Synthesis of *N*-(4-acryloylphenyl)-2,4-dichloro-5-sulfamoylbenzamides with anticancer activity

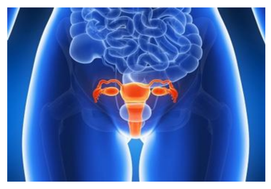
Beata Żołnowska (zolnowska@gumed.edu.pl)*[1], Jarosław Sławiński (jaroslaw@gumed.edu.pl)[2],
Anna Kawiak (anna.kawiak@biotech.ug.edu.pl)[3]
[1] Department of Organic Chemistry, Faculty of Pharmacy, Medical University of Gdańsk, Gdańsk, Poland
[2] Department of Organic Chemistry, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland
[3] Department of Biotechnology, Intercollegiate Faculty of Biotechnology,
University of Gdańsk-Medical University of Gdańsk, Gdańsk, Poland

INTRODUCTION

- Breast, colon and cervical cancer are the most common cancers in women worldwide [1].

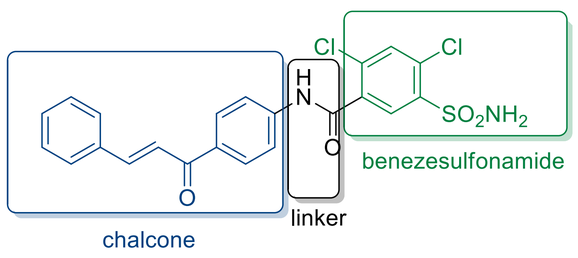

2 261 419 (24,5%)*


865 630 (9,4%)*


604 127 (6,5%)*

*cases in women in 2020 along with the percentage of a given type of cancer

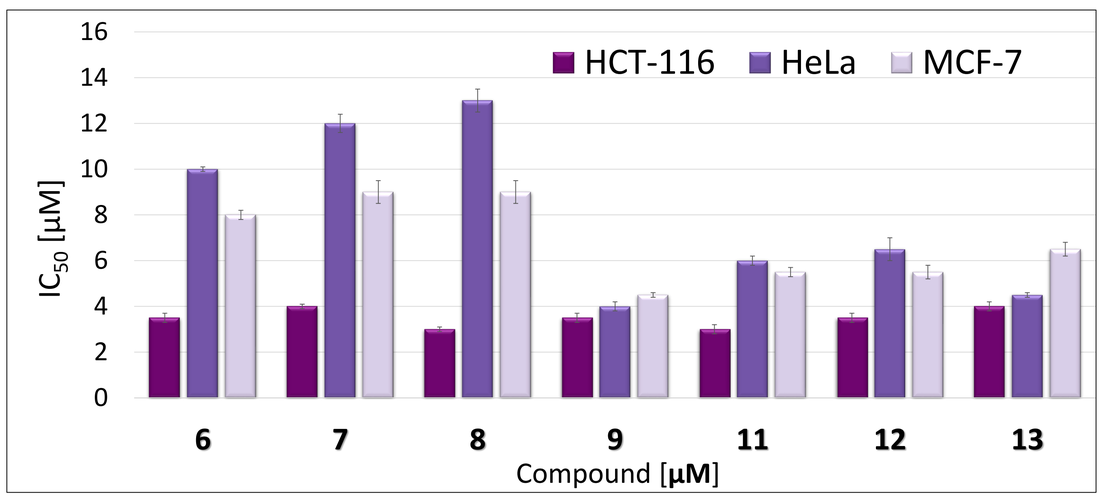
- **Hybrid compounds** - a combination of various components, fragments of known drugs or leading structures into a single molecule [2].



- Synthesis of molecular hybrids of benzenesulfonamide and chalcone to obtain a potential cytotoxic effect against MCF-7, HCT-116 and HeLa cancer cell lines.

RESULTS

- MTT test was performed on cancer cell lines: HCT-116 (colon cancer), HeLa (cervical cancer) and MCF-7 (breast cancer)
- Results were expressed as IC_{50} values (concentration required to inhibit the viability of 50% of the tumor cell population).

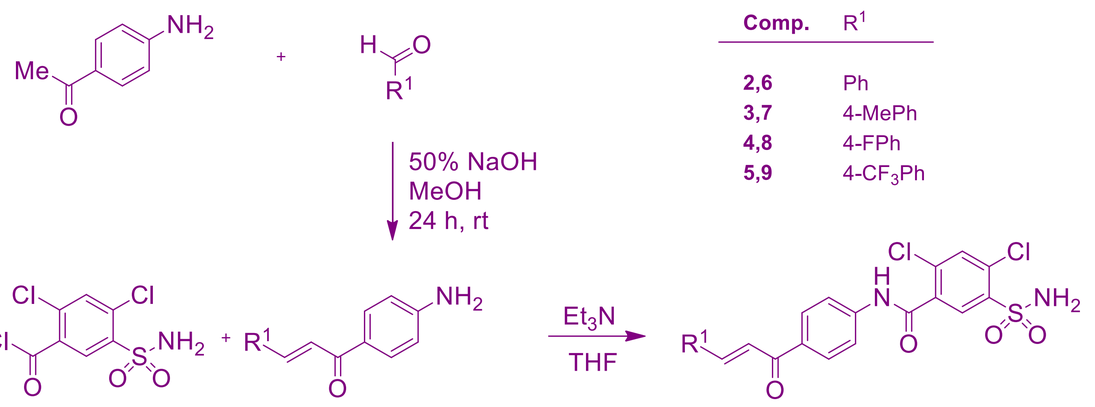


- **HCT-116 cell line** - the highest sensitivity to the compounds - **average IC_{50} = 3.5 μM**, with a minimum and maximum IC_{50} value of 3 μM and 4 μM, respectively.
- **The highest cytotoxic activity towards the HCT-116 cell line** - compounds **8** and **11 (IC_{50} = 3 μM)** containing a fluorine or chlorine atom in their structure in the phenyl substituent of the chalcone system.
- High activity of compounds **6-9, 11-13** towards the MCF-7 cell line IC_{50} = 4.5-9 μM and the HeLa cell line IC_{50} = 4-13 μM.

Literature: **[1]** Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [8 IX 2023]; **[2]** Fortin S, et al. Expert Opin. Drug. Discov. 2013, 8, 1029–1047.; **[3]** Antoine Daina et al. Nucleic Acids Res 2019, 357–364.

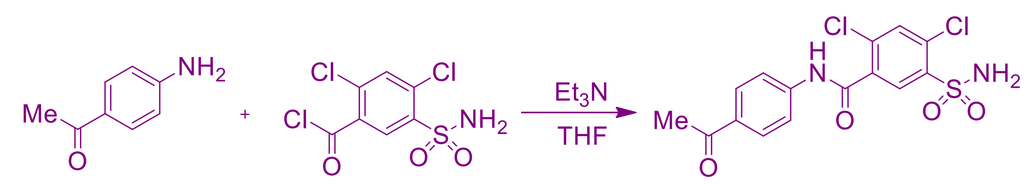
SYNTHESIS

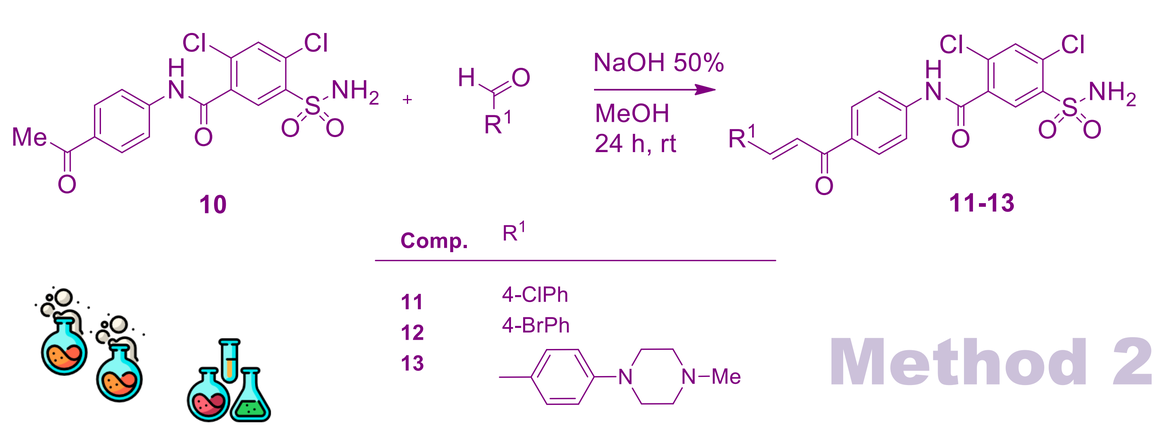
- Two methods for the synthesis of *N*-(4-acryloylphenyl)-2,4-dichloro-5-sulfamoylbenzamide derivatives **6-9** and **11-13**



Comp.	R^1
2,6	Ph
3,7	4-MePh
4,8	4-FPh
5,9	4-CF_3Ph

Method 1





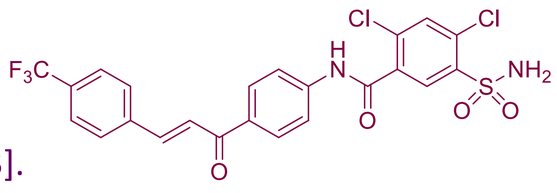
Comp.	R^1
11	4-ClPh
12	4-BrPh
13	

Method 2

CONCLUSINS AND PROSPECTIVES

- The proposed strategy of combining chalcone and benzenesulfonamide fragments resulted in a series of seven structurally modified molecules with anticancer activity.
- The obtained compounds **6-9, 11-13** showed high activity against three tested cancer cell lines, and their **IC_{50} values range from 3 μM to 13 μM**.
- The presence of the substituent R^1 = 4-CF_3Ph has a beneficial effect on the highest cytotoxic activity towards all three tested cell lines, **compound 9** (average IC_{50} = 4 μM).

Compound 9 was predicted for potential molecular targets using the online tool **SwissTargetPrediction** [3].



60% of predicted molecular targets are kinases, including:
Vascular endothelial growth factor receptor 2 (KDR)
Serine/threonine-protein kinase B-raf (BRAF)
Fibroblast growth factor receptor 3 (FGFR3)

Compound 9 was selected for further research focusing on the search for its mechanism of action.