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Synthesis and antitumor activity of substituted triazolo[4,3-*a*]pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety

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ABSTRACT

Chlorosulfonation of 3-methyl[1,2,4]triazolo[4,3-*a*]pyrimidine with chlorosulfonic acid in the presence of thionyl chloride was studied. When triazolo[4,3-*a*]pyrimidines are used as substrates, the substitution occurs at C-6. Also the reactivity of the hydrazides (**7**) towards aldehydes, thioglycolic acid and amines were studies. The newly prepared compounds **10a,d** and **11a,d** demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5} M level and in some cases at 10^{-7} M concentrations.

Cancer encompasses many disease states generally characterized by abnormally proliferating cell and is a major and often fatal disease. A variety of anticancer drugs are currently in clinical use. Some of these compounds can be applied successfully for the treatment of several neoplastic diseases such as leukemias or testicular cancer. However, the effect of anticancer drugs on solid tumors has been poor. Because the response of solid tumors to available anticancer chemotherapy has been reduced, new drugs with improved efficacy are desired.

Pyrimidines nucleus are a pharmacophoric scaffold and represents a class of heterocyclic compounds with a wide range of biological applications. Many of them are widely used as anticonvulsant,[1] analgesic,[2] sedative,[3] anti-depressive,[4] anti-pyretic agents.[5] Some heterocycles containing pyrimidine moiety were reported to possess anti-inflammatory,[6] antiviral,[7] anti-HIV-1,[8] antimicrobial,[9] and anti-tumor activities.[10,11] Other than their biological importance, pyrimidine derivatives are valuable for the preparation of fused ring compounds, such as triazolopyrimidines,[12] thieno-pyrimidines,[13] thiazolo-pyrimidines,[14] and pyridopyrimidines.[15] It has been noticed that introduction of an additional ring to the pyrimidines core tends to exert profound influence in conferring novel biological activities in these molecules. Although many methods for synthesizing triazolopyrimidines ring systems have been reported, they continue to receive a great deal attention.[16–18]

Another class of heterocyclic compounds used as scaffold in medicinal chemistry is devoted to sulfonamide derivatives.[19] They exhibit useful pharmacological properties and clinical applications. In addition to these considerable biological applications, triazolopyrimidines are important intermediates and final products in organic synthesis. In the course of our research and as part of our program involving the synthesis of heterocyclic compounds having potential biological interest, we have already reported the synthesis of many pyridopyrimidine,[20] pyrimido[4,5-*b*]quinoline and its tricyclic derivatives.[21–23]

In pursuance of our interests for investigating the reactivity of pyrimidine-2-thione towards electrophile reagents we now extend the scope of this reactivity towards other active reagents. Also, sulfochlorination reactions are widely used in organic chemistry. Sulfonyl chlorides are intermediates in syntheses of active and dispersible dyes, herbicides, and fungicides.[24] Among six-membered heterocyclic compounds containing two nitrogen atoms, a prominent place is occupied by pyrimidine derivatives used as drugs (sulfamide drug such as sulfadimethoxine, sulfamonomethoxine; antitumor agent fluorouracil; antibiotic Amecytin, etc.).[25] Moreover, triazolo[4,3-*a*]pyrimidin-6-sulfonoamide derivatives were utilized as new pharmacophoric tool for the development of more efficacious antitumor agent. On the basis of the above observations, the development of novel heteroaromatic sulfonamide as potential antitumor agents is very attractive.

Synthetic pathway depicted in Scheme 1 outlines the chemistry of the present work. The key intermediate 7-amino-3-methyl-5*H*-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**3**) was prepared by treating of 2-hydrazino-6-aminopyrimidin-4(4*H*)-one (**2**) with glacial acetic acid. The latter 2-hydrazino compound **2** was obtained from the action of hydrazine hydrate on 2-aminothiouracil (**1**). The reaction of compound **3** with aromatic aldehydes in ethanol and cata-

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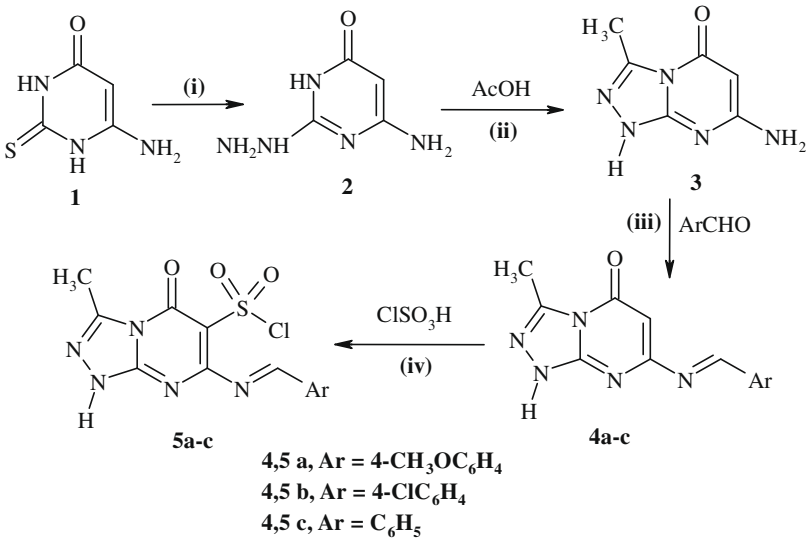


Scheme 1. Reagents and conditions: (i) EtOH (100 mL), $NH_2.NH_2$ (25 mL, 99%), 12 h; (ii) AcOH (30 mL), 16 h; (iii) Ar-CHO, EtOH (30 mL), AcOH (1 mL), 4 h; (iv) $ClSO_3H$, stirring at rt (20–30 min), heated at 75–85 °C for 5–6 h, cooled to 0 °C.

lytic amount of acetic acid yielded triazolo[4,3-*a*]pyrimidine (**4a–c**). According to the literature, the data on chlorosulfonation of pyrimidines are relatively few. As shown in the chemical abstract,[26] uracil and substituted pyrimidines react with a tenfold excess of chlorosulfonic acid to form uracil-6-sulfonyl chloride and 6-methyluracil-5-chlorosulfonyl. We reported here a develop and more efficient procedure for preparation of 7-aryl-methyleneamino-3-methyl-6-chlorosulfonyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**5a–c**). Chlorosulfonic acid in combination with thionyl chloride (1.5:1) considerably increases the rate of formation and yields of (**5a–c**).

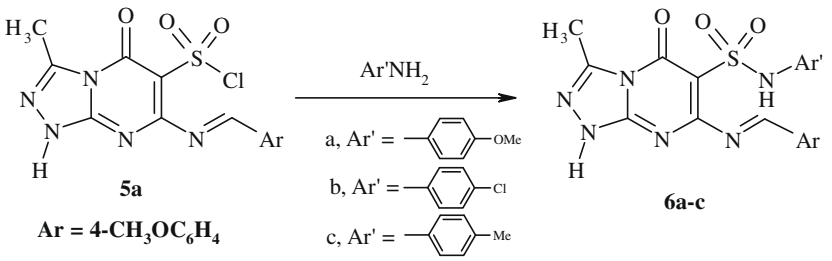
Compounds (**5a–c**) were synthesized by chlorosulfonation of 7-arylmethylene-amino-3-methyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**4a–c**). *C*-Sulphonyl chloride in position 6 of the triazolopyrimidine ring was performed at atmospheric pressure by treatment of **4** with chlorosulphonic acid and thionyl chloride (1.5:1). Treatment of compound **5a** with aryl amine in dry benzene under reflux afforded 7-(4-methoxyphenylmethyleneamino)-3-methyltriazolo[4,3-*a*]pyrimidin-6-*N*-aryl-sulfonoamide (**6a–c**), (Scheme 2). Postulated structures of the newly synthesized compounds **3**, **4**, **5** and **6** are in agreement with their IR, ^{1}H NMR spectral and elemental analysis data.

Simultaneously, the reaction of compound **5a** with hydrazine hydrate (99%) was completed in 5 h, the pure sulphonyl hydrazide **7** was obtained in good yield. The latter hydrazide was treated with aryl aldehydes at room temperature in absolute ethanol affording the corresponding aryl hydrazone derivatives **8a–d** (Scheme 3). The NMR spectrum of **8a**, as an example showed three singlet signals at δ 2.31, 3.93 and 4.00 corresponding to the methyl and two methoxy groups, showed also the aromatic protons at δ 7.52 (d, 2H, J = 8.01 Hz), 7.80 (d, 2H, J = 8.00 Hz), 8.22 (d, 2H, J = 8.01 Hz) and 8.38 (d, 2H, J = 8.00 Hz), the two azomethain protons (–N=CH–) appear at δ 8.81, 8.96 ppm, finally two broad bands corresponding to 2 NH at δ 9.50 and 11.40 which are D_2O exchangeable.

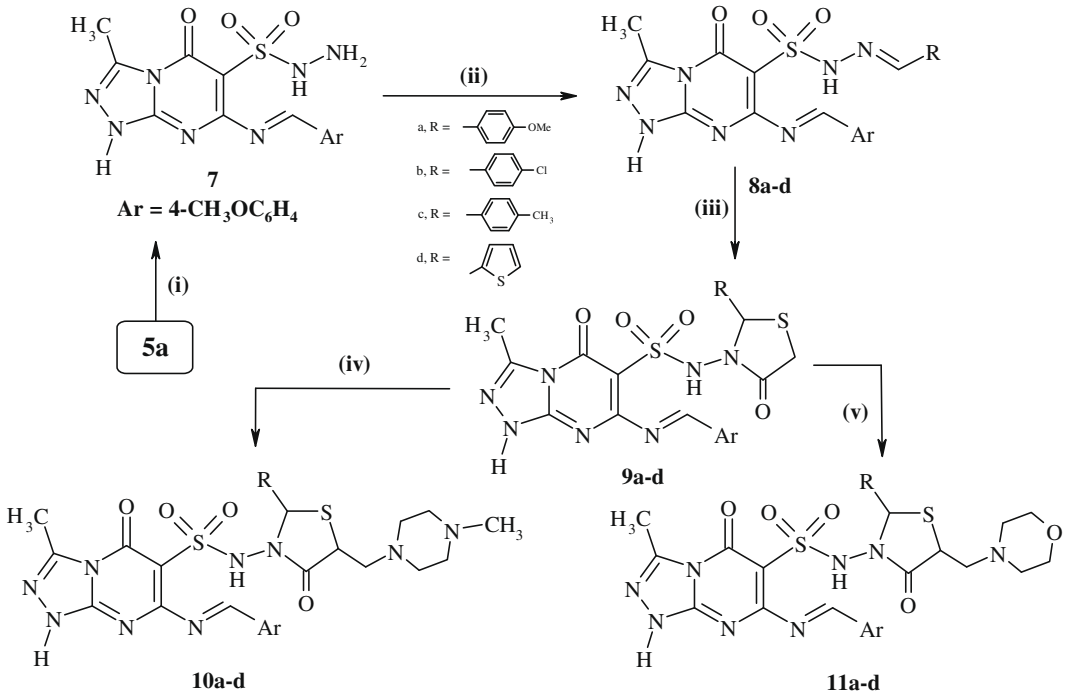
The syntheses of 3-methyltriazolo[4,3-*a*]pyrimidin-6-sulfono[(4-methylpiperazine/or morpholine-1-yl-methyl)-4-oxo-2-(arylthiazolidin-3-yl]amide derivatives (**10** and **11**) were carried out as shown in Scheme 3. The intermediate compounds **9a–d** was synthesized by the nucleophilic cycloaddition of thioglycolic acid in dry benzene under reflux in a water-bath. The structure of **9** was assigned to the isolated products **9a–d** on the basis of elemental analysis, IR and in particular NMR spectra: the latter compound revealed the absence of –CH=N– and appeared the absorption signal corresponding to the methylene proton around δ 4.40 ppm and the singlet signal due to the N–CH–S of thiazolidine proton around δ 8.80 ppm.

6-(4-Methylpiprazin or morpholin)-1-yl-methyl)-derivatives were prepared by the reaction of intermediate **9** with a mixture of paraformaldehyde and *N*-methyl piperazine or morpholine in absolute ethanol. The mixture was refluxed for 7–10 h and left it at room temperature under stirring for 3 days. The structure of compounds **10a–d** and **11a–d** were conformed on the basis of their correct elemental analyses as well as compatible spectral data (general).[31] The ^{1}H NMR spectra of compounds **10** and **11** revealed the absence of the $-CH_2-$ absorption signal of thiazolidine ring and appeared the multiplet absorption signals of the methylene protons (4–CH_2) of piperazine and morpholine.

Evaluation of anticancer activity on thiazolopyrimidines **6–11** was performed at the National Cancer Institute (NCI). First, all



Scheme 2. Reagents and conditions: Ar′-NH_2, dry benzene (50 mL), reflux 3 h.



Scheme 3. Reagents and conditions; (i) NH_2NH_2 (5 mL, 99%), EtOH (30 mL), 5 h; (ii) Ar-CHO, EtOH, (25 mL), rt 48 h; (iii) $SHCH_2COOH$, dry benzrne (25 mL), water-bath 80 °C, 10–14 h.; (iv) *N*-methylpiprazine, HCHO (15 mL), EtOH (25 mL), 30–45 min, then reflux for 7–10 h.; (v) morpholine, HCHO (15 mL), EtOH (25 mL), 30–45 min, then reflux for 7–10 h.

thiazolopyrimidines were evaluated in primary anticancer assay at 10^{-4} M concentration against NCI-H460 (Lung), MCF7 (Breast), and SF-268 (CNS) cell lines (Table 1).

For NCI criteria, compounds, which reduce the growth of any one of the cell lines to approximately 32% or less, are passed on for evaluation in the full panel of cell lines over a 5-log dose range. Sulfonamide derivatives **10a,d** and **11a,d**, which meet these criteria, were evaluated for their anticancer activity following the known in vitro disease-oriented antitumor screening program, which is based upon use of a multiple panels of 60 human tumor cell lines.[27,28] Each compound is tested at a minimum of five concentrations at 10-fold dilution against every cell line in the panel. A 48 h continuous drug exposure protocol is used and a sulforhodamine B (SRB) protein assay is used to estimate cell viability or growth.[29] The anticancer activity of each compound is deduced from dose response curves and is presented in three different tables according to the data provided by NCI.[30] The response parameters GI_{50}, TGI and LC_{50} (Table 2) refer to the drug concentration that produce 50% inhibition, total growth inhibition, and 50% cytotoxicity, respectively, and are expressed in 10^{-5} molar concentrations. In the tables we report only the activity of those compounds which exhibited GI_{50}, TGI, and LC_{50} less than 10×10^{-5} M.

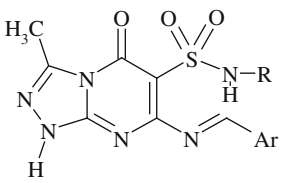
Table 1
Aniproliferative activity of triazolo[4,3-*a*]pyrimidines **6–11** at 10^{-4} M concentration expressed in growth percentage

Compd No.	Cell lines		
	MCF7	NCI-H460	SF-268
6a	86	82	91
6b	87	102	87
6c	83	89	85
7	43	45	55
8a	83	55	85
8b	93	73	101
8c	87	83	93
8d	66	13	62
9a	91	118	94
9b	90	88	84
9c	72	67	63
9d	89	106	98
10a	9	0	18
10b	102	86	106
10c	55	109	102
10d	46	24	58
11a	64	16	75
11b	94	68	95
11c	67	63	82
11d	24	13	56

The GI_{50} data reported in Table 2 indicate that all selected compounds **10a,d** and **11a,d** showed a good level of cytostatic activity at 10^{-5} M and in some cases at 10^{-7} M concentrations against all subpanel cell lines. Compound **10a** displayed a significant growth inhibitory activity on all the 60 cell lines showing GI_{50} values between 5.89 and 37.1×10^{-6} M, and total growth inhibitory activity on 56 cell lines at $2.1–8.94 \times 10^{-5}$ M concentrations. Compound **10a** showed cytotoxic activity against 31 cell lines with particular selectivity against all renal cancer and prostate cancer cell lines. Compound **10d** totally inhibited the growth of 20 cell lines at $0.318–9.73 \times 10^{-5}$ M concentrations, showing a good selectivity on the leukemia panel. In addition, it was not cytotoxic, except for three cell lines of this panel (HL-60TB, K-562, and SR). Compound **11a** showed cytotoxic activity on four leukemia cell lines with LC_{50} values between 7.15 and 8.68×10^{-5} M. Furthermore, **11d** produced 50% growth inhibition of 26 cell lines at micromolar concentrations. The same compound inhibited totally the growth of 24 cell lines at 10^{-5} M concentrations exhibiting high potency against leukemia SR cell line (TGI value 3.18×10^{-6} M and LC_{50} value 9.20×10^{-6} M). Compound **11d** is cytotoxic against HCC-2998 cell line of colon cancer only (LC_{50} value 6.48×10^{-5} M).

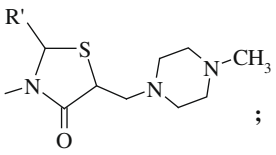
The activity appears to be related to some structural requirements, as the 6-substituent on the 3-methyl-triazolo[4,3-*a*]pyrimidin-6-sulfonoamide ring. In fact, the presence of an 4-methylpiprazin/or

Table 2
GI_{50} values, TGI values and LC_{50} values of compounds **10a**,**d** and **11a**,**d**



Ar = 4-$CH_3OC_6H_4$

R =



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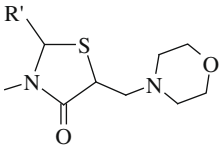

10a, R' = 4-$CH_3OC_6H_4$
10d, R' = 2-C_4H_3S

11a, R' = 4-$CH_3OC_6H_4$
11d, R' = 2-C_4H_3S

Panel/cell line	10a			10d			11a			11d		
Type of test	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
Leukemia												
CCRF-CEM	1.72	4.92	n.t	0.352	1.61	n.t	2.58	7.89	n.t	0.627	–	n.t
HL-60(TB)	2.82	8.68	–	0.341	0.704	3.13	0.98	2.72	7.43	n.t.	n.t.	n.t.
K-562	1.30	2.87	6.33	0.287	0.675	6.82	1.30	3.23	8.05	0.234	1.13	–
MOLT-4	1.78	5.89	–	0.288	1.83	–	1.36	3.44	8.68	0.408	4.06	–
RPMI-8226	1.41	3.90	–	0.256	0.821	–	1.64	4.43	–	0.386	2.62	–
SR	0.772	2.75	8.49	0.079	0.303	1.31	1.17	2.89	7.15	0.110	0.32	0.920
Nn-small cell lung cancer												
A549/AT CC	1.34	5.08	n.t	0.365	–	n.t	2.96	–	n.t	1.91	–	n.t
EKVX	2.59	6.03	n.t	3.970	–	n.t	9.39	–	n.t	5.41	–	n.t
HOP-62	2.02	4.09	8.26	0.170	–	–	8.66	–	–	1.39	–	–
HOP-92	1.78	3.64	7.42	0.941	–	–	3.63	–	–	1.24	–	–
NCI-H226	1.24	3.06	7.57	1.180	–	–	5.36	–	–	2.45	–	–
NCI-H23	2.05	4.81	n.t	0.116	0.911	n.t	8.78	–	n.t	4.45	–	n.t
NCI-H322M	2.11	5.11	n.t	0.818	–	n.t	3.98	–	n.t	5.69	–	n.t
NCI-H460	1.64	4.67	n.t	0.820	–	n.t	8.77	–	n.t	0.532	–	n.t
NCI-H522	2.19	4.77	n.t	0.263	1.33	n.t	3.25	–	n.t	0.435	2.73	n.t
Colon cancer												
COLO 205	3.71	2.61	n.t	0.529	2.10	n.t	6.62	–	n.t	1.49	1.28	n.t
HCC-2998	0.859	2.25	7.19	0.134	1.68	–	2.20	–	–	0.396	3.13	6.48
HCT-116	0.589	4.72	7.15	0.101	2.00	–	2.97	9.73	–	0.472	5.74	–
HCT-15	1.72	7.08	n.t	0.065	–	n.t	2.67	–	n.t	0.452	7.17	n.t
HT29	3.47	n.t	n.t	0.196	n.t	n.t	2.67	n.t	n.t	1.94	n.t	n.t
KM12	2.48	n.t	n.t	0.302	n.t	n.t	3.61	n.t	n.t	0.406	n.t	n.t
SW-620	3.04	n.t	n.t	0.138	n.t	n.t	4.71	n.t	n.t	0.611	n.t	n.t
CNS cancer												
SF-268	1.77	4.20	9.96	–	–	–	–	–	–	1.85	–	–
SF-295	1.68	3.59	7.68	0.102	–	–	3.32	–	–	0.469	–	–
SF-539	0.650	2.18	6.12	0.177	0.558	–	7.51	–	–	0.724	3.04	–
SNB-19	2.57	7.25	n.t	0.714	–	n.t	–	–	n.t	3.45	–	n.t
SNB-75	2.36	5.18	n.t	0.201	–	n.t	5.73	–	n.t	3.55	–	n.t
U251	1.76	4.52	–	0.251	–	–	4.04	–	–	1.56	–	–
Melanoma												
LOX IMVI	0.74	–	n.t	0.216	–	n.t	2.16	6.24	n.t	0.897	–	n.t
M14	1.70	3.65	7.80	0.136	–	–	6.74	–	–	0.679	3.87	–
SK-MEL-2	2.13	4.61	9.94	0.555	–	–	9.93	–	–	0.830	8.19	–
SK-MEL-28	3.03	7.82	n.t	1.640	–	n.t	–	–	n.t	8.21	–	n.t
SK-MEL-5	1.93	3.90	7.85	0.072	0.711	–	1.90	–	–	0.371	2.40	–
UACC-257	2.16	4.47	9.23	0.252	–	–	3.22	–	–	0.677	–	–
UACC-62	1.89	3.84	7.78	0.147	–	–	2.54	–	–	0.370	3.14	–
Ovarian cancer												
IGROV 1	2.10	4.44	9.39	0.078	9.73	–	2.60	9.74	–	0.395	3.48	–
OVCAR-3	2.15	4.02	7.53	0.088	–	–	2.25	6.05	–	0.360	–	–
OVCAR-4	2.33	4.74	9.65	–	–	–	9.44	–	–	–	–	–
OVCAR-5	2.43	4.70	9.07	0.831	–	–	–	–	–	4.34	–	–
OVCAR-8	0.782	4.72	n.t	0.353	4.05	n.t	3.14	–	n.t	6.06	–	n.t
SK-OV-3	2.71	7.33	n.t	0.512	–	n.t	–	–	n.t	2.02	–	n.t
Renal cancer												
786-0	1.62	3.12	5.99	0.393	–	–	6.71	–	–	0.582	–	–
A498	1.29	2.81	6.09	0.050	0.32	–	2.55	6.92	–	0.267	1.55	–
ACHN	1.74	3.45	6.84	0.318	–	–	2.31	9.26	–	0.548	–	–
CAKI-1	2.09	4.03	7.78	0.129	–	–	4.33	–	–	1.21	–	–
RXF 393	1.02	3.11	9.51	0.234	–	–	1.50	–	–	1.66	9.42	–
SN12C	1.86	3.58	6.89	0.468	–	–	5.51	–	–	1.68	8.57	–
TK-10	1.94	3.99	8.21	0.590	–	–	4.01	–	–	2.08	9.20	–
UO-31	2.06	3.81	7.05	0.536	–	–	3.96	–	–	1.45	8.64	–
Prostate cancer												
PC-3	1.47	3.22	7.02	0.289	4.00	–	2.46	–	–	0.392	9.58	–
DU-145	1.18	3.20	8.66	0.522	–	–	2.88	–	–	1.60	–	–

Table 2 (*continued*)

Panel/cell line	10a			10d			11a			11d		
Type of test	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
Breast cancer												
MCF7	1.53	4.78	n.t	0.580	—	n.t	7.73	—	n.t	0.318	—	n.t
NCI/ADR-RES	1.41	4.02	n.t	0.150	0.698	n.t	4.31	—	n.t	0.998	6.48	n.t
MDA-MB-231/ATCC	1.22	3.29	8.86	0.325	4.22	—	2.53	—	—	1.17	5.61	—
HS578T	1.30	3.40	8.87	0.305	—	—	4.11	—	—	1.33	8.21	—
MDA-MB-435	2.41	6.46	n.t	0.032	0.52	n.t	3.50	—	n.t	0.326	3.60	n.t
BT-549	1.91	4.63	n.t	1.130	—	n.t	—	—	n.t	1.80	—	n.t
T-47D	3.12	8.94	nt	—	—	nt	—	—	nt	4.80	—	n.

n.t., means not tested; (—) values >10×10^{-5} M.

morpholine linked to arylthiazolidine on 6-position favorably affects the activity. The introduction in the same position of an 4-chlorphenylthiazol-idine or 4-tolylthiazolidine group (compound **10b,c** and **11b,c**) and also, thiazolidine ring without substitution (compounds **9a–d**) or 3-methyltriazolo[4,3-*a*]pyrimidine (compounds **6a–c, 7**) and 6-arylmethylenesulfonoamide (compound **8a–d**) are detrimental. Among 6-arylthiazolidine derivatives thienyl or 4-methoxyphenyl groups on arylidene moiety were effective in inducing strong antitumoral activity. The best activity is shown by thienyl group in presence of 4-methylpiparazine or morpholine derivatives, whereas the presence of 4-chlorophenyl or 4-methylphenyl group produces variable effects.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.05.126.

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31. *General*: Melting points were measured with Electrothermal IA 9100 apparatus (Shimadzu, Japan). The ^{1}H NMR spectra were recorded on *JEOL* ECA500 MHz. Chemical shifts relative to TMS as internal standard are given as δ values in ppm and recorded in (DMSO-d_6). IR spectra were recorded as KBr pellets on a Nexus FT/IR spectrometer. Mass spectra were recorded on GCMS-QP 1000 EX Shimadzu. Elemental analyses were performed in the Microanalytical Unit at Cairo University (Egypt) and were found within ±0.4% of the theoretical values (*see* Table 3 as Supplementary data). The antitumor screening of the investigated compounds was carried out by the pharmacology Unit, National Cancer Institute (NCI), Cancer Biology Department, Cairo University, Egypt).
Primary anticancer assay: The compounds were tested by NCI in an in vitro three-cell line, one dose primary anticancer assay as a primary cancer screen. The three-cell line panel consists of the MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). Each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at single 10-4 M concentration and the culture is incubated for 48 h. End-point determinations are made with alamar blue.[32] Results for each test agent are reported as the percent of growth of the treated cells when compared to untreated control cells. Compounds, which reduce to growth of any one of cell lines to approximately 32% or less, are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range.
Determination of GI_{50}, TGI and LC_{50} values: A total of 60 human tumor cell lines, derived from nine cancer types (leukemia, lung, colon, brain, melanoma, ovarian, renal, prostate, and breast), formed the basis of this test. The tumor cells were cultured in RPMI1640 medium supplemented with 5% fetal calf serum and 2 mM L-glutamine. The tumor cells are inoculated over a series of standard 96-well microtiter plates in 100 mL of medium.[27,28] Density of inoculums depends on the type of tumor cell and on its growth characteristics.[33] These cells are then preincubated on the microtiter plate for 24 h before adding the compounds. They were tested in DMSO solution at five different concentrations (10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} M). After an incubation of the chemical agent for 48 h with the tumor cell lines, a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The cytotoxic effects are evaluated, and the assay results and dose-response parameters were calculated as previously described.[30]
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