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The S-Methyl-(2-Methoxycarbonylamino-Benzimidazole-5) Thiosulfonate as Potential Anticancer Agents

Lubenets VI * ,Parashchyn ZhD, Vasylyuk SV, Novikov VP

Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Ukraine

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***Corresponding author:** Lubenets VI, Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, Ukraine, Tel: +380973323012; Email: vlubenets@gmail.com

Abstract

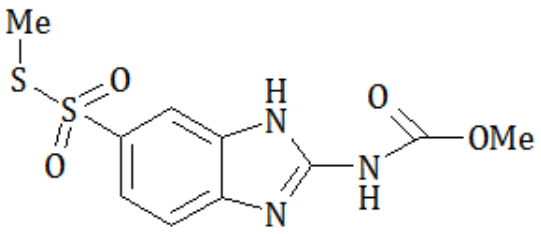
In-vitro anticancer activity of the S-methyl-(2-methoxycarbonylamino-benzimidazole-5) thiosulfonate (NSC NCI code - 713598 - J/1) was tested by the National Cancer Institute and it has revealed the anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines.

Keywords: Thiosulphonates; Anti-cancer activity

Introduction

It is known that sulfur-containing organic compounds, including thiosulfonic acids and their derivatives are potential biologically active compounds with broad spectrum of action based on their ability to participate in nitrogen metabolism, in the synthesis of enzymes, hormones, proteins necessary for normal functioning of body [1]. Given the high synthetic and pharmacological potential of the derivatives of thiosulfonic acids very important is the designing of systems that would contain various combinations of thiosulfonate moiety with heterocyclic systems as this is likely to lead to the emergence of a new or modifications of the existing biological activity.

Taking into consideration the mentioned above, S-methyl-(2-methoxycarbonylamino-benzimidazole-5) thiosulfonate was the object of our researches.



Methods of obtaining the compound and its characteristics are presented in the previous work [2]

Results and Discussion

The S-methyl-(2-methoxycarbonylamino-benzimidazole-5) thiosulfonate (NSC NCI code - 713598 - J/1) was selected by the National Cancer Institute (NCI) within the Developmental Therapeutic Program (www.dtp.nci.nih.gov) for *in-vitro* cell line screening. Anticancer assays were performed according to US NCI protocol, which was described elsewhere [3-6]. Primary anticancer assays of compound at one dose (concentration 10^{-4}M) were performed in the 3-cell line panel consisting of NCI-H460 (Lung), MCF7 (Breast) and SF-268 (CNS) cancer cell lines.

The tested compound showed impressive levels of anticancer activity and it was tested in a five concentrations assay on 60 tumor cell lines over a range of concentrations (10^{-4} - 10^{-8}). The cytotoxic and/or growth inhibitory effects of the reported compound were tested in vitro against the human tumor cell lines derived from nine neoplastic diseases such as leukemia, melanoma, non-small cell lung cancer, breast cancer, colon cancer, ovarian cancer, renal cancer, prostate cancer (Table 1).

Table 1: Total (mean graph) values of the in-depth *in-vitro* screening in 5 concenrations (10^{-4} -10^{-8}M).

Panel	Cell Line	Average Values of the Activity Parameters		
		$log_{10}GI_{50}$	$log_{10}TGI$	$log_{10}LC_{50}$
Leucemia	CCRF-CEM	-5.45	-4.21	> -4.00
	HL-60(TB)	-5.62	-5.09	> -4.00
	K-562	-5.31	> -4.00	> -4.00
	MOLT-4	-5.54	> -4.00	> -4.00
	RPMI-8226	-5.42	> -4.00	> -4.00
	SR	-5.43	-4.20	> -4.00
Non-Small Cell Lung Cancer	A549/ATCC	-5.09	> -4.00	> -4.00
	EKVX	-5.06	-4.20	> -4.00
	HOP-62	-4.68	> -4.00	> -4.00
	HOP-92	-5.20	-4.55	-4.02
	NCl-H226	-5.20	> -4.00	> -4.00
	NCl-H322M	-5.04	> -4.00	> -4.00
	NCl-H460	-5.28	> -4.00	> -4.00
	NCl-H522	-5.36	> -4.00	> -4.00
Colon Cancer	COLO 205	-5.37	> -4.00	> -4.00
	HCC-2998	-4.98	-4.37	> -4.00
	HCT-116	-5.33	-4.61	> -4.00
	HCT-15	-5.41	-4.71	> -4.00
	HT29	-5.48	-4.95	> -4.00
	KM12	-5.26	> -4.00	> -4.00
	SW-620	-5.43	-4.60	> -4.00
CNS Cancer	SF-268	-4.78	> -4.00	> -4.00
	SF-295	-5.11	> -4.00	> -4.00
	SF-539	-5.40	-4.41	> -4.00
	SNB-19	-5.12	> -4.00	> -4.00
	U251	-5.26	-4.52	> -4.00
Melanoma	LOX IMVI	-5.32	-4.66	-4.03
	MALME-3M	-5.01	-4.59	-4.18
	M14	-5.47	-4.74	> -4.00
	SK-MEL-2	-5.14	-4.57	-4.05
	SK-MEL-28	-5.08	-4.60	-4.16
	SK-MEL-5	-5.28	> -4.00	> -4.00
	UACC-257	-4.97	-4.34	> -4.00
	UACC-62	-5.41	-4.65	-4.06
Ovarian Cancer	IGROV1	-5.47	-4.82	-4.22
	OVCAR-3	-5.31	> -4.00	> -4.00
	OVCAR-4	-4.92	-4.07	> -4.00
	OVCAR-5	-4.94	-4.35	> -4.00
	OVCAR-8	-5.29	-4.51	> -4.00
	SK-OV-3	-5.08	-4.37	> -4.00
Renal Cancer	786-0	-5.29	-4.77	-4.36
	A498	-4.79	-4.00	> -4.00
	ACHN	-4.99	-4.62	-4.26
	CAKI-1	-5.31	> -4.00	> -4.00
	RXF393	-5.26	-4.75	-4.35
	SN12C	-4.96	-4.43	> -4.00
	TK-10	-5.09	-4.66	-4.27
Prostate Cancer	PC-3	-5.35	-4.79	-4.33
	DU-145	-5.22	-4.57	> -4.00
Breast Cancer	MCF7	-5.31	-4.57	> -4.00
	NCl/ADR-RES	-5.44	-4.08	> -4.00
	MDA-MB-231/ ATCC	-4.94	-4.40	> -4.00
	HS 578T	-4.69	> -4.00	> -4.00
	MDA-MB-435	-5.57	-4.91	> -4.00
	MDA-N	-5.63	-5.17	-4.40
	BT-549	-5.00	-4.64	-4.29
	T-47D	-5.02	-4.52	-4.03

In this assay three dose-response parameters are obtained:

- growth inhibition of 50% - GI_{50};
- total growth inhibition - TGI;
- LC_{50}.

Whereas the GI_{50} may be viewed as a growth-inhibitory level of effect, the TGI signifies a "total growth inhibition" or cytostatic level of effect. The LC_{50} is the lethal concentration, "net cell killing" or cytotoxity parameter. If tested parameters (log10GI50, log10TGI and log10LC50) specified in negative log units have values -4.00, then these compounds are assigned as active [7,8]. Analyzing the results of a detailed *in-vitro* screening tested S-methyl-(2-methoxycarbonylamino-benzimidazole-5) thiosulfonate (NSC NCI code - 713598 - J/1) showed significant growth inhibition; the average value of $log_{10}GI_{50}$ ranges from -4.00 to -5.63.

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