OPTIMIZATION OF 4-CHLORO-5-(5-(2-ARYLVINYL))- 1,3,4-OXADIAZOL-2-YL)BENZENESULFONAMIDE STRUCTURE TOWARDS ANTICANCER ACTIVITY

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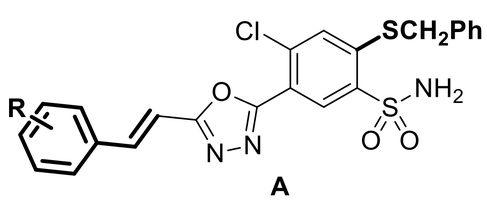
Introduction

In our previous research on the antitumor activity of 2-benzylthio-4-chloro-5-(1,3,4-oxadiazol-2-yl)benzenesulfonamide derivatives it was found that derivatives of type **A** having a styryl substituent in the position 5 of the oxadiazole ring demonstate significant cytostatic activity [1].

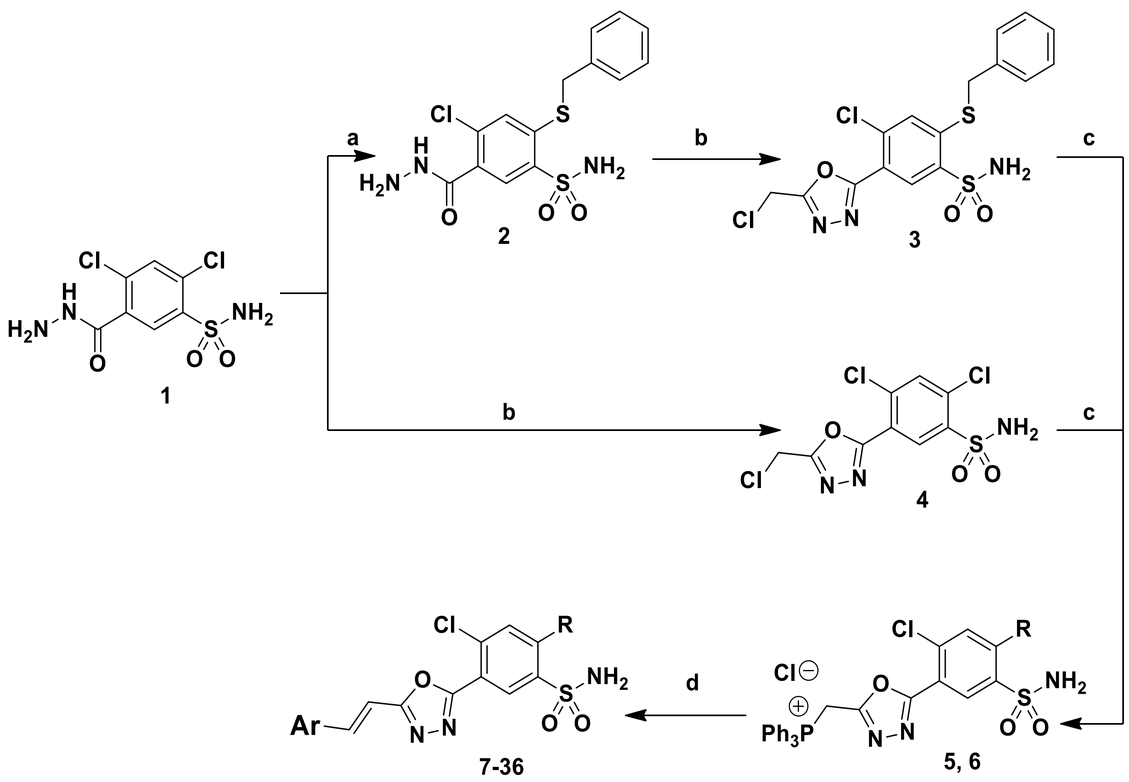


A

IC_{50} MCF7 11-29 μM
HeLa 12-40 μM
HCT-116 12-32 μM

In the present study, in order to optimize the lead structure **A**, a number of new 4-chloro-5-(5-vinyl-1,3,4-oxadiazol-2-yl)benzenesulfonamide derivatives **7**-**36** containing various aromatic and heteroaromatic rings at the vinyl position (Ar) were synthesized. In addition, for each Ar variant its analog devoid of thiobenzyl moiety (R = SBn or Cl) was obteined.

Chemistry



Reaction conditions:

a) K_2CO_3 (2.1 eq.), TBAI (0.01 eq.), phenylmethanethiol (1.0 eq.), $MeCN/H_2O$, r.t., 24 h.

b) 2-chloro-1,1,1-trimethoxyethane (1.5 eq.), 1,4-dioxan, reflux, 18 h;

c) triphenylophsphine (1.15 eq.), MeCN, reflux 18 h;

d) ArCHO (1.2 eq.), *N*,*N*-diisopropylamine (2 eq.), CH_2Cl_2, r.t. 24 h.

R = Cl, SBn

Ar = Ph, 3-ClPh, 4-ClPh, 2,6-diClPh, 4-BrPh, 4-HOPh, 4-CNPh, 4-CF_3Ph, Pyridin-4-yl, Pyridin-3-yl, Pyridin-2-yl, Thiophen-2-yl, 5-Nitrothiophen-2-yl, Furan-2-yl, 5-Nitrofuran-2-yl, Pyrrol-2-yl

Biological studies

Compounds **7-36** were submitted to test towards their effect on growth of human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7, cervical cancer HeLa and noncancerous keratinocyte cell line HaCaT. Cell viability was measured using MTT assay after 72 h of incubation with tested compound in concentration 1 – 100 μM.

Compd.	Ar	R	IC_{50} [μM]			
			HCT-116	MCF-7	HeLa	HaCaT
7	Ph	Cl	86	165	455	
8		SCH_2Ph	**18**	**16**	**14**	20
9	3-Cl-Ph	Cl	24	150	19	98
10		SCH_2Ph	**12**	**11**	**16**	**16**
11	4-Cl-Ph	Cl	22	28	41	
12		SCH_2Ph	**12**	**11**	40	
13	2,6-diCl-Ph	Cl	16	92	25	95
14		SCH_2Ph	32	29	**12**	160
15	4-Br-Ph	Cl	34	41	34	55
16		SCH_2Ph	**15**	**13**	29	31
17	4-OH-Ph	Cl	49	73	99	
18		SCH_2Ph	18	59	18	26
19	4-CN-Ph	Cl	**14**	**10**	117	
20		SCH_2Ph	**10**	**9**	**12**	**20**
21	4-CF_3-Ph	Cl	18	75	90	
22		SCH_2Ph	**15**	30	33	33
23	Pyridin-4-yl	Cl	255	640	740	
24		SCH_2Ph	31	225	135	150
25	Pyridin-3-yl	Cl	220	760	570	
26		SCH_2Ph	85	350	135	
27	Pyridin-2-yl	Cl	117	110	170	
28		SCH_2Ph	25	115	130	
29	Thiophen-2-yl	Cl	108	175	245	
30		SCH_2Ph	32	66	87	
31	5-Nitrothiophen-2-yl	Cl	**0.5**	**4**	**4.5**	
32		SCH_2Ph	17	55	58	57
33	Furan-2-yl	Cl	33	170	210	
34		SCH_2Ph	28	62	85	
35	5-Nitrofuran-2-yl	SCH_2Ph	**4**	150	69	
36	Pyrrol-2-yl	Cl	39	40	73	
Cisplatin			3.8	3	2.2	

Conclusions

- The highest overall activity demonstrate compound **31** with 5-nitrothiophene Ar substituent and devoid of thiobenzyl group.
- Compounds with thiobenzyl moiety in position 2 of benzenesulfonamide scaffold are generally more active than then their 2-Cl analogues.
- Activity of compounds build on the 2,4,-dichlorobenzenesulfonamide scaffold depends much more on the type of aryl substituent.
- Most susceptible to tested compound is HCT-116 cell line.
- Very god selectivity index between (HaCat and cancer cell line) is observed for cervical cancer HeLa – for compounds **9** (x5) and **14** (x13), and for colon cancer HCT-116 for compounds **13** (x6), **14** (x5) and **24** (x5).
- Introduction of pyridine ring (compd. **23**-**28**) causes substantial loss of activity.

Literature: [1] J. Sławiński, K. Szafrański, A. Pogorzelska, B. Żołnowska, A. Kawiak, K. Macur, M. Belka, T. Bączek, Novel 2-benzylthio-5-(1,3,4-oxadiazol-2-yl)benzenesulfonamides with anticancer activity: Synthesis, QSAR study, and metabolic stability, *Eur. J. Med. Chem*. 132 (2017). doi:10.1016/j.ejmech.2017.03.039.

5th International Electronic Conference on Medicinal Chemistry
1-30 November 2019
sponsors: MDPI pharmaceuticals