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5-Substituted-2-thiohydantoin analogs as a novel class of antitumor agents

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Certain series of 2-thiohydantoin derivatives, carrying various substituents at position 5 such as 5-bromo-2-thienylmethylene, 5-(2-carboxyphenylthio)-2-thienylmethylene and 2-methylene-4H-thieno[2,3-*b*][1]benzothiopyran-4-one, were evaluated for their antitumor activity. Compound 5-(5-bromo-2-thienylmethylene)-3-morpholinomethyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)hydantoin proved to possess a broad spectrum antitumor activity against a wide range of different human cell lines of nine tumor subpanels causing both cytostatic and cytotoxic effects, resulting in full panel median growth inhibition (GI_{50}) and total growth inhibition (TGI), with a median lethal concentration (LC_{50}) at 15.1, 41.7 and 83.2 μM, respectively. On the other hand, compound 5-(5-bromo-2-thienylmethylene)-2-thiohydantoin and compound 5-(5-bromo-2-thienylmethylene)-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-thio)hydantoin showed potential selectivity against leukemia cell lines. Further derivatization of these compounds, deduced from the obtained tentative structure activity relationships, may lead to more potent agents.

Key words: Antitumor screening, nucleosides, 2-thiohydantoins.

Introduction

A number of sulfur containing heterocycles have been noted in the literature to possess antitumor activity, i.e. hycanthone (thiaxanthone derivatives),[1–3] sulfadiazine[4] and chloroquinoxaline sulfonamide.[5–7] Recently we have reported on the antineoplastic activity of a series of compounds containing thioether[8] and thioureido[9–11] functions. In the course of synthesizing some thiophene analogs of the 2-thiohydantoin nucleus as antiviral agents[12] (Figure 1), we evaluated these compounds for their antitumor activity, especially those containing 4H-thieno[2,3-*b*][1]benzothiopyran-4-one as a planer tricyclic heterocycle representing a thioxanthone isoster, as well as the *S*-glucosyl hydantoin and *S*-substituted thiosalicylic acid derivatives as thioether analogs. The thiohydantoin nucleus itself is a cyclized thiourea, a synthon proven to contribute dramatically to cytotoxic potency.[9–11]

Figure 1 shows a list of the structures of the compounds investigated in the present study. They were evaluated in the National Cancer Institute's (NCI) *in vitro* disease-oriented antitumor screen, which determines a test agent's effect on growth against a panel of approximately 60 human tumor cell lines.[13,14]

Materials and methods

Source of compounds

The thiohydantoin derivatives used in the present study were previously synthesized and characterized.[12] Their chemical names are shown in the following list and their chemical structures are presented in Figure 1.

(1) 5-(5-Bromo-2-thienylmethylene)-2-thiohydantoin (**1a**)
(2) 5-(5-Bromo-2-thienylmethylene)-3-phenyl-2-thiohydantoin (**1b**)
(3) 5-[5-(2-Carboxyphenylthio)-2-thienylmethylene]-2-thiohydantoin (**2a**)
(4) 5-[5-(2-Carboxyphenylthio)-2-thienylmethylene]-3-phenyl-2-thiohydantoin (**2b**)
(5) 2-[(4-Oxo-2-thioimidozolidin-5-yliden)methylene]-4H-thieno[2,3-*b*][1]benzothiopyran-4-one (**3a**)
(6) 2-[(4-Oxo-3-phenyl-2-thioimidazolidin-5-yliden)methylene]-4H-thieno[2,3-*b*][1]benzothiopyran-4-one (**3b**)
(7) 5-(5-Bromo-2-thienylmethylene)-3-morpholinomethyl-2-thiohydantoin (**4a**)
(8) 5-(5-Bromo-2-thienylmethylene)-3-piperidinomethyl-2-thiohydantoin (**4b**)
(9) 5-(5-Bromo-2-thienylmethylene)-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)hydantoin (**5a**)
(10) 5-(5-Bromo-2-thienylmethylene)-3-phenyl-2-

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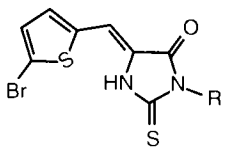
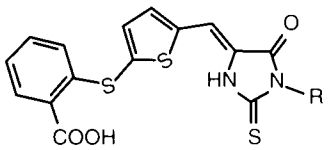


1a, R H; 1b, R Ph



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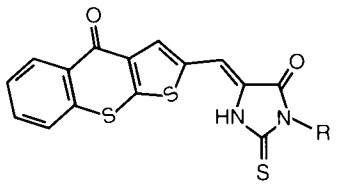
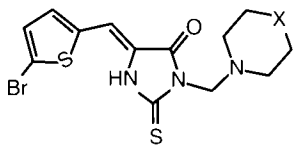
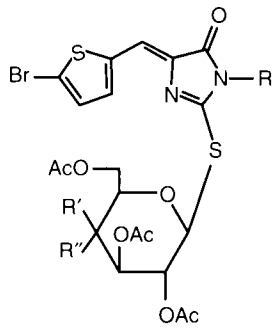


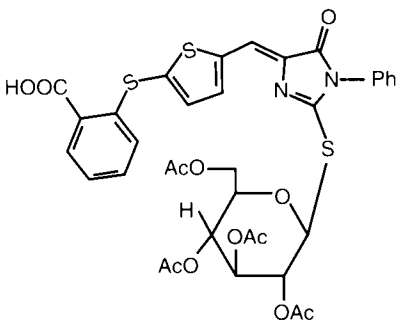
3a, R H; 3b, R Ph



4a, X O; 4b, X CH_2



5a: R R′ = H, R″ = OAc
5b: R Ph, R′ = OAc, R″ = H



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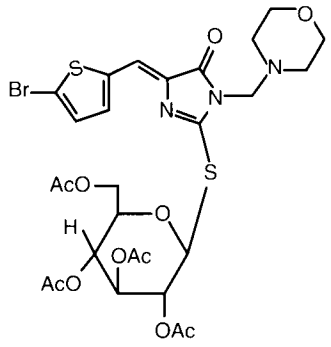

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Figure 1. Structures of 2-thiohydantoin analogs.

(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosylthio)-hydantoin (**5b**)

(11) 5-[5-(2-Carboxyphenylthio)-2-thienylmethylene]-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)hydantoin (**6**)

(12) 5-(5-Bromo-2-thienylmethylene)-3-morpholinomethyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)hydantoin (**7**)

Antitumor biological testing and data analysis

Compounds **1a**–**7** were subjected to the NCI *in vitro* disease-oriented human cells screening panel assay as described elsewhere.[13–15] About 60 cell lines of nine tumor subpanels were incubated with five concentrations (0.01–100 μM) of each agent

and used to create log concentration–% growth inhibition curves. Three response parameters, GI_{50}, total growth inhibition (TGI) and LC_{50}, were calculated for each cell line. The GI_{50} value corresponds to the agent's concentration causing 50% decrease in net cell growth, the TGI value is the agent's concentration resulting in total growth inhibition and the LC_{50} value is the agent's concentration causing a net 50% loss of initial cells at the end of the incubation period (48 h). Subpanel and full panel mean-graph midpoint values (MG-MID) for a certain agent are the average of individual real and default GI_{50}, TGI or LC_{50} values of all cell lines in the subpanel or the full panel, respectively.[15]

Results and discussion

Antitumor screening

The NCI antitumor drug discovery screen has been designed to distinguish between broad spectrum antitumor compounds and tumor- or subpanel-selective agents.[15] In the present study, the 5-substituted-2-thiohydantoin analogs **1a**–**7** showed a distinctive potential pattern of selectivity as well as broad spectrum antitumor activity, e.g. most of the 12 compounds tested produced 50% growth inhibition (GI_{50}) in five or six different cell lines of the leukemia subpanel, at concentrations less than 100 μM, and all of them showed GI_{50} mean-graph values less than 100 μM (Tables 1 and 2). The least effective members of these compounds were **2a** < **1b** < **5a** (these three compounds exhibited GI_{50} values in only two or three cell lines of the leukemia subpanel, Table 2). With regard to selectivity against individual leukemia cell lines, compounds **1a**, **5a**, **5b** and **7** were particularly effective against HL-60(TB) with GI_{50} values of 0.86, 8.5, 3.8 and 3.9 μM, respectively. Compounds **5b** and **7** were effective against PRMI-8226 with GI_{50} values of 8 and 6 μM, respectively, and compound **5b** against SR cell line with a GI_{50} value of 9.7 μM (Table 2). On the other hand, three of the 12 compounds (**4a**, **4b** and **7**) produced TGI of four or five cell lines of the leukemia subpanel at concentrations less than 100 μM (Table 3). Furthermore, compound **7**

Table 1. Subpanel (I IX) and full panel (MG-MID) mean-graph midpoint of median growth inhibitory (GI_{50}) concentration (μM) of 2-thiohydantoin analogs **1a** **7**

Agent	Subpanel tumor cell lines									MG-MID
	I	II	III	IV	V	VI	VII	VIII	IX	
1a	23.9 (2.60)	78.8	90.6	97.5	75.5	83.7	76.5	97.1	72.2	63.1
1b	79.9	65.9	87.1	51.8	77.8	60.9	59.1	> 100	62.7	63.1
2a	87.7	88.9	> 100	> 100	97.9	> 100	96.3	> 100	> 100	95.5
2b	36.2 (2.05)	88.4	89.3	> 100	88.9	74.5	69.7	> 100	97.2	74.1
3a	37.7 (2.08)	60.5	66.8	52.2	75.6	65.7	78.2	86.1	77.9	57.5
3b	38.0 (1.24)	79.0	91.5	34.3 (1.93)	95.7	> 100	79.9	> 100	92.7	66.1
4a	24.1 (1.90)	56.1	48.7	82.3	53.4	60.3	38.4	66.1	55.9	45.7
4b	19.1 (1.40)	39.5	30.0	38.0	26.0	42.2	31.6	33.2	35.4	26.9
5a	56.4	40.9	75.1	37.2 (1.28)	59.5	69.6	37.1 (1.29)	79.3	62.6	47.9
5b	15.6 (2.56)	37.9	43.5	75.5	47.2	52.9	60.2	38.5	44.0	39.8
6	37.4 (2.07)	92.6	86.5	66.0	83.9	87.3	97.7	> 100	87.6	77.7
7	10.5 (1.44)	14.0	16.7	22.8	13.8	21.4	13.8	19.8	20.8	15.1

Tumor cell line subpanel: 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.
Full panel MG-MID/subpanel mean-graph ratio is shown in parentheses.

Table 2. Log median growth inhibitory (GI_{50}) concentration (M) of *in vitro* tumor cell lines by 2-thiohydantoin analogs **1a 7**

Subpanel/cell line	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6	7
Leukemia												
CCRF-CEM	4.60		NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
HL-60(TB)	6.06		4.35	−4.60	4.44	−4.91	−4.62	4.81	5.07	5.42	−4.70	5.42
K-562	4.46	−4.25	4.03	−4.50	4.52	4.39	−4.59	4.64		4.72	4.27	4.99
MOLT-4	4.67			−4.27	4.63	−4.61	4.49	4.63		4.42	−4.69	4.70
PRMI-8226	4.56	4.65		4.39	−4.59		4.78	4.75	4.42	5.10	−4.29	5.22
SR	4.48			4.54	4.64	−4.89	4.67	4.80	4.45	5.01	−4.38	4.90
Non-small cell lung												
EKVX	4.99			−4.01	5.45	4.32	5.08	5.03	4.51	4.47	4.19	5.09
HOP-62		−4.41			4.49	5.30		4.12	4.38	4.26		4.64
HOP-92	4.09	−4.59	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
NCI-H226	4.07						−4.46	4.49	4.33	4.80		4.95
NCI-H23					4.28		4.44	4.49	4.47	4.72		4.90
NCI-H322M		4.19						4.16	4.11	4.09		4.76
NCI-H460	4.15	4.29			4.19		4.30	−4.44	4.52	4.42	−4.08	4.73
NCI-H522	4.08	4.33	−4.66	−4.67	4.15		4.19	4.63	4.59	4.66		5.16
Colon cancer												
COLO 205		−4.07		−4.26	−4.32		4.48	−4.74	4.39	4.24		4.73
HCC-2998	4.24			−4.01	4.15			4.51	4.23	4.44		4.70
HCT-116		−4.35		−4.14	4.44	−4.39	4.50	4.51	4.60	4.21	4.42	4.86
HCT-15	4.04	4.09					−4.52	−4.55		4.17		4.78
HT29	4.07				−4.26		4.45	−4.48		4.54		4.81
KM12							−4.07	4.45		4.35		4.76
SW-620					−4.24		−4.44	−4.48		4.04	4.17	4.83
CNS cancer												
SF-268						−4.26	4.06	−4.41	4.25			4.48
SF-295		−4.36			4.15	−4.18	−4.02	4.52	4.40	4.24		4.71
SNB-19	4.05	4.57			4.48	−4.62		−4.33	4.43	4.25	−4.39	4.70
SNB-75	NT	NT			4.58	−5.29	4.07	4.35	4.60		4.18	4.60
U251		−4.44			−4.51	4.68	−4.37	4.54	4.55	4.20	−4.62	4.79
Melanoma												
LOX IMVI					−4.22		4.61	−4.67	4.32	4.19	4.26	4.89
MALME-3M		4.17						−4.23	4.27	4.30		4.78
SK-MEL-2	4.00			4.65		−4.10	4.14	−6.17	4.49	4.78	4.49	6.42
SK-MEL-28					−4.39		4.39	4.39		4.08		4.80
SK-MEL-5	4.40	4.20				−4.04	4.30	−6.50	4.28	4.37		4.72
UACC-257	4.21	4.18					4.18	−4.48		4.37		−4.78
UACC-62	4.55	4.33	4.07		4.53		4.69	4.58	4.51	4.51		4.81
Ovarian cancer												
IGROVI	4.03	4.16			4.39		−4.24	4.39	4.06	4.38		4.77
OVCAR-3	4.14	4.20		−4.32	4.27		−4.23	4.65	4.04	4.68		NT
OVCAR-4	4.27	4.57		−4.60	4.12		4.21	−4.43	4.38	4.50	4.13	−4.53
OVCAR-5							4.21	4.12			4.20	4.64
OVCAR-8	NT	NT			−4.24		4.21	−4.48	4.55	4.15		4.79
SK-OV-3		4.34	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Renal cancer												
786-0		4.39		4.73	−4.40	−4.63	4.37	4.44	4.75			4.78
A498	−4.46	4.29					4.44	4.64	4.23	4.39		4.69
ACHN		4.49		−4.40	4.22		4.32	−4.34	4.49	−4.28		4.79
CAKI-1	4.15	4.35	−4.15	4.35			−4.60	4.49	4.87	4.07		4.75
RXF 393		−4.52			−4.17	4.81	4.67	4.68	−4.92	5.02	−4.09	5.42
SN12C		4.13					−4.34	4.46	−4.30			4.87
TK-10	4.28			4.12	4.01		−4.30	4.46	4.39	4.22		4.78
UO-31	4.26			−4.10	−4.23		−4.43	−4.61	−4.15	−4.49		−4.81
Prostate cancer												
PC-3	4.03				4.14		4.10	−4.55	4.23	4.47		4.64
DU-145							4.27	4.42		4.37		4.78

Table 2. (*continued*)

Subpanel/cell line	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6	7
Breast cancer												
MCF7		−4.46			−4.45		−4.60	−4.69	−4.38	−4.10	−4.10	−4.81
MCF7/ADR-RES	NT	NT					−4.19	−4.54	−4.39	−4.37		−4.69
MDA-MB-231/ATCC		−4.46				−4.05	−4.00	−4.20	−4.23	−4.37	−4.24	−4.57
HS 578T	−4.47	−4.41			−4.19		−4.19	−4.29	−4.45	−4.32		−4.71
MDA-MB-435	−4.23	−4.06					−4.24	−4.52	−4.06	−4.49		−4.62
MDA-N					−4.06		−4.28	−4.47		−4.26		−4.74
BT-549	−4.39	−4.08			−4.46	−4.29	−4.47	−4.59	−4.38	−4.61	−4.20	−4.83
T-47D	NT	NT		−4.11			−4.30	−4.52	−4.02	−4.56		−4.55
MG-MID	−4.20	−4.20	−4.02	−4.13	−4.24	−4.18	−4.34	−4.57	−4.32	−4.40	−4.11	−4.82

, log GI_{50} of > −4.00.
NT, not tested.
MG-MID, log molar GI_{50} full panel mean-graph midpoint.

Table 3. Log TGI concentration (M) of *in vitro* tumor cell lines by 2-thiohydantoin analogs **1a** **7**

Subpanel/cell line	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6	7
Leukemia												
CCRF-CEM			NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
HL-60(TB)				−4.09		−4.71	−4.20	−4.30		−4.67	4.27	−4.89
K-562							−4.00	−4.22				−4.34
MOLT-4					−4.16			−4.18			−4.26	−4.28
PRMI-8226	−4.09	−4.07					−4.37	−4.29		−4.21		−4.57
SR						−4.30	−4.26	−4.33				−4.46[a]
Non-small cell lung												
EKVX												−4.01
HOP-62												−4.25
HOP-92		−4.15	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
NCI-H226												−4.49[a]
NCI-H23												−4.57[a]
NCI-H322M												−4.45[a]
NCI-H460												−4.41[a]
NCI-H522				−4.41[a]				−4.08		−4.03		−4.63[a]
Colon cancer												
COLO 205							−4.06	−4.43[a]				−4.42[a]
HCC-2998												−4.41[a]
HCT-116												−4.55[a]
HCT-15												−4.31
HT29												−4.47[a]
KM12												4.45[a]
SW-620												−4.41
CNS cancer												
SF-268												−4.09
SF-295								−4.04				−4.28
SNB-19												−4.33
SNB-75	NT	NT			−4.14				−4.21			−4.17
U251											−4.20	−4.49[a]
Melanoma												
LOX IMVI							−4.21	−4.28				−4.57[a]
MALME-3M												−4.45[a]
SK-MEL-2								−4.43		4.31		
SK-MEL-28												−4.48[a]
SK-MEL-5								−4.62[a]				−4.47[a]
UACC-257												−4.49[a]
UACC-62							−4.31					−4.49[a]

Table 3. (*continued*)

Subpanel/cell line	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6	7
Ovarian cancer												
IGROVI												4.33
OVCAR-3								4.22		-4.07		NT
OVCAR-4				4.22								
OVCAR-5												4.14
OVCAR-8	NT	NT										4.43[a]
SK-OV-3			NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Renal cancer												
786-0				-4.45[a]					4.26			4.44[a]
A498								-4.04				4.34
ACHN												4.34
CAKI-1							-4.18	4.23	4.49[a]			4.46[a]
RXF 393							-4.22	-4.22	-4.24			4.70[a]
SN12C												4.49[a]
TK-10												4.46[a]
UO-31								4.12				4.53[a]
Prostate cancer												
PC-3								-4.05				4.26
DU-145												-4.51[a]
Breast cancer												
MCF7							-4.28	-4.24				4.47[a]
MCF7/ADR-RES	NT	NT						-4.01				-4.36[a]
MDA-MB-231/ATCC												
HS 578T									4.11			
MDA-MB-435												
MDA-N												4.32
BT-549								4.01				4.41
T-47D	NT	NT										4.04
MG-MID	-4.00	-4.00	-4.01	4.02	-4.01	-4.01	4.04	-4.08	4.02	-4.02	-4.01	4.38

, log TGI of · 4.00.
NT, not tested.
MG-MID, log molar TGI full panel mean-graph midpoint.
[a]Log molar median lethal concentration (LC_{50}) of · · 4.00.

produced a cytotoxic effect with a median lethal concentration (LC_{50}) of 96.4 μM against SR leukemia cell line (Table 3). When the full panel GI_{50} mean-graph (MG-MID)/leukemia subpanel GI_{50} mean-graph ratio was calculated for all compounds (Table 1) to predict those with selectivity according to Boyed and Paull,[15] it was found that compounds **1a** > **5b** > **3a** > **6** > **2b** showed ratios of 2.05–2.6 indicative of potential selectivity. Compounds with ratios of 3–6 are considered moderately selective and those with ratios of 6 or more are taken as selective.[15] Further derivatization of these compounds may lead to more selectivity against various leukemia tumor cell lines.

Of other tumor subpanel cell lines, non-small cell lung cancer EKVX cell line was particularly sensitive to compounds **3a**, **4a**, **4b** and **7**; HOP-62 was sensitive to compound **3b**; and NCI-H522 was sensitive to compound **7** with GI_{50} values less than 10 μM. CNS cancer, SNB-75 cell line was sensitive to compound **3b** with a GI_{50} value less than 10 μM. Melanoma SK-MEL-2 cell line was highly sensitive to compounds **4b** and **7**; as well as SK-MEL-5 to compound **4b** with GI_{50} values less than 1 μM. Renal cancer, RXF 393 cell line was sensitive to compounds **5b** and **7** with GI_{50} values less than 10 μM (Table 2). On the other hand, compound **5a** showed potential selectivity against renal cancer subpanel cell lines with TGI values against 786-C and RXF 393 as well as TGI and LC_{50} values against CAKI-1 of less than 100 μM (Table 3). It showed, however, a full panel MG-MID/subpanel GI_{50} mean-graph ratio for CNS and renal cancer of only 1.28 and 1.29, respectively (Table 1). The same ratio for compound **3b** against CNS cancer reached 1.93.

Regarding the broad spectrum activity, compound **7** exhibited GI_{50} and TGI values less than 100 μM against all subpanel cell lines tested. It also showed cytotoxic potency in 28 of the tested cell lines (Tables 2 and 3). The full panel mean-graph midpoint MG-MID values of GI_{50}, TGI and LC_{50} were 15.1, 41.7 and 83.2 μM, respectively. Compound **4b**

also showed non-selective growth inhibition (GI_{50}) against all cell lines (Tables 1 and 2). It showed, however, TGI values against some but not all cell lines (Table 3).

Structure–activity relationship

Based on full panel (MG-MID) values (Tables 1 and 2), the activity of the tested 2-thiohydantoin analogs could be correlated to the structure variations and modifications.[15] A tentative SAR could be deduced as follows.

(i) Substitution of the Br atom in **1a** and **1b** (MG-MID values of 63.1 and 63.1 μM) by thiosalicylic acid to form the thioether derivatives **2a** and **2b** (95.5 and 74.1 μM) led to a slight decrease in the antitumor potency.

(ii) Cyclization of the thioethers **2a** and **2b** (95.5 and 74.1 μM) to form the planar tricyclic 4H-thieno[2,3-*b*][1]benzothiopyran-4-one members **3a** and **3b** increased the antitumor activity with MG-MID values of 57.1 and 66.1 μM for **3a** and **3b**, respectively.

(iii) Replacement of the *N*-phenyl moiety on the 2-thiohydantoins **1a** and **1b** by a heterocyclic methylene moiety produced more active compounds as in the case of **4a** and **4b** (45.7 and 26.9 μM). The piperidine analog **4b** proved to be more potent and with a broader spectrum than the morpholine derivative **4a**.

(iv) *S*-glucosylation of compounds **1a** and **1b** (63.1 and 63.1 μM) and **4a** (45.7 μM) gave their corresponding derivatives **5a** and **5b** (47.9 and 39.8 μM) and **7** (15.1 μM) proving that the introduction of such sugar moieties contributes to the enhancement of the antitumor activity. *S*-glucosylation of **2b** (74.1 μM), however, gave compound **6** (77.7 μM) without a noticeable change in activity, which could be attributed to the presence of the thiosalicylic moiety. On the other hand, it seemed that the antitumor activity was better with galactose in **5b** (39.8 μM) than glucose in **5a** (47.9 μM).

(v) Introduction of the thiosalicylic acid moiety to **5a** (47.9 μM) produced compound **6** (77.7 μM) with a decrease in potency confirming what we have mentioned earlier in (i) and (ii)

The findings of the present investigation showed that the most potent member of this series is compound **7** (15.1 μM) which is characterized by the presence of 5-thienylmethylene, 3-morpholinomethyl and *S*-glucosyl functions on a hydantoin nucleus. The broad spectrum antitumor activity as well as potential cytotoxic effects of the lead compound **7** will be of interest for future derivatization in the hope of finding more active compounds in nanomolar concentrations or less. Further derivatization of compounds **1a** and **5b** may provide more selective agents against leukemia cell lines.

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