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Aminoadamantanes containing monoterpene-derived fragments as potent tyrosyl-DNA phosphodiesterase 1 inhibitors

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ABSTRACT

The ability of a number of nitrogen-containing compounds that simultaneously carry the adamantane and monoterpene moieties to inhibit Tdp1, an important enzyme of the DNA repair system, is studied. Inhibition of this enzyme has the potential to overcome chemotherapeutic resistance of some tumor types. Compound (+)-**3c** synthesized from 1-aminoadamantane and (+)-myrtenal, and compound **4a** produced from 2-aminoadamantane and citronellal were found to be most potent as they inhibited Tdp1 with IC_{50} values of 6 and 3.5 μM, respectively. These compounds proved to have low cytotoxicity in colon HCT-116 and lung A-549 human tumor cell lines (CC_{50} > 50 μM). It was demonstrated that compound **4a** at 10 μM enhanced cytotoxicity of topotecan, a topoisomerase 1 poison in clinical use, against HCT-116 more than fivefold and to a lesser extent of 1.5 increase in potency for A-549.

1. Introduction

Tyrosyl-DNA phosphodiesterase 1 (Tdp1) is a member of the phospholipase D superfamily, catalyzes the hydrolysis of a phosphodiester bond between a tyrosine residue and a DNA 3′-phosphate and functions as a DNA repair enzyme that cleaves stalled Top1–DNA complexes. Moreover, Tdp1 is able to initiate cleavage of apurinic/apyrimidinic sites in DNA, abundant DNA lesions appearing spontaneously or during base excision DNA repair. For more details, see the review [1]. It plays a key role in the removal of DNA damage resulting from inhibition of topoisomerase 1 (Topo1) with camptothecin and its clinical derivatives irinotecan and topotecan [2]. It is also involved in the removal of DNA damage caused by chain-terminating nucleoside analogs (CTNAs) widely used as antiviral drugs [3]. Furthermore, Tdp1 is known to be capable of removing the DNA damage induced by other anticancer drugs commonly used in clinical practice (temozolomide, bleomycin, etoposide, etc.) [4]. Relatively few Tdp1 inhibitors have been described in the literature and most of them have modest inhibitory effect [5–11]. Therefore, searching for novel, potent and specific Tdp1 inhibitors is of great interest.

Synthetic transformation of natural biologically active metabolites to design novel drugs is a successful strategy in medicinal chemistry. During the period between the 1940s and 2014, 49% of anticancer pharmaceuticals introduced to clinical practice were either natural compounds or their derivatives [12]. Monoterpenoids, plant secondary metabolites, are known to possess activity against certain tumor types [13], for example, citral (Scheme 1) at 22 μM induced apoptosis in several hematopoietic cancer cell lines [14]. Compounds carrying the adamantane moiety exhibit a broad range of biological activities [15]. Some of them are active against different cancer types: e.g., adaphostin (NSC680410) [16] and adarotene (ST1926) [17] (Scheme 1) are currently undergoing human clinical trials as potential anticancer agents. Therefore, combining these two molecular scaffolds is a promising approach

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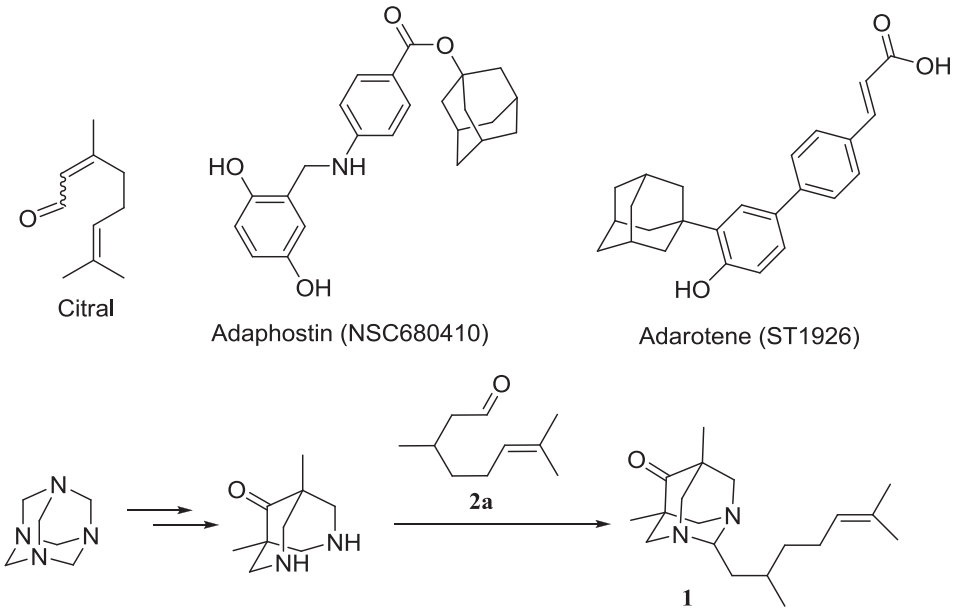

Scheme 1. The structures of citral, adaphostin and adarotene as well as the synthesis of compound **1**.

to develop potent anticancer agents and preliminary molecular modelling investigations suggested favorable binding.

Recently, we synthesized a series of compounds with both the diaza-adamantane and monoterpenoid moieties and tested their inhibitory activity against purified recombinant DNA repair enzyme Tdp1 [18]. Among the substances obtained, compound **1** synthesized using the common monoterpenoid citronellal **2a** (Scheme 1) proved to be the most potent inhibitor with IC_{50} = 15 μM (IC_{50}: concentration of a compound required to reduce the enzyme activity by 50%).

It was found earlier that secondary amines **3** and **4** combining the monoterpenoid and aminoadamantane moieties (Fig. 1), exhibited cytotoxic activity against tumor cell lines, while no genotoxic effect on normal cells was observed [19]. These compounds can be regarded as structural relatives of type **1** diazaadamantanes (except for the keto group whose effect on the Tdp1 inhibition activity is yet to be studied); however, their anti-Tdp1 activity has not been previously investigated. Meanwhile, the Tdp1 inhibitory ability of these compounds, in conjunction with their inherent cytotoxicity, can increase the potency of antitumor drugs such as camptothecin and its analogs, which potency is compromised by Tdp1 activity.

Therefore, the aim of this study is to investigate the ability of compounds comprised of monoterpenoid and aminoadamantane moieties to inhibit Tdp1 and consequently enhance the therapeutic impact of topoisomerase poisons in clinical use.

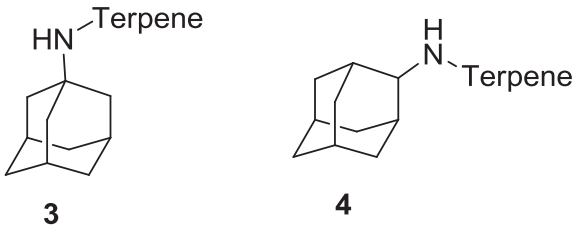

Fig. 1. The general structures of compounds **3** and **4**.

2. Results and discussion

2.1. Chemistry

In addition to the commercially available citronellal **2a**, hydroxycitronellal **2b**, and (−)-myrtenal (−)-**2c**, we synthesized (+)-myrtenal (+)-**2c,** ketoaldehydes (+)- and (−)-**2d** used as aldehyde components of the reaction (see Scheme 1). (+)-Myrtenal (+)-**2c** was obtained by allylic oxidation of (+)-α-pinene (+)-**5** (Scheme 2) according to the procedure [20], and compounds (+)- and (−)-**2d** were synthesized by ozonolysis of (+)- and (−)-α-pinenes (+)- and (−)-**5**, respectively [21].

The target amines **3a–c** and **4a–c** were synthesized by reaction of 1- and 2-aminoadamantane hydrochlorides (**6** and **7**, respectively) with monoterpenoid aldehydes **2a–c** followed by reduction by $NaBH_4$ in accordance with the previously described procedures (Scheme 3) [19,22–24]. The rate of reaction between hydroxycitronellal **2b** and **6** / **7** is significantly higher than that for citronellal **2a**, i.e., complete conversion of the initial reagents was observed after 72 h for **2a**, while hydroxycitronellal **2b** was totally consumed in 15–30 min. The yields of products **3a–c** and **4a–c** varied from 46 to 91%. All the resulting compounds, except for **3b** and **4b**, needed further purification by column chromatography reducing their yields.

When ketoaldehydes (+)- and (−)-**2d** were used, corresponding imines (not shown in Scheme 3) containing a keto group prevented the use of $NaBH_4$ as a reducing reagent. Instead, $(n\text{-}Bu)_4NBH(OAc)_3$ was synthesized by reacting $NaBH_4$ and tetrabutylammonium bromide followed by the reaction with acetic acid [25], was used as an alternative. This acetate is known to reduce selectively aldehydes to alcohols in the presence of a keto group [26]. Using $(n\text{-}Bu)_4NBH(OAc)_3$ for the synthesis of amine (−)-**4d** led to complete conversion of imine in 1.5 h after the reaction started (control by GC), but substantial amounts of byproducts were formed. Purification of compound (−)-**4d** by column chromatography gave the product with the yield of only 3%. For the reason described above, hydrogenation on Pd(10%)/C catalyst in an H-Cube Pro flow reactor was utilized for the synthesis of amines (−)-**3d**, (+)-**3d**, and (+)-**4d**, resulting in yields ranging from 36% to 49% (Scheme 3).