Inorganica Chimica Acta 393 (2012) 276–283

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Synthesis and *in vitro* anticancer activity of ferrocenyl-aminoquinoline-carboxamide conjugates

Adriana Esparza-Ruiz, Christoph Herrmann, Jessie Chen, Brian O. Patrick, Elena Polishchuk, Chris Orvig *

Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

ARTICLE INFO

Article history:
Available online 22 July 2012

Metals in Medicine Special Issue

Keywords:
Aminoquinoline
Carboxamides
Ferrocene
Ferrocenyl-chloroquine conjugates
Cytotoxicity

ABSTRACT

The syntheses and characterization of new multifunctional aminoquinoline-carboxamides and their ferrocene derivatives are reported, as well as their cytotoxicity against human colon adenocarcinoma (Caco-2, HTB-37), human breast carcinoma (HTB-129) and a normal cell line as a control (human normal breast epithelial cells MCF-10A, CRL-10317). All tested compounds showed higher activity against HTB-129 cells than against Caco-2 cells. The ferrocenyl-chloroquine amide conjugates displayed higher activity against both cancer cells than did their parent organic compounds.

1. Introduction

Organometallic compounds that incorporate a ferrocene have attracted considerable attention in medicinal organometallic chemistry; ferrocene has shown itself to be an excellent choice to design new drugs [1–3] due to its small size, aromaticity, hydrophobicity, stability toward air and moisture, and redox behavior. Ferrocene derivatives have shown antimalarial [1,4–17], anticancer [1,2,18–23], antimycobacterial [18,19], antiviral [19], and antibacterial activity [24]. One strategy for improving the activity of biologically active molecules is to incorporate ferrocene into the framework. Some relevant examples are ferrocifen [25,26] and ferroquine derivatives [27,28] (Scheme 1) that have shown higher anticancer and antimalarial activity, respectively, than do their precursor compounds. The biological activity of ferrocenium salts [29] and ferrocene derivatives [1] may be augmented by its capacity to generate hydroxyl radicals ($OH^{\bullet}$) in physiological solutions, inducing oxidative damage to DNA.

Our general aim is the development of methods that provide easy access to anticancer and antimalarial drugs that include ferrocene in their structure and aminoquinolineamide conjugates. Recently, we reported the cytotoxic and antimalarial activities of various ferrocenyl carbohydrate chloroquine conjugates in MDA-MB-435S breast cancer and HTB-37 colon carcinoma cells [17]. The IC_{50} values showed higher anticancer activity in the ferrocene functionalized with chloroquine and carbohydrate groups than in their compounds without chloroquine. In this current work, we report the synthesis and characterization of new aminoquinoline-carboxamides and ferrocenyl-chloroquine amides (Scheme 2) and their *in vitro* anticancer and cytotoxicity activity. We expect that the insertion of amide or ferrocenyl amide groups into the 2-position of chloroquine should improve the biological activity against cancer.

2. Experimental

2.1. Materials and instrumentation

Reagents and analytical grade materials were obtained from commercial suppliers and used without further purification Solvents were dried and distilled prior to use. 3-Chloroaniline, dimethylacetylene dicarboxylate, ferrocene carboxaldehyde, phosphorous(V) oxychloride ($POCl_3$), sodium borohydride ($NaBH_4$), anhydrous ethylenediamine (ETD), anhydrous 1,3-diaminopropane and diphenyl ether (Ph_2O) were purchased from *Sigma–Aldrich*. Reactions in the microwave reactor were performed in a *Biotage* version 2.5. The following instruments were used for physical characterization of the compounds: elemental analyses, *Carlo Erba* Elemental Analyser EA 1108; electrospray ionization mass spectrometry (ESI-MS) spectra, *Micromass* LCT and *Waters* LC–MS; and NMR spectra, Bruker Avance 300 (^1H: 300 MHz and ^{13}C: 75 MHz). Some compounds were separated using a CombiFlash Rf system, *Teledyne Isco*.

2.2. X-ray crystallography

The crystal of **5** was obtained from ethyl acetate. The crystal was mounted on glass fiber, and measurement was made on a

* Corresponding author. Tel.: +1 604 822 4449; fax: +1 604 822 2847.
E-mail address: orvig@chem.ubc.ca (C. Orvig).

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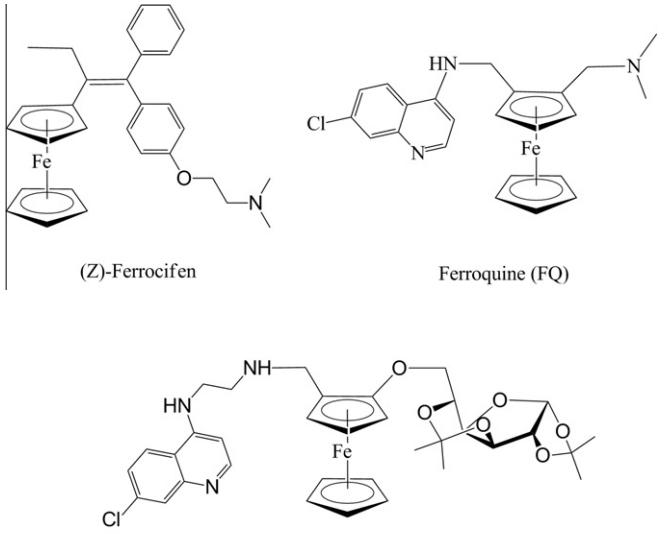
http://dx.doi.org/10.1016/j.ica.2012.06.039

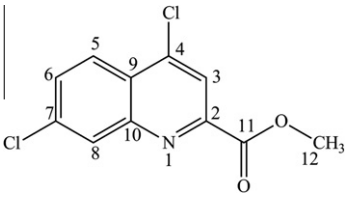


Scheme 1. Ferrocene derivatives with biological activity.

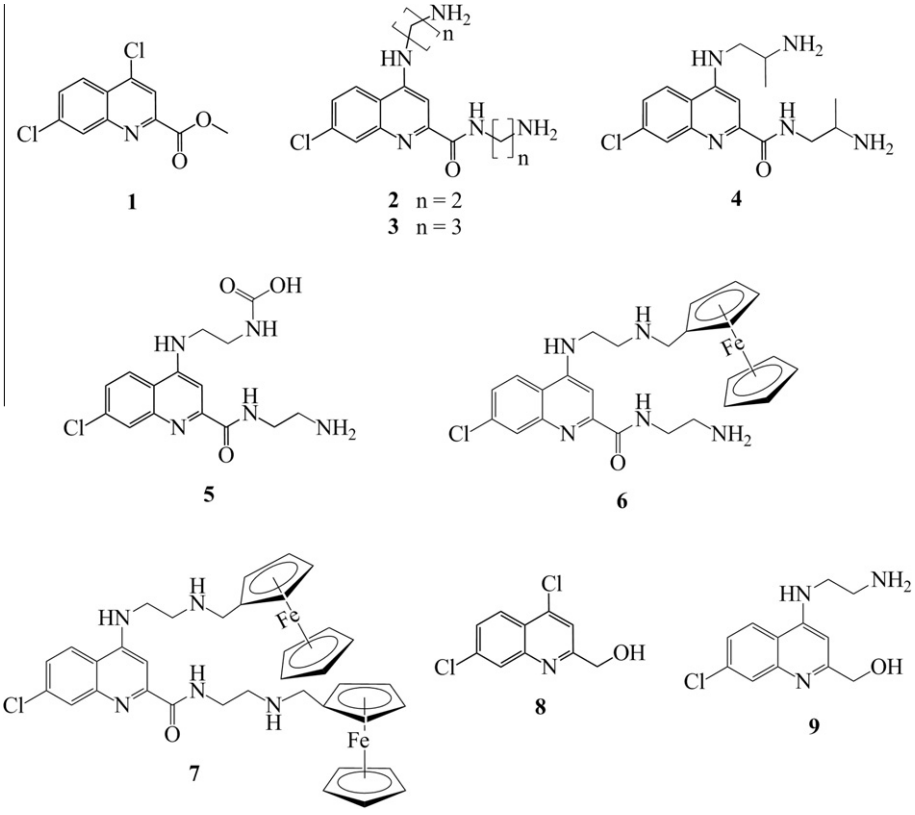
Bruker X8 APEX II instrument using graphite-monochromated Mo Kα radiation. The data were collected at 100 K. The structure was solved with direct methods using SHELX-97 [30]. The material crystallized with two crystallographically independent molecules in the asymmetric unit; the N37-C38-C39-N40 fragment of one molecule is disordered and was modeled in two orientations. Additionally, the material crystallizes with one disordered molecule of methanol in the asymmetric unit. All non-hydrogen atoms were refined anisotropically. All N–H hydrogen atoms were located in difference maps and refined isotropically; however the isotropic thermal parameters were linked to the nitrogens to which they are bonded. The O–H hydrogens were added using the HFIX 147 command. All other hydrogen atoms were placed in calculated positions.

2.3. Synthesis of compounds in Scheme 2

2.3.1. Synthesis of quinoline ester – methyl 4,7-dichloroquinoline-2-carboxylate **1**



Compound **1** was prepared using procedures previously reported [29,30]. 3-Chloroaniline (20.4 mL, 194.3 mmol) was dissolved in MeOH (200 mL), and dimethylacetylene dicarboxylate (25 mL, 203.4 mmol) was then added dropwise (exothermic reaction). The red-brown mixture was heated at reflux for 2 h, and then cooled at rt. After evaporating methanol in vacuum, the solid was dissolved in Ph_2O (50 mL), and added dropwise over 40 min into a solution of Ph_2O (250 °C) with further stirring for 4 h. After, it was cooled at rt. The reaction mixture was filtered and washed with hexane and ether. A yellow solid was obtained (24 g), redissolved in pyridine (150 mL) and refluxed for 1.5 h. The solution was then cooled and the resulting precipitate was filtered, washed with ether, dried under vacuum, and then refluxed with $POCl_3$ (9 mL) for 1 h. After cooling, the excess $POCl_3$ was removed under vacuum, and 1 M NaOH solution was then added to adjust the reaction mixture to pH 8,



Scheme 2. Compounds **1**–**9**.