Synthesis and anticancer activity of 2-(2-arylmethylthio-4-chloro-5-methylbenzenesulfonyl)-1-phenylguanidines

Beata Żołnowska [a], Jarosław Sławiński [a], Anna Kawiak [b]

[a] Department of Organic Chemistry, Faculty of Pharmacy, Medical University of Gdansk

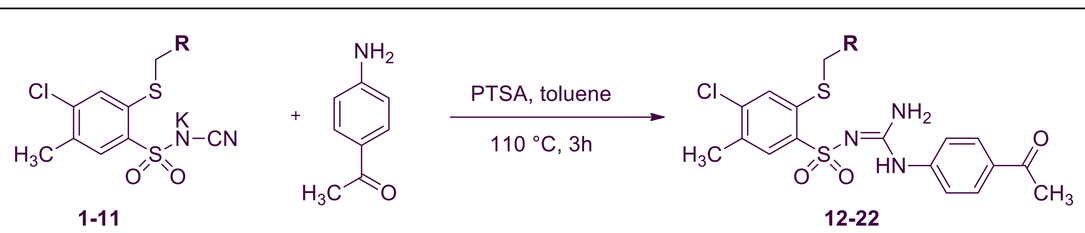
[b] Department of Biotechnology, Intercollegiate Faculty of Biotechnology, University of Gdansk - Medical University of Gdansk

Introduction

Sulfonamides are a classic group of chemotherapeutic drugs with a broad spectrum of pharmacological action includind anticancer activity [1-6]. Cinnamic acid and its natural analogues have been used in the treatment of cancer for over centuries [7]. Natural products containing the cinnamon group attract a lot of attention due to their broad spectrum of biological activity and low toxicity. Thus designing of molecular hybrids, containing in their structure pharmacophore fragments of cinnamic acid and sulfonamide, may lead to compounds with increased biological activity as a result of synergistic effect of both fragments.

Synthesis

The new original compounds **12-30** were molecular hybrids containing the pharmacophore core of 4-chloro-2-mercapto-5-methylbenzenesulfonamide and 4-acetylphenyl moiety or chalcone fragment. Derivatives **12-22** were synthesized by reacting the corresponding monopotassium *N*-(benzenesulfonyl)cyanamide salts [8-13] with 4-aminoacetophenone in the presence of *p*-toluenesulfonic acid (PTSA) and anhydrous toluene (*Scheme 1*). The reaction mixture was heated for 3 h at 110 °C. In order to obtain the second series of compounds **23-30**, aldol condensation reaction has been applied. Compounds **12-19** were treated with benzaldehyde in the presence of NaOH in methanol for 24 h at 65 °C (*Scheme 2*). The structure of the new derivatives was confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectroscopic methods and elemental analysis (C, H, N).



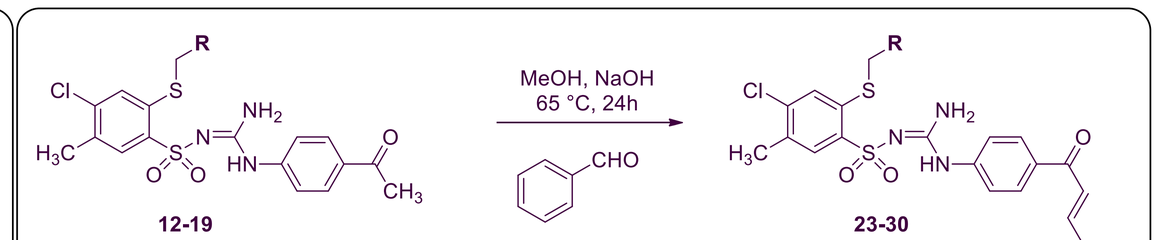
1-11

Comp.	R
1, 12	Ph
2, 13	3-CF_3Ph
3, 14	4-CF_3Ph
4, 15	3-FPh
5, 16	4-FPh

12-22

Comp.	R
6, 17	3-ClPh
7, 18	4-ClPh
8, 19	3-NO_2Ph
9, 20	4-NO_2Ph
10, 21	1-naphthyl
11, 22	2-naphthyl

Scheme 1



12-19

Comp.	R
12, 23	Ph
13, 24	3-CF_3Ph
14, 25	4-CF_3Ph
15, 26	3-FPh

23-30

Comp.	R
16, 27	4-FPh
17, 28	3-ClPh
18, 29	4-ClPh
19, 30	3-NO_2Ph

Scheme 2

Cytotoxic activity against MCF-7, HCT-116, HeLa cell lines

The synthesized compounds **12-30** have been tested for their anticancer activity on three human cancer cell lines: HCT-116 (colon cancer), HeLa (cervical cancer) and MCF-7 (breast cancer). The selectivity of the action of tested compounds was assessed using the HaCaT non-cancer cell line. Analyzes were performed using the MTT assay and results were expressed as IC_{50} values (the concentration required to inhibit the viability of 50% of the tumor cell population) (*Table 1 and 2*).

Table 1

Compound	IC_{50} (μM)				
	R	MCF-7	HeLa	HCT-16	HaCaT
12	Ph	22±0.2	40±2	25±1	56±2
13	3-CF_3Ph	12±0.1	37±1	23±0.5	445±22
14	4-CF_3Ph	38±1	53±1	30±0.6	78±4
15	3-FPh	23±0.5	110±1	72±2	230±12
16	4-FPh	18±1	58±2	26±1	205±11
17	3-ClPh	90±3	28±1	27±1	120±4
18	4-ClPh	182±5	78±5	43±2	250±13
19	**3-NO_2Ph**	**21±1**	**21±1**	**17±1**	**55±3**
20	**4-NO_2Ph**	**13±0.6**	**15±1**	**14±0.7**	**32±2**
21	**1-naphthyl**	**16±0.8**	**15±1**	**10±0.2**	**33±2**
22	2-naphthyl	79±5	38±2	19±1	145±8

Table 2

Compound	IC_{50} (μM)				
	R	MCF-7	HeLa	HCT-16	HaCaT
23	Ph	**5.5±0.2**	**15±0.6**	**5±0.2**	17±1
24	3-CF_3Ph	**4.7±0.2**	**8.5±0.5**	**6±0.2**	23±1
25	4-CF_3Ph	33±1	78±4	58±3	115±6
26	3-FPh	**4.8±0.2**	**5±0.1**	**5.5±0.3**	12±0.6
27	4-FPh	**4.8±0.1**	17±1	14±0.5	27±1
28	3-ClPh	33±2	38±2	24±1	67±2
29	4-ClPh	**4.8±0.1**	16±0.5	15±1	25±1
30	3-NO_2Ph	31±1	28±1	100±3	120±3

Among the tested compounds, derivatives **19**, **20** and **21** deserve special attention, as they showed the highest potency against all tumor cell lines (IC_{50}: 10-21 μM). The high activity of derivatives **19** and **20** was related to the presence of a nitro group in the substituent R, with preferred location of this substituent in *para* position (**20**, IC_{50}: 13-15 μM).

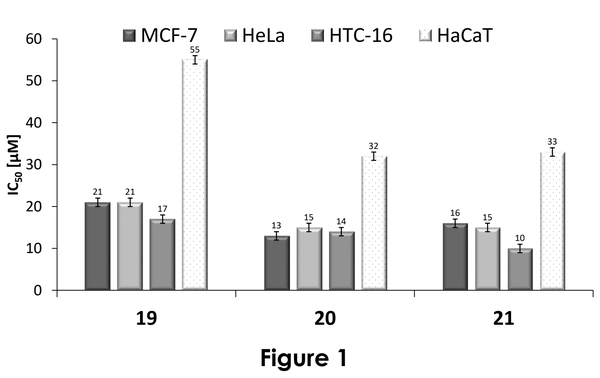


Figure 1

Results obtained from MTT tests against normal HaCaT cells showed lower cytotoxicity compared to neoplastic cells (*Figure 1*), which is a property highly desirable for potential anticancer drugs.

The obtained results showed that derivatives **23-30** exhibited the strongest cytotoxic activity against the MCF-7 cell line, especially compounds **23, 24, 26, 27, 29** with IC_{50} values <10 μM. Moreover, the most active derivatives that inhibit the viability of HeLa cells were **23**, **24** and **26** (IC_{50}: 15; 8.5 and 5 μM), the same compounds also showed high efficacy against the HCT-116 cell line (IC_{50}: 5; 6 and 5.5 μM).

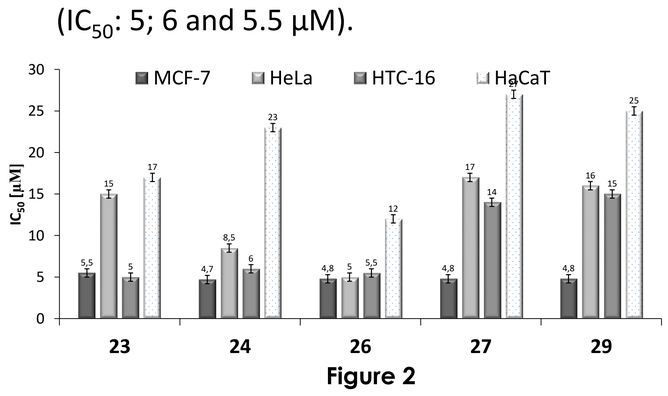


Figure 2

Taking into account the derivatives with the most promising anticancer activity, it was shown that compounds **23, 24, 26, 27, 29** were selective for neoplastic cells rather than normal cells (*Figure 2*).

Literature: **[1]** Drew J. Science 287 (2000) 1960–1964. **[2]** Kaur IP. et. al. Int. J. Pharm. 248 (2002) 1–14. **[3]** Supuran CT. et. al. Eur. J. Med. Chem. 31 (1996) 843–846. **[4]** Wouters J. et. al. Eur. J. Med. Chem. 35 (2000) 923–929. **[5]** Noble S. et. al. Drugs 60 (2000) 1383–1410. **[6]** Scozzafava A. et. al. Curr. Med. Chem. 10 (2003) 925–953. **[7]** De P, et al. Curr Med Chem. 2011;18(11):1672-703. **[8]** J. Sławiński, Polish J. Chem. 2001, 75, 1309–1316. **[9]** J. Sławiński, et al., Monatsh. Chem. 2012, 143, 1705–1718. **[10]** A. Pogorzelska, et al., Eur. J. Med. Chem., 2017, 138, 357–370. **[11]** J. Sławiński, et al., Molecules, 2014, 19, 13704–13723. **[12]** J. Sławiński, et al., Monatsh. Chem. 2012, 143, 1705–1718. **[13]** B. Żołnowska, et al., Molecules 2015, 20, 19101–19129.