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Original article

Cytotoxic, antioxidant activities and structure activity relationship of some newly synthesized terpenoidal oxaliplatin analogs

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Abstract

The terpenoidal oxaliplatin derivatives (**6**) and (**12**) were newly synthesized using 2β,3α-dihydroxy-11-oxo-18β-olean-12-ene-30-oic acid (**1**) and 2α,2β-dihydroxy-18β-ursan-12-ene-28-oic acid (**7**) as starting materials. The synthesized compounds were evaluated for their cytotoxicity and antioxidant activities and were compared to Oxaliplatin® and vitamin C as positive controls. Some of the compounds exhibited better cytotoxicity and antioxidant activities than the reference controls. The detailed synthesis, spectroscopic data, toxicity (LD_{50}) and pharmacological screening for the synthesized compounds were reported.

Keywords: Terpenoid diol; Oxaliplatin derivatives; Cytotoxic; Antioxidant activity

1. Introduction

The 2-benzylidene derivatives of glycyrrhetinic acid and the C-30 esters and amides of glycyrrhetinic acid were prepared [1,2]. The benzylidene derivatives showed potent anti-ulcer activities, while both the ester and amide derivatives showed potent analgesic activities [1,2]. Further chemical alterations on glycyrrhetinic acid and oleanolic acid lead to the synthesis of their 3-menthyl carbonyl derivatives that exhibited potent anti-ulcer activities [3], also synthesis of the ureides derivatives of both glycyrrhetinic acids and oleanolic acid of moderate anti-inflammatory potency has been reported [4]. El-Gamal et al. [5,6] described the synthesis of 2β,3α-glycol derivatives of glycyrrhetic acid but they didnot investigate its anticancer activity. Recently Chao-Mei et al. [7] described the isolation of 2α-hydroxyl-ursolic acid (**7**) from the ethyl acetate extract of the peel of apples (*Malus pumila* Mill). In view of these reports and in continuation of our previous works in chemistry of natural products [8–12], we have synthesized some new compounds containing a terpenoid ring system for biological evaluation against colorectal carcinoma in comparison to Oxaliplatin as the reference drug. Also the antioxidant activities of the newly synthesized compound were estimated and compared to that of vitamin C as positive control. The chemical structures of glycyrrhetinic acid and Oxaliplatin are given in Fig. 1.

2. Results and discussion

2.1. Chemistry

2β,3α-Dihydroxy-11-oxo-18β-olean-12-ene-30-oic acid (**1**) and 2α,2β-dihydroxy-18β-ursan-12-ene-28-oic acid (**7**) were synthesized and isolated according to the literature [5–7] and were used as starting materials. The carboxylic acid derivatives **1** and **7** were esterified with diazomethane in chloroform to give the corresponding methyl ester derivatives **2** and **8** this reaction was completed according to the method given by Dean et al. [13] for the protection of the carboxylic group. The methyl esters **2** and **8** were reacted with sodium azide in the presence of methane sulfonyl chloride and triethylamine to give the corresponding diazide derivatives **3** and **9** according to the literature method [14–17]. The terpenoidal diamine

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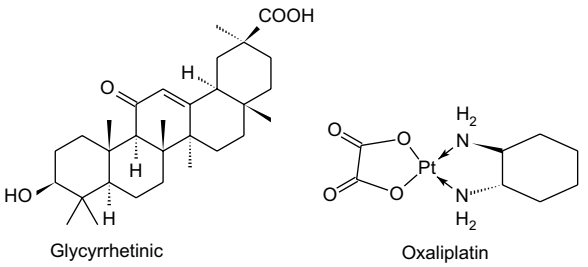


Fig. 1.

ligands **4** and **10** were isolated after catalytic hydrogenation of diazide derivatives **3** and **9** over palladium charcoal (Pd/C) in formic acid [18,19] (Schemes 1 and 2).

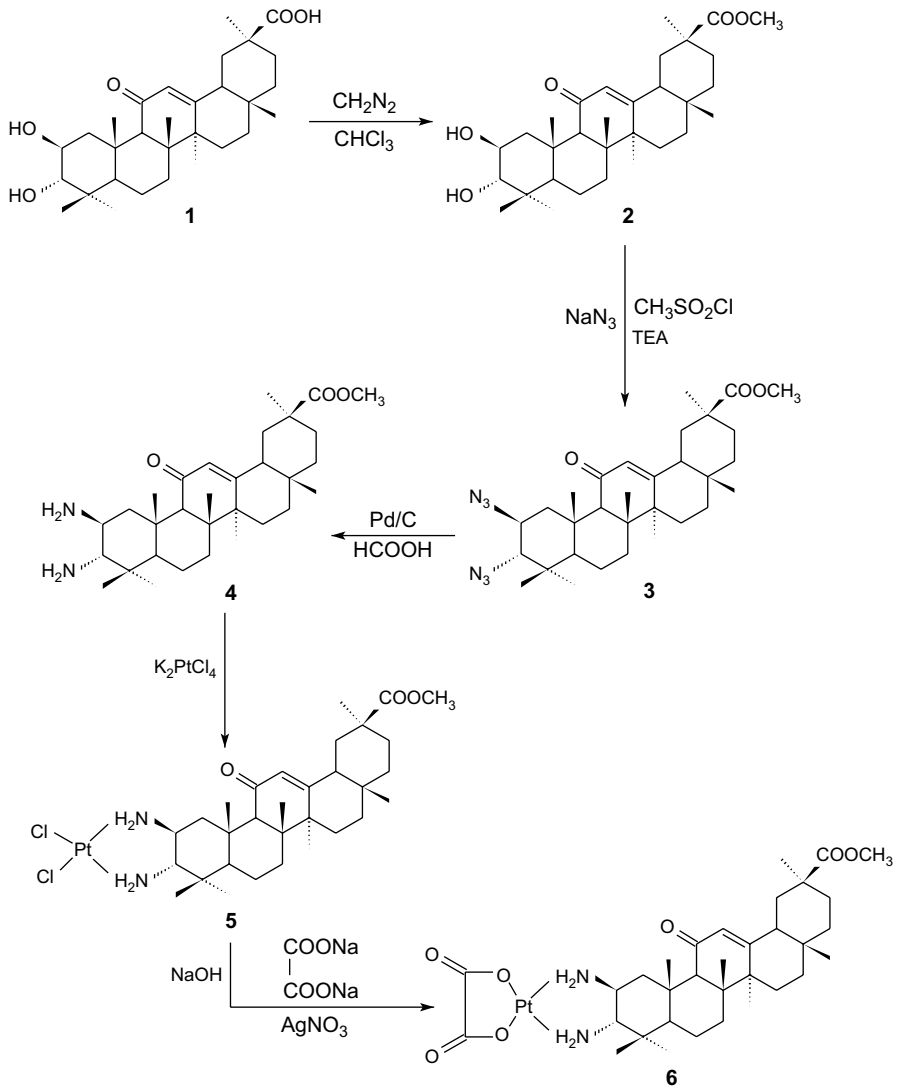
The diaminodichloroplatinum complexes **5** and **11** were synthesized via the reaction of potassium tetrachloroplatinate (II) (K_2PtCl_4) with diamine ligands **4** and **10**. The reaction of sodium oxalate with diaminodichloroplatinum complexes **5** and **11** in water in the presence of silver nitrate ($AgNO_3$) as a precipitating agent for chloride and in the presence of sodium hydroxide, gave the final oxalate complexes **6** and **12** in good yields Schemes 1 and 2.

2.2. Pharmacological screening

Initially, the acute toxicity of the compounds was assayed via the determination of their LD_{50}. All compounds were interestingly less toxic than the reference control (Table 1). The 12 compounds **1**–**12** were further studied for their cytotoxic and antioxidant activities.

2.2.1. Cytotoxic activity

From Table 2, all the newly synthesized tested compounds showed potent cytotoxic activities against HT-29 cell line (colorectal carcinoma). The cytotoxic activities increase as the doses increase, therefore the 150 μg/ml doses induced more cell death than the 100 μg/ml doses and the latters induced more cell death than 50 μg/ml doses. Also the cytotoxic activities increase by increasing the time of contact between cell line and cytotoxic agents at any given dose level. So the cell



Scheme 1.