Synthesis of new *N*-substituted *N*'-(2-methylthio-4-chloro-5-methylbenzenesulfonyl)guanidines with anticancer activity

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Introduction

Cancer is a disease that is spread widely all over the world and requires the development of new anticancer drugs. Curing cancer is a complicated process as the drugs used target human cells and cells that have undergone genetic changes and are dividing at a quick and uncontrolled rate. Thus, there is constant need to develop alternative or synergistic anticancer agents with minimal side effects.

Sulfonamides constitute class of bioactive compounds with wide range of action including the most known diuretic [1], hypoglycemic [2] or anticancer [3] activity. Some of interesting sulfonamides such as indisulam, navitoclax, pazopanib, dabrafenib have been investigated as anticancer drugs in clinical trials.

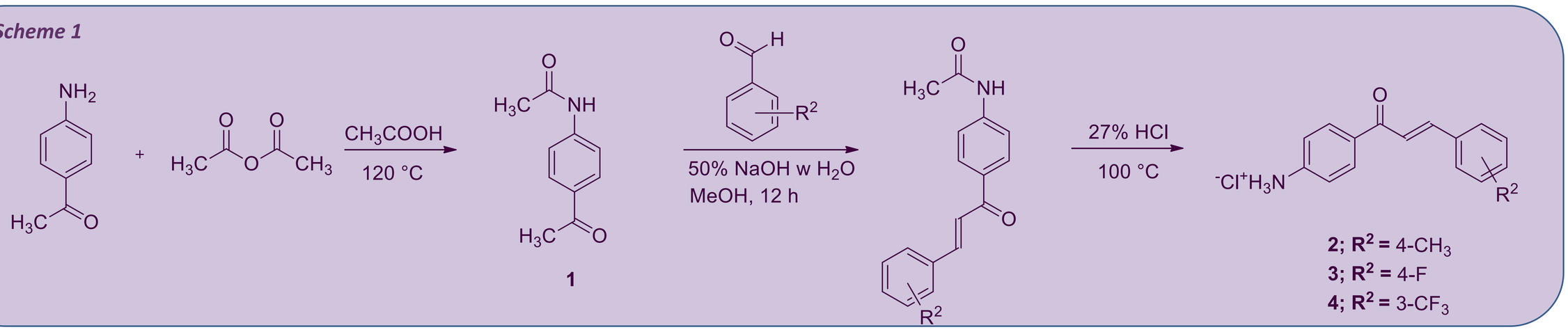
Chalcones are one of the most common naturally occurring flavonoid precursors in plants. These compounds are alpha, beta unsaturated ketones that have two aromatic rings with different substituents in their molecule. Chalcones are subject to research in many directions as they exhibit a number of worthwhile activities. They have been shown to have anti-inflammatory, antibacterial, anticancer and antidiabetic properties [4].

One of the important strategy in the search for chemotherapeutics is the approach based on combining in one molecule fragments of known drugs, leading structures or "hit" structures. The conjugation of two pharmacophores into a molecular hybrid aims at achieving a synergistic effect with increased efficacy compared to the starting compounds [5].

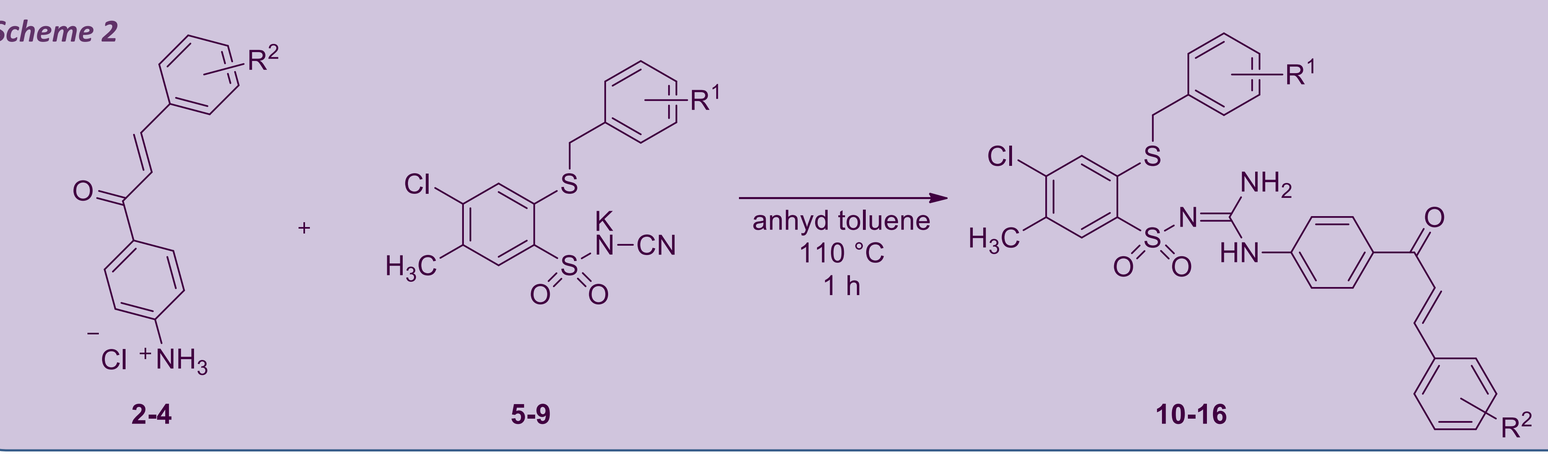
Synthesis

The aim of the work was to synthesize of new *N*-substituted *N*'-(2-methylthio-4-chloro-5-methylbenzenesulfonyl)guanidines with potential anticancer activity, designed as molecular hybrids containing fragments of chalcone and 4-chloro-5-methyl-2-methylthiobenzenesulfonamide. The benzenesulfonamide fragment in position 2 was modified with substituents (R^1) with previously known influence on antitumor activity. The chalcone modifications included the introduction of R^2 substituents containing fluorine and methyl. The methods of synthesis were shown in ***Schemes 1*** and ***2***. The structures of the compounds were confirmed by elemental analysis, spectroscopy (IR, ^{1}H NMR, ^{13}C NMR), X-Ray and mass spectrometry.

Scheme 1



Scheme 2



Comp.	R^1	R^2
2, 5, 10	3-CF_3	4-CH_3
3, 5, 11	3-CF_3	4-F
4, 5, 12	3-CF_3	4-CF_3
4, 6, 13	H	4-CF_3
4, 7, 14	4-Cl	4-CF_3
4, 8, 15	4-F	4-CF_3
4, 9, 16	3-F	4-CF_3

Cytotoxic activity against cancer and non-cancer cell lines

The synthesized compounds **10-16** 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) (Table 1). 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

Compound	R^1	R^2	MCF-7	HeLa	HCT-116	HaCaT
	IC_{50} [μM]					
10	3-CF_3	4-CH_3	**5±0,1**	17±0,7	**5±0,2**	29±1
11	3-CF_3	4-F	**4±0,1**	15±0,6	**2,5±0,1**	22±1
12	3-CF_3	4-CF_3	**4,5±0,2**	15±0,7	**3,5±0,2**	26±1
13	H	4-CF_3	**4,5±0,2**	5±0,2	**4,5±0,2**	17±1
14	4-Cl	4-CF_3	**5±0,1**	15±0,6	**3±0,1**	27±1
15	4-F	4-CF_3	**5±0,1**	11±0,5	**4±0,1**	23±1
16	3-F	4-CF_3	**4,5±0,2**	9±0,4	**4±0,1**	18±0,6

Conclusions

It has been shown that implemented strategy of molecular hybridization gave succesfull result. All sulfonamides were highly active against breast and colon cancer cell lines (IC_{50}: 2.5–5 μM). Additionally, in tests carried out on non-cancer human keratinocyte cell line (HaCaT), it was proved that the tested compounds showed higher cytotoxicity against cancer cells compared to healthy cells (IC_{50}: 17–29 μM). Cytotoxic activity in HeLa cell line ranged from values of IC_{50} from 5 to 17 μM.

Literature: **[1]** Ghiadoni, l. et al. J. Am. Soc. Nephrol. 2006, 17, 26-29. **[2]** Osadebe, P. O. et al. (2014). J. Adv. Med. 2014, 5, 134-159. **[3]** Supuran C.T. Metabolites 2017, 7, 48. **[4]** Salehi B. et al. Front. Pharmacol. 2021, 11, 592654. **[5]** Fortin S, et al. Expert Opin. Drug. Discov. 2013, 8, 1029–1047.