119 (24.30), 118 (24.30), 117 (27.20), 116 (50.00), 109 (12.50), 107 (31.60), 106 (41.90), 105 (24.30), 104 (23.40), 95 (16.90), 93 (27.20), 92 (48.50), 91 (25.00), 90 (25.70), 88 (32.40), 87 (14.00), 80 (16.90), 79 (26.50), 78 (22. 80), 77 (37.50), 76 (19.90), 75 (15.40), 73 (15.40), 69 (30.10), 67 (26.50), 65 (39.70), 64 (37.50), 63 (33.10), 62 (25.70), 57 (63.20), 56 (22.10), 55 (28.70), 52 (22.80), 51 (35.30), 50 (17.60). Anal. Found: C, 52.07; H,4.22; N, 10.56; S, 8.03. $C_{17}H_{17}\ N_3O_6S$ requires: C, 52.17; H, 4.35; N, 10.74; S, 8. 17.

1,5-Diacetyl-3-[(5-bromo-3-methoxy-2-acetoxy-benzylidene)amino]-4-oxo-imidazolidin-2-thione (**7b**) as yellow crystals, yield 61 %, m.p. 140 °C. IR(KBr): 1,162, 1,722, 1,698 (C=O), 1,629 (C=N), 1,603, 1,592 (C=C), 1,325 (C=S), 1,215, 1,317, 1,081 (C–O)cm^{-1}. ^{1}HNMR($CDCl_3$): δ 2.21 (s,3H,$COCH_3$), 2.41 (s,3H,$COCH_3$), 2.56 (s,3H,$OCOCH_3$), 3.96 (s,3H,OCH_3), 5.62 (s,1H,$NCH(CO)_2$), 7.31 (s, 1H,Ar–H), 7.61 (s,1H,Ar-H), 8.41 (s,1H,CH=N) ppm. MS: (*m/z*, %): 471(M^++2,13.10), 469 (M^+,13.20), 468 (M^+−1,10.20), 444 (23.20), 443 (19.20), 442 (12.10), 326 (9.10), 310 (22.20), 309 (13.10), 308 (37.40), 307 (20.20), 306 (19.20), 305 (13.10), 280 (19.20), 279 (17.20), 278 (16.20), 277 (13.10), 265 (6.10), 231 (15.20), 230 (79.80), 229 (51.50), 228 (63.60), 227 (72.70), 216 (16.20), 215 (13.10), 214 (14.10), 213 (18.20), 202 (39.40), 201 (40.40), 200 (38.40), 199 (38.40), 198 (20.20), 197 (13.10), 187 (19.20), 186 (12.10), 171 (20.20), 169 (7.10), 160 (12.10), 159 (18.20), 158 (13.10), 157 (15.20), 150 (12.10), 149 (13.10), 142 (13.10), 141 (27.30), 135 (14.10), 134 (16.20), 131 (14.10), 121 (20.20), 118 (15.20), 116 (13.10), 114 (14.10), 106 (17.20), 105 (13.10), 101 (11.10), 94 (13.10), 93 (14.10), 92 (15.20), 91 (31.30), 90 (19.20), 82 (25.30), 81 (2 3.20), 80 (19.20), 79 (34.30), 78 (32.30), 77 (32.30), 76 (21.20), 75 (34.30), 66 (18.20), 65 (32.30), 6 4 (25.30), 63 (100), 62 (52.50), 61 (34.30), 60 (3 8. 40), 53 (31.30), 51(41.40), 50 (63.40). Anal. Found: C, 43.29; H, 3.21; N, 8.72; S, 6.66. $C_{17}H_{16}\ N_3\ BrO_6\ S$ requires: C, 43.49; H, 3.41; N, 8.95; S, 6.82.

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