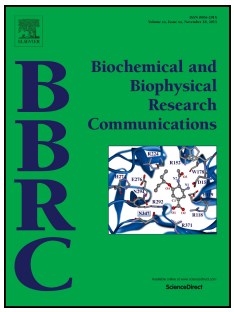
Accepted Manuscript



Anti-tumor activity and cytotoxicity *in Vitro* of novel 4,5-dialkylimidazolium surfactants

Da Wang, Christian Richter, Andreas Rühling, Sabine Hüwel, Frank Glorius, Hans-Joachim Galla

PII: S0006-291X(15)30708-7

DOI: 10.1016/j.bbrc.2015.10.015

Reference: YBBRC 34699

To appear in: *Biochemical and Biophysical Research Communications*

Received Date: 23 September 2015

Accepted Date: 2 October 2015

Please cite this article as: D. Wang, C. Richter, A. Rühling, S. Hüwel, F. Glorius, H.-J. Galla, Anti-tumor activity and cytotoxicity *in Vitro* of novel 4,5-dialkylimidazolium surfactants, *Biochemical and Biophysical Research Communications* (2015), doi: 10.1016/j.bbrc.2015.10.015.

Anti-tumor activity and cytotoxicity *in Vitro* of novel 4,5-dialkylimidazolium surfactants

Da Wang[a], Christian Richter[b], Andreas Rühling[b], Sabine Hüwel[a] ,Frank Glorius[b], Hans-Joachim Galla[a,*]

[a] *Institut für Biochemie, Westfälische Wilhelms-Universität Münster, Wilhelm-Klemm-Straße 2, D-48149 Münster, Germany*

[b] *Organisch Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, D-48149 Münster, Germany*

[*] Corresponding author. Tel.: +49 251 83 33201; fax: +49 251 83 33206.
E-mail address: gallah@uni-muenster.de (H.-J. Galla).

Abstract

Natural monoalkylated imidazolium derivatives exhibit significant anti-tumor activity as well as general cytotoxicity. In the present study, we used a series of newly synthesized imidazolium derivatives bearing two alkyl chains in the backbone of the imidazolium core in 4- and 5-position and either dimethyl- or dibenzyl-substituents at 1- and 3-position. Their anti-tumor activity and cytotoxicity were determined *in vitro* using the lactate dehydrogenase (LDH) assay. The tumor cell line C6 from rat glioma , the non-tumor MDCK cell line (Madin-Darby canine kidney) as well as the mouse embryonic fibroblast cell line (NIH3T3) were used as cellular targets. Surface activity measurements were performed leading to the determination of their critical micelle concentration (CMC) of these new lipid analogues to evaluate the molecular mechanism of the observed cellular effects. We found that 4,5-dialkylation of the imidazole ring enhances the anti-tumor activity compared to simple 1-alkylated imidazoles. The corresponding C_7 homologues are found to be the most potent compounds. Furthermore dibenzyl-substituted imidazolium surfactants exhibit higher surface activity and increased toxicity against tumor cells compared to dimethyl-substituted imidazolium surfactants. In summary the dibenzyl-derivative carrying the two C_7 chains was found to exhibit a drastically increased anti-tumor activity especially compared to so far known monoalkylated species.

Keywords: anti-tumor activity, cytotoxicity, 4,5-dialkylimidazolium salt

Abbrevations: EC_{50}, half maximal effective concentration; NCS, N-chlorosuccinimide; FBS, fetal bovine serum; INT, 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl-2*H*-tetrazolium.

1. Introduction

Imidazolium salts are an important class of biologically active nitrogen-containing heterocycles that have attracted considerable attention due to their significant biological activities, especially their anti-tumor activity and cytotoxicity [1,2]. Alkylated imidazolium derivatives exist in nature exhibit significant anti-tumor activity due to their interactions with biological membranes. Known natural compounds are the imidazolium derivatives Lepidiline A and