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Synthesis and characterization of phenanthrene derivatives with anticancer property against human colon and epithelial cancer cell lines

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ABSTRACT

A variety of polycyclic aromatic hydrocarbons have been synthesized and structurally characterized in our laboratory. Phenanthrene derivatives were efficiently prepared in excellent yields and high purity via a two-step sequence. Heck coupling yielded the corresponding diarylethenes, followed by classical oxidative photocyclization to achieve the expected phenanthrenes. First, we envisioned to synthesize a variety of substituted phenanthrenequinones. Second, we investigated the possibility of a dibenz[*a*,*c*]phenazine formation by addition of *o*-phenylenediamine after completion of the oxidation process. Moreover, because phenanthrenequinones are available so simply, it is likely that other uses will be found for these compounds. For example, 9,10-phenanthrenequinone can be sequentially reduced, alkylated, acetylated, and sulfonated. All the synthesized derivatives were evaluated for cytotoxic activity in vitro against the human epidermoid carcinoma epithelial cells *Hep-2* and human colon carcinoma cells *Caco-2* using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. From the structure–activity point of view, position and nature of the electron donating and electron withdrawing functional groups attached to the phenanthrene skeleton may contribute to the anticancer action. Interestingly, the analysis of the IC_{50} values suggests that most compounds exerted cytotoxic effects with selectivity against both cancer cells. Among them, methyl 8-methyl-9,10-phenanthrenequinone-3-carboxylate **11d** showed the highest potency with IC_{50} values of 2.81 and 0.97 μg/mL.

1. Introduction

Cancer continues to pose significant health problems worldwide. The importance of research of new robust anticancer agents is essential in improving the success rates in treating cancer because chemotherapy used for the cancer victims constantly exhibits some undesirable side effects. The biological activity manifested by many polycyclic aromatic hydrocarbons makes them attractive targets for organic chemists to synthesize medicinal motifs. Cytotoxicity is one of several important biological effects of polycyclic aromatic hydrocarbons. Therefore, many intensive efforts have been made for the discovery and development of new cytotoxic molecules [1,2]. As far as we

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know, phenanthrene derivatives are one of the most stable fused aromatics [3–5]. Therefore, the synthesis and bioactivity evaluation of phenanthrenes received much attention and interests in medicinal chemistry [6–9]. They can be obtained by a near endless list of reactions and transformations [10]. The oxidative photochemical cyclization of stilbenes is an important methodology used to prepare a large number of differently substituted phenanthrenes [11]. By modifying the core phenanthrene structure, it is possible to obtain a wide variety of tricyclic compounds, which have become of particular interest to chemists because of their range of different biological properties [12]. Thus, the construction of an aryl-heteroatom bond is an important study, in particular, the formation of carbon–nitrogen [13] and carbon–oxygen bonds [14]. Such compounds have been demonstrated to possess various biological activities.

A literature survey shows that in phenanthrene **1** the electrophilic aromatic substitution reactions can be performed. However, this compound also gave rise to addition reactions on the double bond between carbons 9 and 10 (Fig. 1), which showed a strong olefinic character [15]. For instance, 9,10-phenanthrenequinone **2** can be prepared from phenanthrene **1** by several methods [16–18] (Fig. 1). Dicarbonylated compound **2** enables several types of chemical reactions of considerable importance in organic synthesis [19–21], especially electrophilic aromatic substitution and condensation, being an excellent starting material to prepare relatively simple and bioactive substances [22,23].

Quinones represent the second widest class of clinically approved antitumor agents [24]. Recently, Afrasiabi et al. [25] synthesized the phenanthrenequinone thiosemicarbazone **3** (Fig. 1) through the condensation reaction between 9,10-phenanthrenequinone **2** and thiosemicarbazide. Compound **3** has been complexed with metals, copper, nickel, and cobalt, and evaluated for anticancer activity in human breast cell line T47D rich in progesterone receptors.

Phenazine derivatives have attracted much attention because of its biological actions [26]. Thus, with the significant advances in the field of molecular biology, Einat et al. [27] prepared the phenazine **4** via condensation reaction of *o*-diaminocyclohexane with 9,10-phenanthrenequinone **2** (Fig. 1). This compound presented an antileukemic activity in vitro against Philadelphia-positive cells in patients with Philadelphia-positive chronic myelogenous leukemia in chronic phase and blastic crisis.

Unfortunately, the number of chemical and pharmacological studies on phenanthrene derivatives is limited, despite being very important with good works. To prepare new compounds with interesting biological activity it is necessary to improve research about synthesis and evaluation of derivate compounds from phenanthrene.

Thereby, with the aim of developing our ongoing research for synthesis of biologically active compounds containing a core phenanthrene structure as promising derivatives for the development of anticancer agents, herein we describe the results of an exploratory study using a simpler procedure for effecting transformations in a variety of phenanthrenes and in vitro cytotoxic activity against two tumor cell lines, including *Hep-2* and *Caco-2* cell lines. The present study is an attempt to investigate whether the different substituents in the phenanthrene skeleton can change or improve the activity to discern structure–activity relationships. Most compounds exerted cytotoxic effects with selectivity against both of the cell lines.

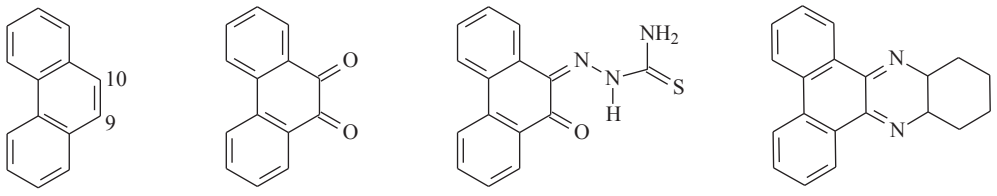
2. Results and discussion

2.1. Synthesis

The starting phenanthrenes **9a–d** have been prepared through a two-step sequence involving the Mizoroki–Heck coupling reaction followed by oxidative photocyclization (see Scheme 1). With respect to the Mizoroki–Heck reaction, this coupling reaction offers a simple and direct approach toward a series of stilbene as precursors for phenanthrene derivatives [28,29]. A great variety of literature conditions for the Mizoroki–Heck reactions can be performed [30,31]. The use of sodium acetate acting as a base, 1 mol % of Herrmann's palladacycle {*trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium} as a catalyst, and *N*,*N*-dimethylacetamide as a solvent allows the straightforward and economic synthesis of substituted stilbenes mainly of (*E*) configuration (Scheme 1) [32,33].

First of all, Wittig reaction of suitable commercially aryl aldehydes **5a–d** with methyltriphenylphosphonium iodide [34] in the presence of K_2CO_3 in DME, provided the matching styrene derivatives **6a–d** as starting materials (Scheme 1). Their palladium promoted Mizoroki–Heck coupling with various bromo benzenes **7a–c** gave the *trans*-stilbene analogues **8a–d** in good yields.

Having obtained the stilbenes precursors, we were able to complete the convergent synthesis of the starting phenanthrenes skeleton **9a–d**. Therefore, each olefin underwent photocyclization in the presence of a catalytic amount of iodine as the oxidizing agent [35]. Photolysis of **8a–d** was performed in toluene on a 500 mg scale per run



1 2 3 4

Fig. 1. Chemical structure of the reported phenanthrene derivatives (**1–4**).