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Substituted thiazoles V. Synthesis and antitumor activity of novel thiazolo[2,3-*b*]quinazoline and pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine analogues

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ABSTRACT

A novel series of thiazolo[2,3-*b*]quinazoline (**14**–**23**, **26** and **27**), and pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine (**34**–**43**, **45** and **46**) analogues were designed and synthesized. The obtained compounds were evaluated for their *in-vitro* antitumor activity at the National Cancer Institute (NCI) 60 cell lines panel assay. Compounds **22**, **38**, **40** and **41** showed remarkable broad-spectrum antitumor activity. Compounds **22** and **38** are almost nine fold more active than 5-FU, with GI_{50}, TGI, and LC_{50} values of 2.5, >100, >100; and 2.4, 9.1, 36.2 μM, respectively; while **40** and **41** are almost seven fold more active than 5-FU, with GI_{50}, TGI, and LC_{50} values of 2.9, 12.4, 46.6 and 3.0, 16.3, 54.0 μM, respectively.

1. Introduction

Cancer is a disease characterized by a shift in the controlled mechanisms that govern cell proliferation and differentiation [1]. Malignancy is caused by abnormalities in cells, which might be due to inherited genes or caused by outside exposure of the body to chemicals, radiation, or even infectious agents [2,3]. Several techniques were adopted for the treatment and eradication of cancerous cells. These techniques involved surgery, radiation, immunotherapy, chemotherapy and chemoprevention. Ideal anticancer drugs would eradicate cancer cells without harming normal tissues. Unfortunately, no currently available agents meet this criterion and clinical use of drugs involves a weighing of benefits against toxicity in a search of favorable therapeutic index [4]. Many of chemotherapeutic agents currently used in cancer therapy are agents which inhibit tumor growth by inhibiting the replication and transcription of DNA.

The wide occurrence of the heterocycles in bioactive natural products made them important synthetic targets. Thiazoles represent a class of heterocyclic compounds of great importance in biological chemistry. They exist in many condensed fused systems that were found to possess a wide range of activity [5,6]. Moreover, fused pyrimidines have drawn the attention of medicinal chemists as chemotherapeutic agents, where several members of this class have earned valued places in chemotherapy as effective agents. Various literature reports displayed numerous fused pyrimidine ring systems and their chemotherapeutic activities as anticancer [7], antibacterial [8], antifungal [9], and antiviral [10] agents. Also, substituted thiazolopyrimidine ring systems were reported to possess antitumor activity [11]. Literature survey has pointed out the inherited antitumor potency in compounds containing α,β-unsaturated ketone [12–15], fused pyridine [14–16], condensed pyrimidine and fused quinazoline moieties [17–24]. The reported significance of such synthons generated the interest to exploit this valuable structure in the designing and the synthesis of new thiazolopyrimidines analogues as antitumor agents.

In continuation to our previous efforts [25–28], new derivatives of thiazolo[3,2-*a*]pyrimidine and thiazolo[2,3-*b*]quinazoline analogues were designed, and synthesized. The new compounds were screened for their *in-vitro* antitumor activity using the NCI's disease-oriented human cell lines assay. The full NCI 60 cell lines panel assay includes nine tumor subpanels namely; leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells [29–31].

2. Results and discussion

2.1. Chemistry

The synthetic strategy to prepare the target compounds **14**–**23**, **26**, **27**, **34**–**43**, **45** and **46** is illustrated in schemes 1 and 2. The

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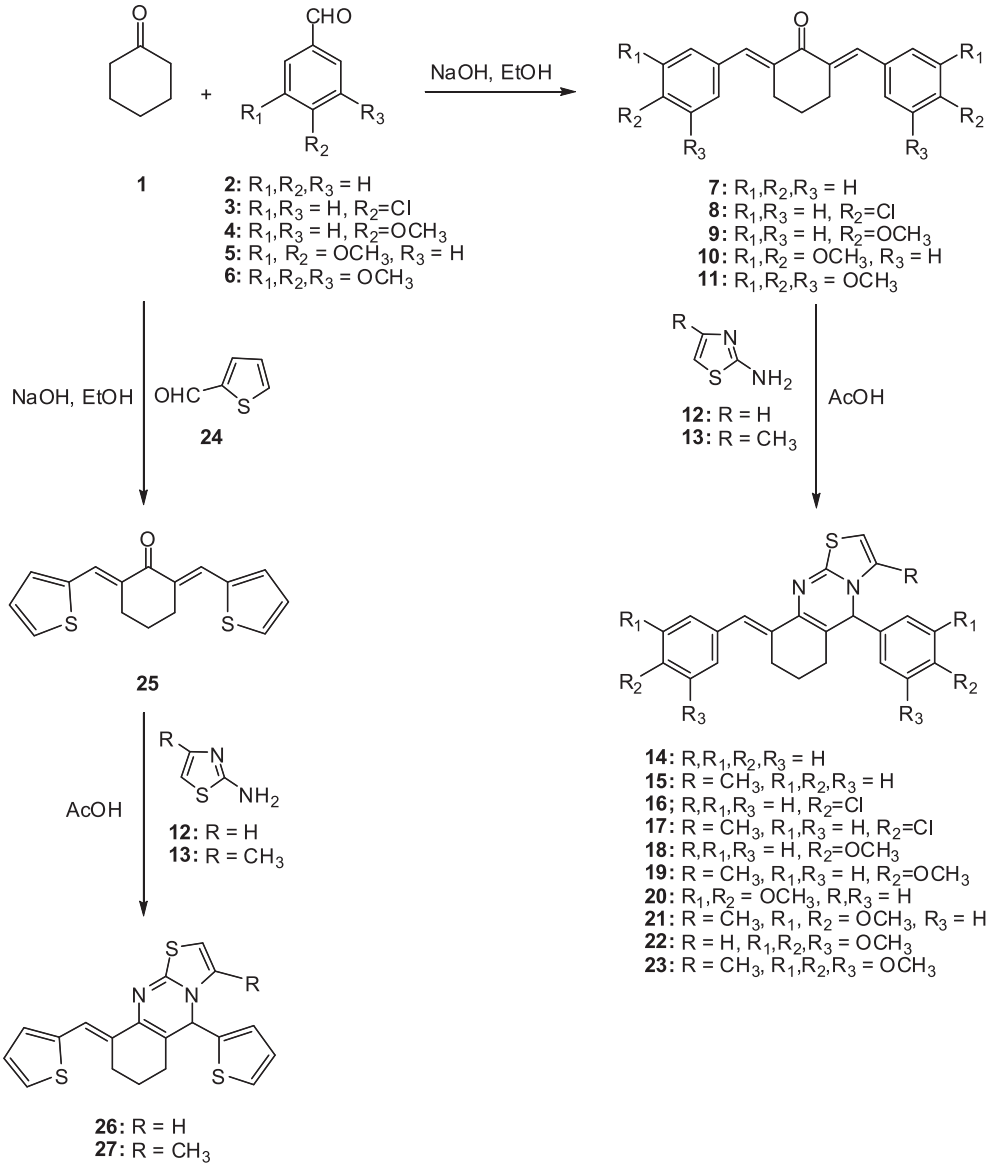


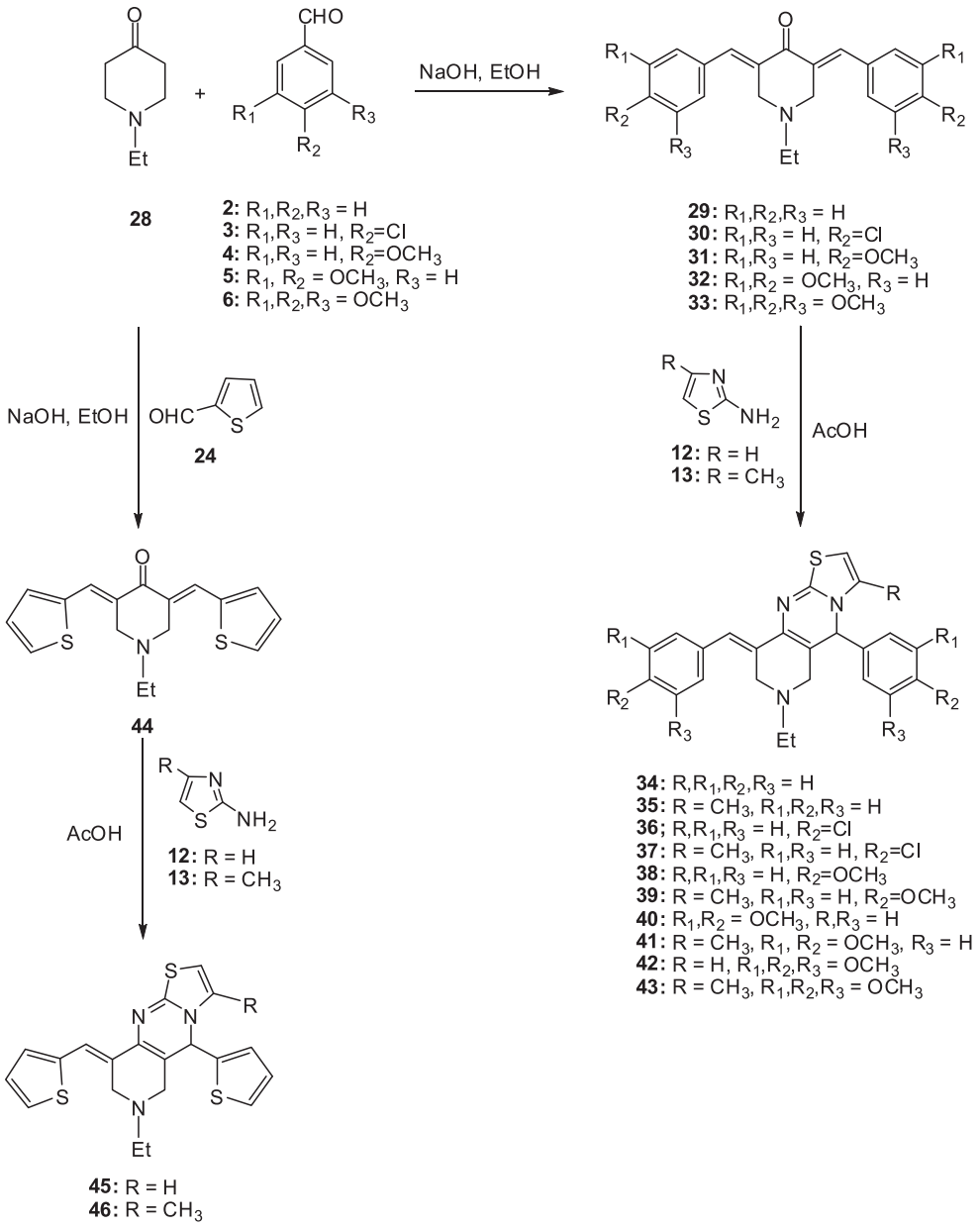
Scheme 1. Synthesis of the target compounds **14**–**23**, **26** and **27**.

reported diarylidene derivatives **7**–**11** and **29**–**33** [12–14,32] as well as the new analogues **25** and **44** were prepared by reacting either cyclohexanone (**1**) or N-ethyl-piperidone (**28**) with various benzaldehyde analogues (**2**–**6**) and 2-thiophen-carboxaldehyde (**24**) in ethanolic solution of sodium hydroxide. The aforementioned target compounds were obtained by reacting 2-amino-thiazole (**12**) or 2-amino-4-methyl-thiazole (**13**) with the α,β-unsaturated ketones **7**–**11**, **25**, **29**–**33** and **44** in glacial acetic acid (schemes 1 and 2, Table 1).

2.2. Preliminary in-vitro antitumor screening

The synthesized compounds **14**, **15**, **18**–**23**, **26**, **27**, **38**–**41**, **45** and **46** were subjected to the NCI's disease-oriented human cell lines screening assay to be evaluated for their *in-vitro* antitumor activity. A single dose (100 μM) of the test compounds were used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels namely; leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells [29–31]. The data reported as mean graph of the percent growth of the treated cells and presented as percentage growth inhibition (GI%). The obtained results of the tested thiazolo[2,3-*b*]quinazoline and pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine analogues showed distinctive potential pattern of selectivity, as well as broad-spectrum antitumor activity (Tables 2 and 3).

Regarding the activity towards individual cell lines; the tested 6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline derivatives showed selective potency against non-small cell lung NCI-H226, CNS cancer SNB-75, and renal cancer UO-31 cell lines. Compounds **15**, **18**, **21**, and **22** showed GI values of 11.2, 21.6, 10.5 and 100% against non-small cell lung NCI-H226, respectively; while compounds **15**, **20**, **22**, **26** and **27** showed GI values of 13.3, 12.4, 65, 10.4 and 16.6% against CNS cancer SNB-75, respectively. Renal cancer cell line UO-31 proved to be selectively sensitive to compounds **14**, **15**, **18**, **19**, **20**, **22**, **23**, **26** and **27** with GI values of 21.4, 28.8, 32.0, 23.3, 27.9, 100, 20.0, 28.7, 24.5%, respectively (Table 2). The tested 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine analogues showed selectivity toward non-small cell lung EKVX, CNS cancer SNB-75, and renal cancer A498 and UO-31 cell lines. Compounds **38**, **40**, **41** and **46** showed GI values of 51.9, 27.1, 37.5 and 17.7% against non-small cell lung EKVX,



Scheme 2. Synthesis of the target compounds **34**–**43**, **45** and **46**.

respectively; while compounds **38**, **39**, **40**, **41**, **45** and **46** showed GI values of 22.3, 12.5, 71.4, 68.1, 14.2 and 13.6% against CNS cancer SNB-75, respectively. Renal cancer cell line A498 proved to be selectively sensitive to compounds **38**, **40**, **41** and **45** with GI values of 11.1, 18.4, 53.8, 21.6%, respectively; while compounds **38**, **39**, **40**, **41**, **45** and **46** inhibited the growth of the renal cancer cell line UO-31 by 100, 35.5, 40.7, 100, 26.2 and 21.8%, respectively (Table 3).

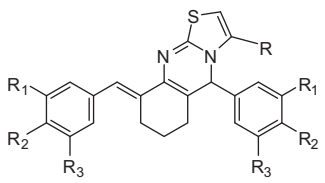
Close examination of the data presented in Tables 2 and 3, revealed that compounds **22**, **38**, **40**, and **41** are the most active members of this study, showing effectiveness toward numerous cell lines belong to different tumor subpanels. The same analogy indicated that compounds **15**, **18**, **20** and **27** possess moderate antitumor activity; while compounds **14**, **19**, **21**, **23**, **26**, **39**, **45** and **46** are the least active antitumors in the present investigation.

Compounds **22**, **38**, **40**, and **41** passed the primary anticancer assay at an arbitrary concentration of 100 μM. Consequently, those active compounds were carried over and tested against a panel of 60 different tumor cell lines at a 5-log dose range [29–31]. Three response parameters, GI_{50}, TGI, and LC_{50} were calculated for each cell line, using the known drug 5-Fluorouracil (5-FU) as a positive control. Compounds **22** and **38** are almost nine fold more active than the positive control 5-FU, with GI_{50}, TGI, and LC_{50} values of 2.5, >100, >100; and 2.4, 9.1, 36.2 μM, respectively; while compounds **40** and **41** are almost seven fold more active than the positive control 5-FU, with GI_{50}, TGI, and LC_{50} values of 2.9, 12.4, 46.6 and 3.0, 16.3, 54.0 μM, respectively (Table 4).

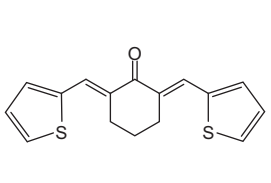
2.3. Structure-activity correlation

Structure-activity correlation, based on the number of cell lines proved sensitive toward each of the synthesized individual compounds, revealed that, 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*d*] thiazolo[3,2-*a*]pyrimidines (**38**–**41**, **45** and **46**) are more active antitumors than their 6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazolines (**14**, **15**, **18**–**23**, **26** and **27**) counterparts.

Table 1
Physicochemical properties of the newly synthesized compounds **14**–**23**, **25**–**27**, **34**–**43**, **44**–**46**.



14-23



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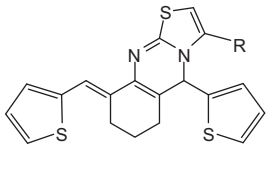
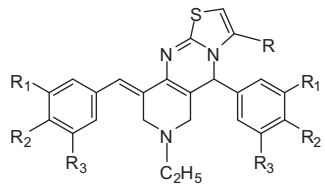
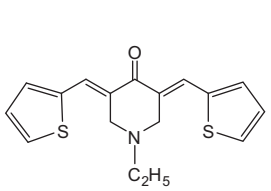


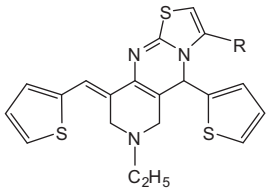
26, 27



34-43



44



45, 46

Compound	R	R_1	R_2	R_3	Yield, %	Mp, °C	Molecular formulae[a]
14	H	H	H	H	64	105–8	$C_{23}H_{20}N_2S$
15	CH_3	H	H	H	71	112–3	$C_{24}H_{22}N_2S$
16	H	H	Cl	H	77	133–5	$C_{23}H_{18}Cl_2N_2S$
17	CH_3	H	Cl	H	68	137–40	$C_{24}H_{20}Cl_2N_2S$
18	H	H	OCH_3	H	84	155–7	$C_{25}H_{24}N_2O_2S$
19	CH_3	H	OCH_3	H	70	143–5	$C_{26}H_{26}N_2O_2S$
20	H	OCH_3	OCH_3	H	61	132–6	$C_{27}H_{28}N_2O_4S$
21	CH_3	OCH_3	OCH_3	H	72	145–7	$C_{28}H_{30}N_2O_4S$
22	H	OCH_3	OCH_3	OCH_3	60	198–201	$C_{29}H_{32}N_2O_6S$
23	CH_3	OCH_3	OCH_3	OCH_3	66	188–90	$C_{30}H_{34}N_2O_6S$
25	–	–	–	–	95	104–6	$C_{16}H_{14}OS_2$
26	H	–	–	–	55	147–50	$C_{19}H_{16}N_2S_3$
27	CH_3	–	–	–	49	138–40	$C_{20}H_{18}N_2S_3$
34	H	H	H	H	43	122–5	$C_{24}H_{23}N_3S$
35	CH_3	H	H	H	51	116–9	$C_{25}H_{25}N_3S$
36	H	H	Cl	H	49	129–32	$C_{24}H_{21}Cl_2N_3S$
37	CH_3	H	Cl	H	55	134–8	$C_{25}H_{23}Cl_2N_3S$
38	H	H	OCH_3	H	57	148–50	$C_{26}H_{27}N_3O_2S$
39	CH_3	H	OCH_3	H	60	161–3	$C_{27}H_{29}N_3O_2S$
40	H	OCH_3	OCH_3	H	72	191–3	$C_{28}H_{31}N_3O_4S$
41	CH_3	OCH_3	OCH_3	H	64	175–8	$C_{29}H_{33}N_3O_4S$
42	H	OCH_3	OCH_3	OCH_3	51	142–6	$C_{30}H_{35}N_3O_6S$
43	CH_3	OCH_3	OCH_3	OCH_3	40	136–9	$C_{31}H_{37}N_3O_6S$
44	–	–	–	–	89	119–21	$C_{17}H_{17}NOS_2$
45	H	–	–	–	31	155–9	$C_{20}H_{19}N_3S_3$
46	CH_3	–	–	–	37	132–6	$C_{21}H_{21}N_3S_3$

[a] Analyzed for C, H, N; results were within ±0.4% of the theoretical values for the formulae given.

Concerning the tested thiazolo[2,3-*b*]quinazoline heterocycles, the un-substituted analogues such as (*E*)-9-benzylidene-5-phenyl-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline (**14**) and (*E*)-5-(thiophen-2-yl)-9-(thiophen-2-yl-methylene)-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline (**26**) proved inactive. The introduction of methyl function to position 3- of **14** and **26** produced compounds **15** and **27** with moderate antitumor potency. Also the introduction of 4-methoxy function to the 5-phenyl and the 9-benzylidene moieties of **14** produced **18** with moderate antitumor activity. Addition of 3-methyl function to **18** converts the compound into the inactive side as in case of **19**. The same was also noticed upon the addition of 3,4-dimethoxy function to the same positions of **14** to produce the moderate active **20** and the inactive compound **21**. Upon the addition of 3,4,5-trimethoxy function to the 5-phenyl and the 9-benzylidene moieties of **14** produced **22** with remarkable antitumor potency. Introduction of methyl group to position 3- of **22** produced the inactive compound **23**, this emphasize that the methyl function at this particular position does not favor the activity in most cases. The same analogy is also applicable, more or less, to the tested pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine heterocycles which netted compounds **38**, **40** and **41** as the remarkably active antitumor agents of this study.

3. Conclusion

Compounds **22**, **38**, **40** and **41** (Fig. 1); are the most active broad-spectrum antitumor agents of this study with GI_{50}, TGI, and LC_{50} values of 2.5, >100, >100; 2.4, 9.1, 36.2; 2.9, 12.4, 46.6 and 3.0, 16.3, 54.0 μM, respectively. The synthesized thiazolo[2,3-*b*]quinazoline and pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine analogues could be considered as useful template for future development to obtain more potent antitumor agent(s).

Table 2
Percentage growth inhibition (GI%) of *in vitro* subpanel tumor cell lines at 10 μM concentration of compounds **14**, **15**, **18**–**23**, **26**, **27**.

Subpanel tumor cell lines	**14**	**15**	**18**	**19**	**20**	**21**	**22**	**23**	**26**	**27**
Leukemia										
CCRF-CEM	–	–	–	–	–	–	**94.1**	–	–	–
HL-60(TB)	–	–	–	–	17.5	–	**L**	–	–	11.4
K-562	–	13.8	–	–	–	–	**L**	–	–	–
MOLT-4	–	–	14.4	–	–	–	**L**	–	–	–
RPMI-8226	–	–	21.0	13.5	–	–	**L**	–	–	–
SR	–	–	–	–	–	–	**L**	–	–	–
Non-small cell lung cancer										
A549/ATCC	–	–	–	–	–	–	**L**	–	–	–
EKVX	–	–	12.5	–	–	11.4	**L**	–	–	–
HOP-62	–	–	–	–	–		**L**		–	11.3
NCI-H226	–	11.2	21.6	–	–	10.5	**L**	–	–	–
NCI-H23	–	–	–	–	–	–	**L**	–	–	–
NCI-322 M	–	–	–	–	–	–	**99.5**	–	–	–
NCI-H460	–	–	–	–	–	–	**L**		–	–
NCI-H522	–	–	–	–	10.3	–	**L**	–	–	–
Colon cancer										
HCT-116	–	–	17.6	–	–	–	**L**	–	–	–
HCC-2998	–	–	–	–	14.9	–	**L**	–	–	–
HT29	–	–	–	–	–	–	**L**	–	–	–
KM12	–	–	–	–	–	–	**L**	–	–	–
CNS cancer										
SF-268	–	–	–	–	-	–	**95.0**	–	–	–
SF-295	–	–	–	–	–	–	**L**	–	–	–
SF-539	–	–	–	–	–	–	**91.3**		–	
SNB-19	–	–	–	–	–	–	79.0	–	–	–
SNB-75	–	13.3	–	–	12.4	–	65.0	–	10.4	16.6
U251	–	–	–	–	–	–	**L**	–	–	–
Melanoma										
LOX IMVI	–	–	–	–	16.4	–	**L**	–	13.0	–
M14	–	–	18.8	–	–	–	**L**	–	–	–
MDA-MB-435	–	–	15.4	–	–	–	**L**	–	–	–
SK-MEL-2	–	–	–	–	–	–	**L**	–	–	–
SK-MEL-28	–	–	–	–	–	–	**89.7**	–	–	–
SK-MEL-5	–	–	–	–	–	–	**L**	–	–	–
UACC-257	–	–	–	–	10.5	–	**L**	–	–	–
UACC-62	–	–	–	–	–	–	**L**	–	–	–
Ovarian cancer										
IGORV1	–	–	–	–	–	–	**L**	–	–	–
OVCAR-4	–	–	15.4	–	–	–	79.5	–	–	–
NCI/ADR-RES	–	–	–	–	–	–	**90.5**	–	–	–
Renal cancer										
A498	–	–	–	36.0	–	–	**L**	–	–	14.3
ACHN	–	–	–	–	–	–	**L**	–	–	–
CAKI-1	–	11.4	11.3	12.5	–	–	**L**	–	–	–
UO-31	21.4	28.8	32.0	23.3	27.9	–	**L**	20.0	28.7	24.5
Prostate cancer										
DU-145	–	–	–	–	–	–	**L**	–	–	–
Breast cancer										
MCF7	–	–	–	–	–	–	76.0	–	–	–
BT-549	–	–	–	–	–	–	**L**	–	–	–
T-47D	–	–	–	–	–	–	69.0	–	–	–

–, GI >10%; nt, not tested; L, compound proved lethal to the cancer cell line.

Table 3
Percentage growth inhibition (GI%) of *in vitro* subpanel tumor cell lines at 10 μM concentration of compounds **38**–**41**, **45**, **46**.

Subpanel tumor cell lines	**38**	**39**	**40**	**41**	**45**	**46**
Leukemia						
CCRF-CEM	**97.3**	–	**94.0**	**97.8**	–	–
HL-60(TB)	**84.0**	–	48.3	72.1	–	–
K-562	**L**	–	**95.2**	**96.4**	–	–
MOLT-4	**90.4**	–	67.9	**L**	–	–
RPMI-8226	**L**	–	**L**	**L**	–	–
SR	**L**	–	**L**	**L**	–	–
Non-small cell lung cancer						
A549/ATCC	66.3	–	61.1	**93.2**	–	–
EKVX	51.9	–	27.1	37.5	–	17.7
HOP-62	**L**	–	**84.7**	**L**	–	–
NCI-H226	**88.0**	–	53.2	**98.2**	–	–
NCI-H23	54.8	–	43.9	67.6	–	–
NCI-322 M	29.0	–	19.1	63.6	–	–
NCI-H460	**L**	–	**L**	**L**	–	–
NCI-H522	52.3	–	46.1	61.7	–	–
Colon cancer						
HCT-116	**L**	–	**L**	**L**	–	–
HCT-15	**L**	–	75.8	**L**	–	–
HT29	**L**	–	**L**	**L**	–	–
KM12	**L**	–	**L**	**L**	–	–
CNS cancer						
SF-268	**85.5**	–	76.0	**89.4**	–	–
SF-295	71.8	–	**82.2**	69.2	–	–
SNB-19	68.3	–	52.9	61.0	–	–
SNB-75	22.3	12.5	71.4	68.1	14.2	13.6
U251	**L**	–	**90.0**	**97.9**	–	–
Melanoma						
LOX IMVI	**L**	–	**L**	**L**	–	–
M14	**97.5**	–	**94.3**	**L**	–	–
MDA-MB-435	**L**	–	**L**	**L**	–	–
SK-MEL-2	–	–	11.5	27.4	–	–
SK-MEL-28	10.9	–	61.3	**96.5**	–	–
SK-MEL-5	74.4	–	60.9	87.2	–	–
UACC-257	44.8	–	63.2	**L**	–	–
UACC-62	49.3	–	62.4	**L**	–	–
Ovarian cancer						
OVCAR-3	**L**	–	**L**	**L**	–	–
OVCAR-8	**L**	–	**95.9**	**96.5**	–	–
NCI/ADR-RES	76.9	–	**91.2**	**L**	–	–
Renal cancer						
786-0	53.2	–	–	69.9	–	–
A498	11.1	–	18.4	53.8	21.6	–
ACHN	83.0	–	79.5	**L**	–	–
CAKI-1	78.3	–	**L**	**L**	–	–
SN12C	96.9	–	**83.1**	**93.7**	–	–
TK-10	70.0	–	46.5	**98.8**	–	–
UO-31	**L**	35.5	40.7	**L**	26.2	21.8
Prostate cancer						
DU-145	**L**	–	**L**	**L**	–	–
Breast cancer						
MCF7	74.3	–	**80.5**	**84.5**	–	–
BT-549	55.2	–	–	57.0	–	–
T-47D	24.4	–	–	26.2	11.4	–

–, GI >10%; nt, not tested; L, compound proved lethal to the cancer cell line.

4. Experimental

Melting points (°C) were determined on Mettler FP80 melting point apparatus and are uncorrected. Microanalyses were performed on a Perkin–Elmer 240 elemental analyzer at the Central Research Laboratory, College of Pharmacy, King Saud University. All of the new compounds were analyzed for C, H and N and agreed with the proposed structures within ±0.4% of the theoretical values. ^{1}H NMR, ^{13}C NMR were recorded on a Bruker 500 MHz FT spectrometer; chemical shifts are expressed in δ ppm with reference to TMS. Mass spectral (MS) data were obtained on a Perkin Elmer, Clarus 600 GC/MS and Joel JMS-AX 500 mass spectrometers. Thin layer chromatography was performed on precoated (0.25 mm) silica gel GF_{254} plates (E. Merck, Germany), compounds were detected with 254 nm UV lamp. Silica gel (60–230 mesh) was employed for routine column chromatography separations. All the fine chemicals and reagents used were purchased from Aldrich Chemicals Co, USA. Compounds **7**–**11**, **29**–**33** were previously reported [12–14,32].

4.1. Chemistry

4.1.1. 2,6-Bis(thien-2-yl-methylene)cyclohexanone (**25**) and 1-ethyl-3,5-bis(thien-2-yl-methyl-ene)-piperidin-4-one (**44**)

A mixture of the appropriate cyclic ketone **1** or **28** (0.01 mol) and 2-thiophene carboxaldehyde (**24**, 0.02 mol) in alcoholic NaOH (10%, 50 ml) was stirred at room temperature for 30 min. The separated solid was filtered off, washed with water, dried and recrystallized from ethanol (Table 1). **25**: ^{1}H NMR (DMSO-d_6) δ 1.66–1.75 (m, 2H,

Table 4
Compounds **22**, **38**, **40** and **41** median growth inhibitory (GI_{50}, μM), total growth inhibitory (TGI, μM) and median lethal (LC_{50}, μM) concentrations of *in vitro* subpanel tumor cell lines.

Compound	Activity	I	II	III	IV	V	VI	VII	VIII	IX	MG-MID[a]
22	GI_{50}	2.0	2.3	1.6	47.8	nt	1.9	1.8	2.0	2.2	2.5
	TGI	[b]	[b]	nt	[b]	nt	[b]	[b]	[b]	[b]	[b]
	LC_{50}	[b]	[b]	nt	[b]	nt	[b]	[b]	[b]	[b]	[b]
38	GI_{50}	2.7	2.5	1.7	4.7	3.5	2.8	2.3	2.8	2.5	2.4
	TGI	81.6	18.3	3.4	9.4	10.9	22.5	6.0	43.9	8.0	9.1
	LC_{50}	[b]	64.9	6.7	68.2	55.0	74.7	24.9	68.1	73.4	36.2
40	GI_{50}	2.6	3.2	2.0	3.3	3.4	3.2	3.1	3.4	19.3	2.9
	TGI	30.7	40.1	4.3	26.7	10.1	48.9	9.8	29.8	43.9	12.4
	LC_{50}	[b]	76.5	29.3	82.8	44.6	90.5	52.8	68.4	74.7	46.6
41	GI_{50}	4.0	3.0	2.1	5.7	2.7	3.8	2.5	2.8	5.7	3.0
	TGI	81.9	44.2	5.6	40.1	10.8	49.7	8.9	53.4	49.5	16.3
	LC_{50}	[b]	86.5	35.3	[b]	54.4	[b]	47.1	79.2	68.2	54.0
5-FU	GI_{50}	15.1	[b]	8.4	72.1	70.6	61.4	45.6	22.7	76.4	22.6
	TGI	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
	LC_{50}	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]

I, leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer.
[a] Full panel mean-graph midpoint (μM).
[b] Compounds showed values >100 μM. nt, not tested.

cyclohexanone-H), 2.01–2.24 (m, 4H, cyclohexanone-H), 6.89 (s, 2H, C=CH), 6.96–7.56 (m, 6H, thienyl-H). ^{13}C NMR δ 21.7, 23.3, 28.2, 76.8, 77, 77.3, 77.9, 127.6, 129.7, 129.9, 130.4, 132.9, 133, 135.7, 139.6, 189. MS *m/z* (%): 286 (12, M^+). **44**: ^{1}H NMR (DMSO-d_6) δ 0.97 (s, 2H, cyclohexanone-H), 1.24 (t, 3H, J = 7.2 Hz, CH_3CH_2), 2.63 (s, 2H, cyclohexanone-H), 3.79–3.81 (q, 2H, CH_2CH_3), 7.49 (s, 2H, C=CH), 7.52–7.63 (m, 6H, thienyl-H). ^{13}C NMR δ 29, 39, 39.1, 39.3, 39.5, 39.7, 39.8, 40, 50.5, 53.7, 128.7, 129.2, 130.4, 133.8, 134.6, 134.7, 186.9. MS *m/z* (%): 315 (3.9, M^+).

*4.1.2. 3-Substituted-9-(substituted benzylidene)-5-(substituted phenyl)-6,7,8,9-tetrehydro-5H-thiazolo[2,3-b]quinazolines (**14**–**23**) and 1-substituted-7-ethyl-5-(substituted benzyl-idene)-9-(substituted phenyl)-6,7,8,9-tetrahydro-5H-pyrido[4,3-d]thiazolo [3,2-a]pyramidines (**34**–**43**)*

A solution of 2-aminothiazole or 2-amino-4-methylthiazole (**12** or **13**, 0.01 mol), the appropriate α,β-unsaturated ketone (**7**–**11**, **29**–**33**, 0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 20 h. Solvent was evaporated under vacuum; the obtained residue was dissolved in chloroform, washed with water, and the organic layer was separated, dried and evaporated. The obtained solid was recrystallized from ethanol to yield compounds **14**–**23** and **34**–**43** (Table 1). **14**: ^{1}H NMR (DMSO-d_6) δ 1.73–1.77 (m, 2H, cyclohexanone-H), 1.88 (t, 4H, J = 5 Hz, cyclohexanone-H), 2.88 (s, 1H, CH), 6.88 (s, 1H, C=CH), 7.02–7.59 (m, 12H, Ar–H and thiazole-H). ^{13}C NMR δ 22.4, 23.9, 27.8, 28.2, 34.7, 38.9, 39.1, 39.3, 39.5, 39.7, 39.8, 40, 55.1, 55.3, 113.2, 114.1, 128, 131.5, 132.2, 134.2, 134.8, 135.4, 159.7. MS *m/z* (%): 356 (9.4, M^+). **15**: ^{1}H NMR (DMSO-d_6) δ 1.72–1.73 (m, 2H, cyclohexanone-H), 1.85–1.86 (m, 4H, cyclohexanone-H), 2.73 (s, 3H, CH_3), 2.91 (s, 1H, CH), 6.74 (s, 1H, C=CH), 7.29–7.55 (m, 10H, Ar–H), 7.64 (s, 1H, thiazole-H). MS *m/z* (%): 370 (5.2, M^+). **16**: ^{1}H NMR (DMSO-d_6) δ 1.72–1.74 (m, 2H, cyclohexanone-H), 1.85–1.86 (m, 4H, cyclohexanone-H), 2.88 (s, 1H, CH), 6.75 (s, 1H, C=CH), 7.37–7.60 (m, 10H, Ar–H and thiazole-H). ^{13}C NMR δ 22.2, 27.7, 28, 34.2, 39, 39.2, 39.3, 39.5, 39.7, 39.8, 40, 62.9, 127,8, 128.6, 131, 132, 133.4, 133.6, 134, 134.5, 135.1, 136.8, 188.7. MS *m/z* (%): 425 (1.39, M^+). **17**: ^{1}H NMR (DMSO-d_6) δ 1.72–1.85 (m, 6H, cyclohexanone-H), 2.72 (s, 3H, CH_3), 2.87 (s, 1H, CH), 6.75 (s, 1H, C=CH), 7.19 (s, 1H, thiazole-H), 7.37–7.60 (m, 8H, Ar–H). MS *m/z* (%): 439 (5.2, M^+). **18**: ^{1}H NMR (DMSO-d_6) δ 1.73–1.75 (m, 2H, cyclohexanone-H), 1.92–2.20 (m, 4H, cyclohexanone-H), 2.88 (s, 1H, CH), 3.80 (s, 6H, OCH_3), 6.65 (s, 1H, C=CH), 6.89–7.59 (m, 10H, Ar–H and thiazole-H). ^{13}C NMR δ 22.4, 24, 27.9, 28.2, 34.7, 39, 39.1, 39.3, 39.5, 39.6, 39.8, 40, 55.1, 113.1, 114.1, 128, 131.5, 132.1, 132.2, 134.2, 134.8, 135.4, 136.1, 136.5, 188.6. MS *m/z* (%): 416 (2.38, M^+). **19**: ^{1}H NMR (DMSO-d_6) δ 1.72–1.91 (m, 6H, cyclohexanone-H), 2.69 (s, 3H, CH_3), 2.90 (s, 1H, CH), 3.81 (s, 6H, OCH_3), 6.56 (s, 1H, C=CH), 6.88–7.59 (m, 9H, Ar–H and thiazole-H). ^{13}C NMR δ 23.9, 27.9, 28.2, 34.7, 39, 39.1, 39.4, 39.5, 39.7, 39.8, 40, 55.1, 55.3, 63, 114.1, 128, 128.3, 131.5, 132.1, 134,2, 134.8, 135.4, 136.1, 136.5, 159.7, 188.6. MS *m/z* (%): 430 (5.09, M^+). **20**: ^{1}H NMR (DMSO-d_6) δ 1.74–1.85 (m, 6H, cyclohexanone-H), 2.92 (s, 1H, CH), 3.79 (s, 12H, OCH_3), 6.65 (s, 1H, C=CH), 6.90–7.18 (m, 6H, Ar–H). 7.40 (d, 2H, thiazole-H). MS *m/z* (%): 476 (0.07, M^+). **21**: ^{1}H NMR (DMSO-d_6) δ 1.74–1.85 (m, 5H, CH_3, cyclohexanone-H), 2.11 (t, 4H, J = 5 Hz, cyclohexanone-H), 2.92 (s, 1H, CH), 3.71–3.81 (m, 12H, OCH_3), 6.65 (s, 1H, C=CH), 6.90–7.40 (m, 6H, Ar–H), 7.60 (s, 1H, thiazole-H). ^{13}C NMR δ 22.5, 27.9, 39, 39.2, 39.3, 39.5, 39.7, 39.8, 40, 55.5, 63, 111.6, 114.1, 123.8, 128.1, 129.3, 131.2, 132, 132.5, 133.9, 134.1, 134.3, 134.7, 135.9, 136.3, 148.5, 149.5, 188.5. MS *m/z* (%): 490 (0.39, M^+). **22**: ^{1}H NMR (DMSO-d_6) δ 1.75–1.89 (m, 6H, cyclohexanone-H), 2.95 (s, 1H, CH), 3.68–3.83

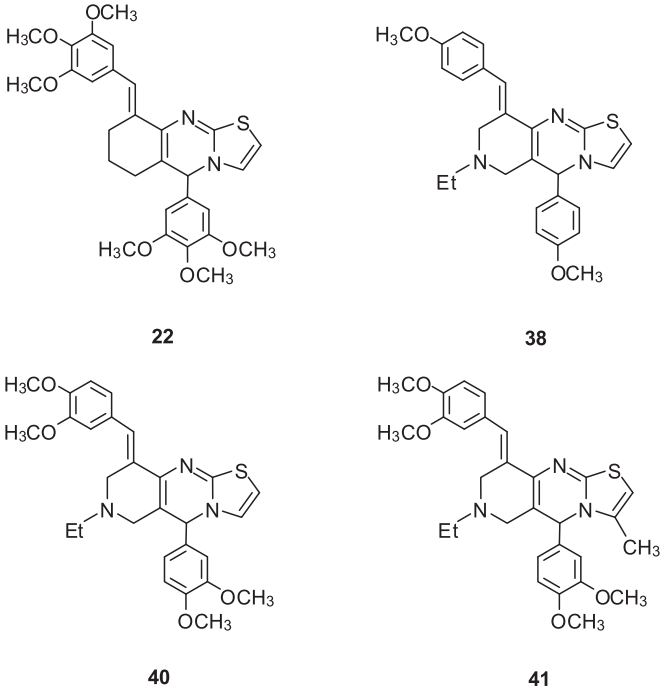


Fig. 1. Structures of the active antitumor agents **22**, **38**, **40** and **41**.

(m, 18H, OCH_3), 6.68 (s, 1H, C=CH), 6.81–6.97 (m, 6H, Ar–H and thiazole-H). MS *m/z* (%): 536 (15.7, M^+). **23**: ^{1}H NMR (DMSO-d_6) δ 1.86–1.90 (m, 6H, cyclohexanone-H), 2.08 (s, 3H, CH_3), 2.95 (s, 1H, CH), 3.67–3.83 (m, 18H, OCH_3), 6.58 (s, 1H, C=CH), 6.79–6.97 (m, 4H, Ar–H), 7.36 (s, 1H, thiazole-H). MS *m/z* (%): 550 (2.7, M^+). **34**: ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3H, CH_2CH_3), 1.14 (s, 4H, cyclohexanone-H), 3.40 (s, 1H, CH), 4.00–4.01 (q, 2H, CH_2CH_3), 7.33 (s, 1H, C=CH), 7.40–7.79 (m, 12H, Ar–H and thiazole-H). ^{13}C NMR δ 22, 29, 38.9, 39.1, 39.3, 39.4, 39.6, 39.8, 39.9, 42.7, 43.3, 43.5, 50.4, 53.5, 127.7, 128.3, 128.8, 129, 130.8, 132.1, 133.5, 133.9, 134.3, 188.4. MS *m/z* (%): 385 (10.5, M^+). **35**: ^{1}H NMR (DMSO-d_6) δ 1.00 (t, 3H, CH_2CH_3), 1.24(s, 3H, CH_3), 2.59 (s, 4H, cyclohexanone-H), 3.70 (s, 1H, CH), 3.76–3.82 (q, 2H, CH_2CH_3), 7.04 (s, 1H, C=CH), 7.48–7.57 (m, 11H, Ar–H and thiazole-H). MS *m/z* (%): 399 (4.33, M^+). **36**: ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.76 (s, 4H, cyclohexanone-H), 2.13 (s, 1H, CH), 3.76–3.92 (q, 2H, CH_2CH_3), 7.17 (d, 4H, J = 5.5 Hz, Ar–H), 7.44 (d, 4H, J = 5.8 Hz, Ar–H), 7.54 (s, 1H, C=CH), 7.58 (s, 2H, thiazole-H). MS *m/z* (%): 454 (6.11, M^+). **37**: ^{1}H NMR (DMSO-d_6) δ 1.58 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.83 (s, 3H, CH_3), 2.95 (s, 4H, cyclohexanone-H), 3.87–3.91 (m, 3H, CH and CH_2CH_3), 6.95 (s, 1H, C=CH), 7.28–7.49 (m, 8H, Ar–H), 7.79 (s,1H, thiazole-H). ^{13}C NMR δ 23.1, 23.6, 28.6, 34.3, 38.2, 39.3, 39.8, 39.9, 40, 42.4, 43.1, 43.5, 43.7, 50.3, 50.8, 124.4, 126.3, 128.6, 128.7, 129, 132.3, 134.4, 136.5, 159.9, 190.2. MS *m/z* (%): 468 (1.12, M^+). **38**: ^{1}H NMR (DMSO-d_6) δ 1.01 (t, 3H, J = 5.5 Hz, CH_2CH_3), 2.57 (s, 4H, cyclohexanone-H), 3.36 (s, 1H, CH), 3.75–3.78 (q, 2H, CH_2CH_3), 3.81 (s, 6H, OCH_3), 6.89 (s, 1H, C=CH), 7.03 (d, 4H, J = 9 Hz, Ar–H), 7.48 (d, 4H, J = 9 Hz, Ar–H), 7.56 (s, 2H, thiazole-H). MS *m/z* (%): 445 (6.11, M^+). **39**: ^{1}H NMR (DMSO-d_6) δ 1.00 (s, 3H, CH_2CH_3), 1.65 (s, 3H, CH_3), 2.59 (s, 4H, cyclohexanone-H), 3.37 (s, 1H, CH), 3.75–3.78 (q, 2H, CH_2CH_3), 3.81 (s, 6H, OCH_3), 6.92 (s, 1H, C=CH), 7.04 (d, 4H, J = 9 Hz, Ar–H), 7.46 (d, 4H, J = 9 Hz, Ar–H), 7.58 (s, 1H, thiazole-H). MS *m/z* (%): 459 (1.37, M^+). **40**: ^{1}H NMR (DMSO-d_6) δ 0.99 (s, 3H, CH_2CH_3), 2.50 (s, 4H, cyclohexanone-H), 3.38 (s, 1H, CH), 3.79 (s, 12H, OCH_3), 3.80–3.82 (q, 2H, CH_2CH_3), 7.07 (s, 1H, C=CH), 7.07–7.10 (dd, 6H, J = 9 Hz, Ar–H), 7.58 (s, 2H, thiazole-H). MS *m/z* (%): 505 (0.59, M^+). **41**: ^{1}H NMR (DMSO-d_6) δ 1.01 (t, 3H, J = 6 Hz, CH_2CH_3), 1.9 (s, 3H, CH_3), 2.06 (s, 4H, cyclohexanone-H), 3.39 (s, 1H, CH), 3.44–3.47 (q, 2H, CH_2CH_3), 3.80 (s, 12H, OCH_3), 7.04–7.08 (m, 6H, Ar–H) 7.10 (s, 1H, C=CH), 7.58 (s, 1H, thiazole-H). MS *m/z* (%): 519 (0.79, M^+). **42**: ^{1}H NMR (DMSO-d_6) δ 1.27 (t, 3H, CH_2CH_3), 1.96 (s, 4H, cyclohexanone-H), 2.98 (s, 1H, CH), 3.89–3.92 (m, 18H, OCH_3), 3.94–4.00 (q, 2H, CH_2CH_3), 6.62 (s, 1H, C=CH), 6.84–7.15 (m, 4H, Ar–H), 7.28 (s, 2H, thiazole-H). ^{13}C NMR δ 23.1, 24.3, 28.5, 28.7, 38.1, 38.3, 39.2, 40.5, 56, 56.2, 61, 63.4, 76.8, 77, 77.2, 107.8, 110.4, 110.9, 112.1, 113.7, 123.9, 124, 129, 134.5, 136.9, 137, 148.7, 149.6, 153, 189.5. MS *m/z* (%): 565 (2.21, M^+). **43**: ^{1}H NMR (DMSO-d_6) δ 1.02 (s, 3H, J = 12 Hz, CH_2CH_3), 2.49 (s, 4H, cyclohexanone-H), 2.59 (s, 3H, CH_3), 3.36 (s, 1H, CH), 3.71 (s, 18H, OCH_3), 3.78–3.82 (q, 2H, CH_2CH_3), 6.77 (s, 1H, C=CH), 6.81 (m, 4H, Ar–H), 7.59 (s, 1H, thiazole-H). MS *m/z* (%): 579 (12.9, M^+).

*4.1.3. 9-(Thien-2-ylmethylene)-5-(thien-2-yl)-3-(substituted-6,7,8,9-tetrehydro-5H-thiazolo[2,3-b]quinazolines (**26**, **27**)) and 7-ethyl-9-(thien-2-ylmethylene)-5-(thien-2-yl)-3-(substituted-6,7,8,9-tetrehydro-5H-pyrido[4,3-d]thiazolo[3,2-a]pyrimidines (**45**, **46**))*

A solution of 2-aminothiazole or 2-amino-4-methylthiazole (**12** or **13**, 0.01 mol), the appropriate α,β-unsaturated ketone (**25**, **44**, 0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 20 h, and continued as mentioned under compounds **14**–**23** and **34**–**43**. **26**: ^{1}H NMR (DMSO-d_6) δ 1.89 (t, 2H, J = 12 Hz, cyclohexanone-H), 2.49–2.51 (m, 2H, cyclohexanone-H), 2.87 (t, 2H, J = 12 Hz, cyclohexanone-H), 3.39 (s, 1H, CH), 7.23 (s, 1H, C=CH), 7.24 (d, 1H, J = 6 Hz, thiazole-H), 7.58 (d, 1H, J = 6 Hz, thiazole-H), 7.86–7.90 (m, 6H, thienyl-H). MS *m/z* (%): 368 (13.2, M^+). **27**: ^{1}H NMR (DMSO-d_6) δ 1.90 (t, 2H, J = 12 Hz, cyclohexanone-H), 2.24 (s, 3H, CH_3), 2.49–2.50 (m, 2H, cyclohexanone-H), 2.87 (t, 2H, J = 12 Hz, cyclohexanone-H), 3.38 (s, 1H, CH), 7.23 (s, 1H, C=CH), 7.26 (d, 1H, J = 6 Hz, thiazole-H), 7.88–7.90 (m, 6H, thienyl-H). MS *m/z* (%): 382 (5.9, M^+). **45**: ^{1}H NMR (DMSO-d_6) δ 1.00 (t, 3H, CH_2CH_3), 1.23 (s, 4H, cyclohexanone-H), 3.79–3.81 (q, 2H, CH_2CH_3), 2.59 (s, 1H, CH), 7.07 (s, 1H, C=CH), 7.11 (d, 2H, J = 8.5 Hz, thiazole-H), 7.59–7.67 (m, 6H, thienyl-H). ^{13}C NMR δ 29, 39, 39.1, 39.3, 39.5, 39.6, 39.8, 40, 50.5, 53.8, 55.5, 111.6, 114.1, 123.7, 127.4, 131.9, 134.8, 148.5, 149.8, 186.4. MS *m/z* (%): 397 (1.2, M^+). **46**: ^{1}H NMR (DMSO-d_6) δ 1.07 (s, 3H, CH_3), 1.14 (t, 3H, CH_2CH_3), 1.82 (s, 4H, cyclohexanone-H), 2.78 (s, 1H, CH), 3.76–3.81 (q, 2H, CH_2CH_3), 6.70 (s, 1H, C=CH), 7.07 (s, 1H, thiazole-H), 7.20–7.28 (m, 6H, thienyl-H). MS *m/z* (%): 411 (0.3, M^+).

4.2. Antitumor screening

Under a sterile condition, cell lines were grown in RPMI 1640 media (Gibco, NY, USA) supplemented with 10% fetal bovine serum (Biocell, CA, USA), 5×10^5 cell/ml was used to test the growth inhibition activity of the synthesized compounds. The concentrations of the compounds ranging from 0.01 to 100 μM were prepared in phosphate buffer saline. Each compound was initially solubilized in dimethyl sulfoxide (DMSO), however, each final dilution contained less than 1% DMSO. Solutions of different concentrations (0.2 ml) were pipetted into separate well of a microtiter tray in duplicate. Cell culture (1.8 ml) containing a cell population of 6×10^4 cells/ml was pipetted into each well. Controls, containing only phosphate buffer saline and DMSO at identical dilutions, were also prepared in the same manner. These cultures were incubated in a humidified incubator at 37 °C. The incubator was supplied with 5% CO_2 atmosphere. After 48 h, cells in each well were diluted 10 times with saline and counted by using a coulter counter. The counts were corrected for the dilution [29–31].

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