Accepted manuscript.

Final version published at:
Bioorganic & Medicinal Chemistry Letters 26: 946-49 (2016)
DOI: 10.1016/j.bmcl.2015.12.059.

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Synthesis, Structure and *in vitro* Cytostatic Activity of Ferrocene - Cinchona Hybrids

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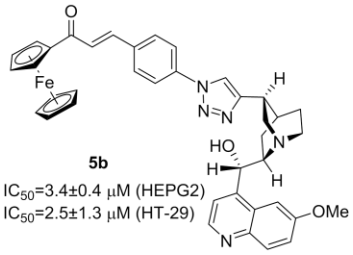

5b

IC_{50}=3.4±0.4 μM (HEPG2)
IC_{50}=2.5±1.3 μM (HT-29)

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Synthesis, Structure and *in vitro* Cytostatic Activity of Ferrocene - Cinchona Hybrids

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Ferrocene
Cinchona
1,2,3-Triazole
Click reaction
Cytostatic activity

ABSTRACT

Exploring copper(I)- and ruthenium(II)-catalyzed azide-alkyne cycloadditions and a Sonogashira protocol, novel cytostatic ferrocene-cinchona hybrids were synthetized displaying significant *in vitro* activity on HEPG-2 and HT-29 cells. Preliminary SAR studies disclosed that compounds incorporating linkers with 1,2,3-triazole and chalchone residues can be considered as promising lead structures. According to the best of our knowledge this is the first report on the incorporation of ferrocene nucleus in the reputed cinchona family *via* triazole and chalcone linkers with established pharmaceutical profile.

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It is a generally accepted view that chemotherapy is one of the essential tools for treatment of malignancies. However, cisplatin, one of the most commonly used chemotherapeutics in the treatment of cancer[1] capable of covalently binding to DNA,[2] causes severe side-effects.[3] In order to overcome the toxic limitations and to broaden the set of treatable malignancies, an intense search was initiated for alternative agents with remarkable structural diversity and led to the development of carboplatin and oxaliplatin, the further emblematic representatives of clinically approved classical metal-complexes,[4] and a wide variety of organometallic and organic potential cytostatic agents. Among organometallics, due to their nontoxic character and chemical stability, ferrocene derivatives with diverse molecular architectures are of pronounced importance. A concept taken into account for the design of compounds was that replacement of an aromatic nucleus of certain organic compounds for a three-dimensional ferrocene unit with tuneable redox character can lead to products possessing unexpected properties which are absent or less manifested in the parent molecule. This view was supported by a number of reviewed examples[5] including ferrocene-containing analogues of the non-steroidal selective estrogen receptor modulator hydroxytamoxifen[6] which display strong cytotoxic and cytostatic effects on hormone-independent MDA-MB-231 breast tumour cells.

Chalcones represent a privileged molecular fragment having a number of interesting biological properties such as antioxidant, cytotoxic, anticancer, antimicrobial, antiprotozoal, antiulcer, antihistaminic and anti-inflammatory activities.[7] There are also remarkable examples of active metallocene derivatives with chalcone analogue structures. For instance, ferrocenylprop-2-en-1-ones were also demonstrated to strongly inhibit the HepG2 cells while having no toxicity towards healthy human fibroblasts.[8]

The potential of simple ferrocene-based heterocycles in fighting cancer,ferrocenylalkyl-substituted azoles were also found to exhibit *in vivo* antitumor activity presenting up to 100% of tumour growth inhibition associated with lower toxicity when compared to clinically used drugs.[9] In this regard, even metal-free organic 1,4-disubstituted 1,2,3-triazoles exhibit significant antiproliferative effect against a wide range of human malignant cell lines.[10] On the other hand, 1,5-disubstituted 1,2,3-triazole analogues of combretastatin A-4 were also found to display marked cytotoxicity on several cancer cell lines.[11]

The structural versatility of deserving therapeutic agents is further demonstrated by several members of natural alkaloids including vinblastine, camptothecine, staurosporine and ellipticin.[12] It is also well-documented that the application of quinine derivatives in the field of cancer diagnosis[13] and in chemotherapy[14] goes far back to the past. Accordingly, we have also prepared cinchona-ferrocene conjugates with amide and urea spacers displaying significant *in vitro* activity against MCF-7 breast adenocarcinoma, HepG2 hepatoma, HL-60 leukemia and SH-SY5Y neuroblastoma human cell cultures characterized by IC_{50} values in the range of 0.1-4.2 μM concentrations.[15] It must be pointed out here that alkaloid chemistry utilizing click strategy seems to have a real potential in searching novel lead structures as demonstrated by the significant *in vitro* antiproliferative effects of cinchona hybrids with 1,4-disubstituted 1,2,3-triazole linker containing nucleoside[10a] or polyether residue.[10b]

Taking all of the aforementioned precedence into account, on the basis of the concept of fragment-based drug design[16] we envisaged the synthesis of novel hybrids of enhanced activity by reasonable chemical combination of modules having themselves well-documented anticancer effects providing a possibility for a synergic mode of action on appropriate biological targets. Thus, here we report on the synthesis, brief structural characterization and *in vitro* evaluation of the first representatives of ferrocene-cinchona hybrids tethered *via* chalcone- and 1,2,3-triazole moieties along with seven chalcone-free triazole derivatives and a chalcone- and triazole-free alkyne serving as reference molecules to establish preliminary structure-activity relationships.

The synthetic pathway leading to fundamental target structures incorporating the entire set of the envisaged building blocks is terminated by the widely used copper(I)-mediated regioselective Sharpless [2+3] cycloaddition,[17] involving the readily available diastereomeric cinchona-derived alkynes **1a**,**b** and ferrocene-containing azido components **2** and **3** (Scheme 1) prepared by base-mediated condensation of acetylferrocene with the corresponding azidobenzaldehyde (For experimental details: cf. Supporting information).

(*To be inserted here*)

Scheme 1. Synthesis of the targeted ferrocene-cinchona hybrids.

The reactions of alkynes **1a**,**b**[18] with azide components **2** and **3**, respectively, conducted in H_2O/*n*-BuOH (1:1, v/v) for 10 h at room temperature in the presence of low catalyst loading (1 mol% of $CuSO_4$, 5 mol% of Na-ascorbate) (Method *i*.) afforded mixtures of diastereomers, which were separated (isolated yields: 23/51% for**4a**/**4c**; 21/39% for**4b**/**4d**; 23/48% for**5a**/**5c**; and 29/44% for **5b/5d**) with significant dominance of the epimerized products stabilized by intramolecular hydrogen bridge between the hydroxyl group and the quinuclidene N1-atom.[19] The partial epimerization of C9 sterogenic center in the cinchona residue takes probably place *via* reversible deprotonation enabled by the coordination of Cu(I)-species to quinoline N1-atom. Supporting this view, a higher catalyst loading (4 mol% of $CuSO_4$) even with a shorter reaction time (2 h) (Method *ii*) gave rise to increase in both conversion and epimerization (isolated yields: 12/82% for **4a**/**4c**; 23/54% for **4b**/**4d**; 17/80% for **5a**/**5c**; and 24/69% for **5b**/**5d**).

In order to obtain further hybrids with complete set of the envisaged building blocks including 1,5-disubstituted 1,2,3-triazole fragment, we performed click reactions of **1a**,**b** and **2** using complex Cp*RuCl(1,5-COD) as catalyst (Method *iii*: Scheme 1).[20] Both reactions proceeded with concomitant Ru(II)-mediated C9-epimerization resulting in the corresponding cinchona product in reasonable yields (46% for **6c** and 57% for **6d**). The facile epimerization accompanying cycloadditions might again be interpreted in terms of coordination between metal-containing species and the quinoline N1-atom. Besides hybrids **6c**,**d** aminochalchone **7**, resulted from the reduction of the azide component **2**, was also formed under the applied conditions and could be isolated in low yield (16-28%). We also attempted to couple **1a**,**b** and **2** in dioxane at 80 ^oC in the presence of complex Cp*RuCl(PPh_3)$_2$ (Method *iv*). While the reaction of **1b** afforded **6d** in low yield (22%) along with a substantial amount of **7** (35%), under the same conditions **1a** proved to be almost completely resistant to ruthenium-catalysis and the reaction led to the isolation of **7** in mediocre yield (45%). Cinchona hybrid **6c** could only be detected by ^{1}H-NMR in traces in the crude product. These findings suggest that – strongly depending on the nature of the spectator ligands – 9-OH group might coordinate to the Ru(II)-centre to form the catalytically active site which can be docked in the proximity of the alkyne residue in the complex derived from **1b**, but in the diastereomeric

counterpart derived from **1a**, being spatially separated from the ethinyl group, the hydroxyl-coordinated metal centre is not capable of catalysing the click reaction. This view can be considered to be in line with the formation of **7** accompanying [2+3] cycloadditions effected by Ru(II)-catalysed azide-reduction[21] which probably involves the cinchona component as a carbinol-based reducing agent being converted into the alkyne analogue of quininone or quinidinone,[22] however, the isolation and identification of these ketones have failed so far.

The copper-mediated [2+3] cycloaddition of azidoferrocene (**8**), azidomethylferrocene (**9**) and 1,1'-*bis*(azidomethyl)ferrocene (**10**) with alkynes **1a,b** conducted under the conditions of Method *i* resulted in the formation of a set of triazoles of types **12-15** as chalchone-free models. In spite of the low catalyst loading, the majority of these click reactions afforded triazole-tethered hybrids in mediocre yields (78% for **12c**; 87% for **13d** and 64% for **14d** along with azidomethyl compound 1**5d** in low yield (16%)), each of them incorporating cinchona residue with reversed configuration at the C9 stereogenic center. On the other hand, besides **13c** with reversed C9-configuration, a small amount of its epimer (**13a**) with retained C9-configuration could also be isolated from the reaction mixture (yields: 15/65% for **13a**/**13c**). The relative stability of the epimers reflected from the stereochemical outcome of the click reactions was also supported by comparative DFT calculations carried out on reasonably simplified models (cf. Supporting information). To our best knowledge, the copper- and ruthenium-mediated reactions discussed in this contribution are the first examples of transition-metal catalyzed C9-epimerization of cinchona derivatives which can be utilized in related synthetic chemistry.

By means of a Sonogashira protocol, employing DIEA as solvent along with catalyst system composed of CuI (2 mol%) and $PdCl_2(PPh_3)_2$ (5 mol%) (Method *iii*), **1b** and iodoferrocene **11** were coupled to give the alkyne-tethered hybrid **16b**, a further reference model, in reasonable yield (76%). Probably due to the use of amine solvent preventing Cu(I)-species to coordinate to quinoline N1-atom, the formation of **16b** was not accompanied by C9-epimerization.

The measured IR- ^{1}H- and ^{13}C-NMR data of the novel compounds listed in the Supporting information are consistent with their structure, only the following remarks about the discrimination between the diastereomeric pairs of types **a**/**c** and **b**/**d** are necessary to make. Indicating its *endo* orientation in compounds type **c**, proton H9 is involved in NOESY correlations with quinuclidine protons H5α-, H6α-, and H7α, while the NOESY spectra of diastereomers type **a** reveal correlation between H9 and H6α, but do not show interaction between proton pairs H9/H5α and H9/H7α, respectively. Accordingly, the approximate *endo* orientation of the hydroxyl group in compounds type **a** is reflected from the signals of the proximal quinuclidine protons H5α-, H6α- and H7α downfield- shifted by 0.2-0.6 ppm relative to those measured for compounds type **c**.

Due to the anisotropic effect of the proximal hydroxyl group, in the ^{1}H NMR spectra of **4b** and **5b** the signal of H2A and H7β protons are downfield-shiftedby ca. 0.1-0.2 ppm relative to those measured for their epimers **4d** and **5d**, in which the hydroxyl group is anchored in a five-membered chelate ring by a hydrogen bond to the quinuclidine N1-atom. Accordingly, in compounds **4d**, **5d**, **6d**, **12d**, **13d**, **14d** and **15d** characteristic NOE was detected between proton pair H9/H7β.

We have determined the *in vitro* cytostatic activity of the novel hybrids expressed as IC_{50}values on HepG2 hepatoma and HT-29 colorectal adenocarcinoma human tumor cell cultures. The cells were treated with the compounds at 10^{-4} to 10^{2} μM concentration range and the viability was determined by MTT-assay.

Table 1. *In vitro* cytostatic effect of the compounds expressed as IC_{50} values±SD [μM].

	HepG2	HT-29
4a	5.5±1.4	5.3±1.6
4b	14.3±14.5	3.9±0.2
4c	4.3±0.4	5.6±1.6
4d	9.9±0.5	4.5±6.5
5a	4.1±1.9	4.4±1.9
5b	3.4±0.4	2.5±1.3
5c	6.1±3.3	4.1±0.1
5d	4.2±1.2	6.6±7.7
6c	4.4±0.3	4.0±0.2
6d	0.7±0.1	1.5±0.2
12c	73.5±1.3	36.2±0.1
13a	52.8±15.8	17.3±5.9
13c	64.8±10.1	20.8±1.1
13d	64.8±10.1	79.4±4.5
14d	22.8±3.3	25.3±10.0
15d	69.9±1.3	23.5±0.6
16b	17.7±9.0	18.3±2.0
2	19.1±1.3	15.8±1.9
7	15.8±0.8	5.8±0.3
3	>100	79.4±4.5
1a	>100	>100
1b	>100	>100
Tamoxifen	20.0±6.5	15.6±5.7

The data summarised in Table 1 show that, irrespective of the relative configuration at positions 8 and 9 and on the substitution pattern of the phenyl ring attached to thetriazolyl-cinchona module, compounds comprising the entire selection of modules (**4a**,**c**, **5a**–**d**, **6c**,**d**) produced characteristic and pronounced *in vitro* cytostatic effect on both cellcultures studied (IC_{50}=0.7±0.1–6.7±7.7 μM), exceeding the activity of Tamoxifen used as reference. It is interesting to note, that, quinidine and 9-epiquinidine derivatives **4b** and **4d** with 1,2-disubstituted benzene ring displayed similar level of activity on HT-29 cells (IC_{50}=3.9±0.2 and 4.5±6.5 μM, respectively) but these compounds exhibited somewhat less marked effect against HepG2 cell culture (IC_{50}=14.3±14.5 and 9.9±0.5 μM, respectively). On the other hand, **6c** and **6d,** the epiquinine and epiquinidine-based models comprising 1,2-disubstituted benzene ring and 1,5-disubstituted 1,2,3-triazoles moiety were found to display comparable activity against both investigated cell cultures. It must also be emphasized that the latter diasteromer with epiquinidine fragment (**6d**) seems to be most promising hybrid in the group of models comprising the entire set of the envisaged building blocks (IC_{50}=0.7±0.1 and 1.5±0.2 μM, for HEPG2 and HT-29, respectively).

Highlighting a significant contribution of the chalcone fragment to cytostatic effect, except for the slightly deactivated *bis*-triazole derivative **14d** with C_2-symmetry, the majority of ferrocenyl- and ferrocenylmethyltriazoles of types **12-15** displayed considerably decreased *in vitro* antitumor effect on HEPG2 cells (IC_{50}=52.8±15.8 –73.5±1.3 μM). On the other hand, the activities of **12c**, **13a**,**c**, **14d** and **15d** were less pronounced against HT-29 cells relative to those measured for chalcones **4a-d** and **5a-d** (IC_{50}=17.3±5.9 –25.3±10.0 μM). It is worth to note that the sluggish activity of **13d** was significantly enhanced by introduction of a further triazolylmethyl group into the η^5-Cp ring of the organometallic fragment to obtain **14d**. The assay carried out with precursors **2** and **3** revealed the importance of the relative position of azido group and the enone fragment in terms of *in vitro* activity: **2** exhibited pronounced effect on both cell cultures, while its regioisomer **3** with spatially separated functional groups displayed a modest activity on HT-29 cells and proved to be essentially inactive on HEPG2 cells. This difference in activity might be attributed to azide-decomposition processes assisted by the proximal carbon-carbon double bond to generate nitrene-derived species including amine **7** with significant activity presented under the conditions of *in vitro* tests (IC_{50}=15.8±0.8 and 5.8±0.3 μM, for HEPG2 and HT-29, respectively). We also observed that contrary to inactive terminal alkynes **1a**,**b** (IC_{50}>100 μM) ferrocenylalkyne **16b** exhibited comparable effect with Tamoxifen, used as reference compound, against both cell lines investigated.

Taken together, this contribution indicates that the concept of fragment-based drug design seems to be applicable for the development of hybrids incorporating chalcone, ferrocene, 1,2,3-triazole and cinchona modules in the proposed molecular architectures. In this regard it is also important to mention that in preliminary studies hybrids **4a-d** proved to be highly active against MDR cancer stem cell lines.[21] We also disclosed structure activity relationship data (SAR) demonstrating the importance of chalcone moiety as well as the cytostatic effect of an alkyne-tethered ferrocene-cinchona hybrid (**16b**). The surprising *in vitro* activity of (*E*)-3-(2-azidophenyl)-1-(ferrocenyl)prop-2-en-1-one (**2**), characterized by pronounced dependence on substitution pattern, might initiate a conceptually novel approach in the search for a novel class of active molecules. Considering the findings presented here we extend systematically the group of modular hybrids and carry out further SAR studies including cellular uptake studies and mechanistic investigation of possible biological targets with the existing set of active compounds.

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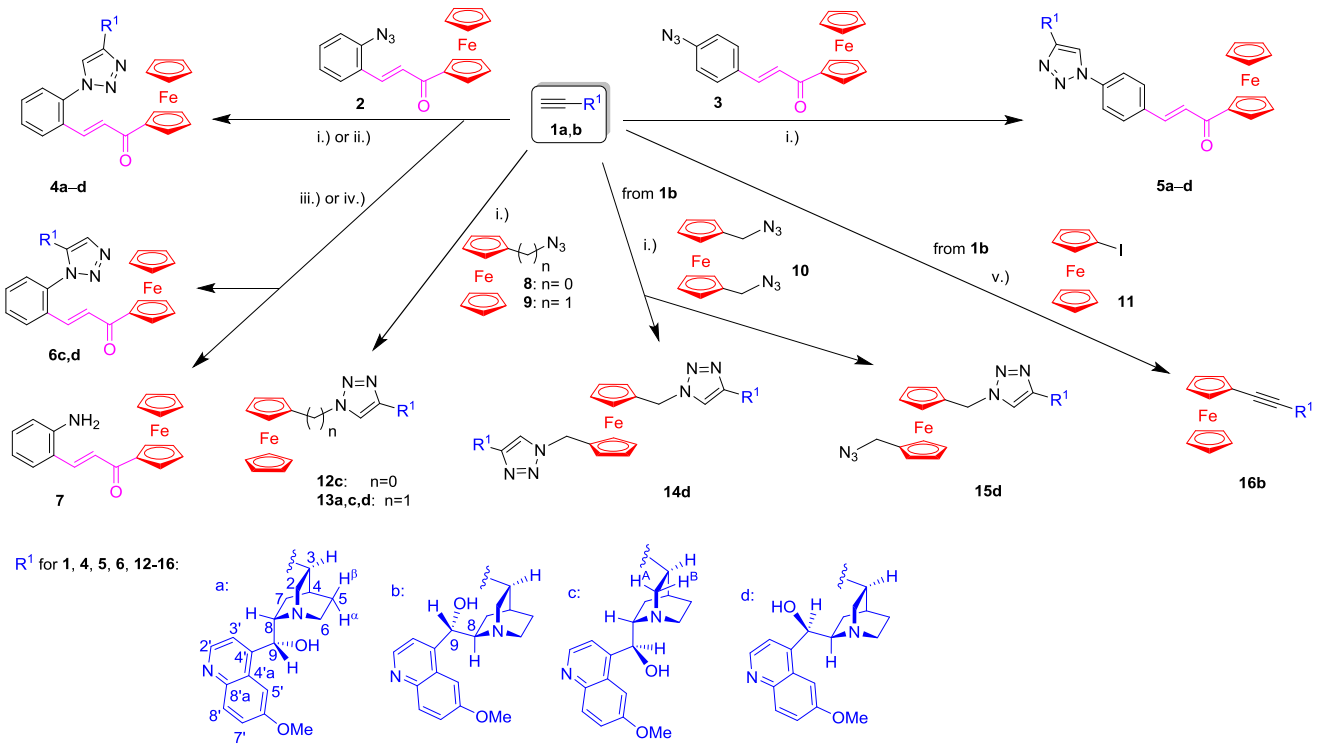

Reaction conditions: i.) $CuSO_4 \cdot 5H_2O$ (1 mol%), Na-ascorbate (5 mol%), H_2O/*n*-BuOH (1:1), rt, 10 h; ii.) $CuSO_4 \cdot 5H_2O$ (4 mol%), Na-ascorbate (20 mol%), H_2O/*n*-BuOH (1:1), rt, 2 h; iii.) Cp*RuCl(1,5-COD) (2 mol%), DCE, 1 h, 45 °C, Ar; iv.) Cp*RuCl(PPh_3)$_2$ (2 mol%), dioxane, 12 h; 60 °C, Ar; v.) CuI (2 mol%), $PdCl_2(PPh_3)_2$ (5 mol%), DIEA, 24 h, 25 °C, Ar.

Scheme 1. Synthesis of the targeted ferrocene-cinchona hybrids.

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Acknowledgments

This work was financially supported by the Hungarian Scientific Research Fund (OTKA K104385, K83874). L K would like to thank the Hungarian Academy of Sciences (MTA) for the 2013 Postdoctoral Fellowship and Domus Hungarica Senior Scholarship.

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Supplementary Material

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