Synthesis, structural characterization and antitumor evaluation of novel 1,2,3-triazole derivatives of benzoxazole

FKITMCMXIX Robert Ostrički[1], Leentje Persoons[2], Els Vanstreels[2], Dirk Daelemans[2], Tatjana Gazivoda Kraljević[3]

PLIVA

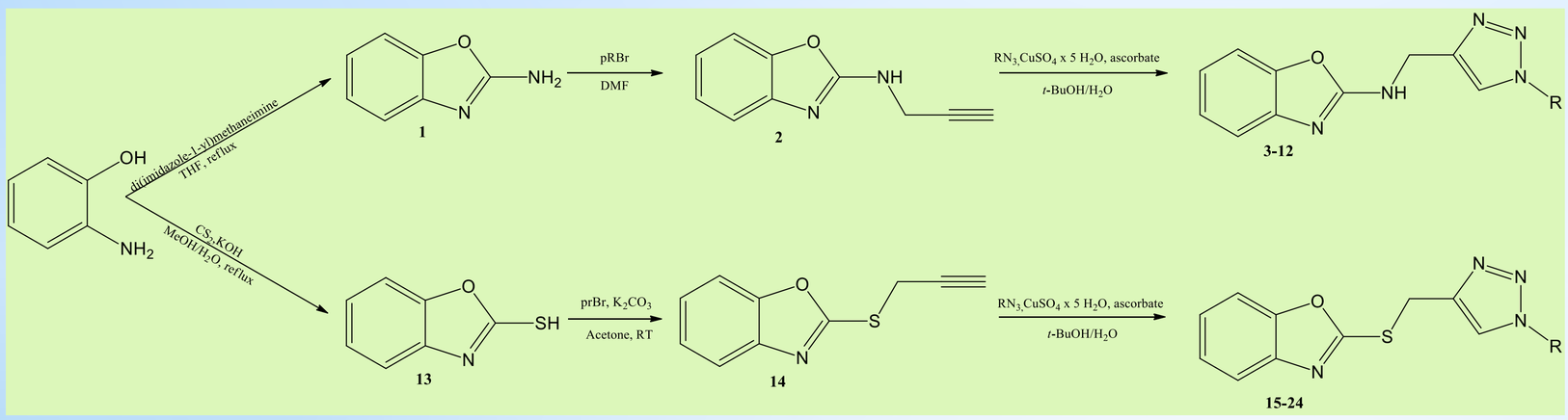
[1]Pliva Hrvatska d.o.o., Prilaz baruna Filipovića 25, 10000 Zagreb
[2]KU Leuven Department of Microbiology, Immunology and Transplantation, Laboratory of Virology and Chemotherapy, Rega Institute, Leuven, Belgium
[3]Department of Organic Chemistry, Faculty of Chemical Engineering and Technology University of Zagreb, Marulićev trg 19, 10000 Zagreb

Background

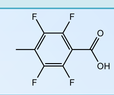
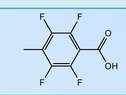
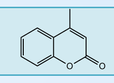
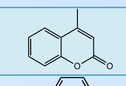
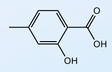
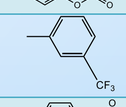
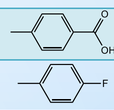
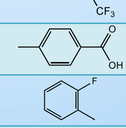
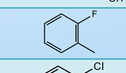
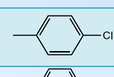
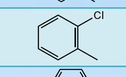
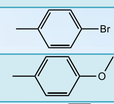
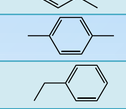
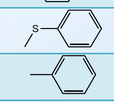
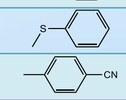
Cancer is one of the main causes of death worldwide along with cardiovascular diseases. Due to its high mortality rate and frequency, medicinal chemists are rapidly developing new, potent antitumor agents. Benzoxazoles are structural isosters of natural nucleotides and represent an important class of heterocyclic compounds exhibiting exceptional pharmacological activities such as anticancer, anti-inflammatory and antiviral. In addition, some of them have found application as fluorescent whitening agents and functional materials.[1-2]
Utilizing conventional and green synthetic methods, novel derivatives of benzoxazole containing 1,2,3-triazole ring as a linker were prepared. Propargylated 2-aminobenzoxazole and 2-thiobenzoxazole were prepared in a two-step reaction including cyclization reaction of 2-aminophenol using di(imidazole-1-yl)methanimine or carbon disulfide, and subsequent N-alkylation reaction with propargyl bromide as an alkylating reagent. 2-amino- and 2-thiobenzoxazole derivatives with 1,2,3-triazole moiety were synthesized by Cu(I) catalyzed click reaction of 2-propargylated benzoxazole derivatives with corresponding azides. The most potent activity against acute lymphoblastic leukemia (DND-41, IC_{50}= 1 μM) showed benzoxazole derivative consisting of coumarin ring linked *via* 1,2,3-triazole.

Results

- Propargylated 2-aminobenzoxazole (2) and 2-thiobenzoxazole (14) were prepared by cyclization reaction of 2-aminophenol using di(imidazole-1-yl)methaneimine (for 1) and carbon disulfide (for 13), followed by alkylation reaction of 1 and 13 with propargyl bromide as an alkylating reagent.
- 1,2,3-triazole derivatives of 2-aminobenzoxazole (3-12) and 2-thiobenzoxazole (15-24) were synthesized by Cu(I) catalyzed click reaction of 2-propargylated benzoxazole derivatives (2 and 14) with corresponding azides (Scheme 1).



Scheme 1. Synthesis of 1,2,3-triazole derivatives of 2-aminobenzoxazole (3-12) and 2-thiobenzoxazole derivatives (15-24)

Compound	X	R	Compound	X	R
3	NH		15	S	
4	NH		16	S	
5	NH		17	S	
6	NH		18	S	
7	NH		19	S	
8	NH		20	S	
9	NH		21	S	
10	NH		22	S	
11	NH		23	S	
12	NH		24	S	

- Formation of the triazole ring is confirmed by the disappereance of the triplet at ~3,2 ppm of the terminal alkyne proton in ^{1}H-NMR spectra of compounds 2 and 14 (Figure 1.) and the appereance of the siglet of the triazole ring proton at ~ 9 ppm in ^{1}H-NMR spectra of compounds 3-12 and 15-24 (Figure 2.).

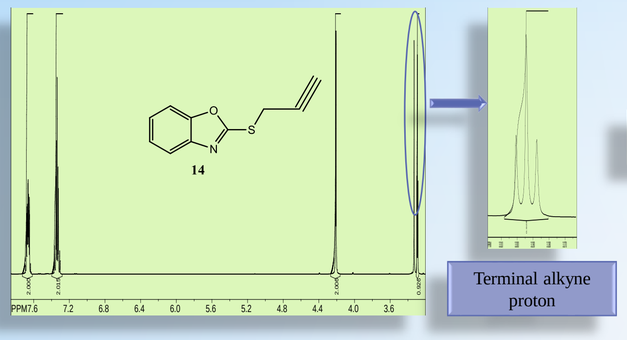


Figure 1. ^{1}H-NMR spectrum of compound 14

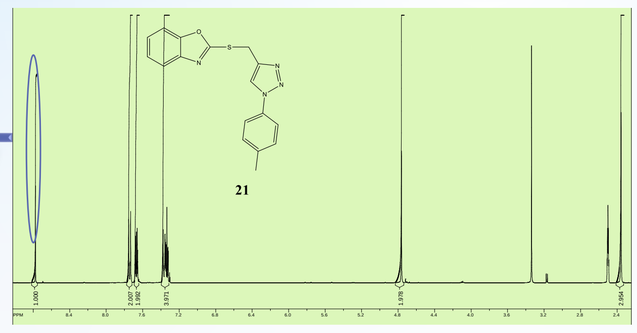


Figure 2. ^{1}H-NMR spectrum of compound 21

Antitumor evaluations

Compound	Concentration unit	IC_{50}							
		LN-229	Capan-1	HCT-116	NCI-H460	DND-41	HL-60	K-562	Z-138
		glioblastoma	*pancreatic adenocarcinoma*	*colorectal carcinoma*	*lung carcinoma*	*acute lymphoblastic leukemia*	*acute myeloid leukemia*	*chronic myeloid leukemia*	*non-Hodgkin lymphoma*
3	μM	>100	85,3	>100	>100	>100	74,9	>100	>100
4	μM	6,7	6,5	24,2	30,5	13,0	48,7	76,2	12,6
5	μM	>100	>100	>100	>100	>100	>100	>100	>100
6	μM	45,9	42,8	>100	>100	>100	>100	>100	>100
7	μM	>100	>100	>100	64,8	>100	>100	>100	>100
8	μM	>100	32,9	52,2	49,8	>100	97,4	>100	90,5
9	μM	>100	81,8	>100	>100	>100	>100	>100	>100
10	μM	>100	>100	>100	>100	>100	>100	>100	>100
11	μM	>100	>100	>100	>100	>100	>100	>100	>100
12	μM	>100	>100	>100	>100	>100	>100	>100	>100
15	μM	>100	48,8	>100	>100	>100	95,9	>100	>100
16	μM	1,8	1,3	1,4	2,1	1,0	1,4	1,6	1,8
17	μM	>100	>100	>100	>100	>100	>100	>100	>100
18	μM	>100	42,9	>100	60,9	>100	66,95	>100	58,3
19	μM	>100	>100	>100	>100	>100	>100	>100	>100
20	μM	>100	>100	>100	>100	>100	>100	>100	>100
21	μM	>100	>100	>100	>100	>100	>100	>100	>100
22	μM	>100	>100	>100	>100	>100	>100	>100	>100
23	μM	>100	>100	>100	>100	>100	>100	>100	>100
24	μM	>100	>100	>100	57,9	>100	>100	>100	>100
Docetaxel	nM	4,1	3,8	2,5	3,4	2,5	2,2	8,5	2,3
Staurosporine	nM	66,8	51,9	70,1	44,8	54,8	58,6	37,4	48,4

Conclusion

- Novel 1,2,3-triazole derivatives of 2-aminobenzoxazole (3-12) and 2-thiobenzoxazole (15-24) have been prepared utilizing „click" chemistry, for the purpose of evaluation of their antitumor activity
- Structures of the prepared compounds were confirmed by ^{1}H and ^{13}C-NMR spectroscopy and mass spectrometry as well.
- 1,2,3-triazolyl benzoxazole derivative with coumarin substituent showed the most potent activity against acute lymphoblastic leukemia (DND-41, IC_{50}= 1 μM).

References

[1] C. P. Kaushik, M. Chahal, *.J. Chem. Sci,*. 2020, *132*, 142
[2] M. Kale, V. Chavan, Mini-Rev. Org. Chem. (2019), 16, 111

Acknowledgements

This work was founded by Pliva Hrvatska d.o.o. and Croatian Science Foundation (HRZZ-IP-2018-01-4682).

teva | api

HRZZ Croatian Science Foundation