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Substituted thiazoles VII. Synthesis and antitumor activity of certain 2-(substituted amino)-4-phenyl-1,3-thiazole analogs

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ABSTRACT

A novel series of 2-acetamido- or 2-propanamido-4-(4-substituted phenyl)-1,3-thiazoles (**11–34**) was designed and synthesized. Compounds were subjected to National Cancer Institute (NCI) in vitro assessment for their antitumor activity, at a single dose of 10 μM. Most of the investigated compounds exhibited broad-spectrum antitumor activity. Compounds **19** and **28** believed to be the most active members in this study, with MG-MID GI_{50}, TGI, and LC_{50} values of 2.8, 11.4, 44.7; and 3.3, 13.1, 46.8, respectively. Compounds **19** and **28** proved to be nine and sevenfold more active than the standard antitumor drug 5-FU, respectively.

Thiazole containing heterocyclic compounds attracted the interest of medicinal chemists due to their synthetic feasibility and their incorporation into variety of therapeutically active agents. They represent a wide range of biological potencies including antibacterial, antifungal, anti-HIV, antihypertension, antiinflammatory, anticancer, anticonvulsant, and antidepressant.[1–6] Meanwhile, DNA is one of the major targets of anticancer drugs since the development of the nitrogen mustards. Targeting DNA of tumor cells has been one of the most effective clinical strategies for many DNA intercalators such as groove binders and anticancer antibiotics.[7–10] In addition, mechanisms of 1,3-thiazole and related heterocycles antitumor activity may be associated with the affinity to anticancer biotargets, such as phosphatase of a regenerating liver (PRL-3),[11,12] non-membrane protein tyrosine phosphatase

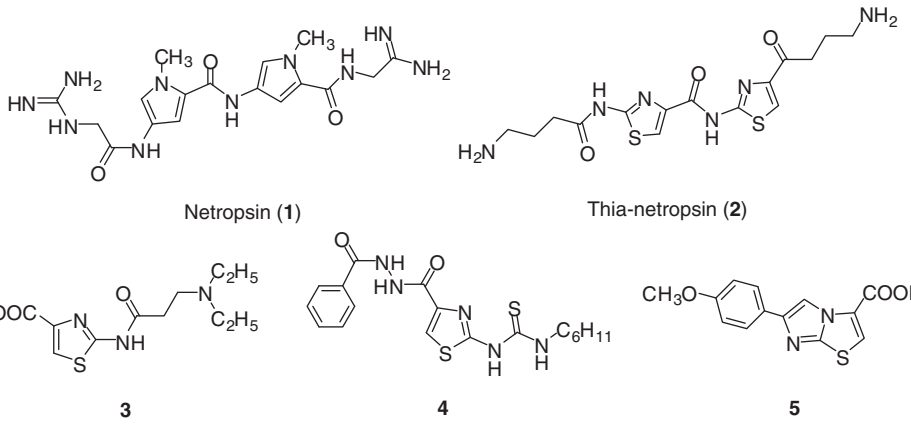

Chart 1. Structures of netropsin (**1**), thia-netropsin (**2**), and some literature thiazole antitumor agents (**3**-**5**).

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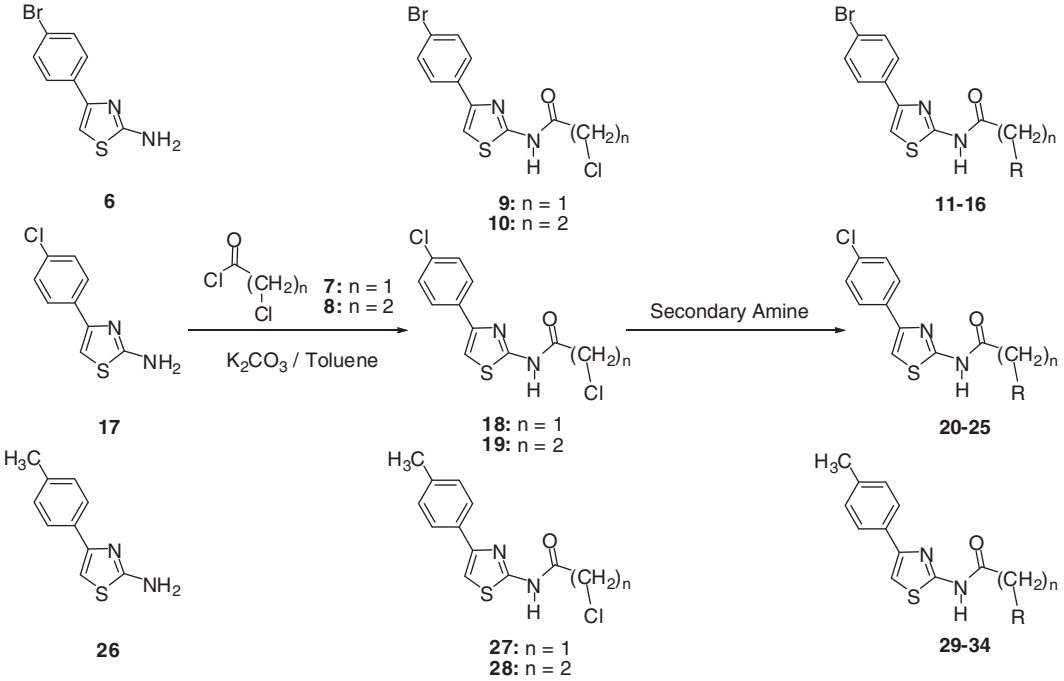


11, 20, 29: R = morpholine, n = 1
12, 21, 30: R = morpholine, n = 2
13, 22, 31: R = N-methyl-piperazine, n = 1
14, 23, 32: R = N-methyl-piperazine, n = 2
15, 24, 33: R = N-phenyl-piperazine, n = 1
16, 25, 34: R = N-phenyl-piperazine, n = 2

Scheme 1. Synthesis of the target compounds **11**–**34**.

(SHP-2),[13] JNK-stimulating phosphatase-1 (JSP-1),[14] tumor necrosis factor TNFa,[15] antiapoptotic biocomplex Bcl-XL-BH3,[16] integrin avb3,[17] etc. Necroptosis inhibitors have been recently identified among 1,3-thiazole related compounds.[18] On the other hand benzothiazole ring belongs to the privilleged scaffolds in modern medicinal chemistry[19] particularly in discovering of new anticancer agents. Various benzothiazole derivatives were proposed as inhibitors of fatty acid amide hydrolase (FAAH),[20] Raf kinase (Raf-1)[21] and B-cell lymphoma protein BCL-2.[22]

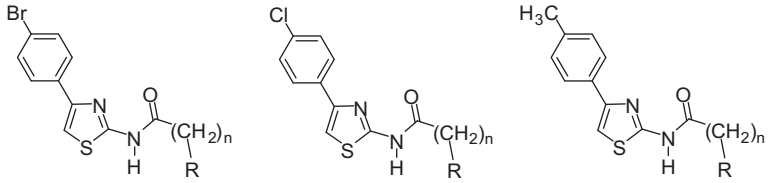
The clinical efficacy of the groove binders tiazofurin, distamycin, netropsin (**1**), thia-netropsin (**2**), and bleomycin pointed out the importance of the 1,3-thiazole moieties and their contribution to enhance the antitumor activity, Chart 1,[23–32] The antitumor activity of 2, 4-disubstituted 1,3-thiazole analogs was reported and well documented.[33–40] Many substituted thiazole analogs were prepared and screened for their antitumor activity, most of them proved to possess promising activity against numerous tumor cell lines. Certain 1,3-thiazole containing derivatives (**3–5**, Chart 1) proved to be effective antitumor agents with GI_{50} range of 0.08–2.9 μM.[35–39]

In view of these facts, an efficient and reproducible synthesis of some 2-(substituted amino)-4-phenyl-1,3-thiazole derivatives has been developed recently in our laboratory as structurally related analogs of the previously mentioned groove binding agents. Those 4-phenyl-1,3-thiazole analogs displayed a broad range of cancer in vitro growth inhibition according to the pattern generated in the NCI-60 cell line screening assay.[40] The finding that aromatic substitution at position 4- of the 1,3-thiazole ring contribute to the antitumor activity encouraged further investigation; some new 2-amino-4-(4-substituted phenyl)-1,3-thiazole analogs bearing 4-chloro-, 4-bromo- or 4-methyl-phenyl moieties, were synthesized to explore the electronic effect of such substituent on the antitumor activity. The 2-amino function of the 4-(4-substituted phenyl)-1,3-thiazoles was also acylated with aliphatic acid chlorides of various length to produce 2-acetamido- or 2-propanamido-analogs fitted at the terminal end with variety of secondary amines as an attempt for isosteric simulation of the amidine and the guanidine functions of netropsin (**1**) with the hope to locate new lead compound(s). The synthesized compounds (Scheme 1, Table 1) were subjected to the NCI in vitro disease-oriented human cells screening panel assay,[41–43] to evaluate the effect of this structural alterations on the antitumor activity. The synthesis of compounds **11**, **20** and **29** were previously reported.[44]

The synthesized compounds **11–34** were subjected to the National Cancer Institute (NCI) in vitro disease-oriented human cells screening panel assay for in vitro antitumor activity. A single dose (10 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.[41–43] The data reported as mean-graph of the percent growth of the treated cells, and presented as percentage growth inhibition (GI%) caused by the test compounds (Table 2).

In the present investigation, most of the tested compounds showed broad spectrum antitumor activity. Compounds **24**, **31,** and **34** displayed modest potency against the tested tumor cell lines and considered to be the least effective members. Concerning activity toward individual cell lines, compound **19** proved to be lethal to Non-small cell lung cancer cell line HOP-92, Renal cancer RXF 393, and Breast cancer MDA-MB-468; while compound **28** proved to be lethal to Non-small cell lung cancer cell line NCI-H23, Renal cancer TK-10, and Breast cancer MDA-MB-468. Colon cancer cell line HT29 proved to be sensitive toward compound **14** with GI value of 80.4%, while Leukemia cell lines CCRF-CEM,

Table 1
Physicochemical properties of the newly synthesized compounds **9–34**



9-16 **18-25** **27-34**

Compound	R	*n*	Solvent	Yield (%)	Mp °C	Molecular formulae[a]
9	Cl	1	Ethanol	66	89–92	$C_{11}H_8BrClN_2OS$
10	Cl	2	Ethanol	60	180–2	$C_{12}H_{10}BrClN_2OS$
11	Morpholine	1	Ethanol	59	115–8	$C_{15}H_{16}BrN_3O_2S$
12	Morpholine	2	Ethanol	68	162–4	$C_{16}H_{18}BrN_3O_2S$
13	*N*-Methylpiperazine	1	Ethanol	73	153–5	$C_{16}H_{19}BrN_4OS$
14	*N*-Methylpiperazine	2	—	62	Oil	$C_{17}H_{21}BrN_4OS$
15	*N*-Phenylpiperazine	1	Ethylacetate	82	144–7	$C_{21}H_{21}BrN_4OS$
16	*N*-Phenylpiperazine	2	Ethanol	67	76–78	$C_{22}H_{23}BrN_4OS$
18	Cl	1	Ethanol	64	169–71	$C_{11}H_8\ Cl_2N_2OS$
19	Cl	2	Ethylacetate	55	164–6	$C_{12}H_{10}Cl_2N_2OS$
20	Morpholine	1	Ethanol	65	132–5	$C_{15}H_{16}ClN_3O_2S$
21	Morpholine	2	Ethanol	59	146–8	$C_{16}H_{18}ClN_3O_2S$
22	*N*-Methylpiperazine	1	Ethanol	70	140–2	$C_{16}H_{19}ClN_4OS$
23	*N*-Methylpiperazine	2	Ethanol	68	128–30	$C_{17}H_{21}ClN_4OS$
24	*N*-Phenylpiperazine	1	Ethanol	71	142–5	$C_{21}H_{21}ClN_4OS$
25	*N*-Phenylpiperazine	2	Ethylacetate	73	181–3	$C_{22}H_{23}ClN_4OS$
27	Cl	1	Ethanol	70	165–7	$C_{12}H_{11}ClN_2OS$
28	Cl	2	Ethanol	73	151–3	$C_{13}H_{13}ClN_2OS$
29	Morpholine	1	Ethylacetate	73	144–6	$C_{16}H_{19}N_3O_2S$
30	Morpholine	2	Ethanol	61	159–60	$C_{17}H_{21}N_3O_2S$
31	*N*-Methylpiperazine	1	Ethanol	64	166–9	$C_{17}H_{22}N_4OS$
32	*N*-Methylpiperazine	2	Ethylacetate	78	155–7	$C_{18}H_{24}N_4OS$
33	*N*-Phenylpiperazine	1	Ethanol	72	151–4	$C_{22}H_{24}N_4OS$
34	*N*-Phenylpiperazine	2	Ethanol	70	134–6	$C_{23}H_{26}N_4OS$

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

Table 2
Percentage growth inhibition (GI%) of in vitro subpanel tumor cell lines at 10 μM concentration of compounds **11–34**

Subpanel tumor cell lines	**1**	**14**	**15**	**19**	**23**	**24**	**25**	**28**	**31**	**33**	**34**
Leukemia											
CCRF-CEM	15.3	24.9	22.2	**88.3**	18.3	—	16.3	**88.3**	—	13.4	—
HL-60(TB)	12.6	37.7	27.1	28.5	20.6	—	19.6	41.4	—	—	—
K-562	25.1	52.4	70.7	63.0	22.4	—	21.6	21.1	11.4	—	—
MOLT-4	33.2	38.1	47.6	61.3	51.8	—	36.3	43.3	13.4	23.7	14.9
RPMI-8226	28.9	30.5	33.6	**92.8**	17.6	—	25.4	**80.9**	—	—	—
SR	—	—	—	77.7	—	—	—	**88.5**	—	—	—
Non-small cell lung cancer											
A549/ATCC	10.3	22.2	30.8	39.9	—	—	12.0	77.3	—	31.4	23.8
EKVX	19.5	10.8	26.7	29.6	11.9	—	—	50.3	—	32.5	16.6
HOP-62	10.9	25.0	—	49.0	19.7	12.7	—	16.2	—	—	—
HOP-92	—	42.7	—	**L**	42.2	60.2	23.7	50.5	—	—	10.2
NCI-H226	14.5	19.1	20.2	51.0	28.0	—	14.1	22.0	—	—	—
NCI-H23	13.9	26.0	22.5	29.0	11.2	—	13.7	**L**	—	18.9	14.5
NCI-322M	11.1	17.2	20.5	16.9	—	—	27.8	55.9	—	21.4	15.6
NCI-H522	28.2	28.5	34.5	**95.6**	31.1	—	18.7	41.0	—	—	—
Colon cancer											
HCC-2998	—	—	21.0	15.8	13.3	—	—	22.5	—	15.2	—
HCT-116	10.7	42.5	33.1	79.3	13.3	16.4	19.4	46.2	—	—	—
HCT-15	—	42.6	26.1	61.4	18.1	—	—	25.9	—	10.6	—
HT29	10.8	80.4	37.7	78.0	23.8	—	18.6	21.0	—	—	—
KM12	—	—	—	43.8	—	—	—	82.4	—	—	—
SW-620	—	—	—	76.0	—	—	—	65.2	—	—	—
CNS cancer											
SF-268	—	12.8	17.0	51.7	14.2	—	—	46.3	—	13.9	—
SF-295	14.4	14.4	20.9	29.8	—	—	24.2	30.2	—	27.3	—
SF-539	—	31.4	—	**94.6**	14.8	—	—	25.2	—	—	—
SNB-19	10.5	20.9	23.9	26.2	19.7	—	—	73.1	—	—	—
SNB-75	29.8	47.9	17.9	58.8	26.8	—	14.9	34.6	42.2	12.1	—
U251	—	33.6	-	55.4	16.5	—	—	48.5	—	—	—

Table 2 (*continued*)

Subpanel tumor cell lines	**1**	**14**	**15**	**19**	**23**	**24**	**25**	**28**	**31**	**33**	**34**
Melanoma											
LOX IMVI	–	31.8	11.6	43.1	12.8	–	–	45.1	–	17.2	–
MALME-3M	12.4	24.6	13.8	44	15.4	–	–	29.1	–	–	12.1
M14	–	33.7	15.7	44.7	15.2	–	–	56.1	–	–	–
MDA-MB-435	–	50.6	23.9	68.1	15.4	–	–	36.9	–	17.6	–
SK-MEL-2	–	–	14.5	72.7	–	–	–	54.2	–	–	–
SK-MEL-28	–	23.4	–	21.2	–	–	–	31.0	–	–	–
SK-MEL-5	23.7	76.2	39.4	46.8	46.1	11.7	10.1	16.6	–	27.6	–
UACC-257	–	36.4	13.7	43.0	–	–	–	41.3	–	–	–
UACC-62	29.0	71.6	40.1	38.7	15.0	20.3	20.5	41.8	–	23.6	16.3
Ovarian cancer											
IGORV1	17.4	20.4	34.3	48.9	18.4	10.4	–	63.1	–	33.8	14.9
OVCAR-3	–	–	–	**89.8**	–	–	–	45.3	–	–	–
OVCAR-4	–	–	–	16.4	–	–	–	81.5	–	28.1	11.1
OVCAR-5	–	15.6	–	35.7	–	–	–	29.3	–	–	–
OVCAR-8	–	–	11.9	52.8	15.6	–	–	60.6	–	–	–
NCI/ADR-RES	17.0	22.9	30.9	51.2	21.9	–	–	55.8	–	21.0	–
SK-OV-3	–	–	–	25.7	–	–	–	63.0	–	–	–
Renal cancer											
ACHN	–	15.9	15.7	39.2	–	–	–	45.1	–	–	–
CAKI-1	28.9	30.2	33.5	52.5	24.2	–	–	55.6	12.0	24.6	14.1
RXF 393	–	38.1	13.6	**L**	47.4	–	–	43.8	–	–	–
SN12C	–	31.9	23.7	48.3	32.9	–	11.9	33.2	10.4	17.0	–
TK-10	–	22.5	28.3	–	20.2	–	–	**L**	–	–	–
UO-31	30.6	50.8	54.6	70.1	48.6	34.4	38.6	61.3	19.9	48.2	41.2
Prostate cancer											
PC-3	17.8	24.6	28.5	59.7	15.3	21.1	12.0	69.5	–	31.1	16.1
Breast cancer											
MCF7	13.7	28.8	41.2	55.8	28	–	10.9	65.9	12.7	20.9	–
MDA-MB-231/ATCC	23.4	64.3	22.2	44.6	25.6	–	–	53.5	34.2	–	–
BT-549	12.9	32.5	13.6	**89.9**	29.1	–	–	72.3	12.8	–	–
T-47D	25.2	34.9	41.8	52.1	28.8	19.0	–	55.2	–	20.8	–
MDA-MB-468	25.7	48.7	55.6	**L**	62.8	–	–	**L**	–	23.1	–

Prominent GI values are bolded.
–, GI <10%; L, compound proved lethal to the cancer cell line.

RPMI-8226; proved to be sensitive toward compound **19** with GI values of 88.3 and 92.8% and **28** with GI values of 88.3 and 80.9%, respectively. Compound **19** exhibited remarkable activity against Non-small cell lung cancer cell line NCI-H522, CNS cancer SF-539; Ovarian cancer OVCAR-3; Breast cancer BT-549 with GI values of 95.6, 94.6, 89.8, 89.9%, respectively (Fig. 1 and Table 2).

Compounds **19** and **28** proved to be the most active member of this study. They passed the primary anticancer assay at an arbitrary concentration of 10 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 monitored for each cell line, using the known drug 5-Fluorouracil (5-FU) as a positive control. Compound **19** proved to be ninefold more active than 5-FU, with MG-MID GI_{50}, TGI, and LC_{50} values of 2.8, 11.4, 44.7 μM, respectively; while compound **28** proved to be sevenfold more active

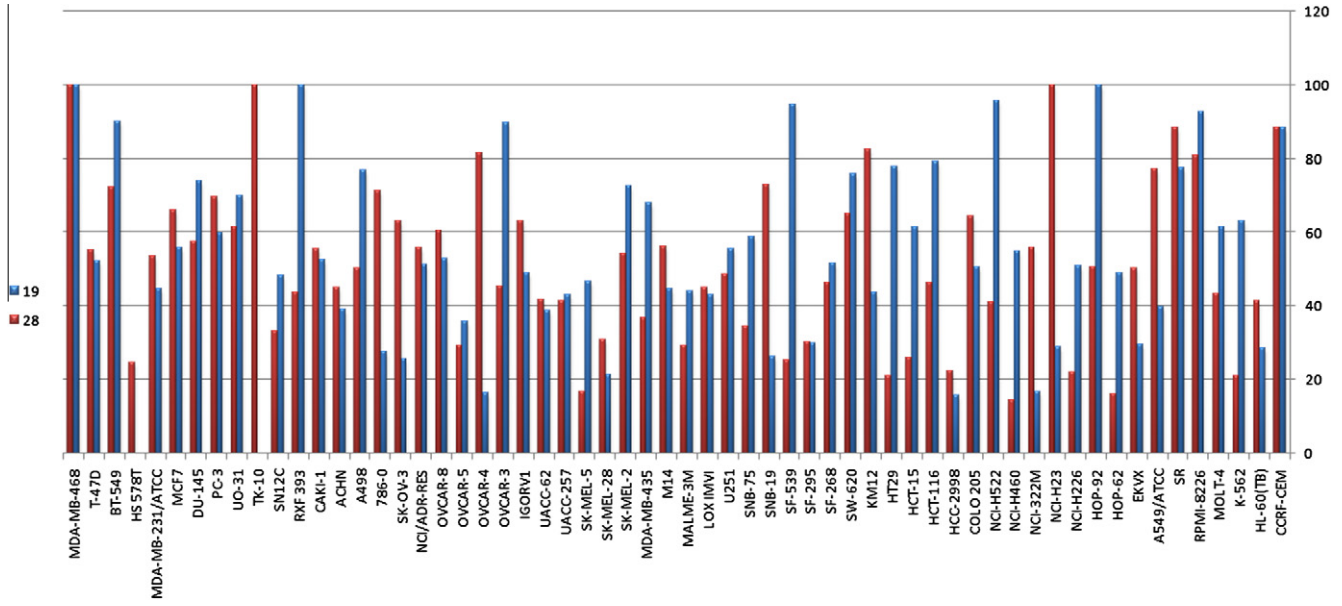


Figure 1. Percentage growth inhibition (GI%) of in vitro subpanel tumor cell lines at 10 μM concentration of compounds **19**, **28**.

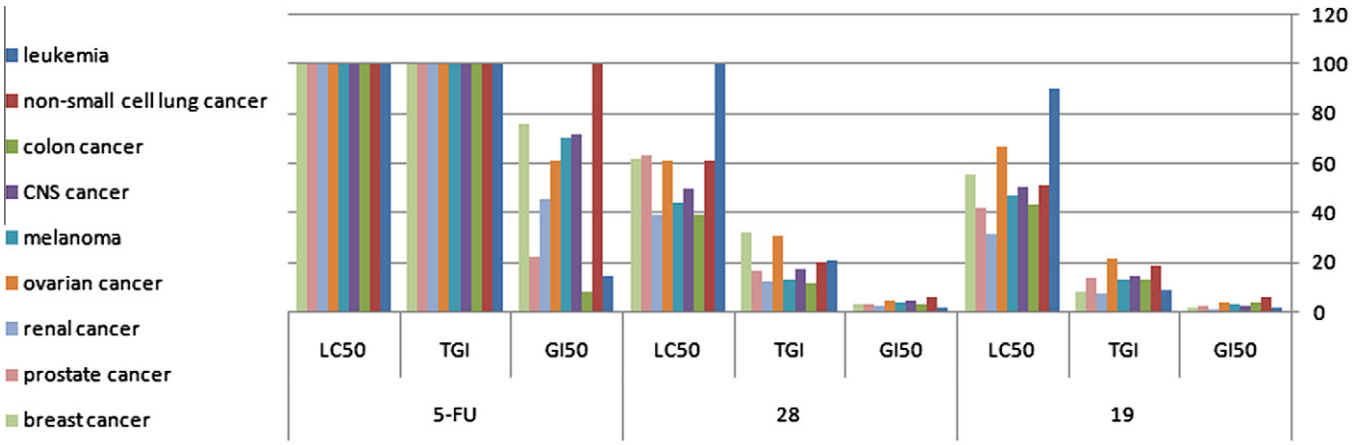


Figure 2. Compounds **19**, **28** median growth inhibitory (GI_{50}, μM), Total growth inhibitory (TGI, μM) and median lethal (LC_{50}, μM) concentrations of in vitro subpanel tumor cell lines.

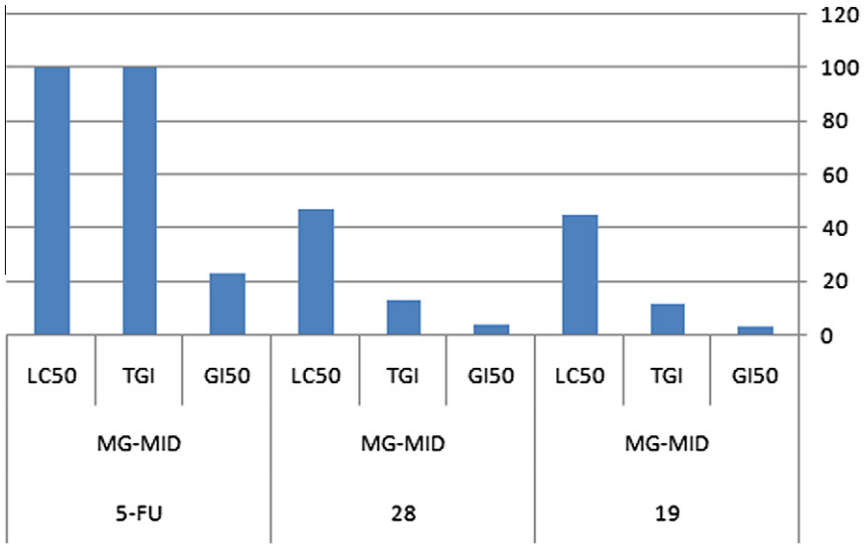


Figure 3. Full panel mean-graph midpoint (μM) of compounds **19, 28** in comparison with 5-FU.

Table 3
Compounds **19**, **28** 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]
19	GI_{50}	2.2	6.1	3.9	3.1	3.2	4.1	1.7	2.8	2.4	2.8
	TGI	8.9	19.0	13.5	14.7	13.1	21.8	7.9	13.8	8.8	11.4
	LC_{50}	90.2	51.5	44	50.9	47.6	67	32.1	42.2	55.9	44.7
28	GI_{50}	2.0	6.3	3.2	4.8	4.2	4.8	2.8	3.8	3.3	3.3
	TGI	21.5	20.3	11.9	17.6	13.4	31.3	12.5	16.8	32.3	13.1
	LC_{50}	[b]	61.5	39.2	50.2	44.3	61.1	39.3	63.4	62.1	46.8
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.

than 5-FU, with MG-MID GI_{50}, TGI, and LC_{50} values of 3.3, 13.1, 46.8 μM, respectively (Figs. 2 and 3, Table 3).

Compounds of the present investigation belong to 2-amino-1,3-thiazole analogs, bearing either to 2-(substituted amino)acetamido- or 3-(substituted amino)propanamido-functions at position 2- and 4-bromo, 4-chloro or 4-methyl-phenyl at position 4. The obtained results revealed that 2-chloro-*N*-[4-(4-substitutedphenyl)-1,3-thiazol-2-yl]-acetamides (**9, 18,** and **27**) devoid of any antitumor potency. Displacement of the chlorine atom of 2-chloroacetamide function of **9, 18,** and **27** with variety of secondary amines produced 2-substituted amino-acetamide analogs with variable potency. Only compounds bearing either morpholine, *N*-methyl-

piperazine or *N*-phenyl-piperazine showed antitumor activity as exemplified by compounds **11**, **15**, **24**, **31** and **34**.

Replacement of the 2-chloroacetamide function of **18** and **27** by 3-chloro-propanamide produced compound **19** and compound **28**, respectively with broad spectrum antitumor activity. Displacement of the chlorine atom of 3-chloropropanamide function of **19** and **28** with variety of secondary amines produced 3-substituted amino-propanamide analogs with either abolished or diminished activity. Only compounds bearing *N*-methyl-piperazine or *N*-phenyl-piperazine proved to be active with diminished potency as shown in **14**, **23**, **25**, and **34**.

In general, the length of the carbon chain linking the 1,3-thiazole nucleus to the terminal secondary amines proved crucial and manipulates the antitumor activity. The propanamide three carbon lengths favor the activity (compounds **19** and **28**) rather than the acetamide two carbon lengths (compounds **18** and **27**). Also, it was proven that bearing either electron withdrawing (4-bromo- or 4-chloro-) or electron donating (4-methyl-) substituent at the 4-phenyl function did not affect the magnitude of antitumor potency of such analogs.

In conclusion, an interesting class of 1,3-thiazole analogs bearing 2-acylamino substituent with different carbon chain length and 4-(4-substitutedphenyl) was designed and synthesized. Antitumor evaluation indicated different pharmacological profiles of these new compounds which substantiate the merits of further exploration. Results revealed that the three carbon chain connecting the thiazole nucleus to the secondary amines has an impact on antitumor activity. 3-chloro-*N*-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]propanamide **(19)** and 3-chloro-*N*-[4-(4-tolyl)-1,3-thiazol-2-yl]propanamide (**28**), displayed broad-spectrum antitumor potency. Compound **19** proved to be ninefold more active than 5-FU, with MG-MID GI_{50}, TGI, and LC_{50} values of 2.8, 11.4, 44.7, respectively; whereas Compound **28** proved to be sevenfold more active than 5-FU, with MG-MID GI_{50}, TGI, and LC_{50} values of 3.3, 13.1, 46.8, respectively. The obtained antitumor potency using 4-aromatic substituent on the 1,3-thiazole core could be considered as useful template for future development and further derivatization or modification to obtain more potent and selective antitumor agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.095.

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