Research Article

Synthesis and biological evaluation of novel ٤-aryl-N-thiazolyl-benzamides

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Abstract
Twelve out of thirty-six thiazole-carboxamide derivatives were selected by the National Cancer Institute (NCI) for *in vitro* anticancer screening. Among these, five derivatives (**٣٣-٣٥, ٣٧, ٣٨**) exhibited significant anticancer activity in the primary assay at concentration $١٠^{-٥}$ M, and further tested against a panel of sixty human tumor cell lines. Compounds **٣٤, ٣٥, ٣٧** and **٣٨** exhibited selective remarkable activity against all Leukemia cell lines, Lung cancer cell line NCI-H٥٢٢ and Renal cancer cell line UO-٣١.

Keywords: Synthesis, anticancer activity, ٢,٤-disubstituted thiazoles, thiazole-carboxamide, galloyl derivatives

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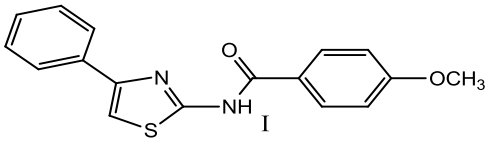
Introduction
Among pharmacologically important heterocyclic compounds, thiazole and its derivatives have been well known in pharmaceutical chemistry because of their wide spectrum of biological activities[١,٢].

Thiazol-٢-yl-benzamides act as glukokinase activators, which are currently under investigation as potential antidiabetic agents by many pharmaceutical companies [٣-٧], and have been recently proposed as a novel promising class of adenosine $A_١$ and $A_٣$ receptor antagonists [٨,٩].

The antitumor activity of ٢, ٤-disubstituted thiazoles containing amide functional group was the subject of many researchers[١٠,١١]. Thiazole-carboxamide derivative II has been identified as a $CDK_٢$-selective inhibitor and has been selected to enter clinical development as an antitumor agent, and has shown superior antitumor efficacy to both flavopiridol and related analogues[١١].



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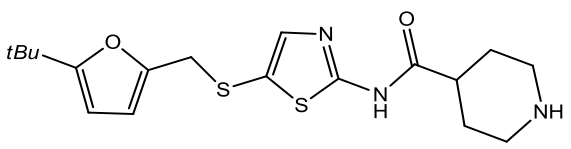
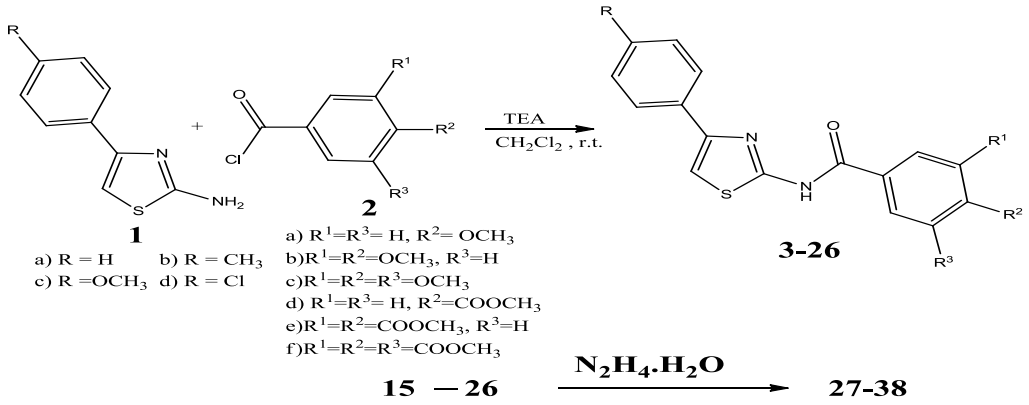


II

Chemistry
The general methods for synthesis of target ٤-aryl-٢-(arylcarboxamido)-١,٣-thiazoles **٣-٣٨** are depicted in Scheme ١. The synthesis of compounds **٣-٢٦** was achieved by a condensation reaction of ٢-amino-٤-arylthiazoles **١a-d** with appropriate acyl chlorides **٢a-f** yielding the corresponding amides **٣-٢٦**. On the other hand, mono- di-, and tri-hydroxy derivatives **٢٧-٣٨** were synthesized by treatment of the ester derivatives **١٥-٢٦** with hydrazine hydrate.



Scheme 1. Synthesis of 4-aryl-N-thiazolyl-benzamides 3-38

Evaluation of anticancer activity *in vitro*

A series of ٤-ary l-٢-(arylcarboxamido)-١,٣-thiazoles **٣-٣٨** were submitted to NCI for antitumor activity evaluation. Compounds **٤, ٥, ٦, ٩, ١٠, ١٣, ١٤, ٣٣, ٣٤, ٣٥, ٣٧,** and **٣٨** were selected for evaluation at single concentration of $١٠^{-٥}$ M towards panel of sixty cancer cell lines. The human tumor cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers. Primary anticancer assays were performed according to the US NCI protocol, which was described elsewhere [١٢]. Compounds **٤, ٥, ٦, ٩, ١٠, ١٣,** and **١٤** have not reduced the growth of any cell lines by ٣٢٪ or less, are inactive. Therefore, only five compounds **٣٣-٣٥, ٣٧** and **٣٨** have been selected for sixty cell line panel assays.

From Table ٢, Compound **٣٣** exhibited a remarkable antitumor activity against Lung and Colon cancers cell lines NCI-H٥٢٢ and HT٢٩ with growth inhibition (GI) values of ٧٨.٥٠ and ٧٤.٤١٪, respectively. However, a moderate activity for the same compound was observed for Leukemia cell lines CCRF-CEM, RPMI-٨٢٢٦, SR as well as Renal cancer cell line UO-٣١,with GI values of ٦٣.٩٢, ٦٣.٨١, ٦٠.٥٣, and ٦٣.٥٦٪, respectively.

Compound **٣٤** showed highest activity against Leukemia cancer cell lines CCRF-CEM, MOLT-٤, SR; Non-small cell lung cancer cell line NCI-H٥٢٢; Ovarian cancer cell line IGROV١, and Renal cancer cell line UO-٣١, with GI values ٨١.٥٦, ٨٢.٩٩, ٨٢.٥٣, ٨٧.٦٨, ٨٩.٢٢, ٨١.١٥٪, respectively.

Beside the remarkable inhibitory activity against all cell lines of Leukemia, and the lethal effect against Lung cancer cell line NCI-H٥٢٢ (Table ٢), compound **٣٥** exhibited a moderate activity against Lung cancer NCI-H٤٦٠; Colon cancer HTC-١١٦, HTC-١٥, SW-٦٢٠; CNS cancer SNB-٧٥, U٢٥١; Ovarian cancer IGROV١, OVCAR-٣; Renal cancer CAKI-١, UO-٣١; Breast cancer T-٤٧D with GI values of ٦٥.٣٠, ٧٤.٠٦, ٧٢.٦٩, ٦٠.٣٢, ٦٦.٨٥, ٦٧.٩٠, ٦٦.٨٤, ٧٧.٧٠, ٧٣.٦٤, ٧٥.٣٦, ٦٨.٧٩٪, respectively.

Compound **٣٧** was found to be a highly active growth inhibitor of Leukemia cell lines CCRF-CEM and SR (GI%; ٨١.٥٢, ٨٥.٤٥), and moderately active against Leukemia MOLT-٤, Colon cancer HCT-١٥ and Renal cancer ACHN, CAK-١ and UO-٣١ with GI values of ٧١.٩٨, ٦٩.٥٨, ٦٤.٠٥, ٦١.٤٢, ٦٩.٦٦٪, respectively, however, it proved lethal effect to Lung cancer NCI-H٥٢٢.

Table (٢): Percentage Growth inhibition (GI%) of *in vitro* Subpanel Tumor Cell Lines at $١٠^{-٥}$ M Concentrations of Compounds ٣٣-٣٥, ٣٧ and ٣٨.

Subpanel tumor cell lines	% Growth Inhibition (GI%)[a] ٣٣	٣٤	٣٥	٣٧	٣٨
Leukemia					
CCRF-CEM	٦٣.٩٢	٨١.٥٦	٩٠.٨٩	٨١.٥٢	٩١.٩٢
HL-٦٠ (TB)	٤٦.٠٣	٧٣.٧٤	٨٧.٣٨	٣٧.٥٨	٨٩.٥٧
K-٥٦٢	٣٠.٠٨	٥٨.٩٠	٨٠.٣٩	٥٥.٢٢	٩٢.٠١
MOLT-٤	٥٨.٠٨	٨٢.٩٩	٨٢.٨٧	٧١.٩٨	٩٥.٣٢
Non-Small Cell Lung Cancer					
A٥٤٩/ATCC	٥٥.٣٠	٦٩.٦٩	٥٣.٨٠	٤١.٣٩	٧٤.٨٥
HOP-٦٢	-	٤٢.٩١	٥٣.٦٠	٣٥.٢١	٦١.٣٩
NCI-H٢٢٦	-	٣٢.٧٧	٣٢.١٠	١٧.٧٢	٢٥.٠٧
Colon Cancer					
COLO ٢٠٥	-	١٠.٨٨	١٥.٥٣	١٨.٦٠	٢٢.٤٠
HCT-١١٦	٥١.٧٤	٧٢.٨٧	٧٤.٠١	٥٠.٤٧	٨٢.٢٨
HCT-١٥	٧٤.٤١	٧٧.١٠	٧٢.٦٩	٦٩.٥٨	٨١.١٦
CNS Cancer					
SF-٢٦٨	٢٣.١٧	٦٠.٤٦	٥٦.٣١	٤٥.٥١	٧٣.٣٢
SNB-١٩	١٠.٣٧	٤١.٧٨	٥٨.٥١	٤٠.١١	٧٤.٠٥
SNB-٧٥	٢٨.٠٣	٦٦.٠١	٦٦.٨٥	٤١.١٨	٦٣.٢٨
Melanoma					
LOX IMVI	٢٢.١٤	٥٤.٨٥	٥٩.٨٤	٤٩.٤١	٩٨.٢٨
M١٤	١٨.٨٦	٤٦.٤١	٤٥.٥٩	٣٦.٨٤	٧٦.٨١
MDA-MB-٤٣٥	٢٤.٣٨	٥١.٦٦	٣٩.٠٠	٣٥.٥٥	٥٩.٠٣
SK-MEL-٢	-	٣١.٦٤	٤٣.١٦	٢٨.٥٧	٦٨.١٠
Ovarian Cancer					
IGROVI	٥٣.٤١	٨٩.٢٢	٦٦.٨٣	٥٣.٥٦	٨٤.٢٦
OVCAR-٣	٣٠.٨٧	٥٠.٢٧	٧٧.٧٠	٢٧.٤٢	٥٩.٩٢
OVCAR-٤	٤٥.٩٦	٥٩.٥٠	٥٥.٥٤	٤١.٤١	٧٢.١٩
OVCAR-٥	-	-	١٠.٥٧	١٣.٩١	٣٧.٣٦
Renal Cancer					
٧٨٦-٠	١٦.٩٣	٤٣.٧٤	٥٨.٣٧	٣٥.٥٦	٨٨.٤٦

A٤٩٨	٣٤.٨٤	٤٠.٣٩	١٤.١٠	-
	٢٢.٨٦			
ACHN	٥١.٦٨	٧٢.٩٧	٥٩.٦٨	٦٤.٠٥
	٨٤.١٤			
CAKI-١	٥١.٦٤	٧٧.٥٦	٧٣.٦٤	٦١.٤٢
	٩١.٣١			
UO-٣١	٦٣.٥٦	٨١.١٥	٧٥.٣٦	٦٩.٦٦
	٩٣.٩٩			
Prostate Cancer				
PC-٣	٢٥.٧٣	٥٠.٠٠	٤١.١٧	٣١.٥٩
	٥٣.٠٨			
DU-١٤٥	١٩.٦٥	٤٩.٨٨	٤٢.٢٦	٣٤.٨١
	٦٤.١٦			
Breast Cancer				
MCF٧	٣٣.٩٠	٥٤.٦١	٤١.٦٣	٣٩.٤١
	٧١.٦٦			
MDA-MB-٢٣١/ATCC	٤٨.٣٦	٤٥.٣٠	٥٥.٩٨	٤٤.٠٤
	٦٣.٩٨			
HS ٥٧٨T	-	٢٥.٩٣	٢٦.٣٦	-
	٣٨.٠٧			
BT-٥٤٩	٢٧.٢٠	٤٥.٩١	٥٤.٠٥	٣٣.١٠
	٧٥.٤٠			
T-٤٧D	٤٨.٨٠	٦٧.٠٩	٦٨.٧٩	٥٥.٣٣
	٧٤.٤٠			
MDA-MB-٤٦٨	٣٩.٠٥	٥٤.٨٣	٥٣.٦٨	٢١.٤٣
	٤٤.١٧			

[a] -, GI<١٠٪; L, compound proved lethal to the cancer cell line.

On the other hand, compound **٣٨** showed a moderate growth inhibitory activity against most of the other cell lines; Lung cancer A٥٤٩/ATCC, HOP-٦٢, Colon cancer SW-٦٢٠, CNS cancer SF-٢٦٨, SF-٢٩٥, SNB١٩, SNB-٧٥, U٢٥١, Melanoma M١٤, SK-MEL-٢, SK-MEL-٥, Ovarian cancer OVCAR-٤, Renal cancer SN١٢C, Prostate cancer DU-١٤٥, Breast cancer MCF-٧, MDA-MB-٢٣١/ATCC, BT-٥٤٩, T-٤٧D with GI values of ٧٤.٨٥, ٦١.٣٩, ٧٤.٦٧, ٧٣.٣٢, ٦٨.٧٨, ٧٤.٠٥, ٦٣.٢٨, ٧٦.٥٧, ٧٦.٨١, ٦٨.١٠, ٧٥.٣٨, ٧٢.١٩, ٧٧.٤٤, ٦٤.١٦, ٧١.٦٦, ٦٣.٩٨, ٧٥.٤٠, ٧٤.٤٠٪, respectively. These compounds were further undergo five dose testing which are illustrated in Table ٣. From Table ٣, we can conclude that, compounds **٣٥**, **٣٧** and **٣٨** showed broad-spectrum anti-tumor activity against nearly all ٦٠ cell lines used in this study, and demonstrated significant activity in the *in vitro* anti-tumor screening expressed by MG_MID $\log_{١٠}$ $GI_{٥٠}$ value of -٥.٤٥, -٥.١٣ and – ٥.٣٨, respectively.

The data in Table ٣ showed that compound **٣٥** possessed a significant activity on Leukemia cell line (CCRF-CEM), Non-small cell Lung cancer cell line (NCI-H٥٢٢) and Renal cancer cell line (UO-٣١) with log $GI_{٥٠}$ values -٦.١٦, -٦.٤٧ and -٦.٢٢, respectively. Furthermore, compound **٣٥** was found to be highly active growth inhibitor of all Leukemia cell lines, Non-small cell lung cancer cell line HOP-٩٢, Colon cancer cell lines HTC-١١٦, HTC-١٥, SW-٦٢٠, where the MG-MID ranged from -٥.٥٠ to -٥.٨٥. Compound **٣٧** is highly active growth inhibitor of Leukemia cell lines CCRF-CEM, MOLT-٤, SR, Non-small cell Lung cancer cell line NCI-H٥٢٢, Renal cancer cell lines CAKI-١, UO-٣١ at MG-MID range from -٥.٥٠ to -٥.٨٨. Compound **٣٨** is highly active growth inhibitor of all Leukemia cell lines, Non-small cell lung cancer cells A٥٤٩/ATCC, HOP-٩٢, NCI-H٥٢٢, Colon cancer cell line HCT-١٥, where the MG-MID ranged from -٥.٥٠ to -٥.٧٥.

Table (٣): Inhibition of *in vitro* cancer cell lines by selected thiazole carboxamide derivatives ٣٤, ٣٥, ٣٧ and ٣٨.

Panel cell line	Response parameters (A) $\log_{١٠}GI_{٥٠}$, (B) $\log_{١٠}TGI$, (C) $\log_{١٠}LC_{٥٠}$, and MG-											
	Compound ٣٤			Compound ٣٥			Compound ٣٧			Compound ٣٨		
	A	B	C	A	B	C	A	B	C	A	B	C
Leokemia												
CCRF-CEM	-٤.١٠	-٣.١٢	>-٢.٣٠	-٦.١٦	-٤.٩٨	>-٤.٠٠	-٥.٨١	-٤.٧٥	>-٤.٤٨	-٥.٦٥	-٥.٠٣	>-٤.٠٠
HL-٦٠(TB)	-٣.٧٥	-٣.٠٤	>-٢.٣٠	-٥.٥٢	-٥.٠٠	>-٤.٠٠	-٥.٠٨	-٤.٦٢	>-٤.٤٨	-٥.٥٤	-٥.٠٢	>-٤.٠٠
K-٥٦٢	-٣-٧٨	>-٢.٣٠	>-٢.٣٠	-٥.٥٦	>-٤.٠٠	>-٤.٠٠	-٥.٣٥	>-٤.٤٨	>-٤.٤٨	-٥.٤٦	-٤.٧٠	>-٤.٠٠
MOLT-٤	-٣.٨٩	-٣.٠٨	>-٢.٣٠	-٥.٨١	-٤.٧١	>-٤.٠٠	-٥.٦٤	>-٤.٤٨	>-٤.٤٨	-٥.٦١	-٤٤.٩١	>-٤.٠٠
RPMI-٨٢٢٦	-٣.٧١	-٢.٧٧	>-٢.٣٠	-٥.٥٢	-٤.٦٦	>-٤.٠٠	-٥.٢٥	>-٤.٤٨	>-٤.٤٨	-٥.٦٧	-٤.٩٧	-٤.٠٤
Non-small cell lung cancer												
A٥٤٩/ATCC	-٣.٥٦	>-٢.٣٠	>-٢.٣٠	-٥.٢٥	-٤.٢٩	>-٤.٠٠	-٤.٩٩	>-٤.٤٨	>-٤.٤٨	-٥.٥٤	-٤.٨٤	-٤.٣٠
HOP-٦٢	-٣.٥٩	-٢.٧٣	>-٢.٣٠	-٥.٢٤	-٤.٥٠	>-٤.٠٠	-٥.٠٥	>-٤.٤٨	>-٤.٤٨	-٥.٣٣	-٤.٧٥	-٤.٣٠
HOP-٩٢	-٣.٩٤	-٢.٩٨	>-٢.٣٠	-٥.٨١	-٥.٠٢	>-٤.٠٠	-٥.٢٨	-٤.٥٨	>-٤.٤٨	-٥.٥٧	-٥.٠٤	-٤.١٨
Colon cancer												
HCT-١٥	-٣.٨٢	>-٢.٣٠	>-٢.٣٠	-٥.٥٠	>-٤.٠٠	>-٤.٠٠	-٥.١٨	>-٤.٤٨	>-٤.٤٨	-٥.٥٠	-٤.٧٤	-٤.٠٤
HT٢٩	-٣.٢٤	-٢.٦٥	>-٢.٣٠	-٥.٢٣	-٤.٣٦	-٤.٠٩	-٤.٧٣	>-٤.٤٨	>-٤.٤٨	-٤.٩٣	-٤.٦١	-٤.٢٨
KM١٢	-٣.٥٠	-٢.٨٤	>-٢.٣٠	-٥.١٠	-٤.٥٧	>-٤.٠٠	-٤.٨٨	>-٤.٤٨	>-٤.٤٨	-٥.٢٧	-٤.٦٧	-٤.١٩
CNS cancer												
SF-٢٦٨	-٣.٨٤	-٢.٨٦	>-٢.٣٠	-٥.٥٧	-٤.٥٠	>-٤.٠٠	-٥.٢٠	>-٤.٤٨	>-٤.٤٨	-٥.٤٥	-٤.٨٦	-٤.٢٩
SF-٢٩٥	-٣.٢٦	-٢.٤٨	>-٢.٣٠	-٥.١٦	-٤.٢٦	>-٤.٠٠	-٤.٧٩	>-٤.٤٨	>-٤.٤٨	-٤.٩٤	-٤.٥٨	-٤.٢٣
SNB-٧٥	-٣.٧٩	-٢.٤٠	>-٢.٣٠	-٥.٧٢	>-٤.٠٠	>-٤.٠٠	-٥.٢٠	>-٤.٤٨	>-٤.٤٨	-٥.٤٩	-٤.٧٦	-٤.٠١
Melanoma												
LOX IMVI	-٣.٧٦	-٣.٠٩	-٢.٤٦	-٥.٤٤	-٤.٤٩	>-٤.٠٠	-٥.١٨	>-٤.٤٨	>-٤.٤٨	-٥.٣٧	-٤.٨٠	-٤.٣٨
MDA-MB-٤٣٥	-٣.٥٨	-٢.٥٣	>-٢.٣٠	-٥.٢٥	-٤.٢٥	>-٤.٠٠	-٥.٠٦	>-٤.٤٨	>-٤.٤٨	-٥.٥٠	-٤.٨٤	-٤.٣٤
SK-MEL-٢٨	-٣.٥٢	>-٢.٣٠	>-٢.٣٠	-٥.١٤	-٤.٢٢	>-٤.٠٠	-٤.٨٨	>-٤.٤٨	>-٤.٤٨	-٥.٤٤	-٤.٧٠	-٤.٢١
SK-MEL-٥	-٣.٧١	-٣.٠٥	-٢.٤٥	-٥.٤٤	-٤.٦٨	-٤.٠٦	-٥.٢٢	>-٤.٤٨	>-٤.٤٨	-٥.٣٣	-٤.٩٢	-٤.٤٢
Ovarian cancer												
IRGOV١	-٣.٧٤	-٣.٠٣	>-٢.٣٠	-٥.٥١	-٤.٦٨	>-٤.٠٠	-٥.١٧	>-٤.٤٨	>-٤.٤٨	-٥.٦٢	-٥.٠٩	-٢.٩٦
	-٢.٤٥	-٥.٤٧	-٤.٨٦	-٤.٠٣	-٤.٩١	>-٤.٤٨	>-٤.٤٨	-٥.٣٠	-٤.٧٤	-٤.٣١		
OVCAR-٤	-٣.٦٥	-٢.٦٠	>-٢.٣٠	-٥.٥٦	-٤.٢٤	>-٤.٠٠	-٥.١٤	>-٤.٤٨	>-٤.٤٨	-٥.٣٦	-٤.٤٤	>-٤.٠٠
OVCAR-٥	-٣.٠٤	>-٢.٣٠	>-٢.٣٠	-٤.٧٤	-٤.٣٢	>-٤.٠٠	> -٤.٤٨	>-٤.٤٨	>-٤.٤٨	-٤.٨٣	-٤.٤٤	-٤.٠٥
Renal cancer												

RXF ٣٩٣	-٣.٧٨	-٣.٠٣	>-٢.٣٠	-٥.٤٥	-٤.٧١	-٤.٠٠	-٥.١٤	>-٤.٤٨	>-٤.٤٨	-٥.٤٢	-٤.٧٧ - ٤.٣٠
SN١٢C	-٣.٧٦	-٢.٤٢	>-٢.٣٠	-٥.٥٠	-٤.٥٢	>-٤.٠٠	-٥.١٣	>-٤.٤٨	>-٤.٤٨	-٥.٤٤	-٤.٨١ - ٤.٣٠
UO-٣١	-٤.٣٠	-٣.٢٤	>-٢.٣٠	-٦.٢٢	-٤.٧١	>-٤.٠٠	-٥.٧٨	>-٤.٤٨	>-٤.٤٨	-٥.٦٤	-٤.٩٨ - ٤.٣٧
Prostate cancer											
DU-١٤٥	-٣.٦١	-٢.٧٣	>-٢.٣٠	-٥.١٩	> ٤.٠٠	>-٤.٠٠	-٥.٠٢	>-٤.٤٨	>-٤.٤٨	-٥.٣٥	-٤.٨٠ - ٤.٣٩
Breast cancer											
MCF٧	-٣.٤٦	>-٢.٣٠	>-٢.٣٠	-٥.٣٣	> ٤.٠٠	>-٤.٠٠	-٤.٩٧	>-٤.٤٨	>-٤.٤٨	-٥.٢٦	-٤.٣٦ >- ٤.٠٠
MDA-MB-٢٣١/ ATCC	-٣.٨٥	-٢.٥٠	>-٢.٣٠	-٥.٨٠	-٤.٦١	>-٤.٠٠	-٥.٢٩	>-٤.٤٨	>-٤.٤٨	-٥.٣٦	-٤.٦٩ - ٤.٢٣
T-٤٧D	-٣.٩٢	-٣.١٧	>-٢.٣٠	-٥.٦٣	-٤.٦٤	>-٤.٠٠	-٥.٢٨	>-٤.٤٨	>-٤.٤٨	-٥.٥٤	-٤.٧٣ >- ٤.٠٠
MG_MID*	**-٣.٦٧**	**-٢.٧٢**	**-٢.٣٢**	**-٥.٤٥**	**-٤.٤٩**	**-٤.٠٢**	**-٥.١٣**	**-٤.٥**	**-٤.٤٨**	**-٥.٣٨**	**-٤.٧٦ - ٤.٢٠**

MG_MID = mean graph midpoint = arithmetical mean value for all tested cell lines.

Conclusion

In conclusion, compounds **٣٥, ٣٧** and **٣٨** -the most active member of this study- exhibited remarkable activity against most of sixty cell lines. All selected compounds possessed selective remarkable activity towards all

Leukemia cell lines, Lung cancer cell line NCI-H٥٢٢, and Renal cancer cell line UO-٣١. The incorporation of galloyl functional groups as well as substitution of the aryl group in ٢-position of thiazole moiety with suitable functionalities would led to more potent and selective antitumor agent.

Experimental

Synthesis of ٢-amino-٤-arylthiazoles (١a-d)

٢-Amino-٤-arylthiazoles **١a-d** were synthesized according to ref. [١١]. ٢-Amino-٤-phenylthiazole (**١a**), m.p. ١٤٥-٦ ^{o}C [Lit. ٢٨, ١٤٩-١٥١ ^{o}C; Lit. ٢٩, ١٤٣-٤ ^{o}C]; ٢-amino-٤-(*p*-methoxyphenyl)thiazole (**١c**), m.p. ٢٠٣-٥ ^{o}C [Lit. ٢٩, ٢٠٥-٢٠٦ ^{o}C]; ٢-amino-٤-(*p*-tolyl)thiazole (**١b**), m.p. ١٣٧ ^{o}C [Lit. ٢٩, ١٣٦-١٣٧ ^{o}C]; ٢-amino-٤-(*p*-chlorophenyl)thiazole (**١d**), m.p. ١٧٥-١٧٧ ^{o}C [Lit.٢٩, ١٧٦-١٧٧ ^{o}C].

٤-Methoxy-N-(٤-phenyl-thiazol-٢-yl)-benzamide (٣)

Compound **٣** was obtained from the reaction of **١a** with **٢a** to yield ٠.٢٩g, white crystals; IR, ν_{max} cm$^{-١}$ =٣٣٥٠, ٣٤٥٠ (NH), ١٧٧٢ (CO);H NMR (٤٠٠ MHz, $CDCl_3$) δ ٨.٠٣ (d, ٢H, J= ٨.٤ Hz, aroyl-H), ٧.٧٣ (d, ٢H, J=٨.٤ Hz, aryl-H), ٧.٣٧ (t, ٢H, J=٨.٤ Hz, aryl-H), ٧.٣٢ (t, ١H, J=٨.٤ Hz, aryl-H), ٧.٠٤ (s, ١H, thiazole-H), ٦.٩١ (d, ٢H, J=٨.٤Hz, aroyl-H), ٣.٨٣ (s, ٣H, OMe); ^{١٣}C NMR (١٥٠.٩١ MHz) δ ١٦٧.٤٩ (CO), ١٦٥.١١ (C٢-thiazole), ١٦٢.٧١ Ar-C-OCH_3), ١٣٣.٢٢ (C٤-thiazole), ١٣١.٨٥, ١٣٠.٧٩ (٢C), ١٢٩.٢٣, ١٢٨.٢٦ (٢C), ١٢٦.٣٢ (٢C), ١٢٤.٤٢, ١١٥.٢٢ (٢C) (Ar-C), ١٠٨.٨٩ (C٥-thiazole), ٥٦.٠٧ (OCH_3); (MS (EI) *m/z* ٣١٠ (M^+, ٨٪). Anal. ($C_{١٧}H_{١٤}N_2O_2S$)C,H, N.

Synthesis of ٣,٤,٥-trimethoxy-N-(٤-phenyl-thiazol-٢-yl)-benzamide (١١)

Compound **١١** was obtained from the reaction of **١a** with **٢c** to yield ٠.٥٥g, white crystals; IR, ν_{max} cm$^{-١}$= ٣٢٤٠ (NH), ١٧٨٣ (CO); H NMR (٤٠٠ MHz, $CDCl_3$) δ ٧.٧٩ (d, ٢H, J= ٨.٧ Hz, aryl-H), ٧.٦٥ (t, ٢H, j= ٨.٧ Hz, aryl-H), ٧.٤٦ (t, ١H, J= ٨.٧ Hz, aryl-H), ٧.٣٢ s, ٢H, aroyl-H), ٧.١٥ (s, ١H, thiazole-H), ٣.٨٩ (s, ٣H, OMe), ٣.٨٥ (s, ٦H, ٢OMe); ^{١٣}C NMR (١٥٠.٩١ MHz) δ ١٦٦.١٤ (CO), ١٦٢.٣٣ (C٢-thiazole), ١٥٣.٣٤ (Ar-C-OCH_3, ٢C), ١٥١.٠٦ (C٤-thiazole), ١٤٤.٠٨ (Ar-C-OCH_3), ١٣٢.٧٦, ١٣٠.٨٥, ١٢٩.٦٢ (٢C), ١٢٦.١٥ (٢C), ١٢٣.٦٢,١٠٨.١٢ (Ar-C), ١٠٥.٢٤ (C٥-thiazole), ٦١.١٠ (OCH_3), ٥٦.٤٧ (٢ OCH_3), ٢٠.٠٨ (CH_3); MS (EI) *m/z* ٣٧٠(M^+, ٢١٪). Anal. ($C_{١٩}H_{١٨}N_2O_4S$) C, H, N.

Synthesis of acetic acid ٤-(٤- *p*-tolyl -thiazol-٢-ylcarbamoyl)-phenyl ester (١٦)

Compound **١٦** was obtained from the reaction of **١b** with **٢d** to yield ٠.٣٧٨g, white crystals; IR, ν_{max} cm^{-1}= ٣٤٥٠, ٣٢٣٠ (NH), ١٦٤٨, ١٦٧٢ (CO); H NMR (٤٠٠ MHz, $CDCl_3$) δ ٧.٨٩ (d, ٢H, J= ٨.٤ Hz, aroyl-H), ٧.٦٢ (d, ٢H, J= ٨.٤ Hz, aryl-H), ٧.١٦ (d, ٢H, J= ٨.٤ Hz, aroyl-H), ٧.١٣ (d, ٢H, J= ٨.٤ Hz, aryl-H), ٧.٠٥ (s, ١H, thiazole-H), ٢.٣٠ (s, ٣H, Me), ٢.٢٦ (s, ٣H, OAc); MS (EI) *m/z* ٣٥٣ (MH^+, ١٩٪). Anal. ($C_{١٩}H_{١٦}N_٢O_٣S$)

Synthesis of acetic acid ٢,٦-diacetoxy-٤-(٤-phenyl-thiazol-٢-ylcarbamoyl)-phenyl ester (٢٣)

Compound **٢٣** was obtained from the reaction of **١a** with **٢f** to yield ٠.٤٥٦g, white crystals; IR, ν_{max} cm^{-1}= ٣٣٠٩, ٣١٠٠ (NH), ١٧٧٨, ١٦٩٠ (CO); H NMR (٤٠٠ MHz, $CDCl_3$) δ ٧.٧٢ (d, ٢H, J= ٨.٦ Hz, aryl-H), ٧.٦٨ (s, ٢H, aroyl-H), ٧.٣٤ (t, ٢H, J= ٨.٦ Hz, aryl-H), ٧.٢٥ (t, ١H, J= ٨.٦ Hz, aryl-H), ٧.١١ (s, ١H, thiazole-H), ٢.٢٤ (s, ٩H, ٣ OAc); MS (EI) *m/z* ٤٥٥ (MH^+, ٢٥ %). Anal. ($C_{٢٢}H_{١٨}N_٢O_٧S$) C, H, N.

Anticancer activity

The methodology of the NCI anticancer screening has been described in detail elsewhere (http://www.dtp.nci.nih.gov) [١٢].

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١٢. Data concerning the NCI screening methods in detail are accessible from the NCI *via* the Internet from the following address http://dtp.nci.nih.gov/branches/btb/ivclsp.html.