Synthesis of ribosylated derivatives of 3-hydroxyquinolin-4 (1*H*)-ones and study of their biological properties.

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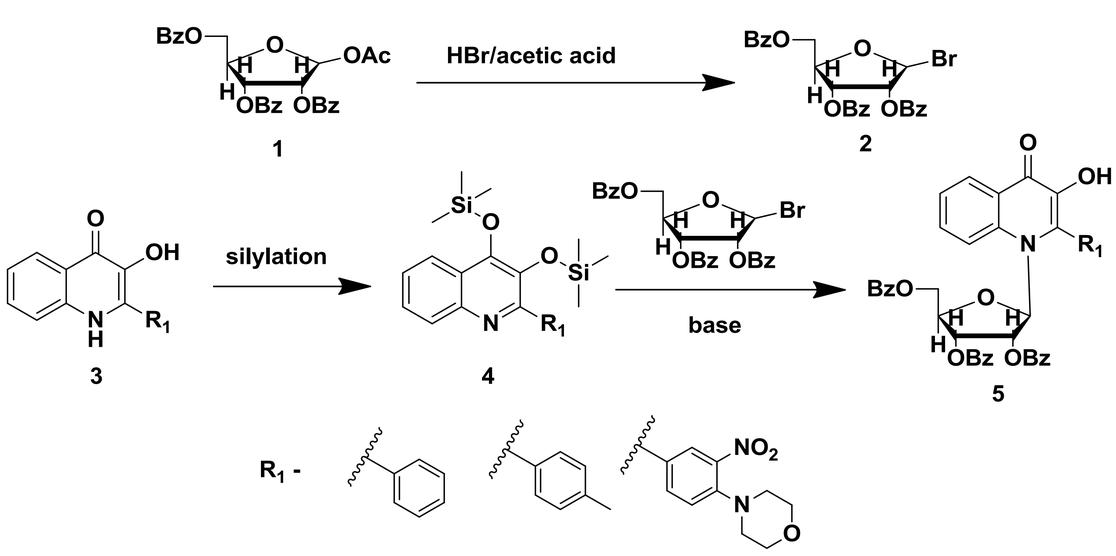
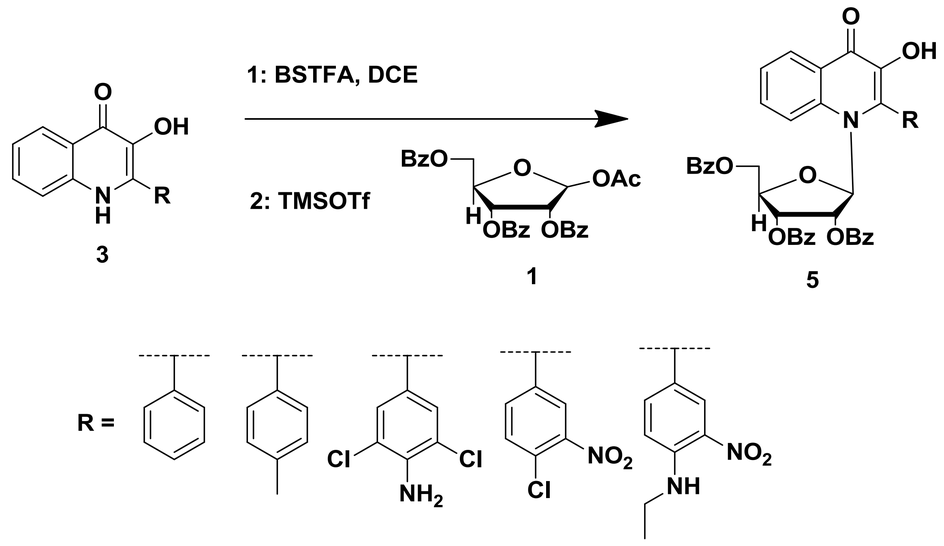
3-hydroxyquinoline-4(1*H*)-ones (3-HQs) (**3**) are the substances with very promising anticancer activity [1]. The practical use of these substances is prevented by low solubility of these derivatives in water and low stability of the 3-HQs at physiological pH. The newly prepared derivatives with the ribose at nitrogen in position 1 solve the problem of solubility and stability. Recently developed conditions using Vorbrügen method of preparation is well applicable to an unsubstituted 2-phenyl-3HQs[2]. Other derivatives of 3HQs do not give good yields or fail completely. We tried a new method of preparation of 3-HQs **5** ribosylated in position 1 by using 2-bromoribofuranose **2**, prepared by bromination of o-acetylribose **1** (**Scheme 1**) . This synthetic route is suitable for preparation of other derivatives with conversion max. 30%. That's why we went back to Vorbrügen method and improved the key step of the reaction - silylation. Using N, O-bis (trimethylsilyl)trifluoroacetamide (BSTFA) as a silylating agent, it was possible to prepare various derivatives with conversion 70 - 85% (**Scheme 2**).



Scheme 1. The preparation of ribosylated 3HQs using 2-bromoribofuranose

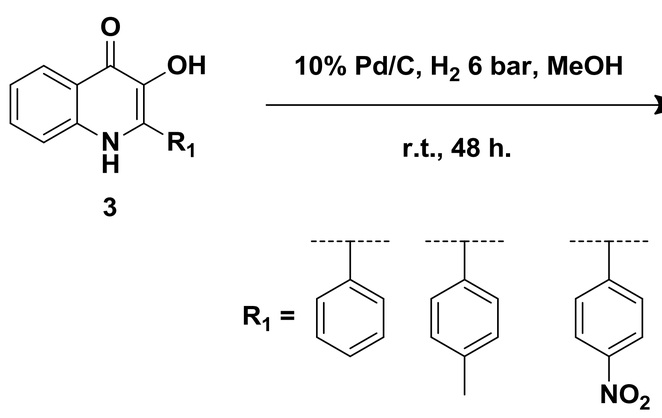


Scheme 2. Ribosylation using modified Vorbrügen method

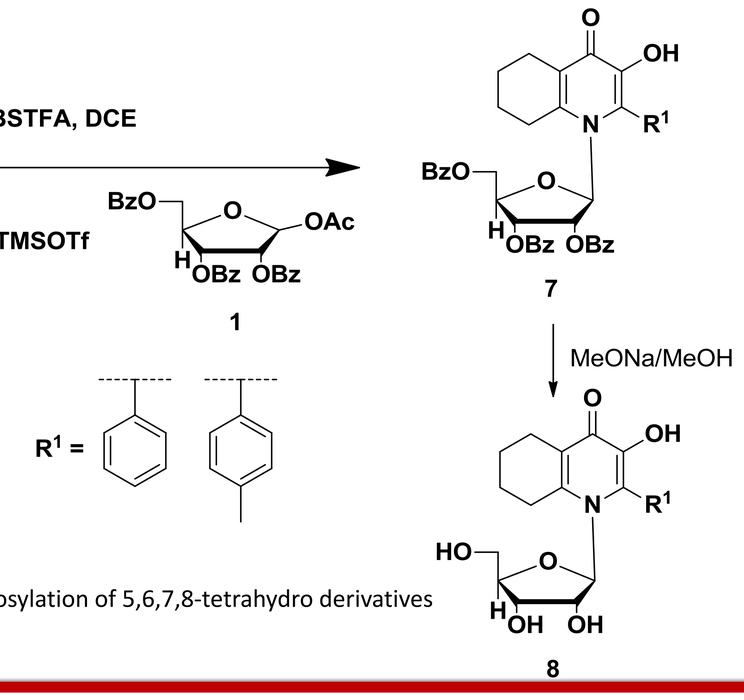
1 – Hradil P., Hlaváč J., Soural M., Hajdúch M., Kolář M., Večeřová R.,*Mini-Rev. Med. Chem*.**2009**, 9, 696 – 702.

2 - Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, 114, 1234

Another modification of the 3-HQs derivatives **3** was their reduction to 5,6,7,8-tetrahydro derivatives **6** (**Scheme 3**) and subsequent ribosylation in position 1 (**Scheme 4**). According to preliminary results 5,6,7,8-tetrahydro-3-HQs **6** have very promising anticancer and antimicrobial activity (**see Table 1-3**).

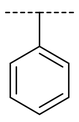


Scheme 3. Reduction of 3HQS



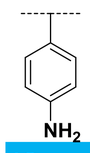
Scheme 4. Ribosylation of 5,6,7,8-tetrahydro derivatives

The reduced derivatives **6** are quite stable within the wide range of pH. Anticancer activity tested against A549, CCRF-CEM, CEM-DNR, HCT116, HCT116, HCT116p53--, K562, K562-TAX cell lines exhibited some very promising results (**see Table 1 and 2**).



	Cell lines						
	CCRF-CEM	K562	K562-TAX	CEM-DNR	A549	HCT116	HCT116 p53--
IC_{50} (μM)	6,367	12,227	7,135	8,298	8,808	6,257	5,129

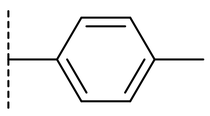
Table 1. Results of anticancer activity of 2-phenyl-5,6,7,8-tetrahydro-3-HQ



	Cell lines						
	CCRF-CEM	K562	K562-TAX	CEM-DNR	A549	HCT116	HCT116 p53--
IC_{50} (μM)	1,439	1,173	6,099	25,523	7,241	1,314	1,525

Table 2. Results of anticancer activity of 2-(4-aminophenyl)-5,6,7,8-tetrahydro-3-I

The reduced derivatives **6** were also tested on antimicrobial activity. Activity of the best derivative is described in Table 3 in comparison to ciprofloxacin used as standard.



			Zone of Growth Inhibition (mm)								
			B. subtilis	*S. aureus*	*M. luteus*	*A. baumannii*	*B. dolosa*	*P. aeruginosa*		*E. coli*	
Compound	Conc.	Solvent	ATCC 6633	SG511	ATCC 10240	ATCC 17961	AU0018	K799/wt	K799/61	DC0	DC2
	2mM	DMSO/ MeOH	17	18	23	14	17	0	h	h	23
ciprofloxacin	5 μg/mL	H_2O	1.66ug/ml 20	19	0	17/20	100ug/ml 18	24	1.66ug/ml 23/28	16	20.5

Table 3. Results of antimicrobial activity of 2-(4-methylphenyl)-5,6,7,8-tetrahydro-3-HQ

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