SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF NEW HYDRAZONE-BRIDGED BENZOTHIAZOLE DERIVATIVES

Ivana Sokol [1], Hanja Mlinar [1], Leentje Persoons [2], Els Vanstreels [2], Dirk Daelemans [2], Tatjana Gazivoda Kraljević [1]

[1]*University of Zagreb Faculty of Chemical Engineering and Technology, Trg Marka Marulića 19, 10 000 Zagreb*

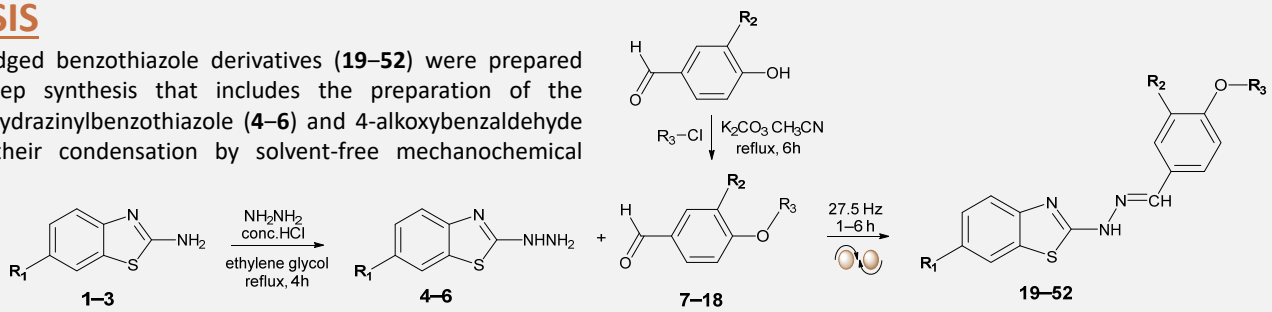
[2]*KU Leuven Department of Microbiology, Immunology and Transplantation, Laboratory of Virology and Chemotherapy, Rega Institute, Leuven, Belgium*

BACKGROUND

Benzothiazole is considered a privileged structure in medicinal chemistry due to its various biological activities such as antimicrobial, antitumor, antituberculostatic, and antimalarial effects. Therefore, this heterocyclic core is often found in drugs available on the market that are used to treat various diseases [1]. Furthermore, the hydrazone moiety has found application in drug delivery to tumor cells due to faster hydrolysis of the imine bond in acidic pH compared to physiological conditions [2].

SYNTHESIS

Hydrazone-bridged benzothiazole derivatives (**19–52**) were prepared by a multi-step synthesis that includes the preparation of the precursors 2-hydrazinylbenzothiazole (**4–6**) and 4-alkoxybenzaldehyde (**7–18**), and their condensation by solvent-free mechanochemical synthesis.



1–3 **4–6** **7–18** **19–52**

CMPD	R_1
1	H
2	Cl
3	OCH_3
4	H
5	Cl
6	OCH_3

CMPD	R_2	R_3
7	H	
8	H	
9	H	
10	H	
11	OCH_3	
12	OCH_3	
13	OCH_3	
14	OCH_3	
15	F	
16	F	
17	F	
18	F	

CMPD	R_1	R_2	R_3	CMPD	R_1	R_2	R_3	CMPD	R_1	R_2	R_3
19	H	H		30	Cl	H		41	OCH_3	H	
20	H	H		31	Cl	H		42	OCH_3	H	
21	H	OCH_3		32	Cl	H		43	OCH_3	H	
22	H	OCH_3		33	Cl	OCH_3		44	OCH_3	H	
23	H	OCH_3		34	Cl	OCH_3		45	OCH_3	OCH_3	
24	H	OCH_3		35	Cl	OCH_3		46	OCH_3	OCH_3	
25	H	F		36	Cl	OCH_3		47	OCH_3	OCH_3	
26	H	F		37	Cl	F		48	OCH_3	OCH_3	
27	H	F		38	Cl	F		49	OCH_3	F	
28	H	F		39	Cl	F		50	OCH_3	F	
29	Cl	H		40	Cl	F		51	OCH_3	F	
								52	OCH_3	F	

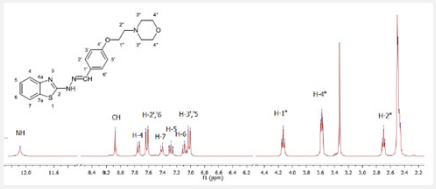


Figure 1. ^{1}H NMR spectrum of compound **20**

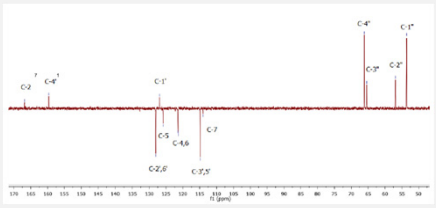


Figure 2. ^{13}C NMR spectrum of compound **20**

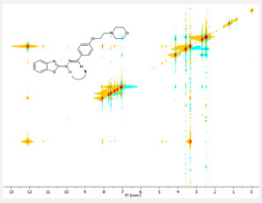


Figure 3. NOESY spectrum of compound **20**

ANTIPROLIFERATIVE ACTIVITY *in vitro*

	IC_{50}/μM							
CMPD	CAPAN-1	HCT-116	LN-229	NCI-H460	DND-41	HL-60	K-562	Z-138
19	2.0	2.5	1.9	1.4	6.5	20.0	5.3	3.6
20	54.8	>100	>100	62.9	90.4	81.6	>100	77.5
21	1.9	2.2	1.7	1.7	2.0	2.3	2.0	2.2
22	2.0	6.0	1.9	2.7	2.1	2.4	2.0	5.2
25	1.4	8.4	2.0	4.2	1.8	5.6	1.8	5.0
26	2.1	1.2	1.8	1.0	2.7	1.9	2.1	2.4
28	1.0	6.7	5.1	5.8	3.8	9.9	4.3	6.6
29	1.9	9.5	3.2	7.7	2.2	3.9	1.9	2.4
30	1.2	5.3	3.0	7.1	2.1	5.0	2.1	6.0
33	1.7	2.4	1.9	4.1	2.2	6.1	2.1	3.0
34	2.5	10.4	9.9	8.1	5.6	10.7	8.4	4.9
37	1.0	1.9	2.0	1.4	1.9	1.9	1.9	1.3
38	0.6	1.4	1.6	0.9	2.5	2.1	1.7	2.2
40	1.9	1.8	1.3	1.8	2.2	5.2	1.6	1.9
41	1.8	1.8	1.6	2.7	2.1	3.5	3.2	3.4
42	1.9	2.6	1.9	6.7	2.1	4.2	1.9	2.0
45	1.9	1.8	1.3	1.8	11.3	1.7	10.4	1.7
46	1.9	2.3	1.8	1.7	1.7	1.6	1.9	1.7
47	1.8	4.9	2.6	1.7	7.3	1.8	2.8	5.1
49	1.8	1.8	1.8	1.4	1.5	1.3	1.8	3.8
50	2.0	2.5	1.8	1.7	2.1	1.8	1.8	3.8
52	1.8	2.0	1.8	1.4	1.9	3.0	3.0	2.1
ETOPOSIDE	0.03	3.4	3.7	6.1	1.0	0.8	4.0	0.7

Antiproliferative activity *in vitro* of newly prepared hydrazone-bridged benzothiazole derivatives (**19–52**) was evaluated against malignant human tumor cell lines: pancreatic adenocarcinoma (CAPAN-1), colon cancer (HCT-116), human brain glioblastoma (LN-229), non-small cell lung cancer (NCI-H460), acute lymphoblastic leukemia (DND-41), acute myeloid leukemia (HL-60), chronic myeloid leukemia (K-562), and non-Hodgkin's lymphoma (Z-138). Of the all evaluated compounds, 2-hydrazone derivatives of benzothiazole presented in table showed pronounced antiproliferative activity.

CONCLUSION

Hydrazone-bridged benzothiazole derivative substituted with chlorine at the C-6 position of benzothiazole and with fluorine at the *meta*-position and *N*,*N*-dimethyl substituent at the *para*-position of the benzene ring **38** showed the most pronounced antiproliferative activities against pancreatic adenocarcinoma cells (CAPAN-1, IC_{50} = 0.6 μM) and non-small lung cancer cells (NCI-H460, IC_{50} = 0.9 μM).

REFERENCES

[1] R. Ali, N. Siddiqui, *J. Chem.* 2013 (2013) 1.
[2] S.J. Sonawane, R.S. Kalhapure, T. Govender, *Eur. J. Pharm. Sci.* 99 (2017) 45.

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