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Original article

Synthesis, anticancer activities and molecular modeling studies of novel indole retinoid derivatives

A. Selen Gurkan-Alp [a,*], Mine Mumcuoglu [b], Cenk A. Andac [c], Emre Dayanc [b], Rengul Cetin-Atalay [b], Erdem Buyukbingol [a]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandogan, Ankara 06100 Turkey
[b] Department of Molecular Biology and Genetics, Faculty of Science, Bilkent University, Bilkent, Ankara 06100 Turkey
[c] Department of Pharmacology, School of Medicine, Dicle University, Diyarbakir 21280, Turkey

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ABSTRACT

In this study, novel *(E)*-3-(5-substituted-1*H*-indol-3-yl)-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-2-en-1-one (**5**(**a**–**e**)) derivatives were synthesized and their anticancer effects were determined *in vitro*. Novel indole retinoid compounds except **5e** have anti-proliferative capacity in liver, breast and colon cancer cell lines. This anti-proliferative effect was further analyzed in breast cancer cell line panel by using the most potent compound **5a**. It was determined that **5a** can inhibit proliferation at very low IC_{50} concentrations in all of the breast cancer cell lines. Here, we present some evidence on apoptotic termination of cancer cell proliferation which may be primarily driven by the inhibition of RXRα and, to a lesser extent, RXRγ.

1. Introduction

The indole ring has been deemed as an important moiety found in many pharmacologically active compounds possessing certain biological activities in which some studies have been attributed to its anticancer effectiveness as described in the literature [1–3]. On the other hand, retinoids, natural and synthetic derivatives of vitamin A and its most active metabolite *all-trans*-retinoic acid have important functions in cell growth, differentiation, modulation of apoptosis and many physiological processes such as vision and embryonic development in vertebrates [4,5]. There are two classes of retinoid nuclear receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs), both having three subtypes (α, β, γ) [6]. Retinoid compounds have shown their biological activities via these receptors in which several mechanistic studies have been relied on the magnitude of their influences on these receptors. The properties of retinoids confer a significant therapeutic potential for the treatment of dermatological diseases [7] and cancer, including chemotherapeutic and chemo-preventive applications [8,9]. There is important evidence that these agents have potent growth inhibiting activities on cancer cell lines *in vitro* and *in vivo* [4]. *In vitro* studies and animal models show that retinoids have ability to inhibit carcinogenesis in different tissues [10]. Retinoids have been evaluated as chemo-preventive agents in cancer treatment and prevention. Retinoid compounds have been used efficiently in the treatment of pre-neoplastic diseases such as cervical dysplasia, leukoplakia and xeroderma pigmentosum. Malignant diseases, especially acute promyelocytic leukemia (APL), a subtype of acute myelogenous leukemia (AML) has been successfully treated with retinoids [11]. Other than leukemia, retinoids have anti-proliferative action in solid tumors such as breast, liver, lung, ovarian, prostate and colon cancer [12,13]. Nevertheless, due to the observation of numerous undesirable side effects i.e. teratogenic activity [14,15], liver and bone toxicity [16], hypervitaminosis A syndrome [17], the short and long term applications of retinoids are limited for the treatment of above-mentioned diseases [18]. Synthesized new retinoid derivatives are required that have increased beneficial properties and reduced adverse effects.

Abbreviations: CPT, camptothecin; DMEM, Dulbecco's modified Eagle's medium; ER, estrogen receptor; FCS, fetal calf serum; MD, molecular dynamics; PBS, phosphate buffered saline; RXR, retinoid X receptor; SRB, sulforhodamine B; TCA, trichloroacetic acid.

* Corresponding author. Tel.: +90 312 2033080; fax: +90 312 2131081.
E-mail address: sgurkan@pharmacy.ankara.edu.tr (A.S. Gurkan-Alp).

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In the present study, a series of novel indole retinoid compounds **5**(**a**–**e**) (Scheme 1) consisting of both indole and tetrahydronaphthalene ring system has been synthesized due to the requirements of finding new compounds in cancer treatments. The indole moiety has been reported to exhibit diverse biological activities including anticancer effects [19]. Therefore, indole ring comprise beneficial features of some of the existing anticancer compounds, such as Panobinostat [20,21], Cediranib [22], indole-3-carbinol [23]. On the other hand, natural and/or synthetic retinoids have been known influences to regulate inner cell functions to interfere for the supression of cancer initiation as well as treatment of the certain cancer occurrences [24]. Therefore, we aimed to combine the structural features of tetrahydronaphthalene ring system (retinoid head) and indole moiety with a linker. The antitumoral profiles of the synthesized compounds were investigated.

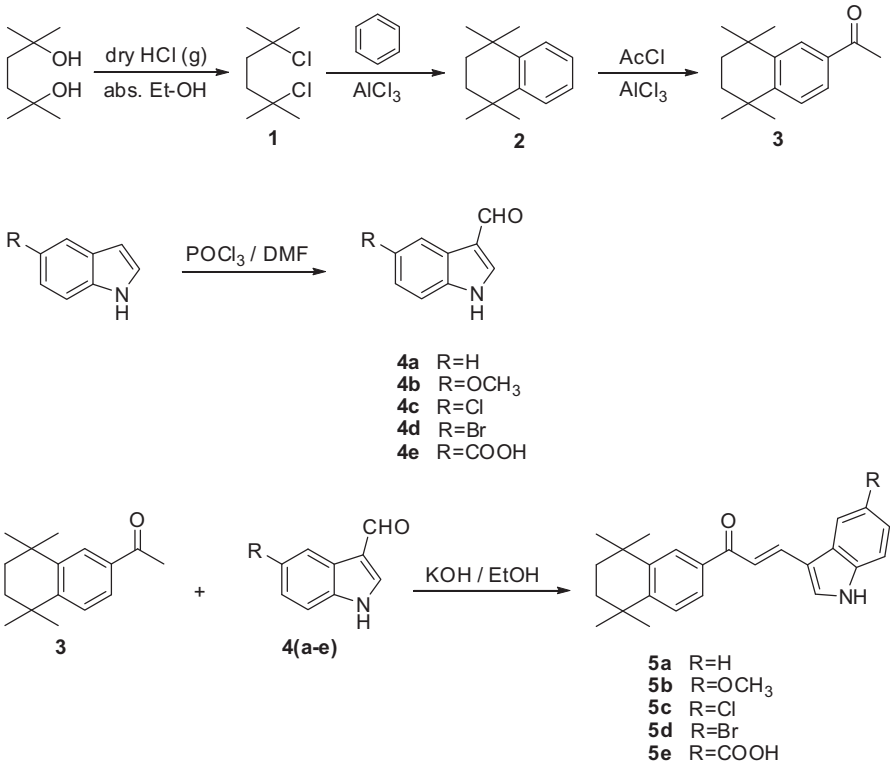
2. Chemistry

The synthetic procedures for the preparation of the compounds **5**(**a**–**e**) are shown in Scheme 1. Commercially available 2,5-dimethyl-2,5-hexandiole and appropriate 5-*substituted* indole derivatives served as starting materials. 2,5-Dichloro-2,5-dimethyl hexane (**1**), was prepared in 55% yield by passing dry hydrogen chloride gas over 2,5-dimethyl-2,5-hexandiole [18,25]. Benzene was alkylated by compound **1** in dichloromethane catalyzed with aluminum chloride to produce 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (**2**), in 48% yield [26]. Then, 1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (**3**) was obtained by acetylation of intermediate **2** with acetyl chloride using $AlCl_3$ as a catalyst [26,27]. On the other hand, the corresponding aldehydes **4**(**a**–**e**) were obtained by treating indole derivatives bearing substituent at position 5 with dimethylformamide, using phosphorus oxychloride as a catalyst according to literature method [28–31]. The final compounds *(E)*-3-(5-*substituted*-1*H*-indol-3-yl)-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-2-en-1-one derivatives **5**(**a**–**e**) were prepared by the condensation of compound **3** with appropriate indole-3-carbaldehyde **4**(**a**–**e**) under basic conditions [32]. Details are stated in the Experimental section.

3. Results and discussion

In this study, we aimed to synthesize novel indole retinoid compounds which are expected to have anticancer properties. To achieve this, five novel indole retinoid derivatives with the substituents at 5th position of the indole ring expected to possess anticancer activity were designed and synthesized. The substitution pattern on the indole ring is thought to have a deterministic factor over the biological effectiveness of the compounds. Due to the distinctive properties of the substituents regarding to their physicochemical behaviors, it might be the way of finding of what relativeness are able to attract activity-inquires leading to exert the desired biological activities. In spite of the fact that the absence of any kind of substitution (hydrogen only) gave the most effectiveness, both electron-donating and electron-withdrawal substitutions had lesser effects in terms of possessing the activity. Actually, this could be a very interesting point of view to support the indole ring system to avoid substituent-inclusion with the enormously activating and/or deactivating substituents rather than using no substitution (like hydrogen only) or with substituents having mild activating/deactivating properties for the future progressions. Thus, more efficiently activating/deactivating substituents could be unfavorable for the biological activity studied.

(E)-3-(5-*Substituted*-1*H*-indol-3-yl)-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-2-en-1-one derivatives **5**(**a**–**e**) were synthesized in four steps (Scheme 1). Synthesized compounds were purified by column chromatography using appropriate solvent systems. Expected chemical structures of the compounds have been deduced by mass, NMR spectral findings and elemental analyses



Scheme 1. Synthesis of novel indole retinoid compounds **5**(**a**–**e**).