

NOVEL 1,2,3-TRIAZOLYL-7-SUBSTITUTED COUMARINS AND **BIS(COUMARIN-TRIAZOLYL)**BENZENES: SYNTHESIS, **PHOTOPHYSICAL PROPERTIES AND CYTOSTATIC EVALUATION**

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INTRODUCTION

Coumarins, with the structure of benzopyrone, are widely studied heterocyclic structures in the fields of biology, medicine, perfumes, cosmetics and environmental chemistry. The favourable photophysical properties validated coumarin derivatives as fluorescent probes in cellular imaging and as good chemosensors of some transition metal ions essential for human health. In addition, "" click"-derived 1,2,3-triazole has become a very common motif from the biological fields to the material sciences. It can interact with biological molecules, organic and inorganic surfaces and materials. Triazole rings have been used as components of fluorogenic probes and as chelating ligands in fluorescent metal sensors.^[1]

Herein, we report the synthesis, spectroscopic study and cytostatic evaluation of some novel coumarin-triazole conjugated heterocycles as well as 1,3- and 1,4-bis(coumarin-triazolyl)benzenes based on Cu(I)-catalyzed azide-alkyne cycloaddition reaction.

MATERIALS AND METHODS

CHEMISTRY

- 7-azido-4-methyl-2*H*-chromen-2-one (**2**) was prepared by diazotation reaction in the presence of ptoluenesulfonic acid and sodium azide in water at room temperature.
- (3-7) • 1,2,3-triazolyl-coumarin derivatives and bis(coumarin-triazolyl)benzenes (8-9) were synthesized 7-azido-coumarine (2) derivative from and corresponding alkynes and dialkynes using ,,click chemistry" approach, with Cu(I) catalyst formed in situ in the presence of Na-ascorbate as reductant and ligand TBTA that promotes catalysis.

SPECTROSCOPIC STUDY

Basic photophysical properties of newly synthesized compounds (3-9), their interaction with heavy metal cations in ethanol, the effect of pH as well as interaction with *ct*-DNA of representative compounds were studied by UV-Vis absorption and fluorescence spectroscopy.



Table 1. Spectral properties of synthesized compounds
 (3-9) in ethanol solution $(10 \mu M)$

	$\lambda_{_{abs}}$ / nm	ε / M⁻¹cm⁻¹	$\lambda_{_{ m emiss}}$ / nm	Stokes shift/nm
3	325	28200	416	91
4	281 325	25300 15500	388	63
5	296	16800	344	48
6	283	38800	374	91
7	285	32800	376	91
8	326	13400	390	64
9	279 330	61200 44900	425	95



Scheme 1. Reagents and conditions: *i*) *p*-TsOH, H₂O, NaNO₂, r.t., *ii*) NaN₃, r.t. *iii*) arylalkynes, *t*-BuOH/H₂O/CH₂Cl₂ (1:2:1), CuSO₄, Na-ascorbate, TBTA, r.t.



Antitumor activity

Compounds **3-9** were evaluated for their cytostatic activities against human tumor cell lines: colon carcinoma (HCT116), breast adenocarcinoma (MCF-7) and lung carcinoma (H 460).



Figure 1. Effect of pH on **a**) absorption and **b**) fluorescence spectra of compound **7** ($c = 10 \mu$ M).



Table 2. Inhibitory effects of the coumarin-triazole derivatives (3-7) and 1,3- and 1,4-bis(coumarin-triazolyl)benzenes (8-9) on the growth of human tumor cell lines

Gl ₅₀ [*] (μM)					
Compound	Cell lines				
	НСТ116	MCF-7	H 460		
3	≥100	23±9	≥100		
4	3±2	0.6±0.1	≥100		
5	≥100	21±0.03	≥100		
6	31±5	19±3	23±10		
7	31±6	3±2	21±7		
8	9±3	0.3±0.2	29±3		
9	7±3	1±0.1	≥100		

 G_{150} ; the concentration that causes 50% growth inhibition

All tested compounds showed pronounced (4, 8, 9) to moderate (3, 5) antiproliferative activity towards tested cell lines. MCF-7 cell line was especially sensitive towards all tested compounds.



Figure 3. Concentration-response profiles for compounds a) 7 and b) 9 tested in vitro on HCT116, MCF-7 and H460 cell lines.



Figure 4. a) Absorbance properties of **7** (20 μ M) and b) emission properties of **8** (2 μ M) upon titration with

Metal sensing properties

Figure 2. Emission properties of a) **7** ($c = 10 \mu$ M) upon titration with Zn²⁺; b) **9** ($c = 10 \mu$ M) upon titration with Fe²⁺.

ct-DNA in BPE buffer solution.

CONCLUSIONS

Novel class of 1,2,3-triazolyl-coumarin conjugates and bis(coumarin-triazolyl)benzenes were synthesized by Cu(I)-catalyzed azide-alkyne cycloaddition reaction and evaluated for their chemosensing and antiproliferative activity.

Spectral characterization showed that compound 7 could be used as potential pH sensor and indicated good sensing properties for Zn²⁺ ions. Titration of compound 9 with heavy metal ions resulted in fluorescence quenching upon addition of Fe²⁺ ions indicating it could be used as potential sensor for Fe²⁺ ions in solution.

Of all evaluated compounds, coumarin-triazolyl derivative 7 containing (benzimidazol-2-yl-thio)methyl side chain showed the most pronounced antiproliferative activity towards tested cell lines as well as changes in apsorption spectra upon titration with *ct*-DNA.

References

^[1] a) C. Le Droumaguet, C. Wang, Q. Wang, Chem. Soc. Rev. 2010, 39, 1233; b) Y. H. Lau, P. J Rutledge, M. Watkinson, M. H. Todd, Chem. Soc. Rev. 2011, 40, 2848.

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