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MEDICINAL CHEMISTRY RESEARCH

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Synthesis and antitumor activity of certain new thiazolo [2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine analogs

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Abstract A novel series of thiazolo[2,3-*b*]quinazoline **(16–19**, **25–28**, and **34–37)** and cyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine **(20–23**, **29–32**, and **38–41)** analogs was designed and synthesized. Structure elucidation of the synthesized compounds was attained by the use of H^1 NMR, C^{13} NMR, and mass spectrometry. The obtained compounds were evaluated for their in vitro antitumor activity using the National Cancer Institute's 60 cell lines' panel assay that included nine tumor subpanels, namely, leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells. Most of the investigated compounds showed a remarkable broad-spectrum antitumor activity. Compounds **19, 28, 32**, and **34** proved to be 10-, 15-, 2-, and 7-fold more active than 5-FU, with GI_{50} MG-MID values of 2.4, 1.5, 11.2, and 3.1 μM, respectively.

Keywords Antitumor activity · Thiazolo[2,3-*b*]quinazoline · Cyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine

Introduction

Cancer is a malignant life-threatening disease which stands next to cardiovascular diseases in terms of morbidity and mortality and is projected to be the primary cause of death worldwide in the future (Harris and Hollstein, 1993; Varmus, 2006). The search for the ideal anticancer drug remains elusive with no drug discovered till date that would eliminate cancerous cells without harming normal tissues. A balance of benefit and toxicity has to be considered for the evaluation of any anticancer agents (Sashidhara *et al.,* 2010).

Thiazole—as a sulfur-containing heterocycle—is widely represented in many biologically active materials, such as the antibacterial sulfathiazole (Bharti *et al.,* 2010; Gouda *et al.,* 2010), the anticonvulsant riluzole (Ergenc and Capan, 1994), the antiparkinsonian talipexole (Gillespie *et al.,* 2008), the antivirals ritonavir and tiazofurin (Bell *et al.,*1995), and the anticancer dasatinib (Cortes *et al.,* 2007). The groove-binding agents dactinomycin, netropsin, and thia-netropsin also represent a group of compounds that contain thiazole moiety and were used as antitumor drugs (Popsavin *et al.,* 2007; Wolter *et al.,* 2009). Furthermore, substituted thiazolo–pyrimidine ring systems were reported to possess antitumor activity (Said *et al.,* 2004).

On the other hand, chalcones constitute an important class of natural products displaying interesting biological activities including anti-inflammatory (Ko *et al.,* 2003), antioxidant, cytotoxic (Go *et al.,* 2005), antimicrobial (Lopez *et al.,* 2001), anti-leishmanial (Nielsen *et al.,* 1998), and anti-tuberculosis (Lin *et al.,* 2002) properties. In addition, they have a recognized synthetic utility in the preparation of numerous pharmacologically interesting heterocyclic systems such as pyrimidines that have drawn the attention of medicinal chemists as chemotherapeutic agents. 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

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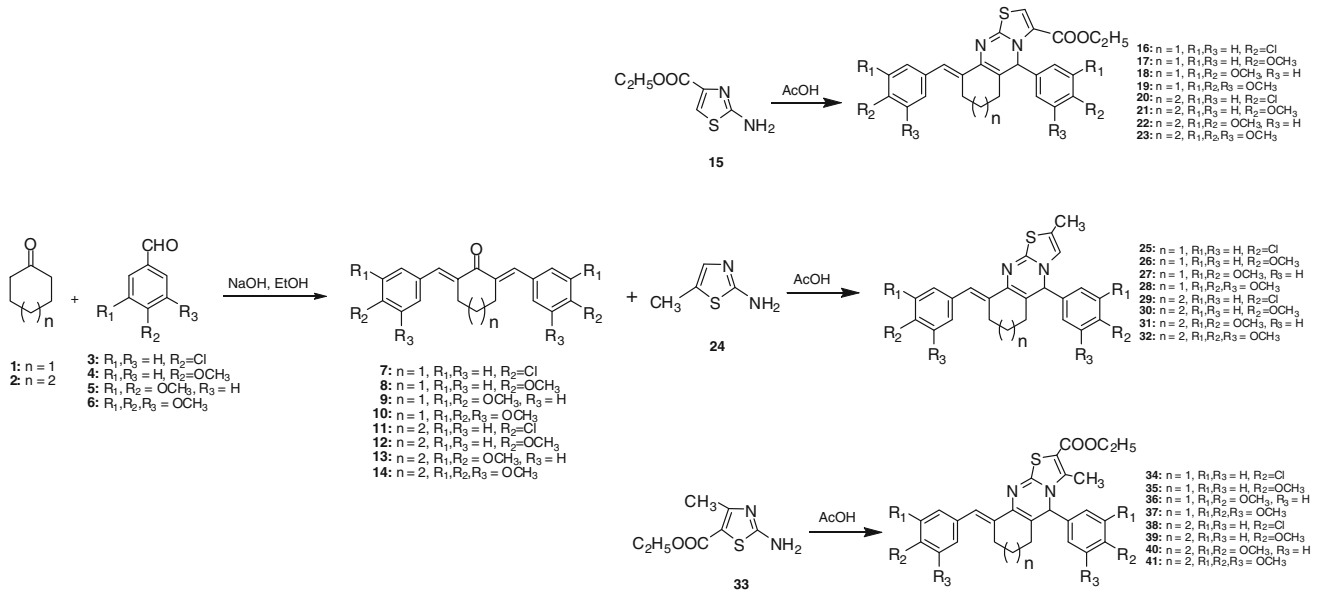


Scheme 1 Synthesis of the target compounds **16–23, 25–32**, and **34–41**

(Habib *et al.,* 2003), antibacterial (El-Bendary *et al.,* 1998), antifungal (Pees and Albert, 1992), and antiviral agents (Abdel-Hafez *et al.,* 2002).

Recently, some hybrid compounds containing thiazolyl–chalcones derivatives have been synthesized and screened for their anticancer activities (Shi *et al.,* 2010). The used chalcone moieties were fitted with methoxy groups, a functional group known to enhance the antitumor potency (Rao *et al.,* 2009; Rostom *et al.,* 2009; Al-Omary *et al.,* 2012). Based on these results and as a continuation to our previous efforts (El-Subbagh *et al.,* 1994; El-Subbagh and Al-Obaid, 1996; El-Subbagh *et al.,* 1999, 2001; El-Messery *et al.,* 2012), a series of new thiazolo[2,3-*b*]quinazoline and cyclohepta[*d*] thiazolo[3,2-*a*]pyrimidine analogs was designed and synthesized. The new compounds incorporated thiazole moiety, chalcone skeleton-bearing methoxy function to produce derivatives that are expected to possess antitumor activity. The new compounds were screened for their in vitro antitumor activity using the National Cancer Institution (NCI)'s disease-oriented human cell line 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 (Grever *et al.,* 1992; Monks *et al.,* 1991; Boyd and Paull, 1995; Skehan *et al.,* 1990).

Results and discussion

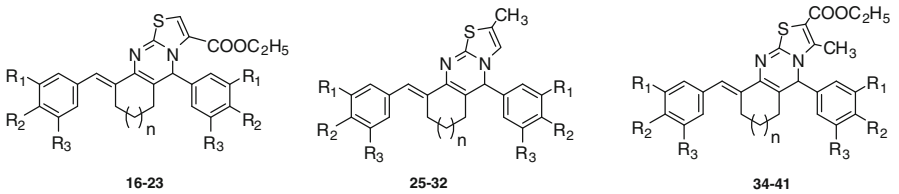
Chemistry

The synthetic strategy to prepare the target compounds (*E*)-ethyl 9-substituted benzylidene-5-substituted phenyl-6,7,8,9-tetrahydro-*5H*-thiazolo[2,3-*b*]quinazoline-3-carboxylates **(16–19)**, (*E*)-ethyl 10-substituted benzylidene-5-substituted phenyl-5,6,7,8,9,10-hexahydrocyclohepta[*d*]thiazolo[3,2-*a*] pyrimidine-3-carboxylates **(20–23)**, (*E*)-9-substituted benzylidene-5-substituted phenyl-2-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-*b*]quinazolines **(25–28)**, (*E*)-10-substituted benzylidene-5-substituted phenyl-2-methyl-5,6,7,8,9,10-hexahydro cyclohepta[*d*]thiazolo[3,2-*a*]pyrimidines **(29–32)**, (*E*)-ethyl 9-substituted benzylidene-5-substituted phenyl-3-methyl-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxylates **(34–37)**, and (*E*)-ethyl 10-substituted benzylidene-5-substituted phenyl-3-methyl-5,6,7,8,9,10-hexa-hydrocyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine-2-carboxylates **(38–41)** is illustrated in Scheme 1. The reported diarylidene derivatives **7–14** were prepared by reacting either cyclohexanone **(1)** or cycloheptanone **(2)** with various benzaldehyde analogs **(3–6)** in ethanolic solution of sodium hydroxide (Al-Omary *et al.,* 2012; Singh *et al.,* 2009, 2011). The target compounds **16–23, 25–32**, and **34–41** were obtained by reacting ethyl 2-aminothiazole-4-carboxylate **(15),** 2-amino-5-methyl-thiazole **(24)**, or ethyl 2-amino-4-methylthiazole-5-carboxylate **(33)** with the α,β-unsaturated ketones **7–14** in glacial acetic acid (Scheme 1). All of the newly synthesized compounds were subjected to structure elucidation using elemental analysis, mass spectrometry,and ^{1}H and ^{13}C NMR (Table 1).

Preliminary in vitro antitumor screening

All of the synthesized compounds **16–23, 25–32**, and **34–41** were selected by the NCI and were subjected to the NCI's disease-oriented human cell line screening assay to

Table 1 Physicochemical properties of the newly synthesized compounds **16–23, 25–32, 34–41**



Compound	*n*	R_1	R_2	R_3	Yield (%)	Mp (°C)	Molecular formulae[a]
16	1	H	Cl	H	74	134–6	$C_{26}H_{22}Cl_2N_2O_2S$
17	1	H	OCH_3	H	66	128–30	$C_{28}H_{28}N_2O_4S$
18	1	OCH_3	OCH_3	H	68	136–8	$C_{30}H_{32}N_2O_6S$
19	1	OCH_3	OCH_3	OCH_3	72	151–2	$C_{32}H_{36}N_2O_8S$
20	2	H	Cl	H	69	164–3	$C_{27}H_{24}Cl_2N_2O_2S$
21	2	H	OCH_3	H	80	152–4	$C_{29}H_{30}N_2O_4S$
22	2	OCH_3	OCH_3	H	75	144–6	$C_{31}H_{34}N_2O_6S$
23	2	OCH_3	OCH_3	OCH_3	71	138–40	$C_{33}H_{38}N_2O_8S$
25	1	H	Cl	H	64	129–31	$C_{24}H_{20}Cl_2N_2S$
26	1	H	OCH_3	H	88	118–20	$C_{26}H_{26}N_2O_2S$
27	1	OCH_3	OCH_3	H	73	121–3	$C_{28}H_{30}N_2O_4S$
28	1	OCH_3	OCH_3	OCH_3	75	158–60	$C_{30}H_{34}N_2O_6S$
29	2	H	Cl	H	80	114–6	$C_{25}H_{22}Cl_2N_2S$
30	2	H	OCH_3	H	69	133–5	$C_{27}H_{28}N_2O_2S$
31	2	OCH_3	OCH_3	H	66	141–3	$C_{29}H_{32}N_2O_4S$
32	2	OCH_3	OCH_3	OCH_3	64	122–5	$C_{31}H_{36}N_2O_6S$
34	1	H	Cl	H	71	161–3	$C_{27}H_{24}Cl_2N_2O_2S$
35	1	H	OCH_3	H	68	143–5	$C_{29}H_{30}N_2O_4S$
36	1	OCH_3	OCH_3	H	64	132–4	$C_{31}H_{34}N_2O_6S$
37	1	OCH_3	OCH_3	OCH_3	80	143–6	$C_{33}H_{38}N_2O_8S$
38	2	H	Cl	H	71	145–7	$C_{28}H_{26}Cl_2N_2O_2S$
39	2	H	OCH_3	H	73	121–3	$C_{30}H_{32}N_2O_4S$
40	2	OCH_3	OCH_3	H	78	166–8	$C_{32}H_{36}N_2O_6S$
41	2	OCH_3	OCH_3	OCH_3	79	175–7	$C_{34}H_{40}N_2O_8S$

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

be evaluated for their in vitro antitumor activity. A single dose (10 μM) of the test compounds was 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 (Grever *et al.,* 1992; Monks *et al.,* 1991; Boyd and Paull, 1995; Skehan *et al.,* 1990). Compounds that satisfied the predetermined threshold inhibition criteria would progress to the five-dose screen. The data were reported as a mean graph of the percent growth of the treated cells are and presented as percentage growth inhibition (GI %). The obtained results of the tested thiazolo[2,3-*b*]quinazoline and cyclohepta[*d*] thiazolo[3,2-*a*]pyrimidine analogs showed a distinctive potential pattern of selectivity as well as broad-spectrum antitumor activity (Tables 2, 3).

Regarding the activity toward individual cell lines, the obtained data revealed that some of the tested subpanel tumor cell lines exhibited variable sensitivity profiles against most of the tested compounds. Among these tumor cell lines, leukemia cell lines including HL-60 (TB), K-562, MOLT-4, RPMI-8226, and SR were found to be sensitive for most of the synthesized compounds and had a range of GI % that started at 10.2 % in compound **40** and reached the lethal effect in compounds **28** and **34**. This sensitivity was obviously expressed by compounds that appeared to be inactive against most of the other cell line subpanels such as compounds **21**, **22**, **31**, and **36** that seem to be selective against the leukemia cell lines. Similarly, the melanoma MALME-3M showed another range of sensitivity toward the tested compounds with GI % that

Table 2 Percentage growth inhibition (GI %) of in vitro subpanel tumor cell lines at 10 μM concentration of compounds **16–23, 25–28**

Subpanel tumor cell lines	% Growth inhibition (GI %)[a]											
	16	17	18	19	20	21	22	23	25	26	27	28
Leukemia												
CCRF-CEM	12.2	10.5	–	83.2	–	–	–	41.3	–	–	–	98.6
HL-60(TB)	20.4	15.4	–	48.5	–	30.5	26.5	44.5	–	23.8	–	**L**
K-562	–	14.8	–	61.3	–	15.5	17.2	64.7	–	–	–	79.6
MOLT-4	17.8	–	–	47.3	–	19.2	17.9	56.3	–	–	–	99.0
RPMI-8226	93.9	26.8	–	77.6	–	11.4	18.0	80.9	60.5	28.8	–	**L**
SR	10.5	–	–	68.8	–	–	13.8	41.9	–	–	–	100
Non-small cell lung cancer												
A549/ATCC	–	–	–	34.9	–	–	–	32.6	–	–	–	**L**
EKVX	–	–	–	–	–	–	–	23.5	–	–	–	80.5
HOP-62	–	–	–	25.5	–	–	–	47.1	–	–	–	**L**
HOP-92	–	23.1	26.0	15.2	–	18.2	10.0	37.5	–	–	**L**	44.6
NCI-H226	–	–	–	32.5	–	–	–	25.6	–	–	–	**L**
NCI-H23	16.2	–	–	47.8	–	–	–	32.1	13.2	–	–	**L**
NCI-322M	–	–	–	–	–	–	–	10.7	–	–	–	–
NCI-H460	–	–	–	76.7	–	–	–	22.8	–	–	–	98.6
NCI-H522	–	–	–	–	11.8	18.0	20.0	36.6	–	10.4	–	**L**
Colon cancer												
COLO 205	–	–	–	47.4	–	–	–	16.4	–	–	–	**L**
HCC-2998	–	–	–	24.9	–	–	–	25.9	–	–	–	**L**
HCT-116	50.3	–	–	80.8	–	–	–	16.9	17.4	–	–	**L**
HCT-15	–	–	–	42.3	–	–	–	38.2	–	–	–	**L**
HT29	17.2	–	–	87.1	–	–	–	21.7	–	–	15.7	**L**
KM12	33.3	–	–	**L**	–	–	–	20.1	–	–	–	**L**
SW-620	–	–	–	55.1	–	–	–	–	–	–	–	**L**
CNS cancer												
SF-268	–	–	–	66.7	–	–	–	11.2	–	–	–	85.3
SF-295	–	–	18.8	44.2	–	21.5	–	21.6	–	–	26.0	97.5
SF-539	–	–	–	50.1	–	–	–	14.8	–	–	–	92.5
SNB-19	18.7	–	–	15.0	–	–	–	10.4	–	–	–	47.3
SNB-75	13.7	10.9	19.6	60.9	–	–	–	–	–	–	–	40.6
U251	–	–	–	–	–	–	–	25.3	–	–	–	–
Melanoma												
LOX IMVI	25.1	–	–	77.0	–	–	–	18.8	14.8	–	–	**L**
MALME-3M	–	–	–	25.4	13.2	20.3	13.9	47.8	–	20.0	13.3	95.2
M14	–	–	–	83.1	–	–	–	–	–	–	–	97.5
MDA-MB-435	20.9	–	–	79.0	–	–	–	21.7	10.6	–	–	98.0
SK-MEL-2	–	–	–	–	–	–	–	10.9	–	–	–	**L**
SK-MEL-28	–	–	–	33.8	–	–	–	25.5	–	–	–	**L**
SK-MEL-5	15.4	–	–	39.7	–	–	11.3	62.0	–	–	–	**L**
UACC-257	14.3	14.5	–	41.9	–	–	–	44.9	–	–	–	**L**
UACC-62	18.0	16.5	–	25.6	–	–	–	42.6	–	–	14.5	–
Ovarian cancer												
IGORV1	–	–	–	10.3	–	–	–	21.6	–	–	–	97.2
OVCAR-3	–	–	–	42.9	–	–	–	26.2	–	–	–	**L**
OVCAR-4	–	–	–	27.7	–	–	18.6	42.6	–	–	–	60.4
OVCAR-5	–	–	–	24.3	–	–	–	–	–	–	–	**L**

Table 2 continued

Subpanel tumor cell lines	% Growth inhibition (GI %)[a]											
	16	17	18	19	20	21	22	23	25	26	27	28
OVCAR-8	–	–	–	86.5	–	–	–	28.7	–	–	–	**L**
NCI/ADR-RES	–	–	–	96.4	–	–	–	32.3	–	–	–	98.3
SK-OV-3	–	–	–	–	–	–	–	13.3	–	–	11.6	80.7
Renal cancer												
786-0	–	–	–	–	–	–	–	–	–	–	–	**L**
A498	21.9	–	17.7	21.7	–	–	–	56.0	13.5	23.2	–	**L**
ACHN	–	–	–	54.1	–	–	–	31.3	–	–	–	**L**
CAKI-1	–	–	–	33.7	–	–	–	26.7	–	–	–	89.0
RXF 393	21.2	–	–	67.4	–	–	–	–	11.8	–	11.7	**L**
SN12C	–	–	–	45.6	–	–	–	24.6	–	–	–	**L**
TK-10	–	–	–	15.3	–	–	–	–	–	–	–	97.8
UO-31	–	13.8	–	30.1	10.9	–	11.5	35.7	–	17.9	–	**L**
Prostate cancer												
PC-3	–	–	–	22.9	–	–	12.8	48.2	–	–	13.0	55.5
DU-145	–	–	–	91.2	–	–	–	–	–	–	–	**L**
Breast cancer												
MCF7	68.7	–	17.8	70.1	–	–	11.9	30.0	31.2	11.2	12.2	84.0
MDA-MB-231/ATCC	–	–	–	25.8	–	–	–	13.8	–	–	–	81.1
HS 578T	–	–	–	53.3	–	–	–	11.0	–	–	–	50.1
BT-549	–	–	–	–	–	–	–	29.1	–	–	–	**L**
T-47D	22.6	–	–	11.1	–	11.4	27.8	53.0	15.5	–	21.3	66.9
MDA-MB-468	15.2	12.5	–	66.2	–	–	–	68.5	–	14.9	–	**L**

L compound proved lethal to the cancer cell line

[a] –, GI < 10 %

ranged from 11.0 % in compound **37** to 95.2 % in compound **28**. Moreover, compounds **23**, **32**, and **41** showed moderate growth inhibitory activity against the same cell line with GI % values of 47.8, 45.5, and 48.3 %, respectively. Furthermore, the growth of the breast cancer MCF 7 was variably affected by the compounds under investigations; it was highly affected by compound **34** and **28** with GI % values of 100 and 84.0 %, respectively, and moderately affected by compounds **16** and **41** with GI % values of 68.7 and 39.1 %, respectively. The breast cancer T-47D showed high sensitivity against compound **32** (GI 71.0 %) and compound **34** (GI 74.7 %), while it expressed moderate activity against compound **23** (GI 53.0 %), **28** (GI 66.9 %), and **41** (GI 54.1 %) (Tables 2, 3).

Concerning the activity of the individual compounds, compounds **23** and **41** showed remarkable activity against most of the tested cell lines. Although they were not selected for the five-dose screen, they can be considered as broad-spectrum antitumor agents. Concerning compound **23**, it showed high activity against leukemia K-562, RPMI-8226, melanoma SK-MEL-5, and breast cancer MDA-MB-468 with GI % values of 64.7, 80.9, 62.0, and 68.5 %, respectively, while it showed moderate activity against leukemia CCRF-CEM, HL-60(TB), MOLT-4, SR, non-small cancer cell HOP-62, Melanoma MALME-3M, UACC-257, UACC-62, Ovarian cancer OVCAR-4, renal cancer A498, prostate cancer PC-3, and breast cancer T-47D with GI % values of 41.3, 44.5, 56.3, 41.9, 47.1, 47.8, 44.9, 42.6, 42.6, 56.0, 48.2, and 53.0 %, respectively. On the other hand, compound **41** showed high activity against leukemia K-562, RPMI-8226, melanoma UACC-62, and breast cancer MDA-MB-468 with GI % values of 68.8, 67.3, 60.1, and 74.8 %, respectively, and it showed moderate activity against leukemia HL-60(TB), MOLT-4, SR, non-small cancer cell HOP-62, NCI-H460, colon cancer HCT-15, CNS cancer SF-295, Melanoma MALME-3M, renal cancer A498, UO-31, prostate cancer PC-3, breast cancer BT-549, and T-47D with GI % values of 50.1, 54.8, 52.6, 50.1, 40.0, 55.2, 43.5, 48.3, 48.0, 45.7, 50.2, 44.9, and 54.1 %, respectively.

On close examination of the data presented in Tables 2 and 3, it was revealed that compounds **19**, **28**, **32**, and **34** are the most active members of this study, showing effectiveness toward numerous cell lines belonging to different tumor subpanels. The same analogy indicated that compounds **16**, **23**, **35**, **40**, and **41** possess moderate

Table 3 Percentage growth inhibition (GI %) of in vitro subpanel tumor cell lines at 10 μM concentration of compounds **29–32, 34–41**

Subpanel tumor cell lines	% Growth inhibition (GI %)[a]											
	29	30	31	32	34	35	36	37	38	39	40	41
Leukemia												
CCRF-CEM	–	–	–	34.2	**L**	23.9	11.3	–	–	–	–	29.1
HL-60(TB)	14.5	33.8	15.0	49.6	**L**	14.4	30.6	–	–	–	10.2	50.1
K-562	–	–	17.5	62.9	**L**	–	–	–	–	–	17.7	68.8
MOLT-4	12.8	–	17.3	64.4	**L**	15.4	16.4	–	–	–	12.0	54.8
RPMI-8226	–	–	15.7	81.6	**L**	81.8	–	–	–	–	15.4	67.3
SR	–	14.4	–	46.2	**L**	12.8	–	–	–	12.4	15.3	52.6
Non-small cell lung cancer												
A549/ATCC	–	–	–	27.2	94.9	11.2	–	–	–	–	–	39.7
EKVX	–	–	–	27.3	35.4	–	–	–	–	–	–	–
HOP-62	–	–	–	32.3	11.8	–	–	–	–	–	–	50.1
HOP-92	–	–	52.4	69.2	–	–	11.7	–	–	–	–	–
NCI-H226	–	–	–	23.1	52.5	–	–	–	–	–	–	–
NCI-H23	–	–	–	33.6	89.1	11.2	–	–	–	–	11.0	38.1
NCI-322 M	–	–	–	12.2	–	–	–	–	–	–	12.6	–
NCI-H460	–	–	–	26.6	48.2	–	–	–	–	–	10.2	40.0
NCI-H522	15.0	–	–	60.3	42.0	16.4	–	–	–	–	–	–
Colon cancer												
COLO 205	–	–	–	–	91.2	–	–	–	–	–	–	18.8
HCC-2998	–	–	–	24.4	**L**	–	–	–	–	–	–	15.0
HCT-116	–	–	–	26.4	**L**	20.2	–	–	–	–	–	32.0
HCT-15	–	–	–	45.4	**L**	–	–	–	–	–	–	55.2
HT29	–	–	–	28.3	**L**	–	–	–	–	–	–	33.2
KM12	–	–	–	25.2	**L**	–	–	–	–	–	–	32.5
SW-620	–	–	–	11.9	**L**	–	–	–	–	–	–	17.5
CNS cancer												
SF-268	–	–	–	36.7	65.3	–	–	–	–	–	–	19.5
SF-295	–	–	20.8	33.4	–	–	–	20.9	–	22.6	–	43.5
SF-539	–	–	–	23.6	58.7	–	–	–	–	–	–	20.1
SNB-19	–	–	–	11.7	44.6	–	–	–	–	–	–	–
SNB-75	–	–	16.2	–	35.8	15.9	10.1	17.5	15.7	–	22.1	10.7
U251	–	–	–	17.2	**L**	–	–	–	–	–	–	32.3
Melanoma												
LOX IMVI	–	–	–	17.5	**L**	–	11.6	–	–	–	–	26.0
MALME-3 M	11.1	–	–	45.5	23.0	16.8	17.4	11.0	–	12.5	14.0	48.3
M14	–	–	–	17.7	**L**	–	–	–	–	–	–	21.0
MDA-MB-435	–	–	–	21.5	**L**	26.9	–	–	–	–	–	31.7
SK-MEL-2	–	–	–	29.1	23.5	–	–	–	–	–	–	–
SK-MEL-28	–	–	–	11.6	51.2	–	–	–	–	–	–	17.2
SK-MEL-5	–	–	–	77.5	59.2	–	10.4	–	–	–	–	–
UACC-257	–	–	–	44.2	74.3	11.3	–	–	–	–	–	–
UACC-62	–	–	17.4	34.4	45.4	18.5	–	16.2	–	16.7	19.1	60.1
Ovarian cancer												
IGORV1	–	–	–	32.0	87.2	–	–	–	–	–	16.6	28.4
OVCAR-3	–	–	–	39.8	**L**	–	–	–	–	–	–	35.5
OVCAR-4	–	–	–	40.6	51.7	20.9	–	–	–	12.2	21.3	30.7
OVCAR-5	–	–	–	–	21.9	–	–	–	–	–	–	14.4

Table 3 continued

Subpanel tumor cell lines	% Growth inhibition (GI %)[a]											
	29	30	31	32	34	35	36	37	38	39	40	41
OVCAR-8	–	–	–	47.0	77.1	–	–	–	–	–	–	36.4
NCI/ADR-RES	–	–	–	29.7	60.6	10.4	–	–	–	–	–	37.9
SK-OV-3	–	–	–	17.7	53.0	–	10.6	11.5	13.4	–	13.9	22.2
Renal cancer												
786-0	–	–	–	17.7	**L**	–	–	–	–	16.0	–	–
A498	–	–	17.0	49.5	96.8	36.0	–	–	–	16.6	14.9	48.0
ACHN	–	–	–	49.3	83.4	–	–	–	–	–	–	30.4
CAKI-1	–	–	–	25.8	37.7	17.8	–	–	–	–	–	34.4
RXF 393	–	–	–	–	**L**	–	–	–	–	–	–	–
SN12C	–	–	–	25.4	41.9	10.2	–	–	–	–	–	24.8
TK-10	–	–	–	30.4	41.8	–	–	–	–	–	–	–
UO-31	–	–	18.8	40.4	46.1	17.1	31.5	21.9	16.8	21.2	31.0	45.7
Prostate cancer												
PC-3	–	–	19.3	52.7	75.7	15.0	–	–	–	–	24.9	50.2
DU-145	–	–	–	–	**L**	–	–	–	–	–	–	14.1
Breast cancer												
MCF7	–	–	–	26.6	**L**	22.0	16.2	–	17.6	10.4	24.8	39.1
MDA-MB-231/ATCC	–	–	–	34.2	28.5	–	–	–	–	–	–	28.1
HS 578T	–	–	–	29.5	48.3	–	–	–	–	–	–	–
BT-549	–	–	–	64.5	**L**	–	–	–	–	–	–	44.9
T-47D	–	–	28.4	71.0	74.7	15.3	–	–	21.4	20.0	37.7	54.1
MDA-MB-468	–	–	21.8	68.4	95.6	15.2	–	–	–	–	21.0	74.8

L compound proved lethal to the cancer cell line

[a] –, GI < 10 %

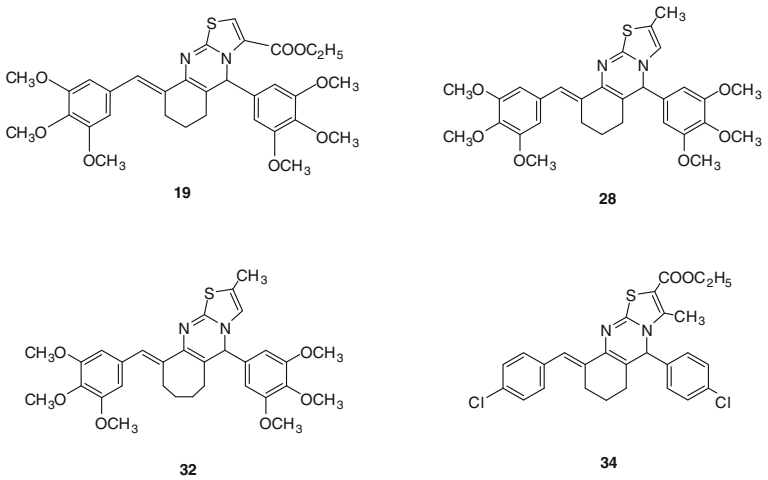


Fig. 1 Structures of the active antitumor agents **19, 28, 32**, and **34**

antitumor activity, while the rest of compounds possess the least active antitumor activity in the present investigation (Fig. 1).

Compounds **19**, **28**, **32**, and **34** 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 (Grever *et al.,* 1992; Monks *et al.,* 1991; Boyd and Paull, 1995; Skehan *et al.,* 1990). 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. Compound **19** is almost tenfold more

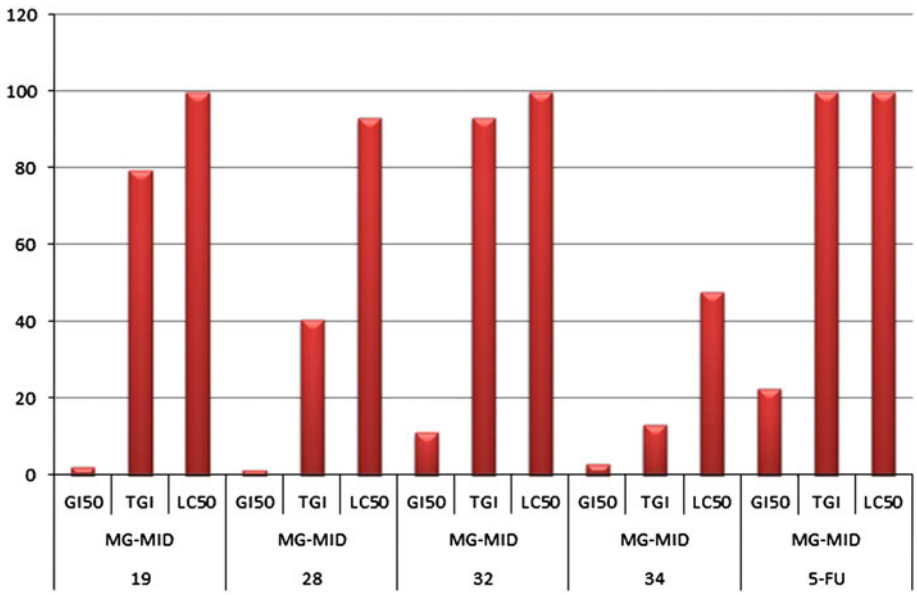


Fig. 2 Full panel mean-graph midpoint (μM) of compounds **19, 28, 32**, and **34** in comparison with 5-FU

active than 5-FU, with GI_{50}, TGI, and LC_{50} values of 2.4, 79.4, and >100, respectively. Compound **28** is 15-fold more active than 5-FU, with GI_{50}, TGI, and LC_{50} values of 1.5, 40.7, and 93.3, respectively, while compounds **32** and **34** are almost double and sevenfold more active than 5-FU, with GI_{50}, TGI, and LC_{50} values of 11.2, 93.3, and >100 and 3.1, 13.2, and 47.9 μM, respectively (Fig. 2; Table 4).

Structure–activity correlation

Structure–activity correlation, based on the number of cell lines proved sensitive toward each of the synthesized individual compounds, revealed that the trimethoxy derivatives of either thiazolo[2,3-*b*]quinazolines (**19** and **28**) or cyclohepta[*d*]thiazolo[3,2-*a*]pyrimidines (**23**, **32**, and **41**) are more active antitumor agents than the other analogs at the same series.

Concerning the tested thiazolo[2,3-*b*]quinazoline heterocycles, the dimethoxy analogs such as (*E*)-ethyl 9-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline-3-carboxylate (**18**), (*E*)-9-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline (**27**), and (*E*)-ethyl 9-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-3-methyl-6,7,8,9-tetrahydro-5*H*-thiazolo [2,3-*b*]quinazoline-2-carboxylate (**37**) proved inactive in comparison with the rest of tested compounds. The para methoxy analogs such as compounds **17** and **35** can be considered as slightly moderate active compounds especially against leukemia cell lines. Regarding the chloro analogs, the replacement of the methyl group at position 2—group of **25** with an ester group at position 3—produced **16** with slightly moderate activity and selectivity against leukemia cell lines, while the introduction of ester group at position 2—and methyl group at position 3—produced **34** with remarkable antitumor activity.

Similarly, by taking a closer look at the cyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine analogs, a pattern had been observed. The chloro derivatives such as (*E*)-ethyl 10-(4-chlorobenzylidene)-5-(4-chlorophenyl)-5,6,7,8,9,10-hexahydrocyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine-3-carboxylate (**20**), (*E*)-10-(4-chlorobenzylidene)-5-(4-chlorophenyl)-2-methyl-5,6,7,8,9,10-hexahydrocyclo-hepta[*d*]thiazolo[3,2-*a*]pyrimidine (**29**), and (*E*)-ethyl 10-(4-chlorobenzylidene)-5-(4-chlorophenyl)-3-methyl-5,6,7,8,9,10-hexahydrocyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine-2-carboxylate (**38**) proved inactive. The introduction of methoxy groups instead of the chloro groups converts the compounds to selective anti-leukemic agent compounds **21**, **22**, **31**, and **40**, while the trimethoxy derivatives such as compounds **23**, **32**, and **41** are considered to have remarkable broad-spectrum antitumor potency.

Conclusions

Compounds (*E*)-ethyl 9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline-3-carboxylate **(19)**, (*E*)-2-methyl-9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quina-zoline **(28)**, (*E*)-2-methyl-10-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-5,6,7,8,9,10-hexahydrocyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine **(32)**, and (*E*)-ethyl 9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-3-methyl-6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazol-ine-2-carboxylate **(34)** (Fig. 1) are the most active broad-spectrum antitumor agents of this study with GI_{50}, TGI, and LC_{50} values of 2.4, 79.4, >100; 1.5, 40.7, 93.3; 11.2, 93.3, >100; and 3.1, 13.2, 47.9 μM, respectively.

Table 4 Median growth inhibitory (GI_{50} ± SD, μM), total growth inhibitory (TGI ± SD, μM), and median lethal (LC_{50} ± SD, μM) concentrations of *in vitro* subpanel tumor cell lines of compounds **19, 28, 32**, and **34**

Compound	Activity	Subpanel tumor cell lines[a]									MG-MID[b]
		I	II	III	IV	V	VI	VII	VIII	IX	
19	**GI_{50}**	1.0 ± 0.62 (0.61)	26.2 ± 7.93 (15.90)	1.7 ± 0.41 (1.03)	3.8 ± 0.63 (2.32)	15.5 ± 3.12 (9.44)	21.4 ± 6.75 (13.03)	19.4 ± 5.00 (11.82)	2.1 ± 0.90 (1.28)	2.9 ± 1.31 (1.77)	2.4 (1.46)
	TGI	2.7 ± 0.51 (1.65)	89.7 ± 5.82 (54.63)	c	c	c	c	c	c	c	79.4
	LC_{50}	c	c	c	c	c	c	c	c	c	c
28	**GI_{50}**	1.2 ± 0.43 (0.66)	1.7 ± 0.74 (0.94)	1.4 ± 0.34 (0.77)	3.1 ± 0.92 (1.71)	1.6 ± 0.20 (0.88)	1.3 ± 0.30 (0.72)	2.5 ± 0.82 (1.38)	2.5 ± 0.76 (1.38)	2.7 ± 0.87 (1.49)	1.5 (0.83)
	TGI	3.7 ± 0.80 (2.04)	80.9 ± 12.7 (44.50)	35.1 ± 8.91 (19.31)	c	nt	80.6 ± 15.1 (44.33)	c	c	c	40.7 (22.39)
	LC_{50}	c	c	68.3 ± 14.2 (37.57)	c	c	c	c	c	c	93.3 (51.32)
32	**GI_{50}**	11.0 ± 2.14 (6.20)	33.3 ± 8.84 (18.78)	60.0 ± 21.1 (33.84)	46.0 ± 19.1 (25.95)	29.6 ± 7.54 (16.70)	32.8 ± 18.7 (18.50)	33.7 ± 10.5 (19.00)	c	7.5 ± 1.80 (4.23)	11.2 (6.32)
	TGI	c	c	c	c	c	c	c	c	c	93.3 (52.62)
	LC_{50}	c	c	c	c	c	c	c	c	c	c
34	**GI_{50}**	2.5 ± 1.19 (1.28)	5.0 ± 2.11 (2.56)	2.1 ± 0.95 (1.07)	4.1 ± 1.66 (2.10)	5.3 ± 2.82 (2.71)	5.9 ± 2.41 (3.02)	3.1 ± 1.60 (1.59)	3.4 ± 1.99 (1.74)	3.1 ± 2.13 (1.59)	3.1 (1.59)
	TGI	7.7 ± 1.97 (3.94)	26.1 ± 12.5 (13.34)	4.5 ± 1.84 (2.30)	49.1 ± 16.3 (25.10)	18.1 ± 9.24 (9.25)	39.0 ± 11.5 (19.93)	29.5 ± 10.8 (15.08)	58.8 ± 18.3 (30.05)	27.6 ± 10.1 (14.11)	13.2 (6.75)
	LC_{50}	84.9 ± 12.8 (43.39)	70.5 ± 19.1 (36.03)	22.4 ± 9.47 (11.45)	c	69.7 ± 13.7 (35.62)	89.3 ± 13.0 (45.63)	54.6 ± 10.8 (27.90)	c	73.3 ± 9.76 (37.46)	47.9 (24.48)
5-FU	**GI_{50}**	15.1 ± 4.20 (1.96)	c	8.4 ± 3.70 (1.09)	72.1 ± 12.7 (9.37)	70.6 ± 15.8 (9.18)	61.4 ± 11.1 (7.98)	45.6 ± 10.3 (5.93)	22.7 ± 9.11 (2.95)	76.4 ± 10.8 (9.93)	22.6 (2.94)
	TGI	c	c	c	c	c	c	c	c	c	c
	LC_{50}	c	c	c	c	c	c	c	c	c	c

Conc. in μg/ml is shown in parentheses

Nt not tested

[a] 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

[b] Full panel mean-graph midpoint (μM)

[c] Compounds showed values >100 μM

The synthesized thiazolo[2,3-*b*]quinazoline and cyclohepta[*d*]thiazolo[3,2-*a*]pyrimidine analogs could be considered as a useful template for future development to obtain more potent antitumor agent(s).

Experimental

Melting points (°C) were determined on a 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 and ^{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 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 a 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 **7–14** were previously prepared (Al-Omary *et al.,* 2012; Singh *et al.,* 2009, 2011).

Chemistry

*(E)-Ethyl 9-substituted benzylidene-5-substituted phenyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazoline-3-carboxylates (**16–19**), (E)-ethyl 10-substituted benzylidene-5-substituted phenyl-5,6,7,8,9,10-hexahydrocyclohepta[d]thiazolo[3,2-a]pyrimidine-3-carboxylates (**20–23**)*

A solution of ethyl 2-aminothiazole-4-carboxylate (**15,** 1.72 g, 0.01 mol) and the appropriate α,β-unsaturated ketone (**7–14**, 0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 24 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 **16–23** (Table 1). ^{1}H NMR (DMSo-d_6); **16:** δ 1.29 (t, 3H, J = 13.5 Hz, CH_3CH_2), 1.72 (t, 2H, J = 5 Hz, cyclohexane-H), 1.84 (t, 2H, J = 5 Hz, cyclohexane-H), 2.87 (t, 2H, J = 5 Hz, cyclohexane-H), 4.25–4.29 (q, 2H, CH_3CH_2), 6.76 (s, 1H, oleifinic-H), 7.48 (d, 4H, J = 8.5 Hz, Ar–H), 7.52 (s, 1H, thiazole-H), 7.59 (d, 4H, J = 15.5 Hz, Ar–H), 8.03 (s, 1H, pyrimidine-H). ^{13}C NMR δ 14.1, 22.2, 22.4, 23.7, 27.7, 28.0, 34.2, 39.0, 40.0, 60.5, 122.5, 127.8, 128.6, 131.0, 132.0, 132.1, 133.4, 133.6, 134.1, 134.5, 134.9, 136.8, 140.8, 158.1, 161.0, 169.0. **MS** *m/z* (%): 497 (13.1, M^+). **17:** δ 1.28 (t, 3H, J = 14 Hz, CH_3CH_2), 1.73 (t, 2H, J = 4.5 Hz, cyclohexane-H), 1.84 (t, 2H, J = 5 Hz, cyclohexane-H), 2.89 (t, 2H, J = 4.5 Hz, cyclohexane-H), 3.82 (s, 6H, OCH_3), 4.27–4.30 (q, 2H, CH_3CH_2), 6.66 (s, 1H, oleifinic-H), 7.02 (d, 4H, J = 7.5 Hz, Ar–H), 7.52 (d, 4H, J = 8 Hz, Ar–H), 7.59 (s, 1H, thiazole-H), 8.03 (s, 1H, pyrimidine-H). ^{13}C NMR δ 14.1, 22.4, 22.5, 23.9, 27.9, 28.2, 34.7, 55.1, 55.3, 60.5, 113.2, 114.1, 122.5, 127.9, 128.2, 131.5, 132.2, 134.2, 135.4, 136.1, 136.5, 140.8, 158.1, 159.2, 161.0, 169.0, 188.6, 191.5. **MS** *m/z* (%): 488 (5.3, M^+). **18:** δ 1.30 (t, 3H, J = 13 Hz, CH_3CH_2), 1.75 (t, 2H, J = 5 Hz, cyclohexane-H), 1.85 (t, 2H, J = 4.9 Hz, cyclohexane-H), 2.69 (t, 2H, J = 4.5 Hz, cyclohexane-H), 3.79 (s, 12H, OCH_3), 4.27–4.29 (q, 2H, CH_3CH_2), 6.66 (s, 1H, oleifinic-H), 6.91 (d, 2H, J = 8 Hz, Ar–H), 7.04 (d, 2H, J = 8 Hz, Ar–H), 7.12 (s, 1H, Ar–H), 7.40 (s, 1H, Ar–H), 7.61 (s, 1H, thiazole-H), 8.01 (s, 1H, pyrimidine-H). ^{13}C NMR δ 14.1, 22.5, 24.0, 27.9, 28.2, 34.9, 55.4, 55.5, 60.5, 110.9, 111.6, 113.4, 114.1, 122.4, 123.7, 123.8, 128.1, 134.3, 135.1, 135.8, 136.3, 136.8, 140.8, 147.7, 148.5, 149.1, 161.0, 169.1, 188.6, 191.8. **MS** *m/z* (%): 548 (3.9, M^+). **19:** δ 1.31 (t, 3H, J = 13 Hz, CH_3CH_2), 1.86 (t, 2H, J = 4.9 Hz, cyclohexane-H), 2.72 (t, 2H, J = 5 Hz, cyclohexane-H), 2.94 (t, 2H, J = 5 Hz, cyclohexane-H), 3.69–3.72 (q, 2H, CH_3CH_2), 3.78 (s, 18H, OCH_3), 6.69 (s, 1H, oleifinic-H), 6.81 (s, 2H, Ar–H), 6.87 (s, 2H, Ar–H), 7.37 (s, 1H, thiazole-H), 7.60 (s, 1H, pyrimidine-H). **MS** *m/z* (%): 609 (8.1, M^+). **20:** δ 1.30 (t, 3H, J = 14 Hz, CH_3CH_2), 1.89 (s, 4H, cycloheptane-H), 2.64 (s, 4H, cycloheptane-H), 4.25–4.27 (q, 2H, CH_3CH_2), 6.15 (s, 1H, oleifinic-H), 7.24 (d, 4H, J = 8 Hz, Ar–H), 7.52 (d, 4H, J = 7.5 Hz, Ar–H), 7.53 (s, 1H, thiazole-H), 8.02 (s, 1H, pyrimidine-H). ^{13}C NMR δ 14.1, 22.4, 22.9, 27.4, 27.7, 60.5, 122.5, 123.5, 128.1, 128.4, 128.7, 129.9, 131.2, 132.3, 132.9, 133.0, 133.4, 134.1, 138.4, 139.2, 140.1, 140.8, 142.0, 158.1, 161.0, 169.0, 197.5. **MS** *m/z* (%): 511 (22.5, M^+). **21:** δ 1.29 (t, 3H, J = 14 Hz, CH_3CH_2), 1.90 (s, 4H, cycloheptane-H), 2.64 (s, 4H, cycloheptane-H), 3.80 (s, 6H, OCH_3), 4.25–4.29 (q, 2H, CH_3CH_2), 7.01 (d, 4H, J = 8.5 Hz, Ar–H), 7.20 (s, 2H, thiazole-H, oleifinic-H), 7.48 (d, 4H, J = 8.5 Hz, Ar–H), 8.03 (s, 1H, pyrimidine-H). ^{13}C NMR δ 14.1, 22.3, 22.9, 27.5, 27.6, 55.2, 55.4, 60.5, 114.2, 122.5, 123.5, 127.8, 128.3, 128.8, 129.2, 129.5, 129.9, 130.2, 131.2, 134.2, 134.8, 139.3, 140.0, 140.8, 158.1, 159.3, 161.0, 169.0, 197.8. **MS** *m/z* (%): 502 (11.1, M^+). **22:** δ 1.30 (t, 3H, J = 14 Hz, CH_3CH_2), 1.94 (s, 4H, cycloheptane-H), 2.67 (s, 4H, cycloheptane-H), 3.80 (s, 12H, OCH_3), 4.25–4.29 (q, 2H, CH_3CH_2), 7.03 (d, 4H, J = 8.5 Hz, Ar–H), 7.11 (s, 2H, thiazole-H, oleifinic-H), 7.21 (s, 2H, Ar–H), 8.03 (s, 1H, pyrimidine-H). ^{13}C

NMR δ 14.1, 22.4, 22.6, 27.7, 27.8, 55.2, 55.3, 55.4, 55.5, 60.6, 111.7, 113.2, 122.5, 122.6, 123.4, 124.5, 127.5, 128.3, 128.5, 129.0, 130.5, 134.6, 135.1, 139.5, 140.8, 148.5, 149.1, 158.1, 161.0, 169.0, 197.8. **MS** *m/z* (%): 562 (5.9, M^+). **23:** δ 1.30 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.97 (s, 4H, cycloheptane-H), 2.69 (s, 4H, cycloheptane-H), 3.70 (s, 9H, OCH_3), 3.82 (s, 9H, OCH_3), 4.25–4.29 (q, 2H, CH_3CH_2), 6.52 (s, 1H, oleifinic-H), 6.83 (s, 4H, Ar–H), 7.22 (s, 1H, thiazole-H), 8.03 (s, 1H, pyrimidine-H). ^{13}C NMR δ 14.1, 22.4, 22.9, 27.8, 28.0, 55.3, 55.5, 55.6, 55.8, 60.1, 60.5, 105.6, 106.9, 111.3, 112.4, 113.8, 114.1, 122.4, 124.1, 125.0, 127.6, 128.4, 129.0, 130.8, 134.8, 137.7, 139.4, 140.8, 142.0, 152.8, 158.1, 161.0, 169.0. **MS** *m/z* (%): 622 (7.4, M^+)

*(E)-9-Substituted benzylidene-5-substituted phenyl-2-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolines (**25–28**), (E)-10-substituted benzylidene-5-substituted phenyl-2-methyl-5,6,7,8,9,10-hexahydrocyclohepta[d]thiazolo[3,2-a]pyrimidines (**29–32**)*

A solution of 2-amino-5-methylthiazole (**24**, 1.14 g, 0.01 mol) and the appropriate α,β-unsaturated ketone (**7–14**, 0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 24 h and prepared as mentioned under compounds **16–23**. ^{1}H NMR (DMSo-d_6); **25:** δ 1.73 (t, 2H, $J = 5$ Hz, cyclohexane-H), 1.85 (t, 2H, $J = 4.9$ Hz, cyclohexane-H), 2.33 (s, 3H, CH_3), 2.88 (t, 2H, $J = 4.9$ Hz, cyclohexane-H), 6.75 (s, 1H, oleifinic-H), 7.11 (s, 1H, thiazole-H), 7.48 (d, 4H, $J = 10$ Hz, Ar–H), 7.57 (s, 1H, pyrimidine-H), 7.59 (d, 4H, $J = 10$ Hz, Ar–H). ^{13}C NMR δ 11.0, 22.2, 22.4, 23.7, 27.7, 28.0, 34.2, 125.8, 127.8, 128.6, 131.0, 132.0, 132.1, 132.3, 133.7, 134.5, 134.9, 136.8, 138.4, 139.2, 156.2, 167.9, 188.7, 191.6. **MS** *m/z* (%): 439 (19.3, M^+). **26:** δ 1.73 (t, 2H, $J = 4.5$ Hz, cyclohexane-H), 1.84 (t, 2H, $J = 5$ Hz, cyclohexane-H), 2.69 (t, 2H, $J = 4$ Hz, cyclohexane-H), 2.89 (s, 3H, CH_3), 3.81 (s, 6H, OCH_3), 6.66 (s, 1H, oleifinic-H), 7.04 (d, 4H, $J = 8$ Hz, Ar–H), 7.41 (s, 1H, thiazole-H), 7.52 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.60 (s, 1H, pyrimidine-H). ^{13}C NMR δ 22.5, 24.0, 27.9, 28.2, 34.7, 38.9, 55.1, 55.3, 113.2, 114.1, 115.9, 125.7, 127.9, 128.2, 131.5, 132.2, 132.3, 134.2, 134.8, 135.4, 136.2, 136.5, 159.2, 159.7, 188.6, 191.6. **MS** *m/z* (%): 430 (12.9, M^+). **27:** δ 1.74 (t, 2H, $J = 14$ Hz, $J = 4.8$ Hz, cyclohexane-H), 1.85 (t, 2H, $J = 4.9$ Hz, cyclohexane-H), 2.33 (s, 3H, CH_3), 2.69 (t, 2H, $J = 4.5$ Hz, cyclohexane-H), 3.81 (s, 12H, OCH_3), 6.65 (s, 1H, oleifinic-H), 7.15 (s, 2H, Ar–H), 7.45 (s, 1H, thiazole-H), 7.52 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.61 (s, 1H, pyrimidine-H). ^{13}C NMR δ 11.0, 22.4, 22.5, 24.0, 27.9, 28.2, 34.9, 55.4, 55.5, 110.9, 111.5, 113.4, 114.1, 123.7, 125.8, 128.1, 132.2, 134.3, 135.1, 136.3, 136.8, 147.6, 148.4, 149.5, 156.2, 167.9, 188.5, 191.8. **MS** *m/z* (%): 490 (4.7, M^+). **28:** δ 1.63 (t, 2H, $J = 5$ Hz, cyclohexane-H), 1.84 (t, 2H, $J = 5$ Hz, cyclohexane-H), 2.96 (s, 3H, CH_3), 2.98 (t, 2H, $J = 5$ Hz, cyclohexane-H), 3.89 (s, 18H, OCH_3), 6.65 (s, 1H, oleifinic-H), 7.26 (s, 2H, Ar–H), 6.91 (s, 1H, thiazole-H), 7.27 (s, 2H, Ar–H), 7.73 (s, 1H, pyrimidine-H). ^{13}C NMR δ 22.9, 28.5, 55.2, 55.5, 56.1, 56.2, 56.3, 61.0, 107.1, 107.6, 107.8, 109.3, 110.0, 110.5, 111.2, 111.4, 122.4, 124.1, 125.3, 128.4, 128.5, 129.7, 131.4, 135.4, 137.1, 138.7, 153.0, 159.1, 189.9, 197.1. **MS** *m/z* (%): 550 (8.4, M^+). **29:** δ 1.89 (s, 4H, cycloheptane-H), 2.33 (s, 3H, CH_3), 2.63 (s, 4H, cycloheptane-H), 6.65 (s, 1H, oleifinic-H), 7.10 (s, 1H, thiazole-H), 7.24 (d, 4H, $J = 7.5$ Hz, Ar–H), 7.35 (d, 4H, $J = 8$ Hz, Ar–H), 7.53 (s, 1H, pyrimidine-H). ^{13}C NMR δ 11.0, 22.4, 27.4, 27.7, 29.2, 111.2, 113.2, 125.8, 128.4, 128.7, 129.9, 131.2, 131.4, 132.0, 133.0, 133.4, 134.2, 134.6, 142.0, 156.2, 158.0, 158.6, 159.0, 167.9, 197.5. **MS** *m/z* (%): 453 (10.0, M^+). **30:** δ 1.74 (s, 4H, cycloheptane-H), 2.11 (s, 3H, CH_3), 2.32 (s, 4H, cycloheptane-H), 3.77 (s, 6H, OCH_3), 6.67 (s, 1H, oleifinic-H), 7.08 (d, 4H, $J = 8$ Hz, Ar–H), 7.11 (s, 5H, Ar–H, thiazole-H), 7.48 (s, 1H, pyrimidine-H). **MS** *m/z* (%): 445 (7.1, M^+). **31:** δ 1.95 (s, 4H, cycloheptane-H), 2.33 (s, 3H, CH_3), 2.68 (s, 4H, cycloheptane-H), 3.81 (s, 12H, OCH_3), 6.65 (s, 1H, oleifinic-H), 7.03 (d, 4H, $J = 7.5$ Hz, Ar–H), 7.10 (s, 3H, Ar–H, thiazole-H), 7.21 (s, 1H, pyrimidine-H). ^{13}C NMR δ 11.0, 22.4, 27.7, 27.7, 29.1, 55.4, 55.5, 111.7, 112.1, 112.5, 113.1, 114.0, 122.6, 123.9, 125.8, 128.0, 129.4, 134.6, 134.7, 135.6, 139.5, 141.1, 141.8, 146.3, 148.5, 149.1, 156.2, 167.9, 197.8. **MS** *m/z* (%): 504 (9.9, M^+). **32:** δ 1.98 (s, 4H, cycloheptane-H), 2.42 (s, 3H, CH_3), 2.70 (s, 4H, cycloheptane-H), 3.69 (s, 18H, OCH_3), 6.65 (s, 1H, thiazole-H), 6.83 (s, 4H, Ar–H), 7.22 (s, 1H, oleifinic-H), 7.51 (s, 1H, pyrimidine-H). ^{13}C NMR δ 11.2, 22.4, 22.5, 27.8, 28.0, 55.3, 55.4, 55.8, 60.1, 106.9, 111.2, 112.0, 122.7, 122.9, 124.7, 126.0, 127.4, 128.1, 128.6, 129.1, 130.7, 131.0, 134.8, 135.0, 136.8, 137.7, 139.0, 140.8, 152.7, 158.3, 197.8. **MS** *m/z* (%): 564 (14.6, M^+).

*(E)-Ethyl 9-substituted benzylidene-5-substituted phenyl-3-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazoline-2-carboxylates (**34–37**), (E)-ethyl 10-substituted benzylidene-5-substitutedphenyl-3-methyl-5,6,7,8,9,10-hexahydrocyclohepta[d]thiazolo[3,2-a]pyrimidine-2-carboxylates (**38–41**)*

A solution of ethyl 2-amino-4-methylthiazole-5-carboxylate (**33**, 1.86 g, 0.01 mol) and the appropriate α,β-unsaturated ketone (**7–14**, 0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 24 h and prepared as mentioned under compounds **16–23**. ^{1}H NMR (DMSo-d_6); **34:** δ 1.25 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.75 (t, 2H, $J = 5.5$ Hz, cyclohexane-H), 1.84 (t, 2H, $J = 4.9$ Hz,

cyclohexane-H), 1.94 (s, 3H, CH_3), 2.84 (t, 2H, $J = 5$ Hz, cyclohexane-H), 4.22–4.25 (q, 2H, CH_3CH_2), 7.43 (s, 1H, oleifinic-H), 7.51 (d, 4H, $J = 8$ Hz, Ar–H), 7.57 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.61 (s, 1H, pyrimidine-H). ^{13}C NMR δ 22.2, 23.7, 27.7, 28.1, 30.7, 34.2, 38.9, 115.3, 116.9, 122.3, 127.8, 128.6, 131.0, 132.0, 132.1, 133.4, 133.7, 134.1, 134.4, 134.9, 136.8, 138.4, 139.2, 139.5, 188.7, 191.6, 206.4. **MS** *m/z* (%): 511 (13.1, M^+). **35:** δ 1.23 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.73 (t, 2H, $J = 5$ Hz, cyclohexane-H), 1.84 (t, 2H, $J = 4.6$ Hz, cyclohexane-H), 2.35 (s, 3H, CH_3), 2.89 (t, 2H, $J = 5.5$ Hz, cyclohexane-H), 3.81 (s, 6H, OCH_3), 4.25–4.32 (q, 2H, CH_3CH_2), 6.65 (s, 1H, oleifinic-H), 7.03 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.53 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.95 (s, 1H, pyrimidine-H). ^{13}C NMR δ 22.5, 24.0, 27.9, 28.2, 30.6, 34.8, 38.9, 40.0, 55.1, 55.2, 113.1, 114.1, 127.9, 128.2, 128.9, 129.3, 131.5, 132.1, 132.2, 134.2, 134.8, 135.4, 136.1, 136.4, 159.2, 159.7, 188.6, 191.5, 206.4. **MS** *m/z* (%): 502 (12.1, M^+). **36:** δ 1.35 (t, 3H, $J = 13.5$ Hz, CH_3CH_2), 1.81 (t, 2H, $J = 5$ Hz, cyclohexane-H), 1.95 (t, 2H, $J = 5.5$ Hz, cyclohexane-H), 2.10 (s, 3H, CH_3), 2.92 (t, 2H, $J = 5$ Hz, cyclohexane-H), 3.81 (s, 12H, OCH_3), 4.32–4.34 (q, 2H, CH_3CH_2), 6.66 (s, 1H, oleifinic-H), 6.93 (d, 2H, $J = 8$ Hz, Ar–H), 7.05 (d, 2H, $J = 8$ Hz, Ar–H), 7.15 (s, 1H, Ar–H), 7.40 (s, 1H, pyrimidine-H), 7.61 (s, 1H, Ar–H). ^{13}C NMR δ 14.2, 17.0, 22.5, 24.0, 27.9, 28.2, 30.6, 34.9, 55.3, 55.4, 55.5, 60.3, 110.9, 111.5, 113.2, 114.0, 114.1, 123.6, 128.1, 134.3, 135.1, 135.8, 136.2, 136.8, 147.6, 148.4, 149.1, 156.2, 162.2, 188.6, 206.4. **MS** *m/z* (%): 562 (4.3, M^+). **37:** δ 1.29 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.86 (t, 2H, $J = 5$ Hz, cyclohexane-H), 2.22 (s, 3H, CH_3), 2.72 (t, 2H, $J = 4.5$ Hz, cyclohexane-H), 2.95 (t, 2H, $J = 5$ Hz, cyclohexane-H), 3.69–3.72 (q, 2H, CH_3CH_2), 3.83 (s, 18H, OCH_3), 6.68 (s, 1H, oleifinic-H), 6.82 (s, 2H, Ar–H), 6.87 (s, 2H, Ar–H), 6.97 (s, 1H, pyrimidine-H). **MS** *m/z* (%): 622 (1.5, M^+). **38:** δ 1.29 (t, 3H, $J = 14.5$ Hz, CH_3CH_2), 1.82 (s, 4H, cycloheptane-H), 2.68 (s, 3H, CH_3), 2.94 (s, 4H, cycloheptane-H), 4.22–4.26 (q, 2H, CH_3CH_2), 6.65 (s, 1H, olefinic-H), 7.23 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.31 (d, 2H, $J = 8$ Hz, Ar–H), 7.36 (d, 2H, $J = 8.5$ Hz, Ar–H), 7.69 (s, 1H, pyrimidine-H), 7.86 (d, 2H, $J = 8.5$ Hz, Ar–H). ^{13}C NMR δ 14.2, 17.1, 22.7, 22.4, 27.7, 38.9, 40.0, 60.3, 113.4, 127.0, 128.4, 128.7, 129.9, 130.8, 131.2, 131.4, 132.0, 133.1, 133.4, 133.9, 134.1, 142.0, 156.2, 160.2, 162.2, 162.5, 169.7, 197.5. **MS** *m/z* (%): 525 (2.9, M^+). **39:** δ 1.28 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.90 (s, 4H, cycloheptane-H), 2.54 (s, 3H, CH_3), 2.65 (s, 4H, cycloheptane-H), 3.80 (s, 6H, OCH_3), 4.22–4.25 (q, 2H, CH_3CH_2), 6.65 (s, 1H, olefinic-H), 7.02 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.20 (s, 1H, pyrimidine-H), 7.50 (d, 4H, $J = 8.5$ Hz, Ar–H). ^{13}C NMR δ 14.2, 17.0, 22.5, 22.9, 27.5, 27.6, 55.2, 55.5, 60.4, 111.9, 112.4, 113.7, 114.1, 122.1, 122.3, 122.9, 123.0, 124.0, 127.8, 131.2, 134.2, 138.5, 138.9, 139.3, 156.1, 159.4, 162.2, 168.0, 169.3, 197.5. **MS** *m/z* (%): 516 (2.6, M^+). **40:** δ 1.28 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.94 (s, 4H, cycloheptane-H), 2.54 (s, 3H, CH_3), 2.65 (s, 4H, cycloheptane-H), 3.65 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3), 4.22–4.25 (q, 2H, CH_3CH_2), 6.65 (s, 1H, olefinic-H), 7.04 (d, 4H, $J = 8.5$ Hz, Ar–H), 7.11 (s, 2H, Ar–H), 7.21 (s, 1H, pyrimidine-H), ^{13}C NMR δ 14.2, 17.0, 22.5, 27.7, 27.8, 55.4, 55.5, 55.8, 56.0, 60.4, 111.7, 112.0, 112.3, 113.1, 114.2, 115.6, 122.5, 122.1, 125.0, 127.5, 128.0, 129.3, 131.0, 132.9, 134.6, 139.5, 141.2, 148.5, 149.1, 156.1, 162.1, 197.9. **MS** *m/z* (%): 576 (11.1, M^+). **41:** δ 1.28 (t, 3H, $J = 14$ Hz, CH_3CH_2), 1.97 (s, 4H, cycloheptane-H), 2.54 (s, 3H, CH_3), 2.69 (s, 4H, cycloheptane-H), 3.70 (s, 9H, OCH_3), 3.82 (s, 9H, OCH_3), 4.23–4.25 (q, 2H, CH_3CH_2), 6.51 (s, 1H, olefinic-H), 6.82 (s, 4H, Ar–H), 7.22 (s, 1H, pyrimidine-H), ^{13}C NMR δ 14.2, 16.9, 22.5, 27.8, 28.0, 55.6, 55.8, 55.9, 60.0, 60.1, 60.4, 105.2, 106.9, 111.2, 112.4, 113.7, 114.0, 122.1, 122.4, 123.8, 128.4, 129.3, 130.8, 134.8, 137.7, 140.8, 141.2, 142.8, 152.8, 156.1, 159.5, 162.1, 169.3, 197.8. **MS** *m/z* (%): 636 (14.4, M^+).

Antitumor screening

Under sterile conditions, cell lines were grown in RPMI 1640 media (Gibco, NY, USA) supplemented with 10 % fetal bovine serum (Biocell, CA, USA) and 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 wells 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 ten times with saline and counted using a coulter counter. The counts were corrected for the dilution (Grever *et al.,* 1992; Monks *et al.,* 1991; Boyd and Paull, 1995; Skehan *et al.,* 1990).

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References

Abdel-Hafez AA, El-Sherief HA, Jo M, Kurokawa M, Shiraki K, Kawahata T, Otake T, Nakamura N, Hattori M (2002) Synthesis and evaluation of anti HIV-1 and anti HSV-1 activities of 4-*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-one derivatives. Arzneimit Forschung 52:833–839

Al-Omary FA, Hassan GS, El-Messery SM, El-Subbagh HI (2012) Substituted Thiazoles V. Synthesis and antitumor activity of novel Thiazolo[2,3-*b*] quinazoline and Pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine analogs. Eur J Med Chem 47:65–72

Bell FW, Cantrell AS, Hogberg M, Jaskunas SR, Johansson NG, Jordan CL, Kinnick MD, Lind P, Morin JM, Noreen R, Oberg B, Palkowitz JA, Parrish CA, Pranc P, Sahlberg C, Ternansky RJ, Vasileff RT, Vrang L, West SJ, Zhang H, Zhou XX (1995) Phenethylthiazolethiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors. 1. Synthesis and basic structure-activity relationship studies of PETT analogs. J Med Chem 38:4929–4936

Bharti SK, Nath G, Tilak R, Singh SK (2010) Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring. Eur J Med Chem 45:651–660

Boyd MR, Paull KD (1995) Some practical considerations and applications of the national cancer institute in vitro anticancer drug discovery screen. Drug Dev Res 34:91–109

Cortes J, Rousselot P, Kim DW, Ritchie E, Hamerschlak N, Coutre S, Hochhaus A, Guilhot F, Saglio G, Apperley J, Ottmann O, Shah N, Erben P, Branford S, Agarwal P, Gollerkeri A, Baccarani M (2007) Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. Blood 109:3207–3213

El-Bendary ER, El-Sherbeny MA, Badria FA (1998) Synthesis and biological evaluation of certain new thiazolopyrimidines. Boll Chim Farm 137:115–119

El-Messery SM, Hassan GS, Al-Omary FA, El-Subbagh HI (2012) Substituted thiazoles VI. Synthesis and antitumor activity of new 2-acetamido- and 2 or 3-propanamido-thiazole analogs. Eur J Med Chem 54:615–625

El-Subbagh HI, Al-Obaid AM (1996) 2,4-Disubstituted thiazoles, II. A novel class of antitumor agents, synthesis and biological evaluation. Eur J Med Chem 31:1017–1021

El-Subbagh HI, El-Naggar WA, Badria FA (1994) Synthesis and biological testing of 2,4-disubstituted thiazole derivatives as potential antitumor antibiotics. Med Chem Res 3:503–516

El-Subbagh HI, Abadi AH, Lehmann J (1999) 2,4-Disustituted thiazoles, III. Synthesis and antitumor activity of ethyl 2-substituted-aminothiazole-4-carboxylate analogs. Arch Pharm Pharm Med Chem 332:137–142

El-Subbagh HI, Al-Khawad IE, El-Bendary ER, Al-Obaid AM (2001) Substituted thiazoles IV. Synthesis and antitumor activity of new substituted imidazo[2,1-*b*]thiazole analogs. Saudi Pharm J 9:14–20

Ergenc N, Capan G (1994) Synthesis and anticonvulsant activity of new 4-thiazolidone and 4-thiazoline derivatives. II Farmaco 49: 449–451

Gillespie RJ, Cliffe IA, Dawson CE, Dourish CT, Gaur S, Giles PR, Jordan AM, Knight AR, Lawrence A, Lerpiniere J, Misra A, Pratt RM, Todd RS, Upton R, Weiss SM, Williamson DS (2008) Antagonists of the human adenosine A2A receptor. Part 2: design and synthesis of 4-arylthieno[3,2-*d*]pyrimidine derivatives. Bioorg Med Chem Lett 18:2920–2923

Go ML, Wu X, Liu XL (2005) Chalcones: an update on cytotoxic and chemoprotective properties. Curr Med Chem 12:483–499

Gouda MA, Berghot MA, El-Ghani GEA, Khalil AM (2010) Synthesis and antimicrobial activities of some new thiazole and pyrazole derivatives based on 4,5,6,7-tetrahydrobenzothiophene moiety. Eur J Med Chem 45:1338–1345

Grever MR, Schepartz SA, Chabner BA (1992) The National Cancer Institute: cancer drug discovery and development program. Semin Oncol 19:622–638

Habib NS, Soliman R, Ismail K, Hassan AM, Sarg MT (2003) Pyrimidines part II: synthesis of novel pyrimidines. 1,2,4-triazolo-[4,3-*a*]pyrimidin-7-ones and pyrimidino[2,1-*c*][1,2,4] triazi-8-ones for their antimicrobial and anticancer activities. Boll Chim Farm 142:396–405

Harris CC, Hollstein M (1993) Clinical implications of the P53 tumor suppressor gene. N Engl J Med 329:1318–1327

Ko HH, Tsao LT, Yu KL, Liu CT, Wang JP, Lin CN (2003) Structure–activity relationship studies on chalcone derivatives: the potent inhibition of chemical mediators release. Bioorg Med Chem 11:105–111

Lin YM, Zhou Y, Flavin MT, Zhou LM, Nie W, Chen FC (2002) Chalcones and flavonoids as anti-tuberculosis agents. Bioorg Med Chem 10:2795–2802

Lopez SN, Castelli MV, Zacchino SA, Dominguez JN, Lobo G, Jaime CC, Cortes JCG, Ribas JC, Devia C, Ana MR, Ricardo DE (2001) In vitro antifungal evaluation and structure–activity relationships of a new series of chalcone derivatives and synthetic analogs, with inhibitory properties against polymers of the fungal cell wall. Bioorg Med Chem 9:1999–2013

Monks A, Scudiero D, Skehan P (1991) Feasibility of a high-flux anticancer drug screen using a diverse panel of cultured human tumor cell lines. J Natl Cancer Inst 83:757–766

Nielsen SF, Christensen SB, Cruciani G, Kharazmi A, Liljefors T (1998) Antileishmaniai chalcones: statistical design, synthesis, and three-dimensional quantitative structure-activity relationship analysis. J Med Chem 41:4819–4832

Pees KJ, Albert G (1992) Triazolopyrimidine derivatives with fungicidal activity. European patent EP 0550113 A2

Popsavin M, Spaić S, Svircev M, Kojić V, Bogdanović G, Popsavin V (2007) Synthesis and antitumour activity of new tiazofurin analogs bearing a 2,3-anhydro functionality in the furanose ring. Bioorg Med Chem Lett 17:4123–4127

Rao YK, Fang S-H, Tzeng Y-M (2009) Synthesis and biological evaluation of 3α,4α,5α-trimethoxychalcone analogs as inhibitors of nitric oxide production and tumor cell proliferation. Bioorg Med Chem 17:7909–7914

Rostom SAF, Hassan GS, Subbagh HI (2009) Synthesis and biological evaluation of some polymethoxylated fused pyridine ring systems as antitumor agents. Arch Pharm Chem Life Sci 342:584–590

Said M, Abouzid K, Mouneer A, Ahmedy A, Osman AM (2004) Synthesis and biological evaluation of new thiazolopyrimidines. Arch Pharm Res 27:471–477

Sashidhara VK, Kumar A, Kumar M, Sarkar J, Sinha S (2010) Synthesis and in vitro evaluation of novel coumarin–chalcone hybrids as potential anticancer agents. Bioorg Med Chem Lett 20:7205–7211

Shi H-B, Zhang S-J, Ge Q-F, Guo D-W, Cai C-M, Hua W-X (2010) Synthesis and anticancer evaluation of thiazolyl–chalcones. Bioorg Med Chem Lett 20:6555–6559

Singh N, Pandey J, Yadav A, Chaturvedi V, Bhatnagar S, Gaikwad AN, Sinha SK, Kumar A, Shukla PK, Tripathi RP (2009) A facile synthesis of α, α'-(EE)-bis(benzylidene)-cycloalkanones and their antitubercular evaluations. Eur J Med Chem 44: 1705–1709

Singh N, Pandey SK, Anand N, Dwivedi R, Singh S, Sinha SK, Chaturvedi V, Jaiswal N, Srivastava AK, Shah P, Siddiqui MI, Tripathi RP (2011) Synthesis, molecular modeling and bio-

evaluation of cycloalkyl fused 2-aminopyrimidines as antitubercular and antidiabetic agents. Bioorg Med Chem Lett 21:4404–4408

Skehan P, Storeng R, Scudiero D, Monks A, McMahon J, Vistica D, Warren JR, Bokesch H, Kenney S, Boyd MR (1990) New colorimetric cytotoxic assay for anticancer drug screening. J Natl Cancer Inst 82:1107–1112

Varmus H (2006) The new era in cancer research. Science 312:1162–1165

Wolter FE, Molinari L, Socher ER, Schneider K, Nicholson G, Beil W, Seitz O, Süssmuth RD (2009) Synthesis and evaluation of a netropsin-proximicin-hybrid library for DNA binding and cytotoxicity. Bioorg Med Chem Lett 19:3811–3815