SYNTHESIS, STRUCTURE AND ANTIPROLIFERATIVE ACTIVITY OF NOVEL CINCHONA-CHALCONE HYBRIDS WITH TRIAZOLYL LINKERS

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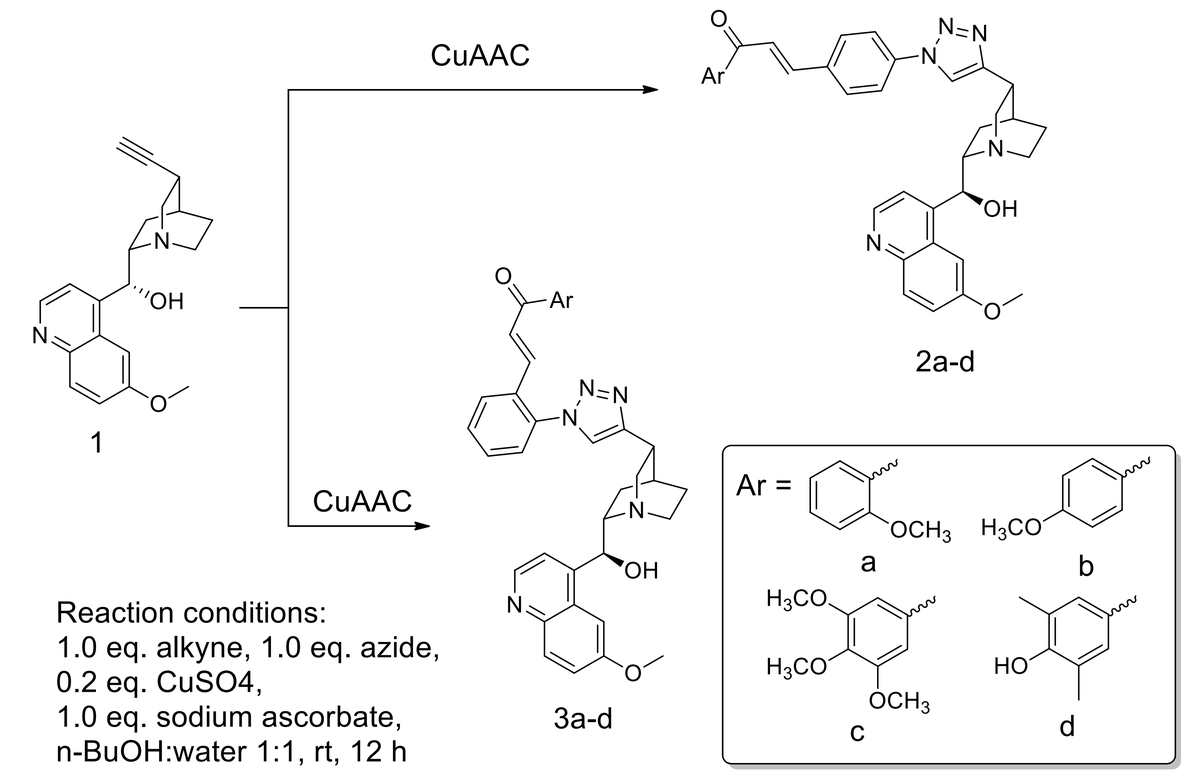
AZ NKFI ALAPBÓL MEGVALÓSULÓ PROJEKT
NEMZETI KUTATÁSI, FEJLESZTÉSI ÉS INNOVÁCIÓS HIVATAL
AZ INNOVÁCIÓ LENDÜLETE

Introduction

It is well-documented that several alkaloids have significant anti-cancer activity, which is widely applied in cancer therapy (eg. vinca alkaloids, taxol, camptothecine, etc.[1]). Cinchona alkaloids have neither cytotoxic nor cytostatic activity against human cancer cell lines, but if they are conjugated to various molecular fragments, the antiproliferative activity of conjugate can be considerably increased compared to parent molecule, as it was proved by our research group[2,3,4]. The main intention of this work was to produce further chalcone-cinchona hybrids of enhanced activity. Accordingly, using easily available building blocks, we synthesized a small molecular library of more potential anti-cancer drug-candidates of which tests may lead to recognition of a novel structure-activity relations.

Results and Discussion

To prepare the target chalcone-cinchona hybrids we have applied Copper(I)-catalyzed Alkine Azide Cycloaddition (CuAAC) reactions. During our previous work[3] we have observed the copper mediated epimerisation of chirality at C-9, which can be



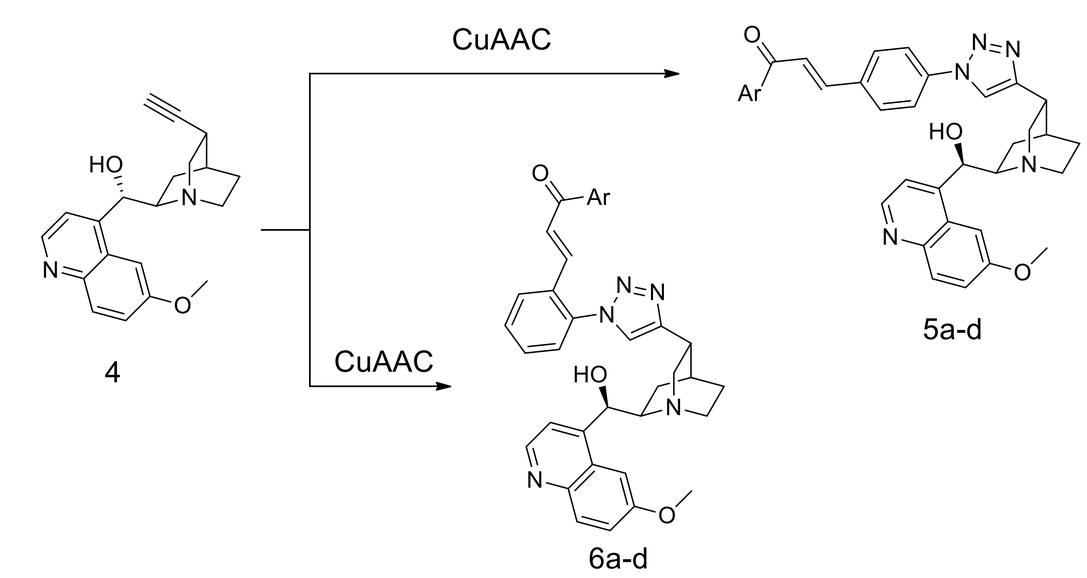


Figure 1: Synthesis of target chalcone-cinchona hydrids

Table 1: Yields and in vitro cytostatic effects expressed in IC_{50} values

Compound	Yield (%)	A5028	PANC-1	COLO-205
		IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
2a	56	3.35	n.d.	n.d.
2b	79	3.67	n.d.	n.d.
2c	61	1.10	2.43	2.21
2d	21	n.d.	n.d.	n.d.
3a	91	2.50	6.83	3.85
3b	72	2.59	8.48	4.62
3c	74	n.d.	n.d.	n.d.
3d	30 + 50[a]	n.d.	n.d.	n.d.
5a	43	3.36	5.06	1.54
5b	62	2.31	n.d.	n.d.
5c	57	0.52	3.72	1.04
5d	24	n.d.	n.d.	n.d.
6a	62	1.49	5.74	4.77
6b	19	n.d.	4.74	5.04
6c	50 + 17[a]	8.15	6.59	1.33
6d	37 + 53[a]	n.d.	n.d.	n.d.

[a]Orientation of 9-hydroxy group is identical to that in natural quinine/quinidine

regulated by the load of copper catalyst, but decreasing of it cause a falling off at yield. To reach the highest yield and an easily purifiable product we have used a relatively high load of catalyst (Figure 1). Nevertheless at compounds **3d**, **6c**, **6d**, we were able to isolate the natural optical isomers along with the target epimer isomer too, presumably because of inhibitory effect of products on copper catalyst by chelate formation (yields are shown in Table 1).

We have investigated the *in vitro* cytostatic activity of novel compounds on A5028 Melanoma, PANC-1 Pancreatic Adenocarcinoma and COLO-205 Colorectal Adenocarcinoma cell lines (data are summarised in Table 1). As our results show all of the investigated hybrids have a low micromolar IC_{50} value on all three cell lines including PANC-1, which is highly resistant against several anti-cancer drugs (eg. Gemcitabine[5]).

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