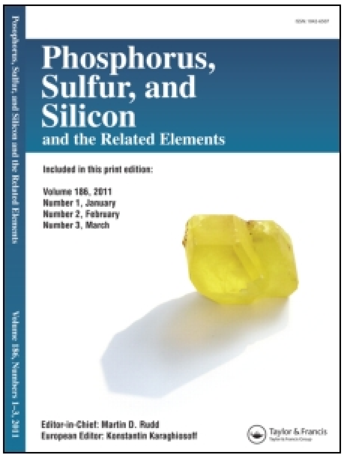

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Synthesis and Anticancer Activities of Some Thiazole Derivatives

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Synthesis and Anticancer Activities of Some Thiazole Derivatives

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In this study, 2-substituted 4-[3/4-(4-arylthiazole-2-yl)aminophenyl]thiazole derivatives and 2-[4-[2-substituted 4-methylthiazole-5-yl]thiazole-2-yl]amino-5-arylidenethiazoline-4-one derivatives have been synthesized. The cytotoxic and/or growth inhibitory effects of the 16 selected compounds were evaluated in vitro against approximately 66 human tumor cell lines derived from nine neoplastic diseases. Some of the compounds were found to act as anticancer agents.

Keywords Anticancer activity; poly-thiazole; thiazolone

INTRODUCTION

Since the initial isolation of the polypyrrole netropsin, **I**, in 1951 and distamycin, **II**, in 1964, the interest in this class of compounds has been increased.[1] These natural antibiotics showed anticancer and antiviral activities by DNA binding.[2] Bleomycins, a group of anticancer antibiotics, also have a bithiazole moiety along with the imidazole and pyrimidine ring systems.[3]

The above observations created the interest for the synthesis of some analogues of netropsin and distamycin, in which the pyrrole rings were replaced by benzene, pyridine, thiophene, thiazole, imidazole, pyrazole, or triazole, to study their anticancer and antiviral activities.[4–13] The studies on the anticancer activity of thia-net, **III**, which is a thiazole-containing analogue of netropsin have been popular recently.[2]

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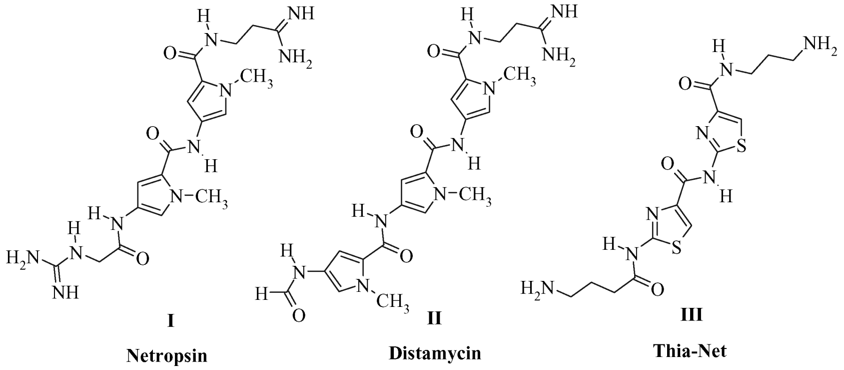
We are now reporting on the syntheses of some new compounds that possess two or three thiazole ring residues along with their anticancer activities.

RESULTS AND DISCUSSION

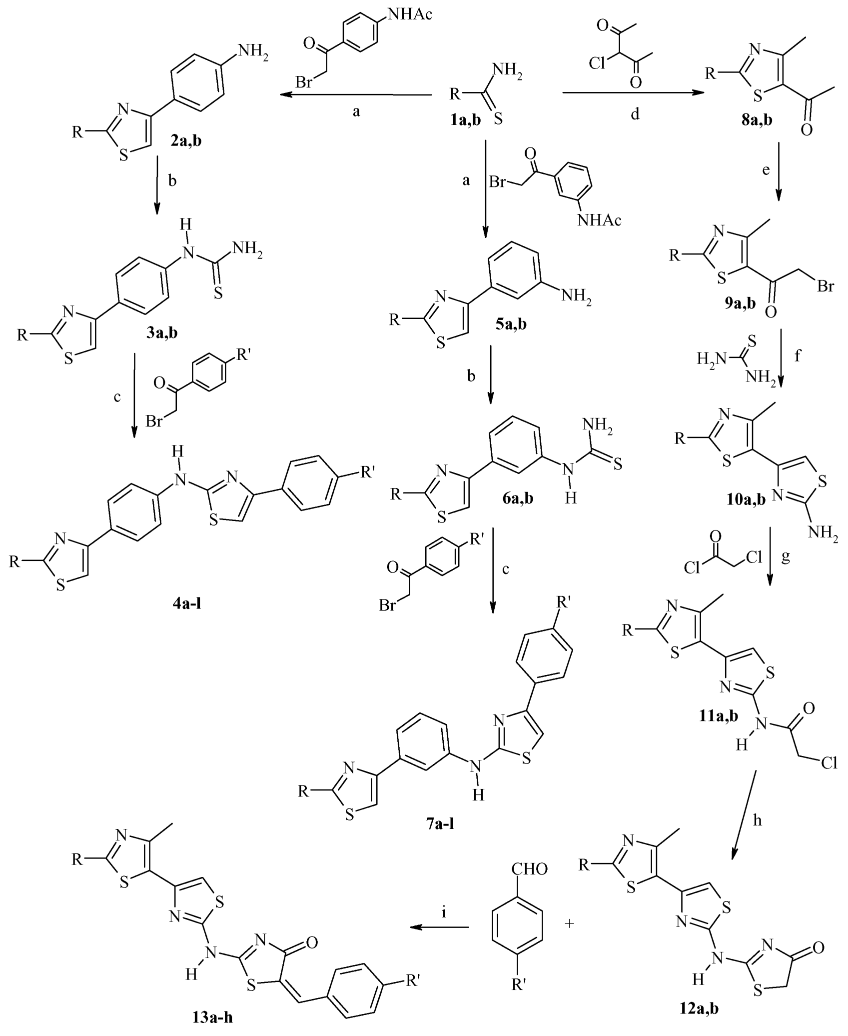
Chemistry

The synthesis of the title thiazole derivatives was accomplished with the sequence of reactions depicted in Scheme 1. To prepare the novel compounds, we have applied the known synthetic routes with minor modifications.[14,15] The first two groups of the compounds are 2-substituted 4[3/4-(4-arylthiazole-2-yl)aminophenyl]thiazole derivatives **4a–l** and **7a–l**, which are isomers of each other. Reaction of 2-bromo-$3'/4'$-acetylaminoacetophenone with the suitable thioamides in benzene afforded 2-substituted 3/4-acetylaminophenylthiazoles. These crude derivatives were hydrolyzed with an aqueous hydrochloric acid solution to afford the corresponding amine derivatives **2a–b**. Then, the amino compounds were treated with ammonium thiocyanate in hydrochloric acid solution, followed by reaction with the suitable $4'$-substituted 2-bromoacetophenones to afford the target compounds **4a–l** or **7a–l** (see Table I).



SCHEME 1

The third group includes 2-[4-[2-substituted 4-methylthiazole-5-yl]thiazole-2-yl]amino-5-arylidenethiazoline-4-one derivatives **13a–h** (Table I). These compounds were obtained by following the common reaction conditions, which have been described in the literature.[14,15] Reaction of 3-chloropentan-2,4-dione with the suitable thioamides



a: i, C_6H_6, reflux, ii, HCl/H_2O; b: NH_4SCN, HCl, H_2O; c: EtOH, d: C_6H_6, reflux, e: Br_2, AcOH, f: EtOH, g: THF, Et_3N; h: NH_4SCN, EtOH; i: AcONa, AcOH.

SCHEME 2

has afforded 2-substituted 4-methyl-5-acetylthiazoles **8a–b**. During the reactions between 3-chloropentan-2,4-dione and thioamides, it is obvious that both of the carbonyl groups can take place in the cyclization reactions. However, this regioselectivity does not cause the

TABLE I Some Characteristics of the Compounds

Comp.	R	R′	mp (°C)	Yield (%)	Molecular formula	Analyses Calc./Found (%)			
						C	H	N	S
4a	CH_3	H	188	72	$C_{19}H_{15}N_3S_2$	65.30	4.33	12.02	18.35
						64.96	4.67	11.86	18.06
4b	CH_3	CH_3	178	75	$C_{20}H_{17}N_3S_2$	66.08	4.71	11.56	17.64
						66.75	5.02	11.91	17.74
4c	CH_3	OCH_3	122	82	$C_{20}H_{17}N_3OS_2$	63.30	4.52	11.07	16.90
						63.56	4.92	10.87	17.20
4d	CH_3	Cl	224	85	$C_{19}H_{14}ClN_3S_2$	59.44	3.68	10.94	16.70
						59.55	3.46	11.12	16 85
4e	CH_3	NO_2	218	80	$C_{19}H_{14}N_4O_2S_2$	57.85	3.58	14.20	16.26
						58.05	4.11	14.47	16.11
4f	CH_3	$NHCOCH_3$	209	77	$C_{21}H_{18}N_4OS_2$	62.05	4.46	13.78	15.77
						61.85	4.35	14.04	16.12
4g	C_6H_5	H	159	65	$C_{24}H_{17}N_3S_2$	70.04	4.16	10.21	15.58
						69.85	4.16	10.25	15.62
4h	C_6H_5	CH_3	225	71	$C_{25}H_{19}N_3S_2$	70.56	4.50	9.87	15.07
						70.45	4.67	9.44	14.93
4i	C_6H_5	OCH_3	193	80	$C_{25}H_{19}N_3OS_2$	68.00	4.34	9.52	14.52
						67.75	4.02	9.55	14.64
4j	C_6H_5	Cl	231	88	$C_{24}H_{16}ClN_3S_2$	64.63	3.62	9.42	14.38
						64.89	4.34	9.32	14.22
4k	C_6H_5	NO_2	224	63	$C_{24}H_{16}N_4O_2S_2$	63.14	3.53	12.27	14.05
						62.84	3.82	12.67	14.15
4l	C_6H_5	$NHCOCH_3$	241	67	$C_{26}H_{20}N_4OS_2$	66.64	4.30	11.96	13.68
						66.45	4.18	12.20	13.74
7a	CH_3	H	172	70	$C_{19}H_{15}N_3S_2$	65.30	4.33	12.02	18.35
						65.71	4.56	12.24	18.77
7b	CH_3	CH_3	147	72	$C_{20}H_{17}N_3S_2$	66.08	4.71	11.56	17.64
						54.75	4.67	11.77	17.72
7c	CH_3	OCH_3	129	78	$C_{20}H_{17}N_3OS_2$	63.03	4.52	11.07	16.90
						62.90	4.55	11.12	17.12
7d	CH_3	Cl	164	83	$C_{19}H_{14}ClN_3S_2$	59.44	3.68	10.94	16.70
						59.45	3.75	11.21	16.90
7e	CH_3	NO_2	194	76	$C_{19}H_{14}N_4O_2S_2$	57.85	3.58	14.20	16.26
						58.15	3.68	14.22	16.26
7f	CH_3	$NHCOCH_3$	111	79	$C_{21}H_{18}N_4OS_2$	62.05	4.46	13.78	15.77
						61.96	4.50	13.80	15.80
7g	C_6H_5	H	202	68	$C_{24}H_{17}N_3S_2$	70.04	4.16	10.21	15.58
						70.14	4.22	10.44	15.80
7h	C_6H_5	CH_3	227	71	$C_{25}H_{19}N_3S_2$	70.56	4.50	9.87	15.07
						70.60	5.60	10.10	14.90
7i	C_6H_5	OCH_3	197	75	$C_{25}H_{19}N_3OS_2$	68.00	4.34	9.52	14.52
						68.41	4.32	9.68	14.60
7j	C_6H_5	Cl	139	80	$C_{24}H_{16}ClN_3S_2$	64.63	3.62	9.42	14.38
						64.68	3.70	9.45	14.44

(Continued on next page)

TABLE I Some Characteristics of the Compounds *Continued*

Comp.	R	R′	mp (°C)	Yield (%)	Molecular formula	Analyses Calc./Found (%) C	H	N	S
7k	C_6H_5	NO_2	187	65	$C_{24}H_{16}N_4O_2S_2$	63.14 63.22	3.53 3.45	12.27 12.33	14.05 14.20
7l	C_6H_5	$NHCOCH_3$	226	67	$C_{26}H_{20}N_4OS_2$	66.64 66.88	4.30 4.28	11.96 12.04	13.68 13.72
13a	CH_3	H	271	78	$C_{18}H_{14}N_4OS_3$	54.25 54.35	3.54 3.60	14.06 14.20	24.14 24.20
13b	CH_3	CH_3	257	77	$C_{19}H_{16}N_4OS_3$	55.32 55.82	3.91 3.85	13.58 13.66	23.32 23.40
13c	CH_3	OCH_3	266	81	$C_{19}H_{16}N_4O_2S_3$	53.25 53.50	3.76 3.90	13.07 13.22	22.45 22.85
13d	CH_3	Cl	287	86	$C_{18}H_{13}ClN_4OS_3$	49.93 50.14	3.03 3.12	12.94 13.12	22.22 21.98
13e	C_6H_5	H	259	63	$C_{22}H_{16}N_4OS_3$	59.98 60.10	3.50 3.60	12.16 12.18	20.88 21.00
13f	C_6H_5	CH_3	243	61	$C_{23}H_{18}N_4OS_3$	60.74 60.55	3.82 3.92	11.80 12.00	20.27 20.30
13g	C_6H_5	OCH_3	218	74	$C_{23}H_{18}N_4O_2S_3$	58.75 58.95	3.70 3.81	11.42 11.60	19.61 19.65
13h	C_6H_5	Cl	276	79	$C_{22}H_{15}ClN_4OS_3$	55.80 55.92	3.05 2.95	11.32 11.53	19.43 19.50

different products because of the symmetry of 3-chloropentan-2,4-dione. The compounds **8a–b** were reacted with bromine to afford the corresponding bromoacetyl derivatives. They were then treated with thiourea to give 2-substituted 4-methyl-5-(2-aminothiazole-4-yl)thiazoles **10a–b**. The aminothiazoles were reacted with chloroacetylchloride in tetrahydrofuran in the presence of triethylamine, followed by reaction with ammonium thiocyanate in ethanol to afford 2-[4-(2-substituted 4-methylthiazole-5-yl)thiazole-2-yl]aminothiazoline-4-ones **12a–b** as starting materials. Finally, the 2-aminothiazoline-4-one derivatives were heated with a suitable aromatic aldehyde in acetic acid in the presence of sodium acetate to give the target compounds **13a–h**.

Pharmacology

The compounds selected by the National Cancer Institute (NCI) and their preliminary anticancer test results as growth percent values obtained against BC, NSCLC, and CNSC cells are given in Table II. It was

TABLE II The Preliminary Test Results

		The growth percentage		
Compounds	Conc. (Molar)	BC MCF7	NSCLC NCI-H460	CNS SF-268
4c	5×10^{-5}	43	42	80
4d	5×10^{-5}	101	99	96
4f	5×10^{-5}	123	110	106
4i	5×10^{-5}	121	120	108
4j	5×10^{-5}	95	85	105
4l	5×10^{-5}	49	70	100
7c	5×10^{-5}	39	20	82
7d	5×10^{-5}	25	5	26
7f	5×10^{-5}	2	0	24
7i	5×10^{-5}	49	70	100
7j	5×10^{-5}	38	7	51
7l	5×10^{-5}	53	12	81
13c	5×10^{-5}	138	122	98
13d	5×10^{-5}	124	120	97
13g	5×10^{-5}	81	61	71
13h	5×10^{-5}	91	83	85

reported that the compounds **4c**, **4l**, **7c**, **7d**, **7f**, **7j**, and **7l** have the remarkable inhibition values for BC and NSCLC, and that **7d**, **7f**, and **7j** have remarkable inhibition values for CNS. These compounds, except **4c**, were accepted for the further screening tests. In this step, the selected six compounds were evaluated in vitro against 66 human tumor cell lines derived from nine neoplastic diseases (see the Experimental section), and the detailed test results are given in Table III.

TABLE III Log_{10} GI_{50} Values

Comp.	L	NSCLC	CC	CNSC	M	OC	RC	PC	BC	MG_MID
4l	−4.66	−4.38	−4.45	−4.77	−4,74	−4.83	−4.80	−4.57	−4.79	−4.75
7c	−6.54	−6.13	−6.21	−5.85	−6.01	−6.12	−5.70	−5.76	−5.92	−6.02
7d	−4.81	−5.10	−4.99	−4.98	−5.06	−4.93	−4.99	−5.03	−4.98	−4.99
7f	−5.35	−5.47	−6.64	−5.70	−6.12	−5.76	−5.68	−5.35	−5.96	−5.81
7j	−4.90	−4.95	−5.00	−4.97	−5.10	−4.81	−4.92	−5.14	−4.93	−4.96
7l	−4.55	−4.58	−4.70	−4.69	−4.93	−4.55	−4.79	−4.74	−4.66	−4.69
A	−5.48	−5.17	−5.11	−5.12	−5.08	−5.18	−4.99	−4.49	−4.79	−5.09
B	−6.39	−6.20	−6.14	−6.18	−6.08	−6.45	−6.17	−6.41	−6.05	−6.20

A: Melphalan, **B**: *Cis*-Diaminodichloroplatinum.

According to the test method, it is stated that the compounds having $\log_{10}$ GI_{50} (GI_{50}: growth inhibition of 50%) values greater than –4 are considered as inactive. It can be seen that all of our compounds' $\log_{10}$ GI_{50} values are smaller than –4. Therefore, we may conclude that all of our compounds provide a notable activity level. Melphalan and *cis*-diaminodichloroplatinum, which are the commonly used clinical chemotherapeutic agents, were used as standard compounds for the test. When the mean graph midpoint (MG-MID) values of the compounds melphalan and *cis*-diaminodichloroplatinum, i.e., –5.09 and –6.20 respectively, are considered, it is observed that our compounds provide high activity levels. The MG-MID value of the compound **7c** is almost equal that of the control compound *cis*-diaminodichloroplatinum. In a similar manner, the activity values of the compounds **7c** and **7f** are higher than that of the other control compound melphalan. When these data are examined according to their activity against various cancer types, it is observed that both the standard and the tested compounds are effective against leukemia for **7c** and colon cancer for **7c** and **7f** in lower concentrations. The most noteworthy compound is **7f**, which is even more active than *cis*-diaminodichloroplatinum against colon cancer. It is noticeable that all of the compounds, except **4l**, under detailed investigation are 1,3-isomers between compounds **4** and **7**. Another noticeable point is that the compounds **13** have the lowest activity values.

EXPERIMENTAL

Chemistry

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments: FTIR: Schimadzu 8400S Spectrophotometer; ^{1}H NMR: Bruker DPX 400 NMR spectrometer. The starting compounds 5-(3/4-aminophenyl)thiazoles **2a**,**b** and **5a**,**b**.[16–18] 1-[4-(2-substituted thiazole-5-yl)phenyl]thioureas **3a**,**b**,[16] 2-substituted 4-methyl-5-acetylthiazoles **8a–b**,[19] 2-substituted 4-methyl-5-(2-bromoacetyl)thiazoles **9a–b**,[20] and 4-(2-substituted 4-methythiazole-2-yl)-2-aminothiazoles **10a**,**b**[20,21] were obtained according to the methods in the literature. The starting compounds **6a**,**b**,**11a**,**b**, and**12a**,**b** were prepared and used according to the steps in this section without any structural identifications. Some characteristics were shown in Table I. The spectral analyses data for prototypes of final compounds **4a–l**, **7a–l**, and **13a–h** are given below.

General Method for the Preparation of 2-Substituted 4[3/4-(4-arylthiazole-2-yl)aminophenyl]thiazole Derivatives 4(a–l) and 7(a–l)

A mixture of 1-[3-(2-substituted thiazole-4-yl)phenyl]thiourea or 1-[4-(2-substituted thiazole-5-yl)phenyl]thiourea derivatives (5 mmol) and a suitable 2-bromoacetophenone (5.5 mmol) in ethanol (50 mL) was refluxed for 4 h. The cooled mixture was filtered and recrystallized from ethanol.

4a: IR (KBr) ν_{max} (cm^{-1}): 3347 (N—H), 1614–1443 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.71 (3H, s, CH_3), 7.31–7.35 (1H, m, Ar-H), 7.38 (1H, s, thiazole C_4-H), 7.43–7.47 (2H, m, Ar-H), 7.78 (1H, s, thiazole C_4-H), 7.80 (2H, d, J = 8.73 Hz, Ar-H), 7.94 (2H, d, J = 8.49 Hz, Ar-H), 7.96 (2H, d, J = 7.12 Hz, Ar-H), 10.43 (1H, s, NH).

4b: IR (KBr)ν_{max} (cm^{-1}): 3354 (N—H), 1614–1442 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.32 (3H, s, CH_3), 2.70 (3H, s, CH_3), 7.24 (2H, d, J = 8.74 Hz, Ar-H), 7.28 (1H, s, Thiazole C_4-H), 7.75 (1H, s, Thiazole C_4-H), 7.78 (2H, d, J = 8.61 Hz, Ar-H), 7.82 (2H, d, J = 8.68 Hz, Ar-H), 7.91 (2H, d, J = 8.55 Hz, Ar-H), 10.39 (1H, s, NH).

4d: IR (KBr) ν_{max}(cm^{-1}): 3346 (N—H), 1616–1462 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.71 (3H, s, CH_3), 7.44 (1H, s, thiazole C_4-H), 7.50 (2H, d, J = 8.79 Hz, Ar-H), 7.78 (1H, s, thiazole C_4-H), 7.80 (2H, d, J = 8.60 Hz, Ar-H), 7.94 (2H, d, J = 8.65 Hz, Ar-H), 7.97 (2H, d, J = 8.50 Hz, Ar-H), 10.45 (1H, s, NH).

4f: IR (KBr)ν_{max} (cm^{-1}): 3362 (N—H), 1672 (C=O), 1610–1472 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.08 (3H, s, $COCH_3$), 2.71 (3H, s, CH_3), 7.23 (1H, s, thiazole C_4-H), 7.67 (2H, d, J = 8.61 Hz, Ar-H), 7.75 (1H, s, thiazole C_4-H), 7.80 (2H, d, J = 8.74 Hz, Ar-H), 7.88 (2H, d, J = 8.58 Hz, Ar-H), 7.93 (2H, d, J = 8.65 Hz, Ar-H), 10.05 (1H, s, CONH), 10.40 (1H, s, NH).

4g: IR (KBr) ν_{max} (cm^{-1}): 3380 (N—H), 1614–1433 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 7.31–7.35 (1H, m, Ar-H), 7.39 (1H, s, thiazole C_4-H), 7.44–7.47 (2H, m, Ar-H), 7.51–7.57 (3H, m, Ar-H), 7.89 (2H, d, J = 8.76 Hz, Ar-H), 7.97 (2H, d, J = 8.33 Hz, Ar-H), 8.03–8.08 (5H, m, Ar-H, thiazole C_4-H), 10.59 (1H, s, NH).

4h: IR (KBr)ν_{max} (cm^{-1}): 3382 (N—H), 1614–1433 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.35 (3H, s, CH_3), 7.27 (2H, d, J:8.08 Hz, Ar-H), 7.31 (1H, s, thiazole C_4-H), 7.55 (3H, d, J = 7.57 Hz, Ar-H), 7.86 (4H, d, J = 8.40 Hz, Ar-H), 8.05 (1H, s, thiazole C_4-H), 8.07 (4H, d, J = 8.57 Hz, Ar-H), 10.45 (1H, s, NH).

4k: IR (KBr) ν_{max}(cm^{-1}): 3378 (N—H), 1612–1438 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 7.51–7.57 (3H, m, Ar-H, thiazole C_4-H), 7.79 (1H, s, thiazole C_4-H), 7.89 (2H, d, J = 8.70 Hz, Ar-H), 8.03–8.08 (5H, m, Ar-H), 8.22 (2H, d, J = 8.92 Hz, Ar-H), 8.32 (2H, d, J = 8.92 Hz, Ar-H), 10.79 (1H, s, NH).

7a: IR (KBr)ν_{max} (cm^{-1}): 3280 (N—H), 1618–1470 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.77 (3H, s, CH_3), 7.33–7.47 (5H, m, Ar-H, thiazole C_4-H), 7.51 (1H, d, J = 7.75 Hz, Ar-H), 7.66, 7.68 (1H, dd, J = 1.98, 2.00 Hz, J = 7.96 Hz, Ar-H), 7.87 (1H, s, thiazole C_4-H), 8.02 (2H, d, J = 7.37 Hz, Ar-H), 8.64 (1H, d, J = 1.55 Hz, Ar-H), 10.41 (1H, s, NH).

7c: IR (KBr) ν_{max} (cm^{-1}): 3276 (N—H), 1617–1468 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.77 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 7.00 (2H, d, J = 8.81 Hz, Ar-H), 7.18 (1H, s, thiazole C_4-H), 7.37–7.42 (2H, m, Ar-H), 7.49–7.52 (1H, m, Ar-H), 7.67, 7.69 (1H, dd, J = 1.54, 1.52 Hz, J:8.01 Hz, Ar-H), 7.87 (1H, s, thiazole C_4-H), 7.94 (2H, d, J = 8.78 Hz, Ar-H), 10.41 (1H, s, NH).

7e: IR (KBr) ν_{max} (cm^{-1}): 3283 (N—H), 1618–1474 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.77 (3H, s, CH_3), 7.41 (1H, t, J = 7.86 Hz, thiazole C_4-H), 7.54 (1H, d, J = 7.73 Hz, Ar-H), 7.67, 7.69 (1H, dd, J = 1.79, 1.80 Hz, J = 7.99 Hz, Ar-H), 7.78 (1H, s, Ar-H), 7.89 (1H, s, Thiazole C_4-H), 8.24 (2H, d, J: = 8.83 Hz, Ar-H), 8.30 (2H, d, J = 8.84 Hz, Ar-H), 8.55 (1H, s, Ar-H), 10.53 (1H, s, NH).

7g: IR (KBr) ν_{max} (cm^{-1}): 3240 (N—H), 1608–1471 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 7.33–7.46 (4H, m, Ar-H, thiazole C_4-H), 7.52–7.58 (3H, m, Ar-H), 7.60–7.64 (2H, m, Ar-H), 8.01 (2H, d, J = 7.18 Hz, Ar-H), 8.05 = 8.08 (3H, m, Ar-H), 8.15 (1H, s, thiazole C_4-H), 8.73 (1H, s, Ar-H), 10.47 (1H, s, NH).

7i: IR (KBr) ν_{max}(cm^{-1}): 3245 (N—H), 1609–1469 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 3.77 (3H, s, OCH_3), 6.93 (2H, d, J:8.73 Hz, Ar-H), 7.21 (1H, s, thiazole C_4-H), 7.41–7.45 (1H, m, Ar-H), 7.50–7.62 (4H, m, Ar-H), 7.94 (2H, d, J = 8.68 Hz, Ar-H), 8.03–8.08 (3H, m, Ar-H), 8.15 (1H, s, Thiazole C_4-H), 8.76 (1H, s, Ar-H), 10.43 (1H, s, NH).

7l: IR(KBr) ν_{max}(cm^{-1}) : 3238 (N—H), 1676 (C=O), 1608–1473 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.08 (3H, s, $COCH_3$), 7.26 (1H, s, thiazole C_4-H), 7.44–7.62 (5H, m, Ar-H), 7.66 (2H, d, J = 8.70 Hz, Ar-H), 7.92 (2H, d, J = 8.64 Hz, Ar-H), 7.98–8.07 (3H, m, Ar-H), 8.15 (1H, s, thiazole C_4-H), 8.62 (1H, s, Ar-H), 10.06 (1H, s, CONH), 10.42 (1H, s, NH).

General Method for the Preparation of 2-[4-(2-Substituted 4-Methylthiazole-5-yl)thiazole-2-yl]amino-5-arylydenethiazoline-4-ones Derivatives 13(a–h)

A mixture of 2-[4-(2-substituted 4-methylthiazole-5-yl)thiazole-2-yl]aminothiazoline-4-one derivative (5 mmol), a suitable 4-substituted benzaldehyde (5.5 mmol) and sodium acetate (15 mmol) in acetic acid (50 mL) was refluxed for 8 h. The cooled mixture was poured into ice water. The precipitate was filtered and crystallized from ethanol.

13a: IR (KBr) ν_{max} (cm^{-1}): 3120 (N–H), 1724, 1688 (C=O), 1590–1430 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.45 (3H, s, CH_3), 2.82 (3H, s, CH_3), 7.31 (1H, s, =CH-), 7.41–7.62 (5H, s, Ar-H), 8.15 (1H, s, thiazole C_4-H), 10.45 (1H, s, NH).

13d: IR (KBr) ν_{max}(cm^{-1}): 3128 (N–H), 1730, 1704 (C=O), 1589–1423 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.44 (3H, s, CH_3), 2.80 (3H, s, CH_3), 7.32 (1H, s, =CH-), 7.45 (2H, d, J = 8.62 Hz, Ar-H), 8.15 (1H, s, thiazole C_4-H), 8.40 (2H, d, J = 8.64 Hz, Ar-H), 10.45 (1H, s, NH).

13g: IR (KBr)ν_{max}(cm^{-1}): 3126 (N–H), 1720, 1683 (C=O), 1589–1461 (C=N, C=C), ^{1}H NMR (400 MHz) (DMSO-d_6)δ (ppm): 2.45 (3H, s, CH_3), 7.12 (2H, d, J = 7.85 Hz, Ar-H), 7.32 (1H, s, =CH-), 7.42–7.50 (3H, m, Ar-H), 7.85–7.95 (2H, m, Ar-H), 8.12 (1H, s, thiazole C_4-H), 8.38 (2H, d, J = 7.90 Hz, Ar-H), 10.43 (1H, s, NH).

Pharmacology

The cytotoxic and/or growth inhibitory effects of the compounds were evaluated in vitro against approximately 66 human tumor cell lines derived from nine neoplastic diseases, namely leukaemia (L), non-small cell lung cancer (NSCLC), colon cancer (CC), central nervous system cancer (CNSC), melanoma (M), ovarian cancer (OC), renal cancer (RC), prostate cancer (PC), breast cancer (BC). The evaluation of anticancer activity was performed at the NCI of Bethesda, Maryland, USA, following the in vitro screening program, which is based upon the use of multiple panels of 66 human tumor cell lines against which our compounds were tested at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. The percentage growth was evaluated spectrophotometrically versus controls not treated with test agents. A 48 h continuous drug exposure protocol was followed, and a sulforhodamine B (SRB) protein assay was used to estimate cell growth.[22,23]

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