ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2016, Vol. 42, No. 1, pp. 100–105. © Pleiades Publishing, Ltd., 2016.

Synthesis and In Vitro Antimicrobial and Antitumor Activity of Some Nitrogen Heterocycles[1]

A. I. El-Shenawy[2]

Department of Chemistry, Faculty of Science, Benha University, Benha, Egypt

Received April 24, 2015; in final form, August 26, 2015

Abstract—5-Phenyl-2-[(3,4,5-trimethoxybenzylidene)hydrazino]-thiazole and 3-[(3,4,5-trimethoxybenzylidene)amino]-4-oxoimidazolidin-2-thione were prepared by cyclization of 1-[(3,4,5-trimethoxybenzyliden)amino]-thiourea with phenacyl bromide and ethyl chloroacetate in the presence of fused sodium acetate. Acetylation of the synthesized compounds with acetic anhydride gave corresponding *N*-acetyl derivatives. Condensation of the synthesized thione with aromatic aldehydes yielded two 3-substituted 5-arylidene-4-oxo-imidazolidin-2-thiones. Acetylation of the latter compounds with acetic anhydride afforded the corresponding *N*-acetyl-4-oxo-imidazolidin-2-thiones. Some of the synthesized compounds exhibited antimicrobial activity. The cytotoxic activity of the prepared thiazole and imidazolidin-2-thione derivatives was studied on several tumor cell lines.

Keywords: nitrogen heterocycles, synthesis, antimicrobial and cytotoxic activities

DOI: 10.1134/S1068162016010040

INTRODUCTION

Because of their interesting biological activities, low molecular weight heterocycles have attracted enormous attention in medicinal chemistry. The hydantoin moiety is an important pharmacophore occurring in various biologically active compounds [1–3]. There is an imminent need to develop new anticancer drugs. In the late 1990s, a new anticancer agent based on the pyridyl cyanoguanidine system was identified by in vitro cytotoxicity screening assays and in vivo preclinical studies [4–7]. Subsequently, we made a drastic change of the parent pyridyl cyanoguanidine core. We supposed that two amino groups of the bridge could serve as sites for additional derivatization through formation of a cyclic structure containing pyridine-4-ylethylidineamino moiety. The structural rigidity imposed by the modification may have imparted a different biological activity to the molecule. It was found that the bulky aryl functionality in position 5 of amino-4-imidazolidin-2-thiones was essential for the cytotoxicity of these heterocyclic compounds.

This paper reports the synthesis of thiazole and 2-thioxoimidazalinone containing 3,4,5-trimethoxybenzylidene amino group from the reaction of 3,4,5-trimethoxybenzaldehyde and thiosemicarbazide as key starting materials. Antimicrobial and antitumor activities of some prepared nitrogen heterocycles are evaluated.

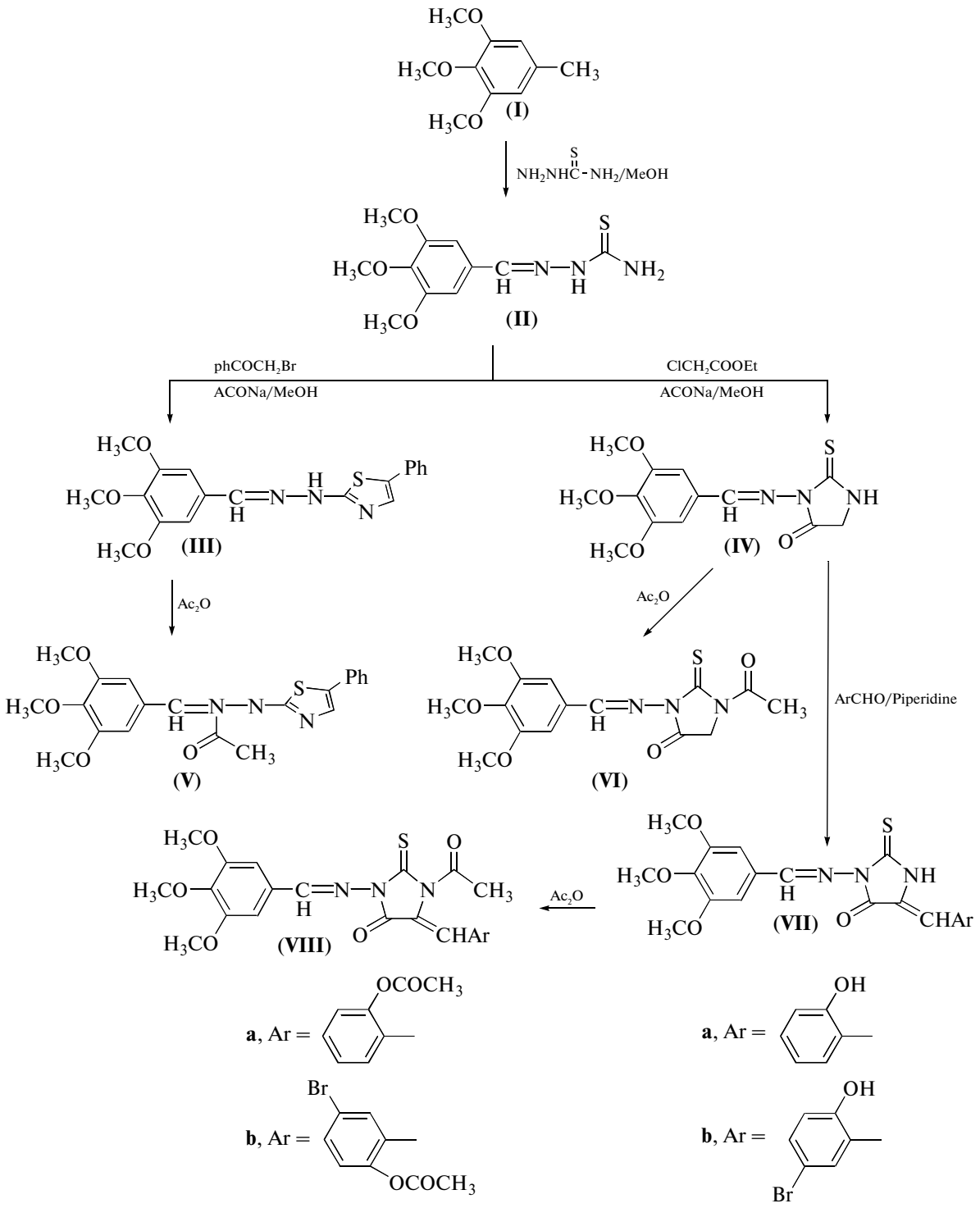
RESULTS AND DISCUSSION

The reaction of 3,4,5-trimethoxybenzaldehyde (**I**) with thiosemicarbazide [8–10] in methanol under reflux gave the corresponding 1-[(3,4,5-trimethoxybenzylidene)-amino]thiourea (**II**). Treatment [11] of thiourea derivatives (**II**) with phenacyl bromide and ethyl chloroacetate in the presence of fused sodium acetate in methanol under reflux yielded the corresponding 5-phenyl-2-[(3,4,5-trimethoxybenzylidene)hydrazino]-thiazole (**III**) and 3-[(3,4,5-trimethoxybenzylidene)amino]-4-oxo-imidazolidine-2-thione (**IV**), respectively. Acetylation of thiazole and imidazolidinone derivatives (**III**) and (**IV**) with acetic anhydride under reflux led to the formation of 5-phenyl-2-[(3,4,5-trimethoxybenzylidene)-acetylhydrazino]thiazole (**V**) and 1-acetyl-3-[(3,4,5-trimethoxybenzylidene)amino]-4-oxo-imidazolidin-2-thione (**VI**), respectively.

Condensation of 3-[(3,4,5-trimethoxybenzylidene)amino]-4-oxo-imidazolidin-2-thione (**IV**) with aromatic aldehydes (2-hydroxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde) in presence of piperidine led to the formation of 3-[(3,4,5-trimethoxybenzylidene)amino]-5-arylidene-4-oxo-imidazolidin-2-thiones (**VIIa**, **b**). Acetylation of compounds (**VII**) with acetic anhydride led to the formation of 1-acetyl-3-[(3,4,5-trimethoxybenzylidene)amino]-5-arylidene-4-oxo-imidazolidin-2-thiones (**VIIIa**, **b**).

[1] The article is published in the original.

[2] Corresponding author: e-mail: aielshenawy@gmail.com.



Scheme.

Antimicrobial Activity

Antimicrobial activities of the synthesized compounds (**II**)–(**VIIIb**) were determined by agar well diffusion method [12, 13]. The compounds were screened in vitro for antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli*, and *Pseudomonas solanarium*. The compounds were tested at different concentrations (100 and 50 μg/100 mL DMSO) and the activity was determined by measuring

Table 1. Antimicrobial activity of compounds **(II)**–**(VIIIb)**

Product	Gram-positive bacteria				Gram-negative bacteria				Antifungal activity			
	Bs		Sa		Ec		Ps		An		Ps	
	10 μg	50 μg	10 μg	50 μg	10 μg	50 μg	10 μg	50 μg	10 μg	50 μg	10 μg	50 μg
(II)	–	8	–	–	1	4	–	2	1	9	1	10
(III)	12	27	10	24	16	20	15	22	12	25	20	29
(IV)	5	11	–	9	5	10	6	9	3	12	10	14
(V)	9	18	6	17	7	11	3	12	9	18	15	26
(VI)	11	24	13	20	13	19	14	19	10	19	19	24
(VIIb)	2	12	7	10	13	14	9	11	5	15	13	17
(VIIIb)	5	20	6	18	10	16	11	17	8	18	15	22
Ciprofloxacin	11	25	9	23	15	19	13	20	–	–	–	–
Fluconazole	–	–	–	–	–	–	–	–	10	21	16	28

Reported is the zone of inhibition expressed in mm. Bs, *Bacillus subtilis*; Sa, *Staphylococcus aureus*; Ec, *Escherichia coli*; Ps, *Pseudomonas* sp.; An, *Aspergillus niger*; Ps, *Penicillium* sp.; –, no activity.

Table 2. Cytotoxicity of thiazole and thiohydantoin derivatives (72 h continuous exposure of HCT-116 tumor cell line)

Compound no.	**(III)**	**(V)**	**(VI)**	**(VIIa)**	**(VIIb)**	**(IIIVa)**	**(IIIVb)**	Vinblastin standard
IC_{50}, μM	6.3	3.1	5.4	1.5	3.0	3.00	3.40	9.80

the zone of inhibition (mm) and compared with the inhibition zones produced by positive controls. The screening results are presented in Table 1. Ciprofloxacin (25 μg/100 mL) was used as a positive control.

Also, compounds **(II)**–**(VI)**, **(VIIb)**, and **(VIIIb)** were evaluated for their in vitro antifungal activity [14, 15] against *Aspergillus niger* and *Penicillium* sp. The screening results are reported in Table 1; activities of the compounds are compared with fluconazole as an antifungal activity positive control. Dimethyl sulfoxide (DMSO, 1%) was used as a negative control.

In comparison with the reference agents (ciprofloxacin and fluconazole), compounds **(III)** and **(VI)** exhibited higher activity against bacteria and fungi; compounds **(V)**, **(VIIb)**, and **(VIIIb)** exhibited moderate antibacterial and antifungal activities, while compounds **(II)** and **(IV)** exhibited weak antimicrobial activity against some bacteria and weak antifungal activity.

Cytotoxicity

Antitumor activity of prepared compounds **(III)**, **(V)**–**(VII)**, and **(VIII)** were assessed according to methods of Masmann [16] and Vijayan [17]. IC_{50} values for the cancer cell line deduced from the figure varied in the range of 1.5–6.3 μM (Table 2). The IC_{50} value is the concentration that induces 50% growth inhibition compared with untreated control cells.

All tested compounds were found to exhibit cytotoxic activity against colon carcinoma cells close to that of a standard antitumor drug vinblastine. Compound **(VIIa)** was the most active.

CONCLUSION

In the present study, we synthesized candidate drugs, namely, thiazole and 2-thioxoimidazalinone heterocycles containing 3,4,5-trimethoxybenzylideneamino groups and evaluate their antimicrobial and anticancer activities. The compounds exhibited high antimicrobial and antifungal activities. Compounds **(III)** and **(VI)** showed the highest activity against bacteria and fungi. Also, cytotoxic activity of synthesized compounds against colon carcinoma cell line (HCT-116) was demonstrated, compound **(VII)** being the most active one.

EXPERIMENTAL

NMR spectra were recorded on a General Electric QE300 instrument in DMSO-d_6 at 500 MHz and chemical shifts are given in δ (ppm) with respect to TMS as internal reference. IR spectra (ν, cm^{-1}) were recorded on a Perkin-Elmer 1420 and a Bio-Rad FTS7 spectrometers in KBr pellets. Mass spectra were obtained on a Joel JMS D-300 spectrometer operating at 70 Ev. Microanalyses were conducted using a Carlo Erba 106 Perkin-Elmer model 240 analyzer. Melting

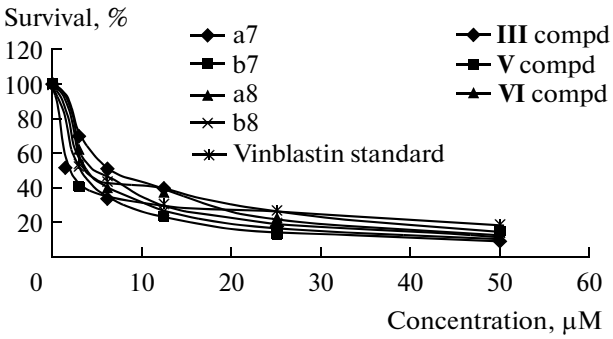
points were determined on a Reicht Hot instrument without correction.

1-[(3,4,5-Trimethoxybenzylidene)amino]thiourea (II). A mixture of 3,4,5-trimethoxybenzaldehyde (0.01 mole) and thiosemicarbazide (0.01 mole) in methanol (50 mL) was heated under reflux for 4 h and then cooled. The solid obtained was filtered off, dried, and purified by recrystallization from methanol to give compound (**II**) as colorless crystals, yield 78%, mp 200°C. IR: 3414, 3150 (NH_2), 3251 (NH), 1625 (C=N), 1605, 1598 (C=C), 1336(C=S), 1225, 1085 (C–O). ^{1}H NMR: 3.71 (s, 3H, OCH_3), 3.82 (s, 6H, $2XOCH_3$), 5.82 (s, 2H, NH_2), 7.23 (s, 2H, Ar-H), 8.31 (s, 1H, CH=N), 9.82 (s, 1H, NH). MS, *m/z* (%): 270 (9.12) [M^++ 1], 269 (100) [M^+], 253 (16.20), 252 (27.20), 213 (11.20), 212 (33.50), 197 (13.20), 196 (53.50), 171 (13.50), 170 (26.30). Found, %: C, 48.98; H, 5.52; N, 15.56; S, 11.78. Calcd., %: $C_{11}H_{15}N_3O_3S$: C, 49.07; H, 5.57; N, 15.61; S, 11.89.

5-Phenyl-2-[(3,4,5-trimethoxybenzylidene)hydrazino]-thiazole (III) and 3-[(3,4,5-trimethoxybenzylidene)amino]-4-oxo-imidazolidine-2-thione (IV). A mixture of compound (**II**) (0.01 mole), phenacyl bromide, and ethyl chloroacetate (0.01 mole) in methanol (50 mL) in presence of fused sodium acetate (0.03 mole) was heated under reflux for 4 h, then cooled, and poured into water. The resulting solid was filtered off, washed with water, dried, and purified by recrystallization from a suitable solvent to give (**III**) and (**IV**).

5-Phenyl-2-[(3,4,5-trimethoxybenzylidene)hydrazino]-thiazole (III). Pale yellow crystals, yield 76%, mp 230°C. IR: 3225 (NH), 1631 (C=N), 1610, 1587 (C=C), 1295, 1125, 1083 (C-O). ^{1}H NMR: 3.70 (s, 3H, OCH_3), 3.83 (s, 6H, $2XOCH_3$), 6.98 (s, 2H, Ar-H), 7.30–7.87(m, 6H, Ar-H and H-thiazole), 8.01 (s, 1H, CH=N), 10.31 (s, 1H, NH). ^{13}C NMR: 15644, 154.32, 153.71, 150.72, 140.53, 134.20, 129.30, 129.21, 128.63, 126.25, 114.55, 105.61 (C-aromatic and C=N), 60.63 (OCH3), 56.42 ($2XOCH_3$). MS, *m/z* (%): 370 (7.20) [M^+ + 1], 369 (33.20) [M^+], 194 (13.20), 193(16.30), 177(2.30), 176 (100), 175 (41.20), 167 (11.30), 163 (12.30), 137 (11.20), 134 (48.50), 133 (12.20), 119 (1.30), 118 (2.10), 117 (4.20), 116 (1.30), 91 (2.10), 89 (7.20), 78 (1.30), 77 (17.80), 63 (2.30), 52 (14.30), 51 (21.20), 50 (11.20). Found, %: C, 61.67; H, 5.03; N, 11.32; S, 8.56. $C_{19}H_{19}N_3O_3S$. Calcd., %: C, 61.79; H, 5.15; N, 11.38; S, 8.67.

3-[(3,4,5-Trimethoxybenzylidene)amino]-4-oxo-imidazolidine-2-thione (IV). Pale yellow crystals, yield 71%, mp 260°C. IR: 3225 (NH), 1631 (C=N), 1698 (C=O), 1626 (C=N), 1605, 1589 (C=C), 1338 (C=S), 1225, 1085, 1037 (C–O). ^{1}H NMR: 3.71 (s, 3H, OCH_3), 3.82 (s, 6H, $2XOCH_3$), 3.88 (s, 2H, NCH_2CO) 7.10 (s, 2H, Ar-H), 8.32 (s, 2H, CH=N), 10.35 (s, 1H, NH). ^{13}C NMR: 169.65 (C=S), 163.78 (C–O), 153.40, 152.36 (C–OCH_3-aromatic), 138.65 (C=N), 131.55, 104.73 (C-aromatic), 74.11 (NCH_2CO). MS, *m/z* (%): 310 (11.30) [M^+ + 1], 309 (76.50) [M^+], 308 (14.20) [M^+ – 1], 295 (13.20), 294 (3.10), 279 (3.20), 278 (5.10), 253 (11.20), 251 (18.20), 194 (100), 193 (67.20), 164 (11.30), 163 (5.20), 137 (11.20), 136 (5.30), 119 (3.10), 118 (4.40), 116 (10.20), 115 (4.70), 102 (3.20), 101 (3.30), 91 (2.00), 90 (1.20), 89 (11.20), 86 (7.20), 78 (1.20), 77(5.50), 76 (6.30), 75 (11.20), 74 (8.20), 63 (11.20), 62 (10.10), 52 (6.70), 51 (8.20), 50 (11.20). Found, %: C, 50.28; H, 4.68; N, 13.35; S, 10.23. $C_{13}H_{15}N_3O_4S$. Calcd., %: C, 50.48; H, 4.85; N, 13.59; S, 10.35.



Cytotoxicity of compounds (**III**), (**V**), (**VI**), (**VIIa, b**), and (**VIIIa, b**) against HCT-118 cells compared to that of vinblastin.

5-Phenyl-2-[(3,4,5,-trimethoxybenzylidene)acetylhydrazino]thiazole (V) and 1-acetyl-3-[(3,4,5,-trimethoxybenzylidene)amino]-4-oxo-imidazolidin-2-thiazole (VI). A solution of compound (**III**) or (**IV**) (0.01 mole) 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 from benzene to give compounds (**V**) and (**VI**), respectively.

5-Phenyl-2-[(3,4,5,-trimethoxybenzylidene)acetylhydrazino]thiazole (V). Pale yellow crystals, yield 63%, mp 180°C. IR: 1705 (C=O), 1625 (C=N), 1605, 1589 (C=C), 1210, 1171, 1078 (C–O). ^{1}H NMR: 2.51 (s, 3H, $COCH_3$), 3.73 (s, 3H, OCH_3), 3.83 (s, 6H, $2XOCH_3$), 7.20 (s, 2H, Ar-H), 7.40–7.92 (m, 5H, Ar-H), 8.12 (s, 1H, H-thiazole), 8.50 (s, 1H, CH=N). ^{13}C NMR: 171.70 (C=O), 156.45, 140.59 (2XC=N), 154.30, 153.70(3X-Ar-C-OCH_3-), 150.73 (C–N), 134.24, 129.31, 129.22, 128.64, 126.27, 114.58, 105.71 (C-aromatic), 60.63 (OCH_3), 56.46 ($2XOCH_3$), 22.86 ($COCH_3$). MS, *m/z* (%): 412 (10.20) [M^+ + 1], 411 (M^+, 37.20) [M^+], 370 (5.60), 369 (68.20), 194 (11.20), 193 (12.30), 177 (2.30), 176 (100), 175 (43.20), 167 (11.20), 163 (13.20), 137 (9.20), 134 (47.20), 133 (13.50), 119 (1.67), 118 (17.20), 117 (5.50), 116 (2.20), 103 (1.20), 102 (10.50), 101 (2.30), 92 (2.20), 91 (11.20), 89 (6.70), 78 (2.10), 77 (45.20), 76 (5.20), 63 (2.30), 62 (4.10), 52 (16.30), 51 (62.20), 50 (42.10). Found, %: C, 61.13; N, 5.01; N, 10.04; S, 7.61. $C_{21}H_{21}N_3O_4S$. Calcd., %: C, 61.31; H, 5.11, N,10.22; S, 7.78.

Acetyl-3-[(3,4,5-trimethoxybenzylidene)amino]-4-oxo-imidazolidin-2-thiazole (VI). Pale crystals, yield 63%, mp 220°C. IR: 1705–1697 (br. CO), 1625 (C=N), 1607, 1589 (C=C), 1338 (C=S), 1215, 1178, 1076 (C–O). ^{1}H NMR: 2.14 (s, 3H, $COCH_3$), 3.66 (s, 3H, OCH_3), 3.78 (s, 6H, $2XOCH_3$), 4.31 (s, 2H, NCH_2CO), 6.91 (s, 2H, Ar-H), 8.10 (s, 1H, CH=N). ^{13}C NMR: 169.20 (C=S), 166.59, 163.79 (C=O), 153.40, 152.38 (Ar-C-OCH_3), 138.63 (C=N), 131.56, 104.77 (C-aromatic), 4.12 (NCH_2CO), 60.39, 56.46 ($3XO-CH_3$), 21.57 ($COCH_3$). MS, *m/z* (%): 352 (12.20) [M^+ + 1], 351 (47.20) [M^+], 309 (100), 308 (16.20), 295 (10.20), 294 (5.10), 279 (4.30), 278 (4.50), 253 (12.20), 251 (16.20), 194 (76.20), 193 (42.10), 164 (10.20), 163 (4.50), 137 (10.30), 136 (4.50), 119 (4.50), 118 (5.30), 117 (1.30), 116 (5.20), 115 (8.30), 103 (2.30), 102 (6.10), 101 (4.20), 92 (1.30), 91 (3.20), 90 (2.20), 89 (1.30), 86 (6.20), 78 (3.10), 77 (3.50), 76 (5.50), 75 (7.10), 74 (6.20), 63 (9.30), 62 (6.50), 52 (6.20), 51 (5.30), 50 (7.30). Found, %: C, 51.09; H, 4.68; N, 11.59; S, 9.02. $C_{15}H_{17}N_3O_5S$. Calcd., %: C, 51.28; H, 4.84; N, 11.96; S, 9.12.

3-[(3,4,5-Trimethoxybenzylidene)amino]-5-arylidene-4-oxo-imidazolidin-2-thiones (VIIa, b). A mixture of compound (**IV**) (0.01 mole), aromatic aldehydes (such as 2-hydroxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde (0.01 mole), and piperidine (1 mL) was fused on a hot-plate at 120–125°C for 1 h. The reaction mixture was cooled and acidified with dilute hydrochloric acid (1 N). The crude product was filtered off, washed with water, dried, and purified by recrystallization from ethanol to give compound (**VII**).

3-[(3,4,5-Trimethoxybenzylidene)amino]-5-(2-hydroxy)benzylidene-4-oxo-imidazolidin-2-thione (VIIa). Yellow crystals, yield 74%, mp 240°C. IR: 3510–2985 (br. OH), 1699 (C=O), 1625 (C=N), 1610, 1607, 1589 (C=C), 1339 (C=S), 1225, 1139, 1076 (C–O). ^{1}H NMR: 3.71 (s, 3H, OCH_3), 3.85 (s, 6H, $2XOCH_3$), 6.98–8.11 (m, 7H, Ar-H and H-olefinic), 8.35 (s, 1H, CH=N), 10.31 (s, 1H, NH), 11.63 (s, 1H, OH). ^{13}C NMR: 164.40 (C=S), 166.59 (C=O), 153.52 (2X aromatic C–OCH_3), 152.35 (aromatic C–OH), 149.30 (aromatic C–OCH_3), 140.16 (C=N), 138.62, 131.56, 128.38, 127.32, 126.05, 124.44, 105.22 (C-aromatic), 60.40 (OCH_3), 3.56 ($2XOCH_3$). MS, *m/z* (%): 414 (6.71) [M^+ + 1], 413 (21.30) [M^+], 412 (1.360), 398 (3.70), 220 (1.30), 219 (13.30), 218 (3.50), 205 (11.30), 204 (4.50), 194 (16.20), 193 (8.30), 177 (16.20), 176 (7.50), 168 (3.50), 167 (11.30), 151 (7.20), 150 (100), 149 (33.50), 138 (3.50), 137 (42.20), 119 (2.30), 118 (3.50), 117 (5.20), 108 (3.30), 107 (13.50), 106 (22.10), 105 (11.30), 104 (3.30), 91 (2.30), 90 (11.30), 89 (8.30), 78 (5.30), 77 (65.30), 76 (11.30), 75 (9.30), 65 (37.50), 64 (12.30), 63 (9.80), 52 (33.50), 51 (36.30), 50 (11.50). Found, %: C, 58.03; H, 4.46; N, 10.02; S, 7.57. $C_{20}H_{19}N_3O_5S$. Calcd., %: 58.11; H, 4.60, N; 10.17; S, 7.75.

3-[(3,4,5-Trimethoxybenzylidene)amino]-5-(bromo-2-hydroxy)benzylidene-4-oxo-imidazolidin-2-thione (VIIb). Yellow crystals, yield 71%, mp 233°C. IR: 3510–2989 (br. OH), 3240 (NH), 1697 (C=O), 1625 (C=N), 1605, 1589 (C=C), 1337 (C=S), 1225, 1167, 1083 C–O). ^{1}H NMR: 3.72 (s, 3H, OCH_3), 3.86 (s, 6H, $2XOCH_3$), 6.97–8.01 (m, 6H, Ar-H and H-olefinic), 8.32 (s, 1H, CH=N), 10.32 (s, 1H, NH), 11.57 (s, 1H, OH). MS, *m/z* (%): 493 (16.20) [M^+ + 2], 492 (8.20) [M^+ + 1], 491 (M^+, 18.30) [M^+], 490 (12.30) [M^+ – 1], 477 (1.30), 476 (2.50), 299 (13.20), 298 (11.20), 297 (16.30), 285 (6.20), 284 (2.50), 283 (7.20), 257 (6.50), 256 (4.20), 255 (8.20), 230 (96.20), 229 (13.20), 228 (100), 227 (47.20), 194 (11.20), 193 (12.20), 185 (2.50), 184 (17.20), 168 (2.50), 167 (11.30), 138 (5.50), 137 (13.20), 108 (1.20), 107 (11.20), 106 (11.50), 92 (3.50), 91 (2.50), 90 (12.60), 78 (1.30), 77 (16.20), 76 (11.20), 75 (11.20), 65 (17.20), 64 (13.20), 63 (10.30), 52 (3.20), 51 (28.30), 50 (17.20). Found, %: C, 48.66; H, 3.44; N, 8.33; S, 6.33. $C_{20}H_{18}N_3BrO_5S$. Calcd., %: C, 48.88; H, 3.66; N, 8.55; S, 6.52.

1-Acetyl-3-[(3,4,5-trimethoxybenzylidene)amino]-5-arylidene-4-oxo-imidazolidin-2-thiones (VIIIa, b). A solution of compound (**VII**) (0.01 mole) in acetic anhydride (25 mL) was heated under reflux for 2 h, then cooled, and poured into ice water. The resulting product was filtered off, washed with water, dried, and purified by recrystallization from benzene to give compound (**VIII**).

1-Acetyl-3-[(3,4,5-trimethoxybenzylidene)amino]-5-(2-acetoxy)benzylidene-4-oxo-imidazolidin-2-thione (VIIIa). Pale yellow crystals, yield 76%, mp 210°C. IR: 1751 (C=O of ester), 1705–1695 (br. C=O), 1623 (C=N), 1607, 1595 (C=C), 1339 (C=S), 1225, 1171, 1082 (C–O). ^{1}H NMR: 2.31 (s, 3H, $COCH_3$), 2.51 (s, 3H, $OCOCH_3$), 3.72 (s, 3H, OCH_3), 3.82 (s, 6H, $2XOCH_3$), 6.81 (m, 7H, Ar-H and H-olefinic), 8.35 (s, 1H, CH=N). ^{13}C NMR: 169.41 (C=S), 167.09, 166.59, 163.79 (C=O), 157.53 (Ar-C-$OCOCH_3$), 153.45 (Ar-C-OCH_3), 149.30 ($2XAr-C-OCH_3$), 140.16 (C=N), 138.63, 131.01, 128.32, 127.33, 126.05, 129.91, 105.37, 104.77 (C-aromatic), 60.61 (Ar-OCH_3), 56.46 ($2XAr-OCH_3$), 21.67 ($COCH_3$), 21.06 ($COCH_3$). MS, *m/z* (%): 498 (13.20) [M^+ + 1], 497 (26.10) [M^+], 496 (11.20) [M^+ – 1], 456 (5.20), 455 (17.30), 454 (6.50), 414 (11.20), 413 (100), 412 (43.20), 398 (1.70), 397 (1.30), 220 (3.20), 219 (16.20), 218 (6.30), 205 (10.50), 204 (3.50), 194 (17.20), 193 (13.30), 177 (11.20), 176 (6.50), 168 (7.50), 167 (17.20), 151 (10.20), 150 (67.30), 149 (36.50), 138 (6.70), 137 (43.20), 119 (4.50), 118 (6.50), 117 (6.30), 108 (4.50), 107 (11.30), 106 (23.30), 105 (16.20), 104 (1.30), 91 (6.50), 90 (6.30), 89 (6.30), 78 (3.20), 77 (67.20), 76 (33.50), 76 (11.50), 75 (11.20), 65 (36.50), 64 (11.30), 63 (13.50), 52 (61.50), 51 (77.20), 50 (17.30). Found, %: C, 57.77;

H, 4.46; N, 8.33; S, 6.22. $C_{24}H_{23}N_3O_7S$. Calcd., %: C, 57.95; H, 4.63; N, 8.45; S, 6.44.

1-Acetyl-3-[(3,4,5-trimethoxybenzylidene)amino]-5-(5-bromo-2-acetoxy)benzylidene-4-oxo-imidazolidin-2-thione (VIIIb). Pale yellow crystals, yield 71.30%, mp 205°C. IR: 1750 (C=O of ester), 1708–1695 (br. C=O), 1627 (C=N), 1608, 1592 (C=C), 1337 (C=S), 1223, 1178, 1095 (C–O). ^{1}H NMR: 2.32 (s, 3H, $COCH_3$), 2.53 (s, 3H, $OCOCH_3$), 3.71 (s, 3H, OCH_3), 3.81 (s, 6H, $2XOCH_3$), 6.83–7.79 (m, 6H, Ar-H and H-olefinic), 8.33 (s, 1H, CH=N). MS, *m/z* (%): 577 (8.92) [M^+ + 2], 576 (3.20) [M^+ + 1], 575 (10.20) [M^+], 535 (6.30), 534 (4.20), 533 (7.20), 793 (5.20), 492 (4.20), 491 (11.20), 490 (6.30), 477 (2.30), 476 (1.50), 299 (16.20), 298 (13.20), 297 (17.20), 285 (7.10), 284 (3.10), 283 (8.30), 257 (16.50), 256 (4.20), 255 (18.50), 230 (17.20), 229 (11.20), 228 (100), 227 (48.50), 194 (16.20), 193 (11.20), 185 (12.50), 184 (16.30), 168 (3.50), 167 (13.50), 138 (3.50), 137 (12.50), 108 (3.20), 107 (12.50), 106 (13.60), 105 (10.50), 104 (7.30), 92 (6.20), 91 (11.50), 90 (11.30), 89 (17.20), 78 (1.60), 77 (46.50), 76 (33.20), 75 (11.50), 65 (11.20), 64 (11.30), 63 (23.30), 52 (13.20), 51 (38.30), 50 (16.20). Found, %: C, 49.94; H, 3.67; N, 7.11; S, 5.35. $C_{24}H_{22}N_3BrO_7S$. Calcd., %: C, 50.08; H, 3.82; N, 7.30; S, 5.56.

Biological Assay

The concentration of the tested compounds was 10 μg/mL. The assay was performed according to a modification of the Kirby-Bauer disk diffusion method. The sterile discs were impregnated with a tested compound (10 μg/disc). Each tested compound was used as a negative control and ciprofloxacin and fluconazole were used as standards. Calculated average diameters (for triplicates) of the zone of inhibition (in mm) for tested samples were compared with those produced by the standard drugs.

Cytotoxicity

Cytotoxic activities of prepared compounds (**III**), (**V**)–(**VII**), and (**VIII**) were assessed according to methods of Masmann [16] and Vijayan [17]. Inhibitory activity against colon carcinoma cells (HCT-116) was registered using different concentrations of the tested compounds (50, 25, 12.5, 6.25, 3.125, and 1.65 μM) and cell viability (%) was determined by colorimetric method.

REFERENCES

1. Wilson, L.J., Li, M., and Portlock, D.E., *Tetrahedron Lett.*, 1998, vol. 39, no. 29, pp. 5135–5138.
2. Belai, I., *Tetrahedron Lett.*, 2003, vol. 44, no. 40, pp. 7475–7477.
3. Brouilette,W.J., Jestkov, V.P., Brown, M.L., Akhtar,M.S., Delorey, T.M., and Brawn, G.B., *J. Med. Chem.*, 1994, vol. 37, pp. 3289–3293.
4. Erik, C.S., Ottosen, R., Petersen, H.J., Bjorking, F., Latini, S., Hjarnaa, V., Bramm, E., and Binderup, L., *Bioorg. Med. Chem. Lett.,* 1997, vol. 7, pp. 3095–3100.
5. Hjarnaa, P.J., Jonsson, E., Latini, S., Dhar, S., Larsson, R., Bramm, E., Skov, T., and Binderup, L., *Cancer Res.,* 1999, vol. 59, pp. 5751–5757.
6. Olsen, L.S., Hijamaa, P.J., Latini, S., Holm, P.K., Larsson, R., Bramm, E., Binderup, I., and Madsen, M.W., *Inc. Cancer*, 2004, vol. 3, pp. 98–105.
7. Mader, M.M., *Curr. Opin. Drug Discov. Devel.*, 2005, vol. 8, pp. 613–618.
8. Ibrahim, H.K., Hasanen, J.A., Zein, M.A., and El-Deen, I.M., *Mens Agitat.*, 2008, vol. 3, pp. 59–72.
9. Aboubshit, S.A. and Aboubshit, H.A., *J. Chem.. Pharm. Res.*, 2012, vol. 4(1), pp. 568–579.
10. Abd El-Moneim, M., *IOSR JAC,* 2014, vol. 7, no. 1, pp. 67–76.
11. El-Sakka, S., *Mens Agitat.*, 2008, vol. 2, pp. 57–68.
12. Schelz, Z., Molnar, J., and Hohmann, J., *Fitoterapia*, 2006, vol. 77, no. 4, pp. 279–285.
13. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing, Informational Supplement M100. S13, 12th ed., NCCLS: Wayne, PA, USA, 2003.
14. Gillespie, S.H., *Antimicrobial Susceptibility in Medical Microbiology, Illustrated*, London: Butterworth Heinemann, 1994, pp. 234–247.
15. Chatterjee, S. and Das, S.N., *Ind. J. Pharmacol.,* 1996, vol. 28, pp. 116–119.
16. Mosmann, T., *J. Immunol. Methods*, 1983, vol. 65, pp. 55–63.
17. Vijayen, P., Raghu, C., Ashok, G., Dhanaraj, S.A., and Suresh, B., *Indian J. Med. Res.*, 2004, vol. 120, no. 1, pp. 9–24.