SYNTHESIS AND BIOLOGICAL EVALUATIONS OF 1,2,3-TRIAZOLYL-TETHERED 4-QUINOLONE–FERROCENE CONJUGATES

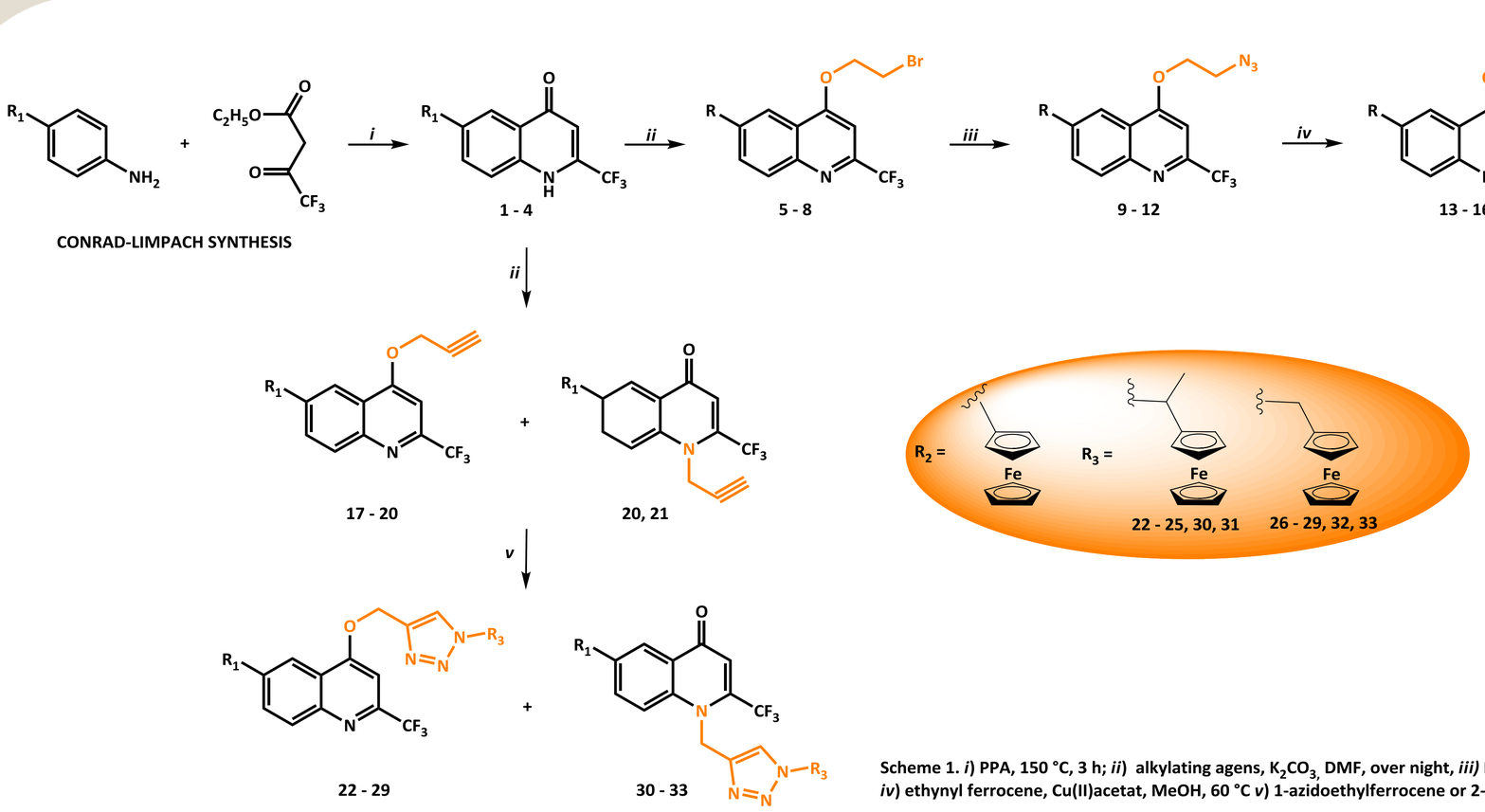
SINTEZA I BIOLOŠKA ISPITIVANJA KONJUGATA 4-KINOLONA I FEROCENA POVEZANIH 1,2,3-TRIAZOLILNOM POVEZNICOM

Silvija Maračić,[1] Senka Djaković,[2] Jasmina Lapić,[2] Valerije Vrček,[3] Silvana Raić-Malić[1]

[1] *University of Zagreb, Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, Marulićev trg 19, HR-10000 Zagreb, Croatia*
[2] *University of Zagreb, Laboratory for Organic Chemistry, Faculty of Food Technology and Biotechnology, Pierottijeva 6, HR-10000 Zagreb, Croatia*
[3] *University of Zagreb, Laboratory for Organic Chemistry, Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, HR-10000 Zagreb, Croatia*

Introduction

1,2,3-Triazoles have attracted considerable attention in recent years because of their wide range of biological activities against various viruses, malignant cells, microorganisms and their inhibitory activities against several enzymes.[1] Advances in the rational design of metalbased therapeutic agents have increased after the discovery of cisplatin, which has been the main impetus for the expansion of metal complexes in cancer and other pathologies. The introduction of a ferrocenyl (Fc) moiety into a drug molecule has now been recognized as a useful approach for the development of more effective therapeutic applications.[2]



Scheme 1. *i*) PPA, 150 °C, 3 h; *ii*) alkylating agens, K_2CO_3, DMF, over night, *iii)* NaN_3, acetone, reflux, over night, *iv*) ethynyl ferrocene, Cu(II)acetat, MeOH, 60 °C *v*) 1-azidoethylferrocene or 2-azidoethylferroceneCu(II)acetat, MeOH, 60 °C

Figure 1. Crystals of compound **26**

R_1	O-propargyl derivative	N-propargyl derivative	O-bromoethyl derivative
H	84 %	3 %	37 %
Cl	74 %	-	26 %
CH_3	75 %	4 %	29 %
Ph	71 %	-	31 %

Chemistry

Novel 4-quinolone–ferrocene conjugates linked *via* 1,2,3-triazolyl scaffold were synthesized by regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition of corresponding azide and alkynyl derivatives. Azido intermediates were synthesyzed from hydroxyl or bromoethyl analogs, while alkynyl derivatives of quinolones were prepared by alkylation in the presence of base. Although *N*-alkylation process of the quinolone system is both thermodynamically and kinetically favored, the introduction of trifluoromethyl group at C2-position makes this reaction kinetically less favored.

Biological evaluations

Results of antiproliferative evaluations of 4-quinolone–ferrocene conjugates on human cervix adenocarcinoma (HeLa), colon adenocarcinoma (CaCo-2) and chronic myeloid leukemia in blast crisis (K562), are presented in the Table 1. Conjugate of nonsubstituited quinolone and ferrocene (**32**) exhibited marked and selective antiproliferative activity against chronic myeloid leukemia in blast crisis (K562, IC_{50} = 7.73 μM).

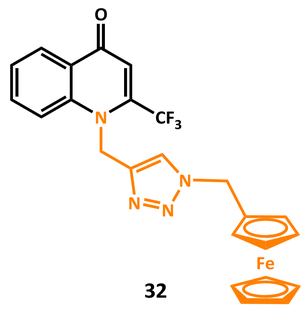


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Table 1. Antiproliferative activities

Compd.	R_1	$IC_{50}{}^{a}$ (μM)		
		CaCo-2	K562	HeLa
22	H	>100	>100	>100
23	Cl	>100	>100	>100
24	CH_3	>100	95.89	>100
25	Ph	>100	>100	>100
26	H	>100	>100	97.04
27	Cl	>100	>100	>100
28	CH_3	>100	97.28	99.86
29	Ph	>100	>100	>100
31	CH_3	57.2	46.21	72.67
32	H	18.53	7.73	49.79
13	H	>100	90.62	70.18
14	Cl	>100	60.26	99.81
15	CH_3	>100	85.16	88.61
16	Ph	>100	80.22	>100

[a] 50% inhibitory concentration or compoundconcentration required to inhibit tumor cell proliferation by 50%.

References

[1] S. Raić-Malić, A. Meščić, *Curr. Med. Chem.* **22** (2015) 1462–1499.
[2] K. Kumar, S. Carrère-Kremer, L. Kremer, Y. Guérardel, C. Biot and V. Kumar, *Dalton Trans.*, **42** (2013) 1492–1500.

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