New *N*-benzenesulfonylguanidine derivatives and their selective growth inhibition of human breast cancer cell line MCF-7 and colon carcinoma HCT-116

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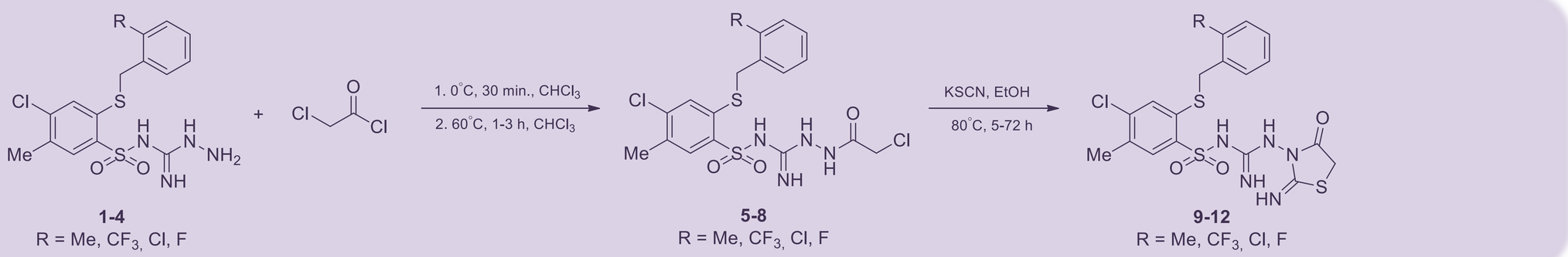
INTRODUCTION:

Benzenesulfonylguanidine derivatives have been shown as potent cytotoxic agents against different types of human cancer cells [1-3]. This important pharmacophore is widely studied in our research team as a basic scaffold for searching new anticancer agents. Here, we described the series of derivatives modified by (2-chloroacetyl)amino and 2-imino-4-oxothiazolidine-3-yl groups.

SYNTHESIS:

The designed derivatives were obtained by a two-step synthesis as was shown at the scheme below. The starting substrates were the appropriate 1-(2-alkylthio-4-chloro-5-methyl)benzenesulfonyl)-3-aminoguanidines **1-4** which were transformed into 1-(2-alkylthio-4-chloro-5-methylbenzenesulfonyl)-3-[(2-chloroacetyl)amino]guanidines **5-8** by a reaction with chloroacetyl chloride. In the next step, the derivatives **5-8** were reacted with potassium thiocyanate yielding 1-(2-alkylthio-4-chloro-5-methylbenzenesulfonyl)-3-(2-imino-4-oxothiazolidine-3-yl)guanidines **9-12**. The compounds **5-8** were obtained with good yields above 79%, while derivatives **9-12** with slightly worse yields about 14-49% after purification. The structures of the synthesized compounds **5-12** were confirmed by IR, ^{1}H NMR, and elemental analyses.



1-4
R = Me, CF_3, Cl, F

5-8
R = Me, CF_3, Cl, F

9-12
R = Me, CF_3, Cl, F

CYTOTOXIC ACTIVITY:

The synthesized derivatives **5-12** were evaluated *in vitro* by MTT assay for their activity against three human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7, and cervical cancer HeLa. The activity against non-cancerous human epidermal keratinocyte line HaCaT was also examined. The data indicate that compounds **5-8** inhibit the growth of cancer cells stronger than derivatives **9-12**. The selective cytotoxic effect against HCT-116 cells was found for benzenesulfonylguanidine **6** containing 2-(trifluoromethyl)benzylthio group at position 2 of benzenesulfonyl scaffold. The IC_{50} value was 13 µM, while IC_{50} for HaCaT cells was 48 µM. Good selectivity was also observed for compound **7**, with 2-chloromethylbenzylthio substituent, against HCT-116 and MCF-7 cells (IC_{50} = 12 and 19 µM, respectively for HCT-116 and MCF-7 cells, IC_{50} = 47 µM for HaCaT cells). Among compounds **9-12**, only compound **9** showed moderate but selective cytotoxicity against MCF-7 cells, with IC_{50} = 18 µM compared with IC_{50} = 54 µM for HaCaT cells.

Compd	R	IC_{50} [µM]			
		HeLa	HCT-116	MCF-7	HaCaT
5	Me	32 ± 1	26 ± 1	25 ± 1	49 ± 3
6	CF_3	30 ± 1	**13 ± 0.4**	25 ± 1	48 ± 3
7	Cl	34 ± 2	**12 ± 0.4**	**19 ± 0.7**	47 ± 3
8	F	73 ± 3	60 ± 3	43 ± 2	92 ± 5
9	Me	37 ± 2	35 ± 1	**18 ± 0.7**	54 ± 3
10	CF_3	54 ± 3	64 ± 4	45 ± 2	101 ± 6
11	Cl	82 ± 4	99 ± 6	51 ± 3	145 ± 8
12	F	97 ± 6	118 ± 6	66 ± 42	Not tested

REFERENCES:

[1] Żołnowska B., Sławiński J., Pogorzelska A. et al. *Eur J Med.. Chem.* **2014**; 71; 135−147. **[2]** Pogorzelska A., Sławiński J., Kawiak A. et al. *Eur. J. Med. Chem.* **2018**; 155; 670–680. **[3]** Sławiński J., Bednarski P., Reszka P. *Polish J Chem.* **2004**; 78; 369−379.