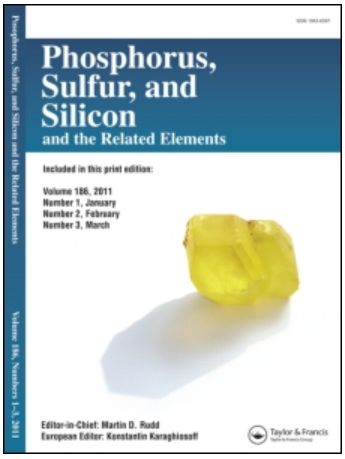

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SYNTHESIS, CONFORMATIONAL ANALYSIS AND ANTITUMOR TESTING OF 5-(*Z*)-ARYLIDENE-4-IMIDAZOLIDINONE DERIVATIVES

A. I. Khodair[ab]; H. I. El-subbagh[c]; A. M. Al-obaid[c]
[a] Chemistry Department, Faculty of Education, Tanta University (Kafr El-Sheikh Branch), Tanta, Egypt [b] Laboratoire de Chimie XII, Université de Poitiers et CNRS. 40 Avenue du Recteur Pineau, Poitiers, France [c] Department of Pharmaceutical Chemistry, College of Pharmacy, P.O. Box 2457 King Saud University, Riyadh, Kingdom of Saudi Arabia

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SYNTHESIS, CONFORMATIONAL ANALYSIS AND ANTITUMOR TESTING OF 5-(*Z*)-ARYLIDENE-4-IMIDAZOLIDINONE DERIVATIVES

A. I. KHODAIR[a*†], H. I. EL-SUBBAGH[b] and A. M. AL-OBAID[b]

[a]*Chemistry Department, Faculty of Education, Tanta University (Kafr El-Sheikh Branch), Tanta, Egypt and* [b]*Department of Pharmaceutical Chemistry, College of Pharmacy, P.O. Box 2457 King Saud University, 11451 Riyadh, Kingdom of Saudi Arabia*

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A series of 5-(Z)-arylidene-2-amino-4-imidazolidinones **16–34,** 5-*(Z)*-arylidene-2-(2-carboxyphenylamino)-4-imidazolidinones **35–41,** 5-*(Z)*-arylidene-3-aminomethyl-2-thioxo-4-imidazolidinones **42–55** and 5-*(Z)*-arylidene-3-aminomethyl-2-methylmercapto-4-imidazolidinones **56–67** have been synthesized *via* two different routes. Conformational analysis and antitumor activities have been studied. The antitumor activity of these compounds showed broad spectrum of activity against a wide range of different human cell lines of nine tumor subpanels causing both cytostatic and cytotoxic potency.

Keywords: 2-Thioxo-4-imidazolidinone; 5-*(Z)*-arylidene-4-imidazolidinone derivatives; conformational analysis and antitumoral activity

INTRODUCTION

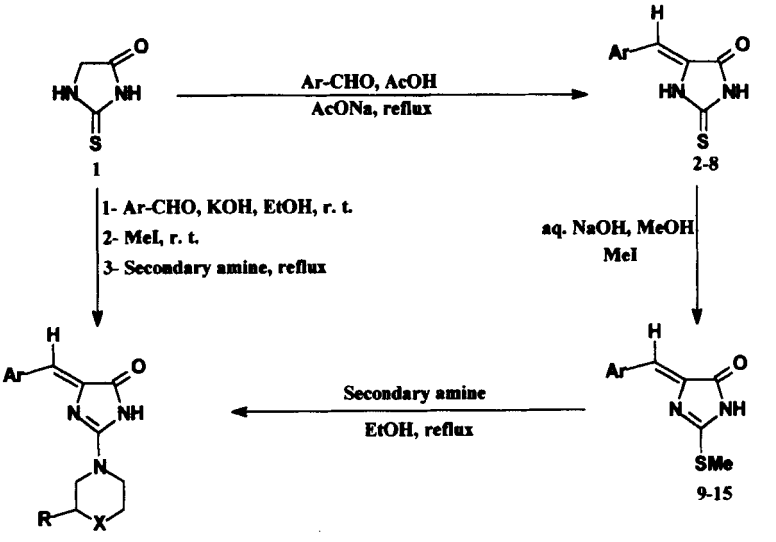
There has been considered interest in the synthesis and biological evaluation of the derivatives of imidazolidinone. They are not only feasible synthetic intermediates but also have been found to be a useful therapeutic agents possessing anticonvulsant[1], antfinflammatory[2,3], antitumor[4–6] and antiviral activities[7–9]. In the course of identifying new chemical

* Present address: Laboratoire de Chimie XII, Université de Poitiers et CNRS, 40 Avenue du Recteur Pineau, F-86022 Poitiers, France. Fax: (00) 33 (05) 49 45 35 01, E-Mail: ahmed.khodair @mailexcite.com.
† Corresponding author.

structures which may serve as leads for designing novel antitumors agents, we were particularly interested in imidazolidinones. In this respect, the linking of this synthon to an hydrophilic and lipophilic moieties such as a hydroxymethylpiperidine, morpholine, piperidine and aminobenzoic acid were considered. The present work describes the synthesis, conformational analysis and biological testing of 5-*(Z)*-arylidene-2-amino-4-imidazolidinones **16–34,** 5-*(Z)*-arylidene-2-(2-carboxyphenylamino)-4-imidazolidinones **35–41,** 5-*(Z)*-arylidene-3-aminomethyl-2-thioxo-4-imidazolidinones **42–55** and 5-*(Z)*-arylidene-3-aminomethyl-2-methylmercapto-4-imidazolidinones **56–67.**

RESULTS AND DISCUSSION

Aromatic aldehydes were condensed with 2-thioxo-4-imidazolidinone **1** by refluxing in a solution of sodium acetate and acetic acid to give 5-arylidene-2-thioxo-4-imidazolidinones **2–8**[10,11]. Compounds **2–8** were reacted with iodomethane in the presence of aqueous methanolic sodium hydroxide to obtain 5-arylidene-2-methylmercapto-4-imidazolidinones **9–15**[10,11]. The appropriate secondary amines such as morpholine, piperidine and 3-hydroxymethylpiperidine were reacted with **9–15** by refluxing in anhydrous ethanol to afford 5-*(Z)*arylidene-2-morpholino-4-imidazolidinones **16–22,** 5-*(Z)*-arylidene-2-piperidino-4-imidazolidinones **23–28** and 5-*(Z)*arylidene-2-(3-hydroxymetylpiperidino)-4-imidazolidinones **29–34,** respectively. Compounds **16–34** were also independently synthesized through another pathway *via* the condensation of 2-thioxo-4-imidazolidinone **1** with aromatic adehydes in the presence of ethanolic potassium hydroxide at room temperature followed by the addition of iodomethane at room temperature and finally followed by the addition of secondary amine under reflux. The structure of compounds **16–34** were established on the basis of their elemental analysis and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The IR spectrum of compound **29** was characterized by the presence of absorptions at 3430, 3190 and 1717 cm^{-1} due to OH, NH and C=O groups, respectively. The ^{1}H-NMR spectrum of compound **29** showed a triplet-doublet at 1.27,1.49 ppm with coupling constant 10.50 Hz was assigned to H-4′. The triplet-triplet at 2.86, 3.06 ppm with J = 11.30 Hz was due to H-2′. The singlet at δ 4.63 ppm was assigned to *OH* group (exchangeable with D_2O). The singlet at δ 6.28 ppm was



2-18	Ar	R	X
2	C_6H_5		
3	4-$MeOC_6H_4$		
4	4-MeC_6H_4		
5	4-ClC_6H_4		
6	4-HOC_6H_4		
7	2-thienyl		
8	2-furyl		
9	C_6H_5		
10	4-$MeOC_6H_4$		
11	4-MeC_6H_4		
12	4-ClC_6H_4		
13	4-HOC_6H_4		
14	2-thienyl		
15	2-furyl		
16	C_6H_5	H	O
17	4-$MeOC_6H_4$	H	O
18	4-MeC_6H_4	H	O

19-34	Ar	R	X
19	4-ClC_6H_4	H	O
20	4-HOC_6H_4	H	O
21	2-thienyl	H	O
22	2-furyl	H	O
23	C_6H_5	H	CH_2
24	4-$MeOC_6H_4$	H	CH_2
25	4-MeC_6H_4	H	CH_2
26	4-ClC_6H_4	H	CH_2
27	2-thienyl	H	CH_2
28	2-furyl	H	CH_2
29	C_6H_5	CH_2OH	CH_2
30	4-$MeOC_6H_4$	CH_2OH	CH_2
31	4-MeC_6H_4	CH_2OH	CH_2
32	4-ClC_6H_4	CH_2OH	CH_2
33	4-HOC_6H_4	CH_2OH	CH_2
34	2-thienyl	CH_2OH	CH_2

SCHEME 1

assigned to the vinyl proton, indicating the presence of a *E*-configuration for the exocyclic double bond, in agreement with the ^{1}H-NMR spectra of 5-*(E)*- and 5-*(Z)*-arylidene-2,4-imidazolidinedione derivatives whose vinyl protons respectively appear at δ 6.10–6.35 and 6.40–6.75 ppm[12–14]. The

singlet at δ 11.25 ppm was assigned to N_3-H, in agreement with the ^{1}H-NMR spectra of 5-*(E)*- and 5-*(Z)*-arylidenehydantoin derivatives whose N_1-H and N_3-H respectively appear at δ 10.29–10.72 and 11.10–11.38 ppm[12–14]. The ^{13}C-NMR spectrum of compound **29** showed the presence of a signal at 111.07 ppm was assigned to the vinilic carbon, indicating the presence of a *Z*-configuration for the exocyclic double bond, in agreement with the ^{13}C-NMR spectra of 5-*(Z)*- and 5-*(E)*-arylidene-2,4-imidazolidinedione derivatives respectively give signals at δ 105–112 ppm and 113–120 ppm[12–14] (Scheme 1).

At this stage, calculations at the AM1 level[15] were considered in order to determine the relative energies of the possible tautomeric forms. These also allow determination of the relative energies of the *E* and *Z* isomers of arylidenehydantoin derivatives. It was found that the *Z*-isomer is more stable by 2–4 kca/mol for **29** and thus no double bond isomerisation is anticipated. For compound **29,** the 4 tautomeric forms α, β, γ, and δ were considered. This result confirms that the exocyclic double bond must be *Z*. It was also found that the internal $C=N_1$ double bond is most stable $C=N_3$. Those results show that **29** must be present as α form and can be applied to compounds **16–34**.

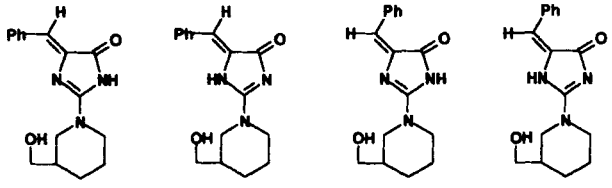
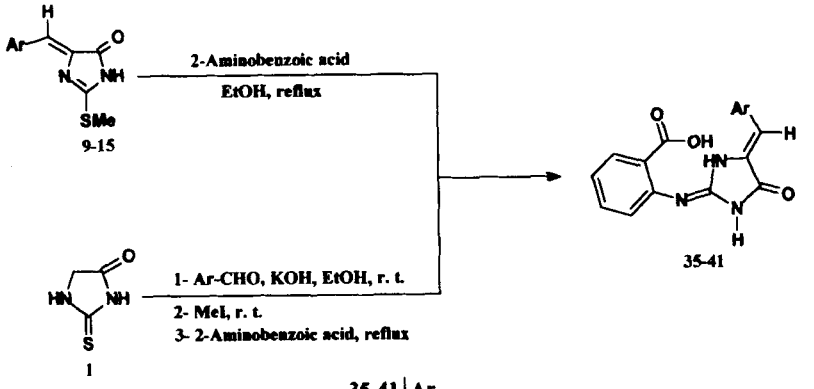


FIGURE 1 Relative energies (kca/mol) of toutomers (α-δ) for compound **29**

It was reported that 5-arylidene-2-methylmercapto-4-imidazolidinone **9–15** were reacted with 2-aminobenzoic acid by fusion at 150 °C or by boiling in glacial acetic acid to give arylideneimadazoquinazolinedione derivatives[16], which proved to possess variety of biological activities[17]. We have found that when the same above reactants were carried out in boiling ethanol, the corresponding 5-*(Z)*-arylidene-2-(2-carboxyphenylamino)-4-imidazolidinones **35–41** were obtained instead of the anticipated arylideneimadazoquinazolinediones[16]. Compounds **35–41** were

also independently synthesized through another pathway *via* the condensation of 2-thioxo-4-imidazolidinone **1** with aromatic adehydes in the presence of ethanolic potassium hydroxide at room temperature followed by the addition of iodomethane at room temperature and finally followed by the addition of 2-aminobenzoic acid under reflux. The structures of **35–41** were confirmed based on elemental analysis and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The IR spectrum of compound **35** was characterized by the presence of the absorption bands at 1704 and 1657 cm^{-1} were due to the presence of C=O and COOH groups. The ^{1}H-NMR spectrum of compound **35** showed a singlet at 6.63 ppm was assigned to the vinylic proton, indicating the presence of a *Z*-configuration for the exocyclic double bond. The singlet at 8.65 ppm was due to the carboxylic proton (exchangeable with D_2O). The broad singlets at 10.96 and 11.60 ppm were assigned to N_1-H and N_3-H, respectively. The ^{13}C-NMR spectrum of compound **36** showed the presence of a signal at 114.46 ppm was assigned to the vinilic carbon, indicating the presence of a *E*-configuration for the exocyclic double bond, in agreement with the ^{13}C-NMR spectra of 5-*(Z)*- and 5-*(E)*-arylidene-2,4-imidazolidinedione derivatives respectively give signals at δ 105–112 ppm and 113–120 ppm[12–14] (Scheme 2). At this stage, acidic hydrolysis of **36** was considered. It was found that the acidic hydrolysis of **36** gave the corresponding 5-(Z)-(4-methoxybenzylidene)-2,4-imidazolidinedione[12] (Scheme 2).

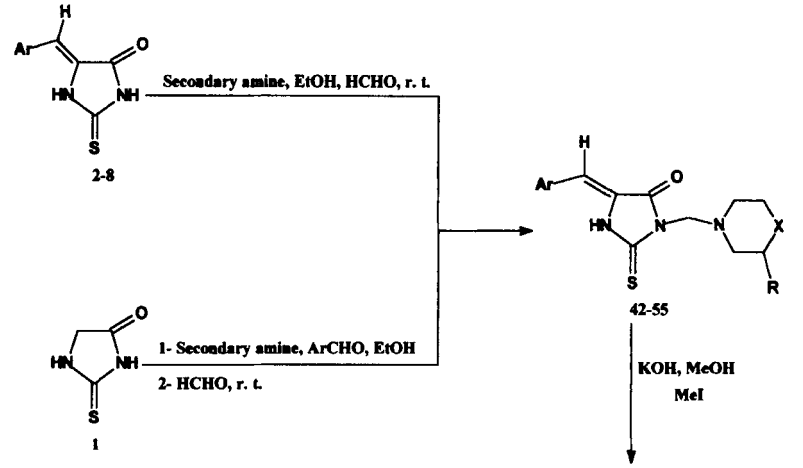
5-*(Z)*-Arylidene-3-aminomethyl-2-thioxo-4-imidazolidinones **42–55** were prepared from the direct condensation of the corresponding 5-*(Z)*-arylidene-2-thioxo-4-imidazolidinones **2–8** with formaldehyde solution and secondary amines in ethanol at room temperature. Compounds **42–55** could be prepared from the indirect condensation of 2-thioxo-4-imidazolidinone **1** with aromatic aldehydes in the presence of a secondary amines in ethanol, followed by the addition of aqueous formaldehyde at room temperature. Compounds **42–55** were reacted with iodomethane in anhydrous methanol, in the presence of sodium methoxide, to yield the corresponding 5-*(Z)*-arylidene-3-aminomethyl-2-methyl-mercapto-4-imidazolidinones **56–67**. Compounds **56–67** were independently synthesized through another pathway *via* condensation of 5-arylidene-2-methylmercapto-4-imidazolidinone **9–15** with formaldehyde solution and secondary amines. The structure of compounds **56–67** could be established and confirmed for the reaction products on the bases of spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The IR spectrum of compound **56** was



35-41	Ar
35	C_6H_5
36	4-$MeOC_6H_4$
37	4-MeC_6H_4
38	4-ClC_6H_4
39	4-HOC_6H_4
40	2-thienyl
41	2-furyl

SCHEME 2

characterized by the absence of a signal for an NH group and the presence of the carbonyl group at 1712 cm^{-1}. The ^{1}H-NMR spectrum of compound **56** showed a singlet at 2.69 ppm was assigned to SCH_3 group. The singlet at 6.63 ppm was assigned to the vinylic proton, indicating the presence of a *Z*-configuration for the exocyclic double bond. The singlet at 4.29 ppm was due to the methylene group. The ^{13}C-NMR spectrum of compound **58** showed the presence of a signal at 124.42 ppm was assigned to the vinilic carbon, indicating the presence of a E-configuration for the exocyclic double bond, in agreement with the ^{13}C-NMR spectra of 5-*(Z)*- and 5-*(E)*-arylidene-2,4-imidazolidinedione derivatives respectively give signals at δ 105–112 ppm and 113–120 ppm[12–14] (Scheme 2). At this stage, basic hydrolysis of **58** was considered. It was found that the basic hydrolysis of **58** gave the corresponding 5-*(Z)*-(4-methylbenzylidene)- 2,4-imidazolidinedione[12] (Scheme 3).



42-55	Ar	R	X
42	C_6H_5	H	O
43	4-$MeOC_6H_4$	H	O
44	4-MeC_6H_4	H	O
45	4-ClC_6H_4	H	O
46	2-thienyl	H	O
47	2-furyl	H	O
48	C_6H_5	H	CH_2
49	4-$MeOC_6H_4$	H	CH_2
50	4-MeC_6H_4	H	CH_2
51	4-ClC_6H_4	H	CH_2
52	4-HOC_6H_4	H	CH_2
53	2-thienyl	H	CH_2
54	2-furyl	H	CH_2
55	4-MeC_6H_4	CH_2OH	CH_2

56-67	Ar	X
56	C_6H_5	O
57	4-$MeOC_6H_4$	O
58	4-MeC_6H_4	O
59	4-ClC_6H_4	O
60	2-thienyl	O
61	2-furyl	O
62	C_6H_5	CH_2
63	4-$MeOC_6H_4$	CH_2
64	4-MeC_6H_4	CH_2
65	4-ClC_6H_4	CH_2
66	2-thienyl	CH_2
67	2-furyl	CH_2

SCHEME 3

TABLE I Characterization data for compounds 16–67

Compd.	*mp (°C)*	*Yield (%)*		*Mol. formula*	*Calcd / Found (%)*			M^+ *(m/z)*
					C	*H*	*N*	
16	232	90[a]	72[b]	$C_{14}H_{15}N_3O_2$ (257.29)	Ref. 18			
17	263	88[a]	76[b]	$C_{15}H_{17}N_3O_3$ (287.31)	62.7/36.0	6.0/6.2	14.6/14.9	287
18	299	96[a]	73[b]	$C_{15}H_{17}N_3O_2$ (271.31)	66.4/66.6	6.3/6.7	15.5/15.6	271
19	308	96[a]	75[b]	$C_{14}H_{14}ClN_3O_2$ (291.73)	Ref. 18			
20	262	73[a]	68[b]	$C_{14}H_{15}N_3O_3$ (273.29)	61.5/61.4	5.5/5.7	15.4/15.2	273
21	275	89[a]	65[b]	$C_{12}H_{13}N_3O_2S$ (263.31)	54.7/55.0	5.0/5.1	16.0/15.8	263
22	272	70[a]	60[b]	$C_{12}H_{13}N_3O_3$ (247.25)	58.3/59.1	5.3/5.5	17.0/17.1	247
23	198	86[a]	73[b]	$C_{15}H_{17}N_3O$ (255.31)	Ref. 18			
24	192	78[a]	76[b]	$C_{16}H_{19}N_3O_2$ (285.34)	67.3/67.2	6.7/6.8	14.7/14.8	285
25	231	77[a]	74[b]	$C_{16}H_{19}N_3O$ (269.34)	71.3/71.5	7.1/7.2	15.6/15.5	269
26	233	79[a]	76[b]	$C_{15}H_{16}ClN_3O$ (289.76)	Ref. 18			
27	175	78[a]	70[b]	$C_{13}H_{15}N_3OS$ (261.34)	59.7/59.6	5.8/5.9	16.1/16.0	261
28	207	77[a]	71[b]	$C_{13}H_{15}N_3O_2$ (245.28)	63.7/63.9	6.2/6.2	17.1/17.2	245
29	198	74[a]	75[b]	$C_{15}H_{17}N_3O$ (255.31)	70.6/70.4	6.7/6.7	16.5/16.8	255
30	229	92[a]	73[b]	$C_{17}H_{21}N_3O_3$ (315.37)	64.7/65.0	6.7/6.6	13.3/13.5	315
31	250	88[a]	76[b]	$C_{17}H_{21}N_3O_2$ (299.37)	68.2/68.2	7.1/7.1	14.0/14.2	299
32	238	88[a]	77[b]	$C_{16}H_{18}ClN_3O_2$ (319.79)	60.1/60.1	5.7/5.8	13.1/13.1	319
33	170	87[a]	75[b]	$C_{16}H_{19}N_3O_3$ (301.34)	63.8/64.0	6.4/6.5	13.9/14.0	301
34	220	89[a]	72[b]	$C_{14}H_{17}N_3O_2S$ (291.36)	57.7/57.7	5.9/5.9	14.4/14.4	291
35	302	75[a]	65[b]	$C_{17}H_{13}N_3O_3$ (307.30)	66.4/66.4	4.3/4.2	13.7/13.8	307
36	262	66[a]	68[b]	$C_{18}H_{15}N_3O_4$ (337.33)	64.1/64.2	4.5/4.6	12.5/12.4	337

Compd.	mp (°C)	Yield (%)		Mol. formula	Calcd / Found (%)			M^+ (m/z)
					C	H	N	
37	330	79[a]	70[b]	$C_{18}H_{15}N_3O_3$ (321.34)	67.3/67.3	4.7/4.8	13.1/13.2	321
38	335	81[a]	73[b]	$C_{17}H_{12}ClN_3O_3$ (341.75)	59.7/60.0	3.5/3.8	12.3/12.5	341
39	326	75[a]	72[b]	$C_{17}H_{13}N_3O_4$ (323.30)	63.2/63.2	4.1/4.2	13.0/13.1	323
40	234	73[a]	70[b]	$C_{15}H_{11}N_3O_3S$ (313.33)	57.5/57.5	3.5/3.5	13.4/13.4	313
41	221	68[a]	65[b]	$C_{15}H_{11}N_3O_4$ (297.27)	60.6/60.6	3.7/3.7	14.1/14.2	297
42	188	83[a]	80[b]	$C_{15}H_{17}N_3O_2S$ (303.37)	59.4/59.5	5.6/5.7	13.9/14.0	303
43	195	90[a]	85[b]	$C_{16}H_{19}N_3O_3S$ (333.40)	57.6/57.8	5.7/5.7	12.6/12.5	333
44	177	90[a]	82[b]	$C_{16}H_{19}N_3O_2S$ (317.40)	60.5/60.6	6.0/6.0	13.2/13.2	317
45	184	86[a]	86[b]	$C_{15}H_{16}ClN_3O_2S$ (337.82)	53.3/53.3	4.8/4.7	12.4/12.4	337
46	160	92[a]	82[b]	$C_{13}H_{15}N_3O_2S_2$ (309.40)	50.5/50.6	4.9/5.0	13.6/13.4	309
47	177	82[a]	80[b]	$C_{13}H_{15}N_3O_3S$ (293.34)	53.2/53.3	5.1/5.2	14.3/14.3	293
48	220	80[a]	84[b]	$C_{16}H_{19}N_3OS$ (301.41)	Ref. 19			
49	217	81[a]	82[b]	$C_{17}H_{21}N_3O_2S$ (331.43)	Ref. 19			
50	222	76[a]	80[b]	$C_{17}H_{21}N_3OS$ (315.43)	64.7/64.4	6.7/6.8	13.3/13.5	315
51	222	77[a]	85[b]	$C_{16}H_{18}ClN_3OS$ (335.85)	57.2/57.5	5.4/5.3	12.5/12.6	335
52	182	78[a]	81[b]	$C_{16}H_{19}N_3O_2S$ (317.40)	60.5/60.5	6.0/6.0	13.2/13.2	317
53	204	78[a]	80[b]	$C_{14}H_{17}N_3OS_2$ (307.43)	54.7/54.8	5.6/5.7	13.7/13.6	307
54	207	79[a]	86[b]	$C_{14}H_{17}N_3O_2S$ (291.37)	57.7/57.6	5.9/6.0	14.4/14.6	291
55	182	87[a]	82[b]	$C_{18}H_{23}N_3O_2S$ (345.45)	62.6/62.4	6.7/6.8	12.2/12.3	345
56	110	70[a]	83[b]	$C_{16}H_{19}N_3O_2S$ (317.41)	60.5/60.6	6.0/6.1	13.2/13.3	317
57	137	92[a]	85[b]	$C_{17}H_{21}N_3O_3S$ (347.43)	58.8/58.7	6.1/6.0	12.1/12.1	347
58	150	86[a]	81[b]	$C_{17}H_{21}N_3O_25$ (331.43)	61.6/61.7	6.4/6.5	12.7/12.8	331

Compd.	*mp (°C)*	*Yield (%)*		*Mol. formula*	*Calcd / Found (%)*			M^+ *(m/z)*
					C	*H*	*N*	
59	138	98[a]	84[b]	$C_{16}H_{18}ClN_3O_2S$ (351.85)	54.6/54.9	5.2/5.3	11.9/12.1	351
60	139	75[a]	80[b]	$C_{14}H_{17}N_3O_2S_2$ (323.43)	52.0/52.1	5.3/5.5	13.0/13.2	323
61	132	73[a]	81[b]	$C_{14}H_{17}N_3O_3S$ (307.37)	54.7/54.6	5.6/5.6	13.7/13.8	307
62	175	78[a]	82[b]	$C_{17}H_{21}N_3OS$ (315.43)	64.7/64.8	6.7/6.7	13.3/13.3	315
63	157	81[a]	86[b]	$C_{18}H_{23}N_3O_2S$ (345.46)	62.6/62.7	6.7/6.8	12.2/12.3	345
64	176	68[a]	84[b]	$C_{18}H_{23}N_3OS$ (329.46)	65.6/65.8	7.0/7.2	12.8/13.1	329
65	189	77[a]	87[b]	$C_{17}H_{20}ClN_3OS$ (349.88)	58.5/58.5	5.8/5.9	12.0/12.0	349
66	177	75[a]	83[b]	$C_{15}H_{19}N_3OS_2$ (321.46)	56.0/56.2	5.9/6.1	13.1/13.2	321
67	148	72[a]	80[b]	$C_{15}H_{19}N_3O_2S$ (305.39)	59.0/59.1	6.3/6.4	13.8/13.9	305

[a] Yield obtained from method A. [b] Overall yield obtained from method B.

TABLE II IR and ^{1}H NMR data for the compounds listed in TABLE I

Compound	*IR (KBr) (cm^{-1})*	*^{1}H-NMR (Me_2SO) / δ*
16	3152 (NH), 1710 (CO).	3.36 (4H, t, J = 4.8 Hz, H-2′, H-6′), 3.66 (4H, t, J = 4.6 Hz, H-3′, H-5′), 6.35 (1H, s, =CH), 7.28–8.08 (5H, m, H-Ar), 11.20 (1H, s, N_3-H).
17	3158 (NH), 1712 (CO).	3.35 (4H, t, J = 4.9 Hz, H-2′, H-6′), 3.64 (3H, s, OCH_3), 3.77 (4H, t, J = 4.5 Hz, H-3′, H-5), 6.35 (1H, s, =CH), 6.88, 6.99 (4H, 2d, H-Ar), 11.21 (1H, S, N_3-H).
18	3150 (NH), 1700 (CO).	2.30 (3H, s, CH_3), 3.36 (4H, t, J = 4.5 Hz, H-2, H-6′), 3.65 (4H, t, J = 4.4 Hz, H-3′, H-5′), 6.34 (1H, s, =CH), 7.16, 7.90 (4H, 2d, H-Ar), 11.20(1H, s, N_3-H).
19	3157 (NH), 1708 (CO).	3.34 (4H, t, J = 4.7 Hz, H-2′, H-6′), 3.66 (4H, t, J = 4.5 Hz, H-3′, H-5′), 6.33 (1H, s, =CH), 7.40, 8.10 (4H, 2d, H-Ar), 11.22 (1H, s, N_3-H).
20	3420 (OH), 3150 (NH), 1705 (CO).	^{1}H-NMR δ 3.51 (4H, t, J = 4.8 Hz, H-2′, H-6′), 3.63 (4H, t, J = 4.6 Hz, H-3′, H-5′), 6.32 (1H, s, =CH), 6.76, 7.90 (4H, 2d, H-Ar), 10.40 (2H, br. s, OH, N_3-H).
21	3160 (NH), 1715 (CO).	3.35 (4H, t, J = 4.9 Hz, H-2′, H-6′), 3.65 (4H, t, J = 4.5 Hz, H-3′, H-5′), 6.70 (1H, s, =CH), 7.05 (1H, t, H-4"), 7.40 (1H, d, H-3"), 7.60 (1H, d, H-5"), 11.50 (1H, s, N_3-H).
22	3156 (NH), 1712 (CO).	3.35 (4H, t, J = 4.8 Hz, H-2′, H-6′), 3.65 (4H, t, J = 4.3 Hz, H-3′, H-5′), 6.29 (1H, s, =CH), 6.60 (1H, t, H-4"), 7.08 (1H, d, H-3"), 7.70 (1H, d, H-5"), 11.32 (1H, s, N_3-H).
23	3198 (NH), 1715 (CO).	0.82–1.63 (6H, m, H-3′, H-4′, H-5′), 3.24 (4H, m, H-2′, H-6′), 6.27 (1H, s, =CH), 7.28–8.00 (5H, m, H-Ar), 10.63 (1H, s, N_3-H).
24	3192 (NH), 1710 (CO).	0.91–1.65 (6H, m, H-3′, H-4′, H-5′), 3.36 (4H, m, H-2′, H-6′), 3.78 (3H, s, OCH_3), 6.27 (1H, s, =CH), 6.80, 7.82 (4H, 2d, H-Ar), 10.63 (1H, s, N_3-H).
25	3152 (NH), 1710 (CO).	0.82–1.63 (6H, m, H-3′, H-4′, H-5′), 2.30 (3H, s, CH_3), 3.36 (4H, m, H-2′, H-6′), 6.25 (1H, s, =CH), 7.22, 7.80 (4H, 2d, H-Ar), 10.71 (1H, s, N_3-H).
26	3196 (NH),1717 (CO).	0.82–1.63 (6H, m, H-3′, H-4′, H-5′), 3.35 (4H, m, H-2′, H-6′), 6.25 (1H, s, =CH), 7.34, 8.01 (4H, m, H-Ar), 10.82 (1H, s, N_3-H).
27	3195 (NH),1712 (CO).	0.82–1.65 (6H, m, H-3′, H-4′, H-5′), 3.27 (4H, m, H-2′, H-6′), 6.61 (1H, s, =CH), 7.35 (1H, t, H-4"), 7.52 (1H, d, H-3"), 7.60 (1H, d, H-5"), 10.76 (1H, s, N_3-H).
28	3190 (NH),1708 (CO).	0.82–1.53 (6H, m, H-3′, H-4′, H-5′), 3.37 (4H, m, H-2′, H-6′), 6.19 (1H, s, =CH), 6.63 (1H, t, H-4"), 7.05 (1H, d, H-3"), 7.8 (1H, d, H-5"), 10.90 (1H, s, N_3-H).

Compound	*IR (KBr) (cm^{-1})*	*^{1}H-NMR (Me_2SO) / δ*
29	3434 (OH), 3190 (NH), 1717(CO).	1.32–1.69 (5H, m, H-3′, H-4′, H-5′), 2.70–3.10 (4H, m, H-2′, H-6′), 4.10 (2H, t, CH_2OH), 4.55 (1H, s, OH), 6.28 (1H, s, =CH), 7.27–8.15 (5H, m, H-Ar), 11.24 (1H, s, N_3-H).
30	3436 (OH), 3188 (NH), 1715(CO).	1.35–1.72 (5H, m, H-3′, H-4′, H-5′), 2.70–3.00 (4H, m, H-2′, H-6′), 3.77 (3H, s, OCH_3), 4.10 (2H, t, CH_2OH), 4.54 (1H, s, OH), 6.28 (1H, s, =CH), 6.94, 8.00 (4H, 2d, H-Ar), 11.00 (1H, s, N_3-H).
31	3430 (OH), 3198 (NH), 1715(CO).	1.30–1.80 (5H, m, H-3′, H-4′, H-5′), 2.30 (3H, s, CH_3), 2.60–3.00 (4H, m, H-2′, H-6′), 4.10 (2H, t, CH_2OH), 4.60 (1H, s, OH), 6.27 (1H, s, =CH), 7.20, 7.82 (4H, 2d, H-Ar), 11.20 (1H, s, N_3-H).
32	3436 (OH), 3192 (NH), 1715 (CO).	1.20–1.71 (5H, m, H-3′, H-4′, H-5′), 2.70–3.00 (4H, m, H-2′, H-6′), 4.10 (2H, t, CH_2OH), 4.60 (1H, s, OH), 6.26 (1H, s, =CH), 7.40, 8.00 (4H, 2d, H-Ar), 11.25 (1H, s, N_3-H).
33	3430 (OH), 3198 (NH), 1719(CO).	1.25–1.70 (5H, m, H-3′, H-4′, H-5′), 2.60–3.00 (4H, m, H-2′, H-6′), 4.10 (2H, t, CH_2OH), 4.60 (1H, s, OH), 6.25 (1H, s, =CH), 6.80, 7.90 (4H, 2d, H-Ar), 9.67 (1H, s, OH-Ar), 11.10 (1H, s, N_3-H).
34	3438 (OH), 3192 (NH), 1712(CO).	1.50–1.82 (5H, m, H-3′, H-4′, H-5′), 2.70–3.00 (4H, m, H-2′, H-6′), 4.10 (2H, t, CH_2OH), 4.50 (1H, s, OH), 6.63 (1H, s, =CH), 7.04 (1H, t, H-4"), 7.35 (1H, d, H-3"), 7.56 (1H, d, H-5"), 11.10 (1H, s, N_3-H).
35	3286 (NH), 1775, 1718(2CO).	6.63 (1H, s, =CH), 7.20–9.00 (10H, m, H-Ar, COOH), 11.05 (1H, s, N_1-H), 11.45 (1H, s, N_3-H).
36	3284 (NH), 1776, 1719(2CO).	3.81 (3H, s, OCH_3), 6.60 (1H, s, =CH), 7.01–8.94 (9H, m, H-Ar, COOH), 11.07 (1H, s, N_1-H), 11.54 (1H, s, N_3-H).
37	3284 (NH), 1780, 1718(2CO).	2.35 (3H, s, CH_3), 6.61 (1H, s, =CH), 7.18–8.90 (9H, m, H-Ar, COOH), 11.05 (1H, s, N_1-H), 11.50 (1H, s, N_3-H).
38	3290 (NH), 1772, 1715(2CO).	6.70 (1H, s, =CH), 7.22–9.27 (9H, m, H-Ar, COOH), 11.20 (1H, s, N_1-H), 11.73 (1H, s, N_3-H).
39	3288 (NH), 1775, 1717 (2CO).	6.59 (1H, s, =CH), 6.74–9.50 (9H, m, H-Ar, COOH), 10.15 (1H, s, OH), 10.50 (1H, s, N_1-H), 11.26 (1H, s, N_3-H).
40	3292 (NH), 1768, 1719 (2CO).	6.58 (1H, s, =CH), 7.02–9.70 (8H, m, H-Ar, COOH), 10.35 (1H, s, N_1-H), 111.26 (1H, s, N_3-H).
41	3290 (NH), 1770, 1717 (2CO).	6.50 (1H, s, =CH), 6.64–9.30 (8H, m, H-Ar, COOH), 10.35 (1H, s, N_1-H, 11.25 (1H, s, N_3-H).
42	3152 (N_1-H), 1710 (CO).	2.62 (4H, m, H-2′, H-6′), 3.52 (4H, m, H-3′, H-5′), 4.70 (2H, s, N-CH_2-N), 6.50 (1H, s, =CH), 7.39–7.84 (5H, m, H-Ar), 12.33 (1H, s, N_1-H).

Compound	*IR (KBr) (cm^{-1})*	*^{1}H-NMR (Me_2SO) / δ*
43	3168 (N_i-H), 1712 (CO).	2.59 (4H, m, H-2′, H-6′), 3.56 (4H, m, H-3′, H-5′), 3.82 (3H, s, OCH_3), 4.69 (2H, s, N-CH_2-N), 6.60 (1H, s, =CH), 7.00, 7.80 (4H, 2d, H-Ar), 12.29 (1H, s, N_1-H).
44	3154 (N_1-H), 1709 (CO).	2.59 (4H, m, H-2′, H-6′), 3.32 (3H, s, CH_3), 3.57 (4H, m, H-3′, H-5′), 4.69 (2H, s, N-CH_2-N), 6.59 (1H, s, =CH), 7.20, 7.74 (4H, 2d, H-Ar), 12.29 (1H, s, N_1-H).
45	3170 (N_1-H), 1717 (CO).	59 (4H, m, H-2′, H-6′), 3.53 (4H, m, H-3′, H-5′), 4.70 (2H, s, N-CH_2-N), 6.61 (1H, s, =CH), 7.75, 7.82 (4H, 2d, H-Ar), 12.43 (1H, s, N_1-H).
46	3166 (N_1-H), 1715 (CO).	2.60 (4H, m, H-2′, H-6′), 3.53 (4H, m, H-3′, H-5′), 4.69 (2H, s, N-CH_2-N), 6.76 (1H, s, =CH), 7.87- 7.93 (3H, m, H-3", H-4", H-5"), 12.20 (1H, s, N_1-H).
47	3159 (N_1-H), 1710 (CO).	2.55 (4H, m, H-2′, H-6′), 3.53 (4H, m, H-3′, H-5′), 4.69 (2H, s, N-CH_2-N), 6.54 (1H, s, =CH), 6.68- 7.90 (3H, m, H-3", H-4", H-5"), 12.08 (1H, s, N_1-H).
48	3172 (N_1-H),1712 (CO).	0.68–1.63 (6H, m, H-3′, H-4′, H-5′), 2.50 (4H, m, H-2′, H-6′), 5.08 (2H, s, N-CH_2-N), 6.64 (1H, s, =CH), 7.40–7.86 (5H, m, H-Ar), 12.36 (1H, s, N_1-H).
49	3170 (N_1-H),1717 (CO).	0.66–1.62 (6H, m, H-3′, H-4′, H-5′), 2.50 (4H, m, H-2′, H-6′), 3.83 (3H, s, OCH_3), 5.07 (2H, s, N-CH_2-N), 6.62 (1H, s, =CH), 7.05, 7.80 (4H, 2d, H-Ar), 12.28 (1H. s, N_1-H).
50	3168 (N_1-H), 1709 (CO).	0.67–1.65 (6H, m, H-3′, H-4′, H-5′), 2.48 (3H, s, CH_3), 2.50 (4H, m, H-2′, H-6′), 5.06 (2H, s, N-CH_2-N), 6.60 (1H, s, =CH), 7.25, 7.68 (4H, 2d, H-Ar), 12.27 (1H, s, N_1-H).
51	3166 (N_1-H),1711(CO).	0.67–1.70 (6H, m, H-3′, H-4′, H-5′), 2.50 (4H, m, H-2′, H-6′), 5.06 (2H, s, N-CH_2-N), 6.62 (1H, s, =CH), 7.43, 7.88 (4H, 2d, H-Ar), 12.36 (1H, s, N_1-H).
52	3158 (N_1-H), 1710 (CO).	0.65–1.60 (6H, m, H-3′, H-4′, H-5′),), 2.54 (4H, m, H-2′, H-6′), 5.06 (2H, s, N-CH_2-N), 6.77 (1H, s, =CH), 6.87,7.64 (3H, 2d, H-Ar), 10.10 (1H, s, OH), 12.32 (1H, s, N_1-H).
53	3160 (N_1-H), 1711 (CO).	0.88–1.60 (6H, m, H-3′, H-4′, H-5′),), 2.52 (4H, m, H-2′, H-6′), 5.06 (2H, s, N-CH_2-N), 6.77 (1H, s, =CH), 7.20–7.97 (3H, m, H-3", H-4", H-5"), 12.13 (1H, s, N_1-H).
54	3156 (N_1-H), 1707 (CO).	0.65–1.60 (6H, m, H-3′, H-4′, H-5′),), 2.50 (4H, m, H-2′, H-6′), 5.05 (2H, s, N-CH_2-N), 6.55 (1H, s, =CH), 7.17–7.90 (3H, m, H-3", H-4", H-5"), 12.06 (1H, s, N_1-H).
55	3435 (OH), 3152 (NH), 1713 (CO).	1.46–3.94 (14H, m, H-3′, H-4′, H-5′, H-2′, H-6′, CH_3, CH_2OH), 4.35 (1H, s, OH), 4.73 (2H,s, N-CH_2-N), 6.54 (1H, s, =CH), 7.23, 7.67 (4H, m, H-Ar), 12.15 (1H, s, N_1-H).

Compound	*IR (KBr) (cm^{-1})*	*^{1}H-NMR (Me_2SO) / δ*
56	1712 (CO).	2.53 (4H, m, H-2′, H-6′), 2.70 (3H, s, SCH_3), 3.56 (4H, m, H-3′, H-5′), 4.28 (2H, s, N-CH_2-N), 6.88 (1H, s, =CH), 7.40–8.29 (5H, m, H-Ar).
57	1715 (CO).	2.51 (4H, m, H-2′, H-6′), 2.69 (3H, s, SCH_3), 3.56 (4H, m, H-3′, H-5′), 3.82 (3H, s, OCH_3), 4.28 (2H, s, N-CH_2-N), 6.86 (1H, s, =CH), 7.00, 8.20 (4H, 2d, H-Ar).
58	1715 (CO).	2.37 (3H, s, CH_3), 2.61 (4H, t, H-2′, H-6′), 2.78 (3H, s, SCH_3), 3.67 (4H, t, H-3′, H-5′), 4.34 (2H, s, N-CH_2-N), 6.93 (1H, s, =CH), 7.27, 8.13 (4H, 2d, H-Ar).
59	1712 (CO).	2.51 (4H, m, H-2′, H-6′), 2.71 (3H, s, SCH_3), 3.55 (4H, m, H-3′, H-5′), 4.29 (2H, s, N-CH_2-N), 6.88 (1H, s, =CH), 7.50, 8.25 (4H, 2d, H-Ar).
60	1710 (CO).	2.51 (4H, m, H-2′, H-6′), 2.71 (3H, s, SCH_3), 3.56 (4H, m, H-3′, H-5′), 4.28 (2H, s, N-CH_2-N), 7.17- 7.91 (4H, m, =CH, H-3", H-4", H-5").
61	1712 (CO).	2.51 (4H, m, H-2′, H-6′), 2.69 (3H, s, SCH_3), 3.56 (4H, m, H-3′, H-5′), 4.27 (2H, s, N-CH_2-N), 6.74- 7.93 (4H, m, =CH, H-3", H-4", H-5").
62	1715 (CO).	0.75–1.60 (6H, m, H-3′, H-4′, H-5′), 2.52 (4H, m, H-2′, H-6′), 2.72 (3H, s, SCH_3), 4.61 (2H, s, N-CH_2-N), 6.90 (1H, s, =CH), 7.41–8.30 (5H, m, H-Ar).
63	1714 (CO).	0.73–1.62 (6H, m, H-3′, H-4′, H-5′), 2.51 (4H, m, H-2′, H-6′), 2.70 (3H, s, SCH_3), 3.81 (3H, s, OCH_3), 4.58 (2H, s, N-CH_2-N), 6.72 (1H, s, =CH), 7.05, 8.16 (4H, 2d, H-Ar).
64	1708 (CO).	0.67–1.65 (6H, m, H-3′, H-4′, H-5′), 2.48 (3H, s, CH_3), 2.51 (4H, m, H-2′, H-6′), 2.70 (3H, s, SCH_3), 4.28 (2H, s, N-CH_2-N), 6.88 (1H, s, =CH), 7.45, 8.24 (4H, 2d, H-Ar).
65	1712 (CO).	0.73–1.60 (6H, m, H-3′, H-4′, H-5′), 2.50 (4H, m, H-2′, H-6′), 2.71 (3H, s, SCH_3), 4.59 (2H, s, N-CH_2-N), 6.89 (1H, s, =CH), 7.45, 8.27 (4H, 2d, H-Ar).
66	1710 (CO).	0.73–1.60 (6H, m, H-3′, H-4′, H-5′), 2.50 (4H, m, H-2′, H-6′), 2.71 (3H, s, SCH_3), 4.58 (2H, s, N-CH_2-N), 7.11–7.90 (4H, m, =CH, H-3", H-4", H-5").
67	1709 (CO).	0.65–1.60 (6H, m, H-3′, H-4′, H-5′), 2.50 (4H, m, H-2′, H-6′), 2.69 (3H, s, SCH_3), 4.57 (2H, s, N-CH_2-N), 6.70–7.93 (4H, m, =CH, H-3", H-4", H-5").

TABLE III ^{13}C NMR data for some selected compounds listed in TABLE I

Compound	*^{13}C-NMR (Me_2SO) / δ*
28	10.99 (C-4'), 22.45 (C-3', 5'), 43.43 (C-2', 6'), 94.51 (C-4"), 111.67 (=CH), 112.45 (C-3"), 129.73 (C-5), 143.74 (C-2"), 150.50 (C-5"), 167.01 (C-2), 176.07 (C-4).
29	24.29 (C-4'), 26.73 (C-3'), 38.61 (C-5'), 45.66 (C-2'), 48.23 (C-6'), 63.49 (CH_2OH), 111.07 (=CH), 127.20, 128.46, 130.13, 136.37, 141.68 (C-5, C-Ar), 158.55 (C-2), 172.45 (C-4).
32	24.00 (C-4'), 26.42 (C-3'), 38.32 (C-5'), 45.31 (C-2'), 47.96 (C-6'), 63.13 (CH_2OH), 108.93 (=CH), 125.35, 128.19, 131.07, 131.27, 135.07, 141.89 (C-5, C-Ar), 158.45 (C-2), 171.98 (C-4).
34	23.96 (C-4'), 26.40 (C-3'), 45.36 (C-5'), 38.27 (C-2'), 47.96 (C-6'), 63.18 (CH_2OH), 105.69 (=CH), 125.37, 126.92, 128.79, 139.34 (C-5, C-Ar), 157.36 (C-2), 171.24 (C-4).
36	55.73 (OCH_3), 114.46 (=CH), 122.08, 125.71, 127.89, 131.52, 132.39, 132.41, 132.43, 132.47, 132.54, 134.68, 141.45, (C-5, C-Ar), 159.79 (C-2), 165.50 (C-4), 170.03 (COOH).
55	21.10 (CH_3), 24.61 (C-4'), 26.50 (C-3'), 51.94 (C-5'), 54.94 (C-2'), 62.73 (C-6'), 64.25 (CH_2OH), 112.75 (=CH), 129.32, 129.54, 130.10, 130.23, 139.22 (C-5, C-Ar), 165.23 (C-4), 179.99 (C-2).
58	13.37 (SCH_3), 21.64 (CH_3), 50.89 (C-2', 6'), 62.46 (N-CH_2-N), 66.70 (C-3', 5'), 124.42 (=CH), 129.45, 131.91, 132.00, 140.34 (C-5, C-Ar), 164.84 (C-4), 170.54 (C-2).

ANTITUMOR ACTIVITY

Compounds **16–67** were subjected to the NCI in *vitro* disease-oriented human cells screening panel assay[20,21]. About 60 cell lines of nine tumor subpanels (leukemia, colon, melanoma, CNS, breast, prostate, ovarian, renal and small cell lung cancers) were incubated with five concentrations (0.01–100 μM) for each compound and were used to create log concentration – % growth inhibition curves. Three response parameters (GI_{50}, TGI and LC_{50}) were calculated for each cell line. The GI_{50} value corresponds to the compounds concentration causing 50% decrease in net cell growth. The TGI value is the compounds concentration resulting in total growth inhibition and the LC_{50} value is the compounds concentration causing a net 50% loss of initial cells at the end of the incubation period (48 h). Full panel mean-graph midpoint value (MG-MID) for certain agents are the

average of individual real and default GI_{50}, TGI or LC_{50} values of all cell lines in the full panel[21].

The GI_{50} (MG-MID) and TGI (MG-MID) values of 2-morpholino **16–22,** 2-piperidino **23–28** and 2-(3-hydroxymethyl)piperidino **29–34** derivatives of 5-*(Z)*-arylidene-4-imidazolidinone are shown in Table IV. Among the 2-morpholino series **16–22** only compounds **20** (Ar = 4-HOC_6H_4) and **21** (Ar = 2-thienyl) showed GI_{50} (MG-MID) values of 89.8 and 90.6 μM, respectively. Replacement of the morpholino group **of 16–22** by piperidino **23–28** increased the antitumor activity, as represented by compounds **24, 25, 26** and **28.** Compound **26**, 5-*(Z)*-(4-chlorobenzylidene)-2-piperidino-4-imidazolidinone; is the most active member of this series with GI_{50} (MG-MID) and TGI (MG-MID) values of 44.1 and 95.2 μM, respectively. The introduction of the hydroxymethyl moiety at the 3-position of the piperidine nucleus **29–34** resulted in substantial decrease in activity (Table IV).

The GI_{50} (MG-MID) and TGI (MG-MID) values of 5-*(Z)*-arylidene-2-(2-carboxyphenylamino)-4-imidazolidinones **35–41** are shown in Table IV. The type of the arylidene group at position 5 seemed to influence the magnitude of activity as it varies from 95.2 and 91.9 μM as in **40** and **41** (Ar = 2-thienyl or 2-furyl), respectively; to 23.5 and 25.4 μM as in **37** and **38** (Ar = 4-MeC_6H_4 or 4-ClC_6H_4), respectively. 5-*(Z)*-(4-methylbenzylidene)-2-(2-carboxyphenylamino)-4-imidazolidinone **37** with GI_{50} (MG-MID) and TGI (MG-MID) values of 23.5 and 62.8 μM and 5-*(Z)*-(4-chlorobenzylidene)-2-(2-carboxyphenylamino)-4-imidazolidinone **38** with GI_{50} (MG-MID), TGI (MG-MID) and LC_{50} (MG-MID) values of 25.4, 74.5 and 93.1 μM ; respectively are the most active members of this series (Table IV).

The GI_{50} (MG-MID) and TGI (MG-MID) values of 3-morpholinomethyl **42–47,** 3-piperidinomethyl **48–54** and 3-(3-hydroxymethylpiperidino)methyl **55** derivatives of 5-*(Z)*-arylidene-2-thioxo-4-imidazolidinone are shown in Table IV. Only compounds **45** and **46** among 3-morpholinomethyl series **42–47** showed GI_{50} (MG-MID) < 100 μM, meanwhile compounds **48–54** of the 3-piperidinomethyl series showed GI_{50} (MG-MID) ranging from 33.9 to 64.1 μM and TGI (MG-MID) from 87.0 to 100 μM. 5-(Z)-(4-Chlorobenzylidene)-3-(piperidinomethyl)-2-thioxo-4-imidazolidinone **51** proved to be the most active member of this group with GI_{50} (MG-MID), TGI (MG-MID) and LC_{50} (MG-MID) values of 33.9, 87.0 and 97.4 μM, respectively. The introduction of the hydroxymethyl moiety at 3-position of the piperidino group produced **55** with reduced activity (Table IV).

TABLE IV In *vitro* growth inhibition concentrations (μM)[a] for compounds 16–67

Compound	GI_{50}[b] *(MG-MID)*	*TGI*[c] *(MG-MID)*	*Compound*	GI_{50}[b] *(MG-MID)*	*TGI*[c] *(MG-MID)*
16	-[d]	-[d]	**42**	-[d]	-[d]
17	-	-	**43**	-	-
18	-	-	**44**	-	-
19	-	-	**45**	97.4	-
20	89.8	-	**46**	93.3	-
21	90.6	-	**47**	-	-
22	-	-	**48**	93.3	-
23	-	-	**49**	44.2	88.7
24	89.8	-	**50**	47.1	97.4
25	94.3	-	**51**	33.9	87.0[e]
26	44.1	95.2	**52**	64.1	-
27	-	-	**53**	64.1	97.4
28	95.2	-	**54**	62.6	-
29	-	-	**55**	-	-
30	-	-	**56**	59.1 I	-[d]
31	-	-	**57**	49.8	97.4
32	90.9	-	**58**	53.5	97.4
33	-	-	**59**	29.7	95.8
34	-	-	**60**	38.9	93.6
35	38.6	90.9	**61**	43.2	85.8[e]
36	65.4	-[d]	**62**	51.1	97.4
37	23.5	62.8	**63**	86.2	-
38	25.4	74.5	**64**	78.7	-
39	36.2	90.9	**65**	37.7	91.7
40	95.2	-	**66**	56.8	97.4
41	91.9	-	**67**	75.8	-

[a]Data obtained from NCI's in *vitro* disease-oxiented human tumor cell screen. [b]GI_{50} (μM) full panel mean-graph midpoint. [c]TGI (μM) full panel mean-graph midpoint. [d](-) values> 100 μM. [e]Compound showed LC_{50} (full panel mean-graph midpoint) value of 97.4 μM.

The antitumor screening results GI_{50} (MG-MID) and TGI (MG-MID) of 3-morpholinomethyl **56–61** and 3-piperidinomethyl **62–67** analogs of 5-*(Z)*-arylidene-2-methylmercapto-4-imidazolidinone are shown in

Table IV. Methylation of the 2-thioxo function of the 4-imidazolidinone **42–55** into the 2-methylmercapto analogs **56–67** increased the antitumor activity. Compounds **59, 60** and **65** showed a distinguish anticancer potency with GI_{50} (MG-MID) values of 29.7, 38.9, 37.7 μM and TGI (MG-MID) values of 95.8, 93.6, 91.7 μM, respectively (Table IV).

The activity of the tested compounds could be correlated to structure variations and modifications, the introduction of the secondary amine to the 2-position of the 4-imidazolidinone nucleus produced few active compounds as in case **16–34** (Table IV), on the other hand the introduction of the anthranilic acid produced the intermediate of the quinazolin-2,5-dione analogs **35–41** with pronounced potency **37** GI_{50} (MG-MID), TGI (MG-MID); 23.5, 62.8 μM, respectively and **38** GI_{50} (MG-MID), TGI (MG-MID and LC_{50} (MG-MID); 25.4, 74.5, 93.1 μM, respectively]. Moving the 2° amine moiety to 3-position of the 2-thioxo-4-imadazolidinone nucleus afforded more active compounds such as **51** [GI_{50} (MG-MID), TGI (MG-MID) and LC_{50} (MG-MID); 33.9, 87.0, 97.4 μM ; respectively]. Methylation of 2-thioxo-4-imidazolidinone analogs yielded more potent compound as **59, 60, 65** with GI_{50} (MG-MID) of 29.7, 38.9, 37.7 μM, respectively; and TGI (MG-MID) of 95.8, 93.6, 91.7 μM, respectively. It is worth mentioning that most of the active compounds such as **26, 38, 51** and **65** carry a 4-chlorophenyl moiety at the 5-*(Z)*-arylidene area which gave the impression that halogen substitution might be essential for activity.

In conclusion, the results obtained from this study revealed that 5-*(Z)*-arylidene-2-(2-(carboxyphenylamino)-4-imidazolidinone nucleus represented by compounds **37** and **38,** also 5-*(Z)*-arylidene-3-aminomethyl-2-methylmercapto-4-imidazolidinone nucleus represented by compound **59** can be considered as a two ring systems that deserves additional derivatization in the hope to obtain more potent antitumor agents.

EXPERIMENTAL

General method. The ^{1}H- and ^{13}C-NMR spectra were measured on a Varian XL-200, 250 MHz and a Bruker Advance DPX 300 MHz spectrometers for solutions in DMSO-d_6 using TMS as internal standard and the chemical shifts are given as δ values and the J values are given in Hz. Mass spectra were recorded on a Finnigan MAT-INCOS 500 spectrometer with ionization by electron impact (70 eV). IR spectra (KBr disc) were

obtained on a Pye Unicam Spectra 1000. Analytical data were obtained from the Microanalytical Center at College of Pharmacy, King Saud University. Melting points (°C, uncorrected) were recorded on a Gallenkamp melting point apparatus. Aluminum sheets coated with silica gel 60 F_{254} (Merk) were used for TLC. Detection was effected by viewing under a short wavelength UV lamp.

5-Arylidene-2-thioxo-4-imidazolidinones 2–8

A mixture of 2-thioxo-4-imidazolidinone **1** (1.16 g, 10 mmol), anhydrous sodium acetate (2.8 g, 34 mmol) and the appropriate aromatic aldehyde (10 mmol) in glacial acetic acid (15 ml) was refluxed for 2 h until the starting material was consumed (TLC). The reaction mixture was poured into cold water. The yellow solid obtained was filtered off and recrystallized from ethanol to give the products 2–8. They were identical with authentic samples by melting points, mixed melting points and TLC determinations[10,11].

5-(Z)-Arylidene-2-methylmercapto-4-imidazolidinones 9–15

5-Arylidene-2-thioxo-4-imidazolidinones **2–8** (10 mmol) were suspended in aqueous sodium hydroxide (12.60 %, 3.50 ml) at room temperature. To this suspension was added methanol (25 ml), and the mixture became clear after stirring 5 min. Methyl iodide (1.56g, 11 mmol) was added, and the mixture was stirred 4 h at room temperature until the starting material was consumed (TLC). The precipitated solid was collected by filtration and recrystallized from methanol to give the products **9-15.** They were identical with authentic samples by melting points, mixed melting points and TLC determinations[10,11].

5-(Z)-Arylidene-2-morpholino-4-imidazolidinones 16–22, 5-(Z)-arylidene-2-piperidino-4-imidazolidinones 23–28 and 5-(Z)-arylidene-2-(3-hydroxymethyl)piperidino-4-imidazolidinones 29–34

General procedures. Method A

A mixture of 5-arylidene-2-methylmercapto-4-imidazolidinones **9-15** (10 mmol) and the appropriate secondary amine mainly morpholine, pipe-

ridine and 3-hydroxymethylpiperidine (10 mmol) in anhydrous ethanol (30 ml) was heated under reflux for 24 h, after cooling. The separated solid was collected and recrystallized from ethanol to give **16–34** in a quantitative yields (Table I).

Method B

2-Thioxo-4-imidazolidinone **1** (1.16 g, 10 mmol) was dissolved in ethanolic potassium hydroxide (2 %, 30 ml) at room temperature. To this solution was added the appropriate aldehyde (11 mmol) and the mixture was stirred overnight at room temperature. To this mixture was added methyl iodide (1.56 g, 11 mmol) and the mixture was stirred at room temperature for 4 h. To this mixture was added the appropriate secondary amine mainly morpholine, piperidine and 3-hydroxymethylpiperidine (10 mmol) and the mixture was heated under reflux for 24 h until the starting material was consumed (TLC). The precipitated solid was collected by filtration and recrystallized from ethanol to give the products **16–34** in a quantitative yields (Table I).

5-(Z)-Arylidene-2-(2-carboxyphenylamino)-4-imidazolidinones 35–41

General procedures. Method A

A mixture of 5-arylidene-2-methylmercapt-4-imidazolidinones **9–15** (10 mmol) and antharanilic acid (1.37 g, 10 mmol) in anhydrous ethanol (30 ml) was heated under reflux for 24 h until the starting material was consumed (TLC). The precipitated solid was collected by filtration and recrystallized from dimethylformamide to give the products **35–41** in a quantitative yields (Table I).

Method B

2-Thioxo-4-imidazolidinone **1** (1.16 g, 10 mmol) was dissolved in ethanolic potassium hydroxide (2 %, 30 ml) at room temperature. To this solution was added the appropriate aldehyde (11 mmol) and the mixture was stirred overnight at room temperature. To this mixture was added methyl iodide (1.56 g, 11 mmol) and the mixture was stirred at room temperature for 4 h. To this mixture was added antharanilic acid (1.37 g, 10 mmol) and the mixture was heated under reflux for 24 h until the starting material was consumed (TLC). The precipitated solid was collected by fil-

tration and recrystallized from dimethylformamide to give the products **35–41** in a quantitative yields (Table I).

5-(Z)-Arylidene-3-morpholinomethyl-2-thioxo-4-imidazolidinones 42–47, 5-(Z)-arylidene-3-piperidinomethyl-2-thioxo-4-imidazolidinones 48–54 and 5-(Z)-(4-methylbenzylidene)-3-(3-hydroxymethylpiperidino) methyl-2-thioxo-4-imidazolidinone 55

General procedures. Method A

A mixture of 5-arylidene-2-thioxo-4-imidazolidinones **2–8** (10 mmol), the appropriate secondary amine mainly morpholine, piperidine and 3-hydroxymethylpiperidine (10 mmol) in anhydrous ethanol (30 ml) and aqueous formaldehyde (1 ml) was stirred for 6 h at room temperature until the starting material was consumed (TLC). The separated solid was collected and recrystallized from ethanol to give **42–55** in a quantitative yields (Table I).

Method B

A solution of 2-thioxo-4-imidazolidinone **1** (1.16 g, 10 mmol), the appropriate secondary amine mainly morpholine, piperidine and 3-hydroxymethylpiperidine (10 mmol) in anhydrous ethanol (30 ml). To this solution was added the appropriate aldehyde (11 mmol) and the mixture was stirred overnight at room temperature. To this mixture was added aqueous formaldehyde (1 ml) and the mixture was stirred at room temperature for 6 h until the starting material was consumed (TLC). The precipitated solid was collected by filtration and recrystallized from ethanol to give the products **42–55** in a quantitative yields (Table I).

5-(Z)-Arylidene-3-morpholinomethyl-2-methylmercapto-4-imidazolidinones 56–61 and 5-(Z)-arylidene-3-piperidinomethyl-2-methylmercapto-4-imidazolidinones 62–67

General procedures. Method A

A mixture of 5-arylidene-2-methylmercapto-4-imidazolidinones **9–15** (10 mmol), the appropriate secondary amine mainly morpholine, piperidine and 3-hydroxymethylpiperidine (10 mmol) and aqueous formaldehyde

(1 ml) in anhydrous ethanol (30 ml) was stirred at room temperature for 12 h until the starting material was consumed (TLC). The precipitated solid was collected by filtration and recrystallized from ethanol to give the products **56–67** (Table I).

Method B

5-(Z)-Arylidene-3-aminomethyl-2-thioxo-4-imidazolidinones **42–55** (10 mmol) were dissolved in ethanolic 2% potassium hydroxide (30 ml) at room temperature. To this solution was added methyl iodide (1.56 g, 11 mmol) and the mixture was stirred at room temperature for 4 h. until the starting material was consumed (TLC). The precipitated solid was collected by filtration and recrystallized from ethanol to give the products **56–67** (Table I).

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References

[1] N. Mehta, C. A. Risinger and F. E. Soroko, *J. Med. Chem.*, **24,** 465 (1981).
[2] I. P. Singh, A. K. Saxena, J. N. Sinha and K. Shanker, *Eur. J. Med. Chem.*, **20,** 283 (1985).
[3] A. Mignot, M. Miocque, P. Binet, J. R. Rapin, P. Rinjard, M. Roux, M. J. Cals and J. C; Ekindjian, *Eur. J. Med. Chem.*, **15,** 33 (1980).
[4] S. A. Grawal, N. K. Singh, R. C. Aggarwal, A. Sodhi and P. Tandon, *J. Med. Chem.*, **29,**129 (1986).
[5] J. P. Scovill, *J. Med. Chem.*, **25,** 2161 (1982).
[6] A. M. Al-Obaid, H. I. El-Subbagh and A. I. Khodair, *Anti-Cancer Drugs.*, **7,** 873 (1996).
[7] K. R. Bharucha, V. Pavilines, D. Ajdukovic and H. M. Shrenk, *Ger. Often,* **2,** 329, 745 (1974); Chem. Abstr., **80,** 95948d (1974).
[8] A. A. El-Barbary, A. I. Khodair, E. B. Pedersen, C. Nielsen, *J. Med. Chem.*, **37,** 73 (1994).
[9] A. I. Khodair, H. I. El-Subbagh and A. A. El-Emam, *Boll. Chim. Farm.*, **136,** 561 (1997).
[10] A. F. A. Shalaby, H. A.Daboun and M. A. Abdel Aziz, Z. *Naturforsch,* **33b,** 937 (1978).
[11] N. S.Girgis, G. E. H.Elgemeie, G. A. Nawar, and M. H. Elnagdi, *Lieb. Ann. Chem.*, 1468 (1983).
[12] S. F. Tan. K. P. Ang and Y. F. Fong, *J. Chem. Soc., Perkin Trans.* **II,** 1941 (1986).
[13] A. A. El-Barbary, A. I. Khodair and E. B. Pedersen, *J. Org. Chem.*, **58,** 5994 (1993).
[14] A. A. El-Barbary, A. I. Khodair, E. B. Pedersen and C. Nielsen, *Arch. Pharm. (Weinheim),* **327,** 633 (1994).
[15] Calculations were carried out with the Hyperchem 4® software (Hypercube Inc.).

[16] H. A.Daboun, A. M. Abd-Elfattah, M. M. Hussein and A. F. A. Shalaby, *Z. Naturforsch,* **36b,** 937 (1981).
[17] J. K. Wojciechowska, W. Kwiatkowski and K. K. Konowics, *Pharmacie,* **50,** 114 (1994).
[18] M. R. Salem, H. A. Abdel-Hamid and A. A. Shaker, *Egypt. J. Chem.,* **26,** 323 (1983); Chem. Abstr., **101,** 230410s (1984).
[19] A. F. Shalaby, H. A.Daboun and M. A. Abd Elaziz, *Z. Naturforsch,* **31b,** 111 (1976).
[20] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Poull, D. Vistica, C. Hose, J. Langly, P. Cronise, A. Viagro-Wolff M. Gray-Goodrish, H. Compell, M. Boyd, *J. Natl. Cancer Inst.,* **83,** 757 (1991).
[21] M. R. Boyd, K. D. Poull, *Drug Dev. Res.,* **34,** 91 (1995).