5-Arylideneimidazolones as a potential solution for multi-drug resistance in cancer cells

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Introduction

One of a serious threats in treatment of cancer diseases is multi-drug resistance (MDR). MDR of cancer cells is a significant problem of chemotherapy failure and is growing rapidly. Thus, searching for compounds able to block at least one mechanism of cancer MDR is an important goal of medicinal chemistry [1]. Such activity was described previously for imidazolones *e.g.* 5-arylideneimidazolone presented in Fig. 1 [2].

Aim

The aim of our research is searching for compounds able to inhibit MDR in cancer cells in the group of 5-arylideneimidazolones.

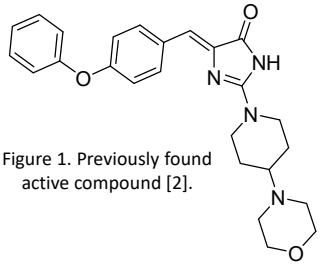


Figure 1. Previously found active compound [2].

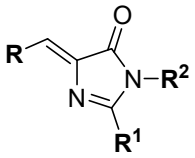
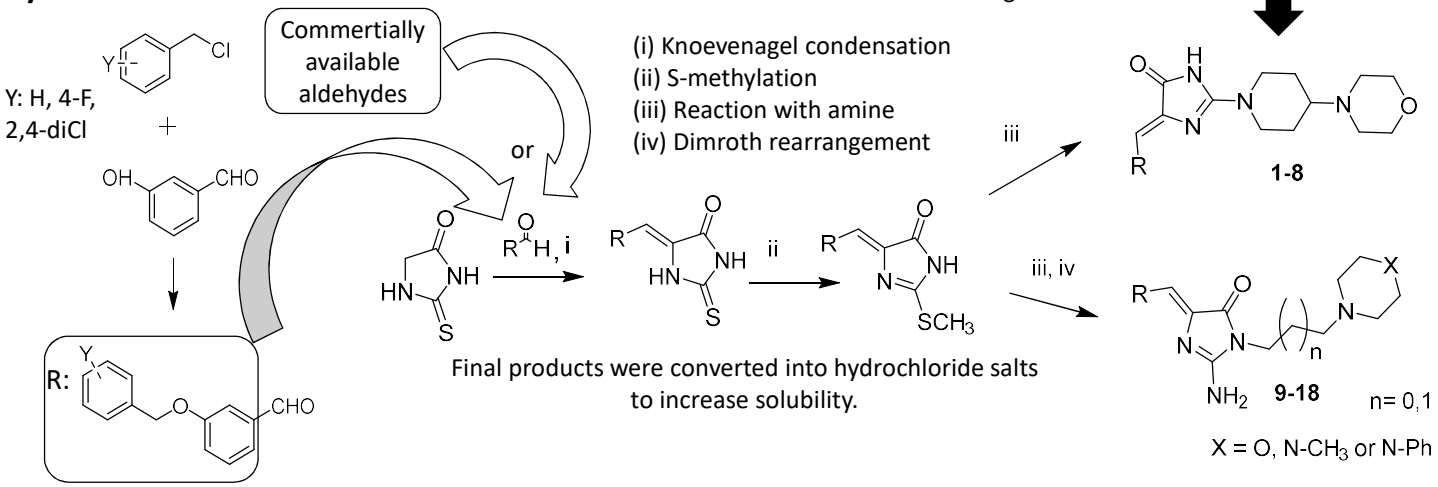


Figure 2. General structure.

Synthesis



Final products were converted into hydrochloride salts to increase solubility.

Accumulation assay

Final compounds were tested in rhodamine 123 accumulation assay using both, sensitive and Pgp overexpressing MDR, mouse T-lymphoma cell lines. Results for the most active compounds in MDR cancer cells in tested concentrations are presented in Table 1.

Table 1. Active compounds **6, 8, 16, 18** in MDR cancer cells.

Compound	FAR	
	2 μM concentration	20 μM concentration
6	**15.147**	**28.269**
8	1.952	**5.976**
16	2.224	**11.331**
18	**15.807**	**30.860**
Tariquidar	-	**34.809**

Cytotoxicity toward cancer cells

Table 2. The most cytotoxic compounds from this group.

Compounds	PAR (IC_{50} μM)		MDR (IC_{50} μM)	
	Mean	SD	Mean	SD
9	>100	-	**2,15**	0,03
10	>100	-	**2,37**	0,11

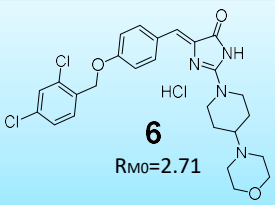
Lipophilicity

RP-TLC method

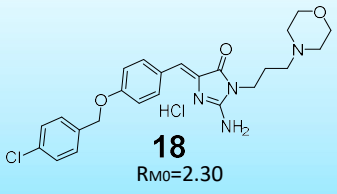
All tested compounds proved "drug-like" lipophilicity (R_{M0} = 1.48-3.35)

Conclusions

Two of tested 5-arylideneimidazolones (**6** and **18**):
- ✓ displayed strong activity in MDR cancer cells
- ✓ did not show cytotoxicity,
- ✓ proved „drug-like" lipophilicity.



6
R_{M0}=2.71



18
R_{M0}=2.30

Bibliography

[1] Szakács G. et al. *Nature Reviews Drug Discovery* **5** (2006) 219.
[2] Kaczor A. et al. *Molecules* **25** (2020) 2258.

Acknowlegments

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