European Journal of Medicinal Chemistry 87 (2014) 735–744

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis of cyclic 1,9-acetal derivatives of forskolin and their bioactivity evaluation

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ARTICLE INFO

Article history:
Received 10 June 2014
Received in revised form
2 October 2014
Accepted 6 October 2014
Available online 7 October 2014

Keywords:
Forskolin
Acetal derivatives
Ceric ammonium nitrate
Anticancer activity
α-Glucosidase activity

ABSTRACT

A new series of 1,9-acetals of forskolin were synthesized by treating with aromatic and aliphatic aldehydes using Ceric ammonium nitrate as catalyst and evaluated for anticancer and α-glucosidase inhibition activities. Among the synthesized compounds **2a**, **2b** and **3a** showed potential cytotoxic activity towards human cancer cell lines MCF-7 (Human Breast Adenocarcinoma), MDA-MB (Human Breast Carcinoma), HeLa (Human Cervix Adenocarcinoma), A498 (Human Kidney Carcinoma), K562 (Human Erythromyeloblastoid leukemia), SH-SY5Y (Human Neuroblastoma), Hek293 (Human Embryonic Kidney) and WRL68 (Human Hepatic) with IC_{50} values ranging between 0.95 and 47.96 μg/ml. Osmotic fragility test revealed compound **3a** as non-toxic to human erythrocytes at the tested concentrations of 50 and 100 μg/ml. Compounds **1g** (IC_{50} value 0.76 μg/ml) and **1p** (IC_{50} value 0.74 μg/ml) significantly inhibited α-glucosidase in *in vitro* system. *In silico* based docking, ADME and toxicity risk assessment studies also showed discernible α-glucosidase activity for compounds **1g**, **1p** compared to standard acarbose.

1. Introduction

Generally, synthesis of natural products proceeds *via* protection and deprotection sequences [1–3]. In the recent years, much attention has been focused on the synthesis of acetal protected compounds [4–6], due to their significant biological activity. Many semi synthetic derivatives of natural products having the acetal moiety showed either enhanced or a different activity altogether. For example, semisynthetic acetal derivatives of Podophyllotoxin [7,8], andrographolide [9] and taxanes [10] (Fig. 1), are currently used in the treatment of a variety of malignancies.

Forskolin **1**, is a highly oxygenated major labdane type diterpenoid present in the roots of *Coleus forskohlii* [11,12]. Forskolin exerts most of its biological activity by stimulation of adenylate cyclase by increasing cellular concentrations of the second messenger, cyclic AMP [13]. It also displays a wide variety of physiological activities such as branchospasmolytic [14], antihypertensive, inotropic [15,16], antiglaucoma [17], cardiovascular [18], antiobesity [19] and anticancer [20,21] activity etc. 7-deacetylforskolin **2**, another major phytochemical of the plant, displays a lowering of blood pressure although less intense than that of forskolin, but equipotent in spontaneously hypertensive rats [14,15]. The third major phytoconstituent, isoforskolin **3** was found to stimulate cyclic AMP and therefore, decrease blood pressure and produce an inotropic effect lesser than that produced by forskolin [15,22,23]. Considering the various biological potentials exhibited by forskolins (**1**, **2** and **3**) and their high natural abundance in the plant, authors felt to synthesize their 1,9-acetal derivatives and screen them for *in vitro* anticancer and antidiabetic potentials.

The most commonly used methods [24] for the synthesis of acetals involves the catalytic condensation of either 1,2 or 1,3-diols with aldehydes or dimethyl/diethyl acetals in the presence or absence of dehydrating agents. These methods suffer harsh reaction conditions, use of toxic catalysts, acidic reaction conditions and competitive products formation by elimination, dehydration, isomerization, decomposition etc. Hence, these methods are not

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http://dx.doi.org/10.1016/j.ejmech.2014.10.013
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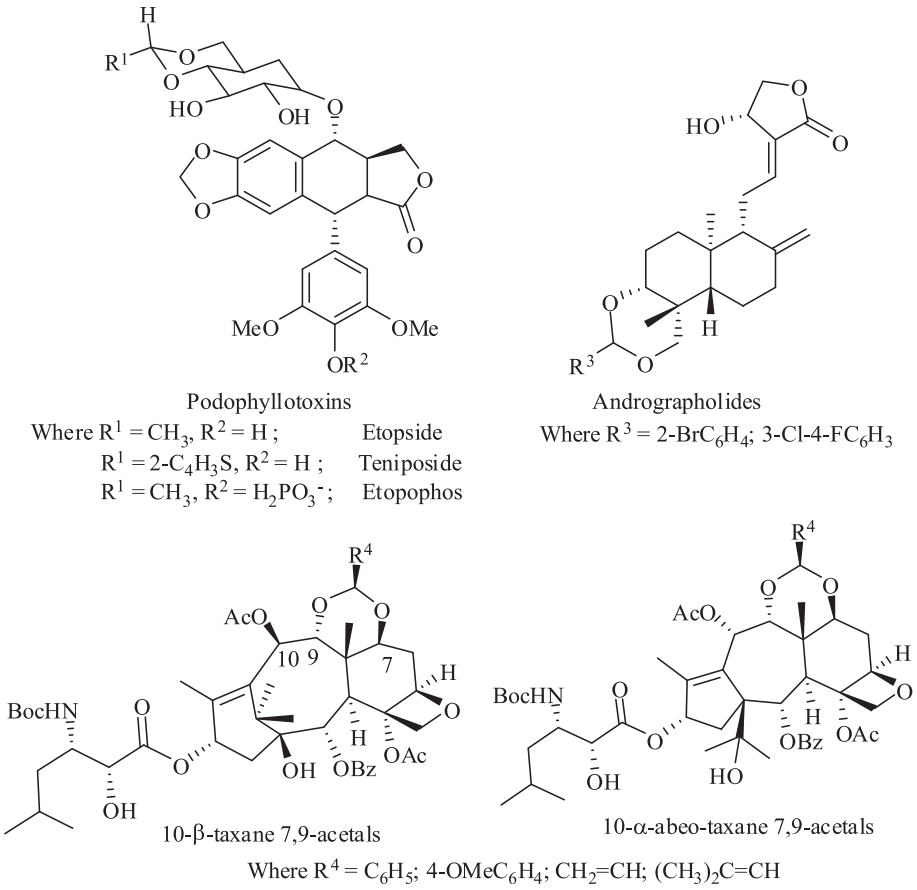

Fig. 1. Semisynthetic derivatives of Podophyllotoxin, Andrographolide and Taxanes.

applicable for natural products especially with acid sensitive functional groups. Ceric ammonium nitrate (CAN) [25] is the most notable one electron oxidant and has been utilized extensively for a broad variety of oxidative transformations in synthetic chemistry. Additional advantages such as excellent solubility in water, inexpensiveness, ecofriendly nature and high reactivity makes CAN a potent catalyst in organic syntheses. CAN is also used as a powerful catalyst in oxidation [26], nitration [27], 1,3-dipolar cycloaddition [28], thiocyanation [29], esterification [30], 1,4-addition [31] and in the biginelli reaction [32]. In the present work, we have synthesized a series of novel 1,9-acetal derivatives of forskolins (**1**, **2** and **3**) isolated from *C. forskohlii*, using CAN as a catalyst, and evaluated for *in vitro* anticancer and α-glucosidase inhibition activity. Compounds exhibiting potent cytotoxic activity against human cancer cell lines were further evaluated for their toxicity on human erythrocytes by performing osmotic fragility test and compounds showing potential α-glucosidase inhibition were also confirmed by docking and ADMET studies.

2. Result and discussion

2.1. Chemistry

The synthetic strategy was as depicted in Scheme 1, forskolin **1** was treated with a series of aliphatic/aromatic aldehydes **a**–**p** in the presence of CAN (30 mol %) in acetonitrile at room temperature for 12–24 h and, as envisaged, the reactions proceeded smoothly to afford the corresponding forskolin-1,9-acetals (**1a**–**1p**) in excellent yields. Acetonitrile was the best solvent for acetal formation amongst methanol, ethyl acetate, chloroform or water. Although the amount of catalyst has been optimized to 30 mol % but, lesser amounts like 5, 10 or 20 mol % also worked with longer reaction times. The reaction was chemoselective for the aldehydes when carried out as a mixture of benzaldehyde **a** and acetophenone during the synthesis of compound **1a**. Also, the reaction was highly regioselective, when 7-deacetylforskolin **2** was reacted with **a** and **b**, at same reaction conditions, compounds **2a** and **2b** were formed by protecting *cis*-1,9 diol without affecting *cis*-6,7 or *trans*-7,9-diols. Similarly, when isoforskolin **3** was treated with **a** and **b**, under above conditions, compounds **3a** and **3b** were formed majorly without affecting *trans*-7,9 diol. The catalyst CAN's ability of regioselectivity was also proved when **1a** and **3a** were deacetylated with methanolic KOH to get compound **2a** in good yields (Scheme 2).

Structures of all the derivatives were elucidated by ^{1}H, ^{13}C NMR, MS and IR spectral data. Further, the structure and stereochemistry of compounds **2a** and **3b** were also confirmed by single crystal X-ray diffraction studies. The perceptive view of **2a** and **3b** given in Fig. 2 and the new stereo centre formed in cyclic 1,9-acetals is confirmed as (*S*) conformation.

2.2. Biology

2.2.1. In vitro anticancer screening

Forskolins and all acetal derivatives were screened for *in vitro* cytotoxic activity by performing MTT assay against various human cancer cell lines including MCF-7 (Human Breast Adenocarcinoma), MDA-MB (Human Breast Carcinoma), HeLa (Human Cervix