Novel *N*-(2-mercaptobenzenesulfonyl)guanidine derivatives modified by nitrogene-containing heterocycles – synthesis and antiproliferative activity against human cancer cell lines

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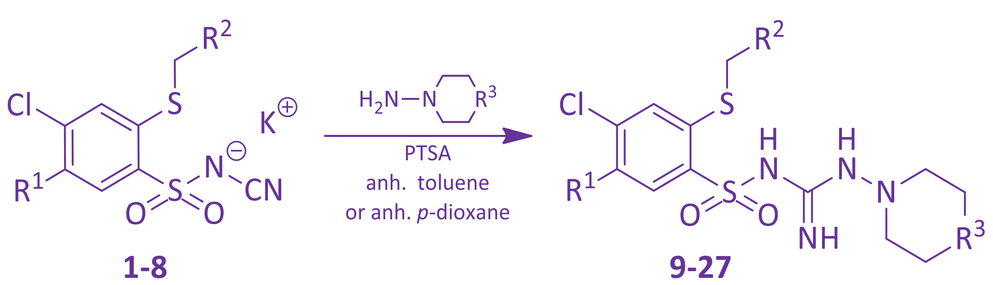
INTRODUCTION:

Benzenesulfonylguanidine derivatives inhibit growth of humar cancer cells belonging to different tumor types [1-3], and can consequently serve as the basis for the development of novel anticancer agents. Continued our research for searching new antiproliferative compounds bearing benzenesulfonylguanidine scaffold, we designed and synthesized the series of derivatives modified by important pharmacophore such as morpholine, 4-methylpiperazine and piperidine.

SYNTHESIS:

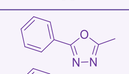
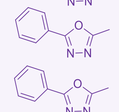
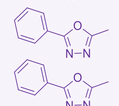
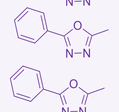
The planned *N*-(2-mercaptobenzenesulfonyl)guanidine (**9**-**27**) have been obtained by reaction of *N*-(2-mercaptobenzenesulfonyl)cyanamide potassium salts (**1**-**8**) with 1-aminopiperidine, 4-aminomorpholine or 1-amino-4-methylpiperazine, using 4-toluenesulfonic acid (PTSA) as a protonating agent. The synthesis were carried out in anhydrous toluene or *p*-dioxane in ACE pressure tube (Sigma-Aldrich). The temperature of oil bath was 110 °C. The reactions lasted for 1-24 h, and, in most cases, the yields were higher than 50 %. The structures of new compounds were confirmed by spectroscopic methods, IR and ^{1}H NMR, as well as elemental analyses.



1-8 **9-27**

Nr	R^1	R^2	R^3
9	Me	Ph	O
11	Me	Ph	CH_2
10	Me	Ph	NMe
12	Me	2-$CF_3C_6H_4$	O
14	Me	2-$CF_3C_6H_4$	CH_2
13	Me	2-$CF_3C_6H_4$	NMe
15	Me	2-FC_6H_4	O

Nr	R^1	R^2	R^3
17	Me	2-FC_6H_4	CH_2
16	Me	2-FC_6H_4	NMe
18	Me	2-ClC_6H_4	O
19	Me	2-ClC_6H_4	CH_2
21	Me	2-ClC_6H_4	NMe
20	Me	2-MeC_6H_4	O
22	Me	2-MeC_6H_4	CH_2

Nr	R^1	R^2	R^3
23		Ph	O
24		Ph	NMe
25		2-ClC_6H_4	CH_2
26		2-ClC_6H_4	NMe
27		2-MeC_6H_4	CH_2

CYTOTOXIC ACTIVITY:

Compounds **9-27** have been studied *in vitro* for their antiproliferative activity against three human cancer cel lines: colon cancer HCT-116, breast cancer MCF-7 and cervical cancer HeLa. Evaluations were made by MTT assays and incubation time was 72 h. The experiment was performed in triplicate and, as a result, IC_{50} values were estimated as the mean ± SD.

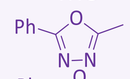
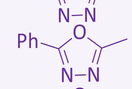
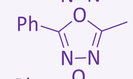
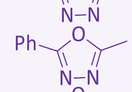
The obtained results indicate that R^3 modification is the most important for cytotoxic effect. It may be statement that *N*-methylpiperazine residue is essential for antiproliferative activity. Derivatives **17**, **20**, **24** and **26** display the best anticancer activity, with IC_{50} values lower than 20 µM against three tested cel lines. An exception is compound **14**, which displays slightly higher activity toward two lines HCT-116 (IC_{50} = 17 µM) and HeLa (IC_{50} = 13 µM), as well as compound **11** with IC_{50} in the range of 20-35 µM against all studied cell lines.

Compounds with piperidine fragment display moderate activity. In this series only **13** and **25** do not display significant cytotoxic effect. Other derivatives **10**, **16**, **19**, **22** and **27** inhibit the growth of at least two cancer cel lines with IC_{50} from 17 to 92 µM. Additionally, compounds with piperidine residue are slightly more selective toward HCT-116, which is quite clear for derivatives **19** and **27**.

From the compounds containing morpholine scaffold only **21** and **23** dsiplay some antiproliferative activity. The derivative **20** shows growth inhibition of three tested cel lines with IC_{50} in the range of 43-92 µM. In turn, the compound **23** display significant selective cytotoxic activity against HCT-116 cells with IC_{50} = 18 µM.

Nr	R^1	R^2	R^3	IC_{50} [µM]		
				HeLa	HCT-116	MCF-7
9	Me	Ph	O	*	*	*
10	Me	Ph	CH_2	*	44 ± 0,5	44 ± 1
11	Me	Ph	NMe	**20 ± 0,5**	**35 ± 2**	**35 ± 2**
12	Me	2-$CF_3C_6H_4$	O	*	*	*
13	Me	2-$CF_3C_6H_4$	CH_2	*	*	*
14	Me	2-$CF_3C_6H_4$	NMe	**13 ± 0,5**	**17 ± 1**	**28 ± 1**
15	Me	2-FC_6H_4	O	*	*	*
16	Me	2-FC_6H_4	CH_2	45 ± 1	34 ± 2	42 ± 2
17	Me	2-FC_6H_4	NMe	**15 ± 0,5**	**14 ± 1**	**15 ± 1**
18	Me	2-ClC_6H_4	O	*	*	*
19	Me	2-ClC_6H_4	CH_2	65 ± 2	28 ± 1	92 ± 1

* $IC_{50} \geq 100$ µM

Nr	R^1	R^2	R^3	IC_{50} [µM]		
				HeLa	HCT-116	MCF-7
20	Me	2-ClC_6H_4	NMe	**16 ± 1**	**13 ± 0,5**	**17 ± 1**
21	Me	2-MeC_6H_4	O	68 ± 3	43 ± 1	92 ± 5
22	Me	2-MeC_6H_4	CH_2	44 ± 1	29 ± 1	*
23		Ph	O	*	**18 ± 1**	*
24		Ph	NMe	**16 ± 1**	**15 ± 0,3**	**17 ± 1**
25		2-ClC_6H_4	CH_2	*	*	*
26		2-ClC_6H_4	NMe	**16 ± 1**	**16 ± 0,5**	**16 ± 1**
27		2-MeC_6H_4	CH_2	49 ± 1	**17 ± 1**	43 ± 1
Cisplatin				2,2 ± 0,1	3,8 ± 0,2	3,0 ± 0,1

* $IC_{50} \geq 100$ µM

REFERENCES:

[1] Żołnowska B., Sławiński J., Pogorzelska A. et al. *Eur J Med Chem.* **2014**; 71; 135−147. [2] Brożewicz K, Sławiński J. *Eur J Med Chem.* **2012**; 55; 384−394.
[3] Sławiński J, Bednarski P, Reszka P. *Polish J Chem.* **2004**; 78; 369−379.

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