European Journal of Medicinal Chemistry 78 (2014) 248–258

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Biological evaluation of new mimetics of annonaceous acetogenins: Alteration of right scaffold by click linkage with aromatic functionalities

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ARTICLE INFO

Article history:
Received 18 October 2013
Received in revised form
19 March 2014
Accepted 20 March 2014
Available online 21 March 2014

Keywords:
Annonaceous acetogenins
Quinone
Aromatic functionalities
Click chemistry
Cytotoxicity

ABSTRACT

A small library of analogues of annonaceous acetogenins through click linkage with aromatic moieties is established using a convergent modular fragment-assembly approach. These analogues exhibited low micromolar inhibitory activities against the proliferation of several human cancer cell lines. Structure–activity relationship (**SAR**) of these analogues indicates that replacement of the methoxy groups of ubiquinone ring with methyl groups is proved to be a useful strategy for improving the anticancer activity of quinone–acetogenin hybrids.

1. Introduction

Annonaceous acetogenins, a large unique family of natural polyketides with more than 400 members, have been isolated and characterized from *Annonaceous* plants growing in tropical and subtropical regions in the past three decades [1–3]. Most acetogenins exhibit a broad spectrum of bioactivity such as antitumor, immunosuppressive, antimalarial, antifeedant, and insecticidal activities, among which their antitumor activities are probably most attractive. It is generally accepted that the main mode of action of acetogenins is the blockage of complex **I** (**NADH**-ubiquinone oxidoreductase) in mitochondria [4,5]. Due to their unique chemical structures and excellent antitumor activities, annonaceous acetogenins have been attracting worldwide attention [1,2,6]. We have engaged in simplifying the structure of natural acetogenins with medicinal considerations for several years [7–15]. In our previous studies, a mimic of naturally occurring acetogenins-AA005 have been successfully developed by replacement of the THF rings of natural bullatacin with an ethylene glycol ether unit and exhibited very potent antitumor activity against a variety of human cancer cell lines in low to medium nanomolar range, whereas it had low cytotoxicity against normal human cells [8–10]. Subsequently, we also developed a new mimic **1** bearing a biphenyl moiety in the left hydrocarbon chain part, which was identified to show more potent inhibitory activity and higher selectivity against cancer cells than normal cells by comparison with AA005 [16].

The γ-lactone moiety of most natural acetogenins was suggested to probably interact with the quinone binding site of complex **I**. To clarify the mode of action of acetogenins, Koert et al. designed two hybrid analogues in which the γ-lactone moiety was replaced with the quinone portion of ubiquinone, a natural substrate of complex **I**. The hybrid analogue quinone–mucocin showed

Abbreviations: NADH, nicotinamide adenine dinucleotide; THF, tetrahydrofuran; TMS, trimethylsilyl; DCM, dichloromethane; DIPEA, Ethyldiisopropylamine; TBAF, tetrabutylammonium fluoride; MOMCl, chloromethyl methyl ether; BTEAC, benzyltriethylammonium chloride; DMF, N,N-dimethylformamide.

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http://dx.doi.org/10.1016/j.ejmech.2014.03.062
0223-5234/

10 times more potent complex **I** inhibitory activity than that of natural mucocin [17–19]. This mentioned that exchange of the γ-lactone moiety of natural acetogenins with other aromatic structural equivalents might remain the bioactivity. Click chemistry has been increasingly applied as a useful tool in biomedical research and drug discovery in the past two decades. It greatly simplifies compound synthesis, providing the means for faster lead discovery and optimization. For lead optimization, it enables rapid SAR profiling, through generating analog libraries quickly and reliably by joining small units together [20–23]. According to the structural characteristics of compound **1**, we wish to explore small focused library of annonaceous acetogenin analogues by replacing the γ-lactone moiety with various aromatic functionalities with Click chemistry (Fig. 1). Practically, generation of proper aromatic moieties in the right region of compound **1**-like molecules using two pre-functionalized fragments alkynes and azides would provide a new convergent access to this class of anticancer compounds. Herein, we report our results from this approach, by which the γ-

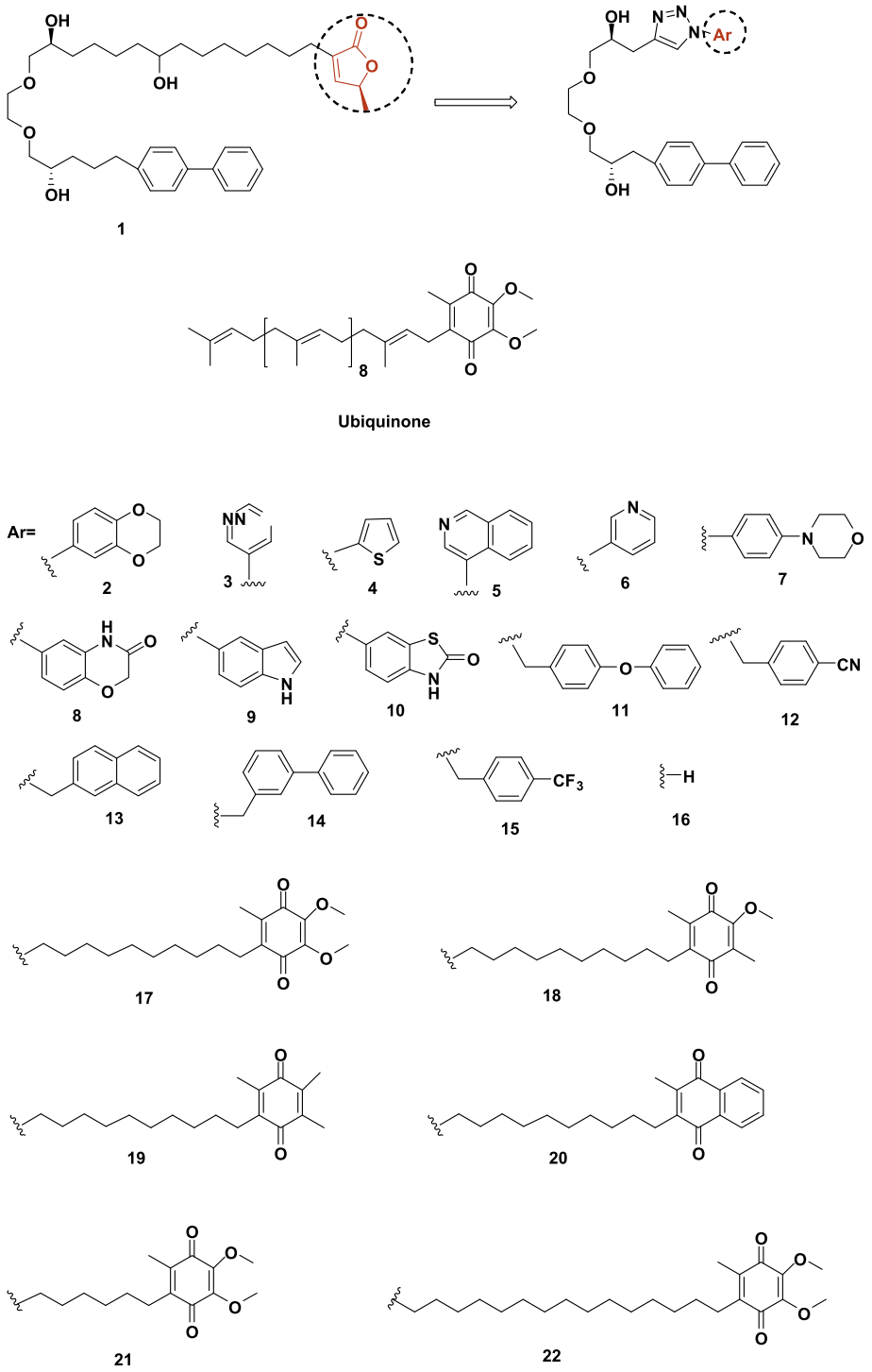

Fig. 1. Design of acetogenin analogues by click linkage with aromatic functionalities.