Bioorganic & Medicinal Chemistry Letters 28 (2018) 2023–2028

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Investigation of chemical reactivity of 2-alkoxy-1,4-naphthoquinones and their anticancer activity

Manoj Manickam, Pulla Reddy Boggu, Jungsuk Cho, Yeo Jin Nam, Seung Jin Lee, Sang-Hun Jung *

College of Pharmacy and Institute of Drug Research and Development, Chungnam National University, Daejeon 34134, Republic of Korea

ARTICLE INFO

Article history:
Received 22 February 2018
Revised 20 April 2018
Accepted 25 April 2018
Available online 26 April 2018

Keywords:
2-Alkoxy-5-hydroxy-1,4-naphthoquinone
Anticancer activity
Chemical reactivity

ABSTRACT

To establish the structure-activity relationship of 5-hydroxy-1,4-naphthoquinones toward anticancer activity, a series of its derivatives were prepared and tested for the activity (IC_{50} in μM) against three cell lines; colo205 (colon adenocarcinoma), T47D (breast ductal carcinoma) and K562 (chronic myelogenous leukemia). Among them **2** (IC_{50}: 2.3; 2.0; 1.4 μM), **6** (IC_{50}: 1.9; 2.2; 1.3 μM), **9** (IC_{50}: 0.7; 1.7; 0.9 μM) and **10** (IC_{50}:1.7; 1.0; 1.2 μM) showed moderate to excellent activity. Our perception toward the DNA substitution of alkoxy groups at the C2 position of these naphthoquinones for the anticancer activity led us to investigate their reactivity of substitution toward dimethylamine as a nucleophile. The ease of the substitution of alkoxy groups at the C2 position with dimethylamine is strongly accelerated by hydroxyl group at C5 position and is well correlated with the found anticancer activity results.

Cancer is a major health problem worldwide and the second most common cause of death.[1] The number of people living beyond a cancer diagnosis reached nearly 14.5 million in 2014 and is expected to rise to almost 19 million by 2024.[1] Screening for new anticancer drugs is still important and is one of the major goals in medicinal chemistry.[2] Mass screening programs of natural products by the National Cancer Institute have identified the quinone moiety as an important pharmacophoric element for cytotoxic activity.[3] Quinones are widely distributed in nature,[4] and are represented in many clinically used drugs (e.g. doxorubicin, daunorubicin, mitoxantrone, mitomycin-C (Fig. 1)).[5,6] Two major mechanisms have been proposed for the anticancer action of quinones in a variety of cell systems. First, quinones undergo one electron reduction by enzymes such as microsomal NADPH-cytochrome P-450 reductase or mitochondrial NADH-ubiquinone oxidoreductase, yielding the corresponding semiquinone radicals.[7,8] Under aerobic conditions, the semiquinone radical then participates in redox cycling to generate superoxide anion, all of which are believed to be responsible for most of the drug activity.[9,10] Second, quinones are potent electrophiles, capable of reacting with the thiol groups in proteins as well as GSH.[11,12] Depletion of GSH has been associated with menadione-induced cytotoxicity.[11,13] In addition, cytotoxic quinone derivatives were proven to be topoisomerase I and II inhibitors.[14] Among the quinones, 1,4-naphthoquinones have been found to possess a diverse range of biological activities, in particular, they exhibit potent anticancer activity.[15–19] For example, starting from simple menadione to calothrixins A and B (Fig. 1), they exhibit potent anticancer activities.[20,21] The attachment of variety of functional groups such as amines, esters, sulfonamides, to the 1,4-naphthoquinone system are proven to improve their anticancer activities.[22–25] In a similar fashion, the fusion of many heterocycles to 1,4-naphthoquinone system such as furan, pyran etc., have also been synthesized and checked for anticancer activity.[26] An interesting subgroup of 1,4-naphthoquinones is 5-hydroxy-1,4-naphthoquinones. For e.g. juglone and plumbagin possess anticancer property (Fig. 1).[27–30] Some of the esters attached to 5-hydroxy-1,4-naphthoquinone have also been prepared and showed anticancer activity. [31]

Since 5-hydroxy-1,4-naphthoquinones are not well explored for its anticancer activity, we were interested to design and synthesis a series of 5-hydroxy-1,4-naphthoquinone analogs and establish its structure-activity relationship.

Scheme 1 represents the preparation of compounds **1**–**5**. Compounds **1** and **4** were prepared according to the literature procedure with slight modifications.[32] The commercially available juglone (**11**) was reacted with dimethylamine at −20 °C to obtain **12** as major product and **13** as minor product. Both the products upon refluxing with 10% HCl yielded the corresponding **1** and **4**. Compounds **1** and **4** on methylation with methyl iodide in presence of sodium carbonate yielded **2** and **5**, respectively. The dimethoxy derivative **3** was prepared by the methylation of **2** with methyl iodide using potassium carbonate as base.

* Corresponding author.
E-mail address: jungshh@cnu.ac.kr (S.-H. Jung).

https://doi.org/10.1016/j.bmcl.2018.04.060
0960-894X/

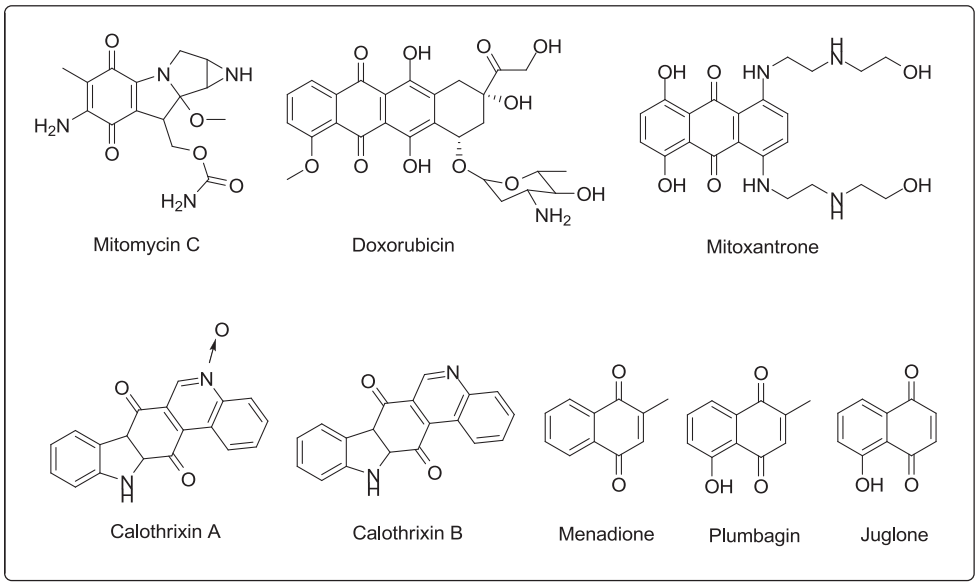
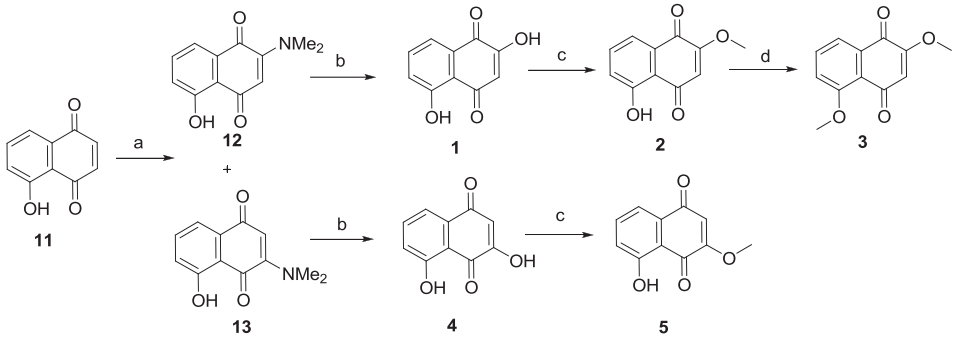
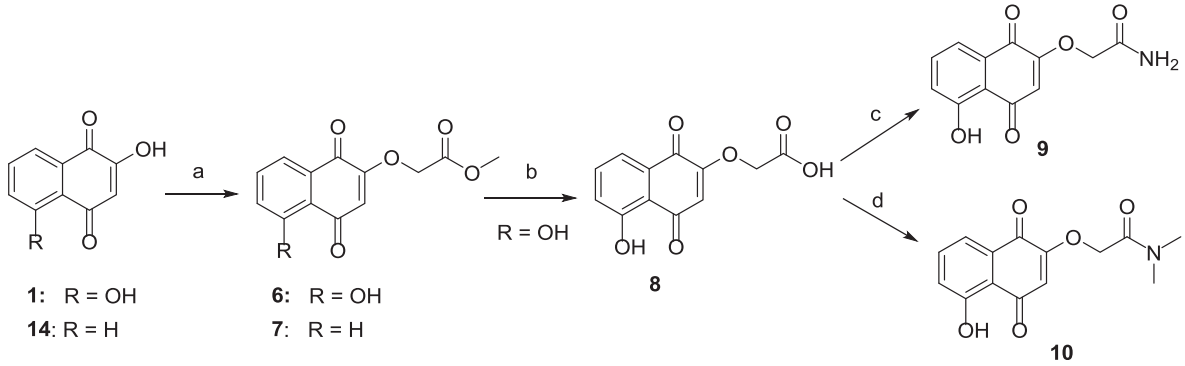


Fig. 1. Anticancer 1,4-naphthoquinones and 5-hydroxy-1,4-naphthoquinones.



Scheme 1. Preparation of compounds **1**–**5**. *Reagents and condition:* a) Dimethylamine (2M in THF), toluene, −20 °C, 24 h b) 10% HCl, dioxane, reflux, 5 h c) CH_3I, Na_2CO_3, DMF, RT, 10 h d) CH_3I, K_2CO_3, DMF, RT, 15 h.



Scheme 2. Preparation of compounds **6**–**10**. *Reagents and condition:* a) $BrCH_2COOCH_3$, Na_2CO_3, DMF, 0 °C to RT, 5 h b) 3 M H_2SO_4, 10 h, RT c) (i) $SOCl_2$, DCM, reflux, 2 h (ii) NH_4OH, 0.5 h, RT d) dimethylamine (2M in THF), DCC, HOBT, THF −5 °C to RT, 8 h.

The synthesis of compounds **6**–**10** is denoted in Scheme 2. The prepared compound **1** (R = OH) and the commercially available compound **14** (R = H) on reaction with methyl bromoacetate using sodium carbonate as base afforded the corresponding C2-O-alkylated analogs **6** and **7**. The occurrence of O-alkylation at C2-position of **1** to form **6** was supported by the literature.[31] Further it was substantiated by the assignment through NOESY spectrum. The one proton singlet at 3rd position (H-3) of the naphthoquinone appears at δ 5.99 ppm. The OCH_2 proton at 2nd position appears δ 4.75 ppm and has a correlation with H-3 at δ 5.99 ppm as shown in the NOESY spectrum (see Supporting Information).

The hydrolysis of the methyl ester of **6** to its carboxylic acid **8** was carried out using 3 *M* sulfuric acid at ambient temperature. The carboxylic acid **8** was converted to its amide **9** by refluxing