Synthesis of Novel *N*-{[4-(1,2,3-Triazol)pyridin-3-yl]sulfonyl}urea Derivatives With Potential Anticancer Activity

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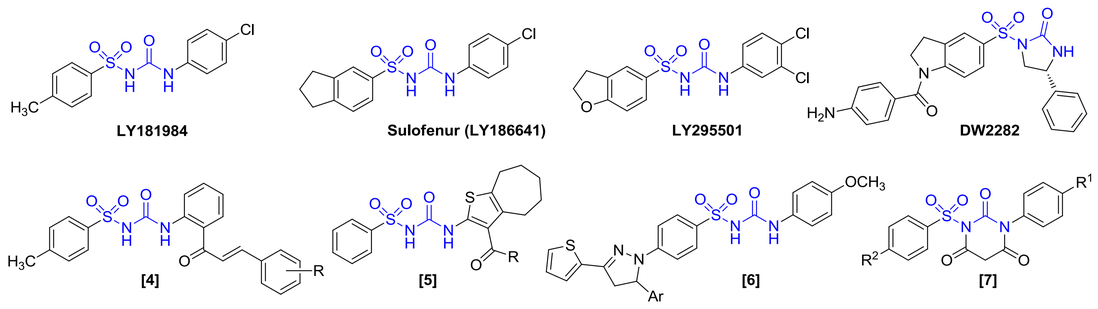
Introduction

Diarylsulfonylureas (DSUs) are a group of compounds which, unlike the *N*-alkyl sulfonylurea derivatives with hypoglycaemic activity, exhibit high potential as antineoplastic compounds [1]. The discovery of the compound LY181984, followed by the clinical trials of the compound LY186641 (sulofenur), initiated a series of studies on the antitumor activity of sulfonylurea derivatives (Figure 1).

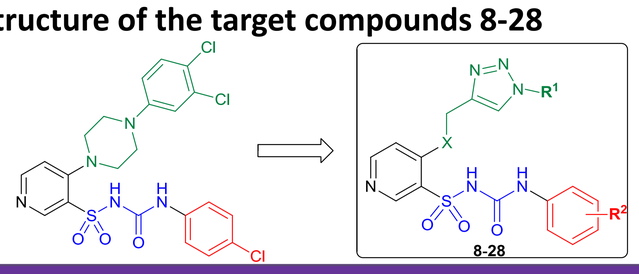
Figure 1. Sulfonylureas with anticancer activity



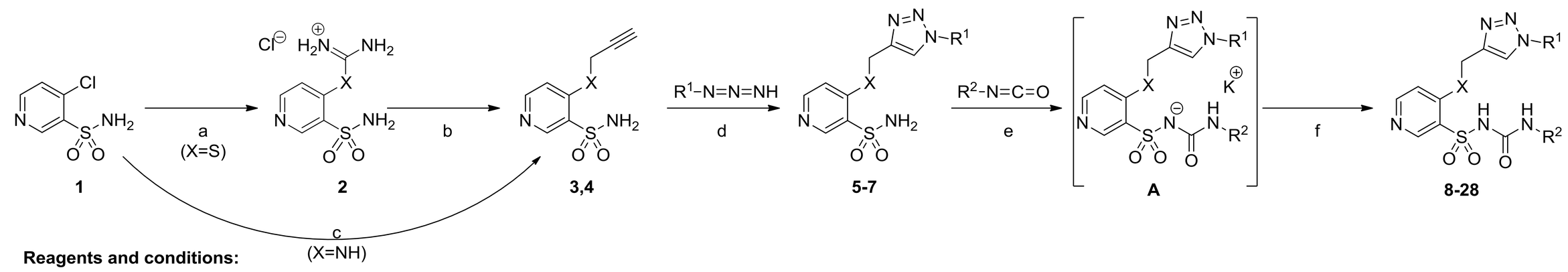
Continuing our previous studies, in which we have shown a significant potency for antitumor activity of 1-(4-substituted pyridine-3-sulfonyl)-3-phenylureas [2], we have undertaken the synthesis and evaluation of cytostatic activity of novel series of *N*-{[4-(1,2,3-triazol)pyridin-3-yl]sulfonyl}urea derivatives. The presence of the 1,2,3-triazole linker at the position 4 of the pyridine ring, which has a significant influence on the antitumor activity [2,3], allows easy functionalization of the basic scaffold by the copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC).

Figure 2. Most active previous *N*-(pyridin-3-yl)sulfonylurea derivative and structure of the target compounds 8-28

Cancer type	no. of cell lines	IC_{50} [uM]
leukemia	5	3,0 - 19,9
NCLC	7	13,4 - 19,9
colon cancer	7	6,4 - 16,8
CNS cancer	4	12,2 - 19,1
melanoma	4	1,5 - 18,9
ovarian cancer	4	16,3 - 18,6
renal cancer	6	6,3 - 18,4
prostate cancer	2	14,4 - 17,3
breast cancer	5	13,9 - 19,7



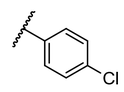
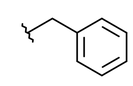
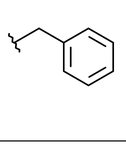
Synthesis



Reagents and conditions:

a) thiourea (1,05 eq), MeCN, 3h reflux.; **b)** propargyl bromide (4 eq), NaOH THF/H_2O, 24h 0° - 20°C; **c)** propargylamine (2 eq), EtOH, 10h reflux;

d) R_1-N_3 (1,2 eq), $CuSO_4$ sodium ascorbate (0,1 eq), DMSO/H2O, 3h r.t.; **e)** R_2-NCO (1,1 eq), K_2CO_3, acetone, 24h r.t., **f)** 4%HCl pH=2, H_20, 24 h r.t.

X	R^1	R^2	compd	yield	Molecular formula	M.W.	m.p. [°C]	logP*
N		Ph	**8**	88%	$C_{21}H_{18}ClN_7O_3S$	483,93	160-162	2,32
		4-ClPh	**9**	85%	$C_{21}H_{17}Cl_2N_7O_3S$	518,37	161-163	2,93
		4-BrPh	**10**	91%	$C_{21}H_{17}BrClN_7O_3S$	562,83	174-175	3,09
		4-FPh	**11**	86%	$C_{21}H_{17}ClFN_7O_3S$	501,92	186-188	2,46
		4-CH_3Ph	**12**	85%	$C_{22}H_{20}ClN_7O_3S$	497,96	172-174	2,84
		4-CF_3Ph	**13**	78%	$C_{22}H_{17}ClF_3N_7O_3S$	551,93	164-166	3,20
		cyclohexane	**14**	76%	$C_{21}H_{24}ClN_7O_3S$	489,98	188-190	2,29
N		Ph	**15**	77%	$C_{22}H_{21}N_7O_3S$	463,52	164-166	1,78
		4-ClPh	**16**	67%	$C_{22}H_{20}ClN_7O_3S$	497,96	167-169	2,39
		4-BrPh	**17**	68%	$C_{22}H_20BrN_7O_3S$	542,41	166-168	2,55
		4-FPh	**18**	84%	$C_{22}H_{20}FN_7O_3S$	481,51	164-166	1,93
		4-CH_3Ph	**19**	91%	$C_{23}H_{23}N_7O_3S$	477,54	134-137	2,30
		4-CF_3Ph	**20**	67%	$C_{23}H_{20}F_3N_7O_3S$	531,51	167-169	2,66
		cyclohexane	**21**	82%	$C_{22}H_{27}N_7O_3S$	469,56	179-181	1,75
S		Ph	**22**	83%	$C_{22}H_{20}N_6O_3S_2$	480,56	167-170	3,15
		4-ClPh	**23**	81%	$C_{22}H_{19}ClN_6O_3S_2$	515,00	158-162	3,76
		4-BrPh	**24**	67%	$C_{22}H_{19}BrN_6O_3S_2$	559,46	146-148	3,92
		4-FPh	**25**	55%	$C_{22}H_{19}FN_6O_3S_2$	498,55	164-167	3,29
		4-CH_3Ph	**26**	79%	$C_{23}H_{22}N_6O_3S_2$	494,59	190-192	3,67
		4-CF_3Ph	**27**	72%	$C_{23}H_{19}F_3N_6O_3S_2$	548,56	183-184	4,03
		cyclohexane	**28**	82%	$C_{22}H_{26}N_6O_3S_2$	486,61	167-170	2,93

*Calculated using JChem for Office 17.14.0, 2017, ChemAxon (http://www.chemaxon.com)

Starting from 4-chloropyridine-3-sulfonamide **1** in the first step, 4- (2-propyn-1-yl-thio/ amino) pyridine-3-sulfonamides were obtained. Either by previously reported method (**a** and **b** on scheme) or by the simple aromatic nucleophilic substitution (method **c**). Subsequent reaction of alkynes **3** and **4** with 4-chloroazide benzene or azidophenylmethane was carried out in standard CuAAC conditions in DMSO and water using copper (II) sulphate and sodium ascorbate to generate Cu^+ ions, giving compounds **5-7**.

The desired, sulfonylurea derivatives **8-28** were obtained by treatment of primary sulfonamides **5-7** with the appropriate isocyanates in dry acetone at r.t. in the presence of anhydrous potassium carbonate. The initially formed intermediate potassium salts of type **A** was acidified with diluted hydrochloric acid to pH 2, to afford products in good yields (55-91%).

Biological studies

Compounds **8-28** were submitted to test towards their effect on growth of human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7 and cervical cancer HeLa. Cell viability was measured using MTT assay after 72 h of incubation with tested compound in concentration 1 – 100 µM.

Preliminary results for compounds **15**-**18** and **22**-**25** show their moderate activity (IC50> 100 µM).

Table. Percent of growth inhibition (GI%) of human cancer cell lines incubated with tested compounds 15-18 and 22-25 in concentration 10 µM.

compd.	HCT-116	HeLa	MCF-7
15	28	34	13
16	20	23	9
17	17	24	11
18	18	21	15
22	17	12	40
23	6	4	21
24	5	9	3
25	1	0	12

Literature: [1] Pasello G, et al. Oncologist **2013**; *18:* 1118–1125. [2]Szafrański K, Sławiński J. Molecules. **2015**; 20**;** 12029–12044. [3]Sławiński J, et al. Eur J Med Chem. **2013**;69:701–710. [4]V.R. Avupati et al. **2012**, 22, 1031-1035 [5]M.A. El-Sherbeny, et al. *Eur. J. Med. Chem*., **2010**, 45, 689-697. [6]C. Kharbanda et al. *Bioorg. Med. Chem. Lett*., **2014**,24, 5298-5303.; [7]I.M. El-Deeb et al. *Eur. J. Med. Chem*., **2010**, 45, 2516-2530

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