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Studies on the synthetic and structural aspects of benzosuberones bearing 2, 4-thiazolidenone moiety as potential anti-cancer agents

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ABSTRACT

Novel representative of the important group of biologically active benzosuberones bearing 2, 4-thiazolidenone moiety was synthesized as potential anticancer agents (**6a**–**j**). These compounds were synthesized in good yields from Knoevenagel condensation of compounds **2a**–**b** with thiazolidenone derivatives **3a**–**e** in the presence of sodium acetate and glacial acetic acid. The *in vitro* cytotoxicity of these compounds was evaluated against different human cancer cell lines (A549, HeLa, MDA-MB-231, MCF-7) and normal cell line, HEK293. Compound **6a** exhibited promising cytotoxicity with IC_{50} values ranging from 2.98 to 13.34 μM against all the tested cancer cell lines, HeLa, A549, MCF-7 and MDA-MB-231, while compound **6g** showed potent cytotoxicity against human breast adenocarcinoma cell line (MCF-7, IC_{50} value of 1.91 μM).

1. Introduction

Benzosuberone derivatives possess potential bacteriostatic, anti-inflammatory, anti-pyretic, anti-ulcer, CNS-depressant, CNS-stimulant and anti-convulsant activities. Some of the derivatives are also known for anti-tumor activity in murine P388 cell line tests [1]. Tricyclic antidepressants containing dibenzosuberone moieties mostly effect the autonomic and central nervous systems, and traditional anti-depressants, like amitriptyline [2], imipramine [3] and noxiptiline [4] which continue to be used as first-line drugs in treating depressive disorders.

Thiazolidenone templates are a privileged structure fragments in modern medicinal chemistry considering its broad spectrum and affinity for various bio-targets of this class of heterocyclic compounds. Thiazolidenone derivatives are well known class of biological active substances that became basic for the whole number of innovative medicinal agents, such as hypoglycaemic thiazolidenones (pioglitazone and its analogues) [5], aldose reductase inhibitors (Epalrestat) [6]. In the recent years, research on thiazolidenone derivatives has gained immense interest and proven promising for oncology. Since the two heterocyclic moieties, benzosuberone and thiazolidenone, constitute two active pharmacophores that are highly active against tumour cell lines and microbes. In view of this fact, these two moieties were combined to obtain synthons which would plausibly have a synergistic effect on their biological properties. The reported significance of such synthons generated the interest among medicinal chemists in the recent years to exploit this valuable structure in the design and synthesis of new benzosuberone derivatives bearing 2, 4-thiazolidenone moieties.

In continuation to our on-going research programme [7–13] to discover and develop tumour growth inhibitors and apoptotic inducers as potential new anti-cancer agents, we designed and synthesized novel benzosuberone bearing 2, 4-thiazolidenone moieties having cytotoxic properties. Analysis of the structure–activity relationships (SARs) identified the benzosuberone derivatives with thiazolidine-2, 4-dione nucleus as being essential for this promising activity, and the substitution at the head group of the benzosuberone ring when condensed with 3-(2-oxo-2-phenylethyl)thiazolidine-2, 4-dione moiety (**3a**–**e**) increases the cytotoxicity against human breast cancer cell lines like MDA-MB-231 and MCF-7 more efficiently, when compared to the isolated fragments, **3a**–**e**, **8a** and **8b**. Among the intermediate fragments,

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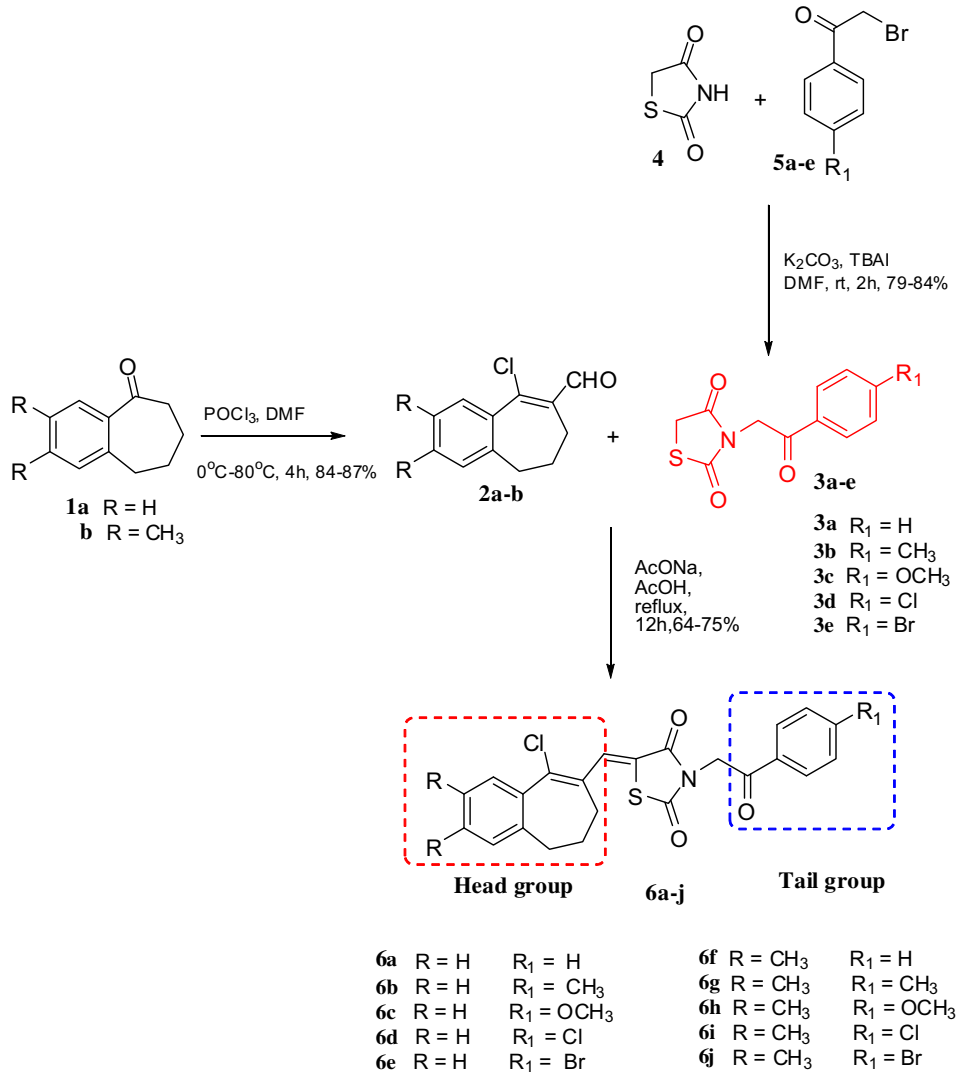

Scheme 1. Synthesis of compounds **6a**–**j**.

only **8b** showed cytotoxicity against A549, HeLa, and MDA-MB-231 cell lines. The compounds **6a** and **6g** showed promising cytotoxicity against MCF-7 with IC_{50} values of 5.31 and 1.9 μM, respectively.

2. Chemistry

2.1. Synthesis of (Z)-5-(((Z)-9-chloro-6,7-dihydro-5H-benzo[7]annulen-8-yl)methylene)-3-(2-oxo-2-phenylethyl)thiazolidine-2, 4-dione

The synthetic route of target compounds was obtained in Scheme 1. A series of target compounds **6a**–**j** were synthesized by Knoevenagel condensation of compounds **2a**–**b** with thiazolidenone derivatives (**3a**–**e**) in glacial acetic acid, in the presence of sodium acetate. The yields were in the range of 64–75% (Scheme 1). The structures of all the synthesized compounds were confirmed by spectral data (FTIR, ^{1}H NMR, ^{13}C NMR and ESI-MS). The target model compound **6b** was evident from the appearance of $[M + H]^+$ peak at m/z 438 in the mass spectrum (ESI), –C=O stretching at 1682 cm^{-1} in IR and the appearance of characteristic methine proton as singlet at δ 8.37 in ^{1}H NMR. The structure of the product **6b** was further confirmed by X-ray crystallographic analysis. In another route, the synthesis of target compounds by Knoevenagel condensation of compounds **2a**–**b** with thiazolidine-2, 4-dione **4** gave the desired compounds **8a**–**b** with yields of only 24% (Scheme 2).

2.2. Synthesis of (Z)-9-chloro-6,7-dihydro-5H-benzo[7]annulene-8-carbaldehydes

The compounds **2a**–**b** were synthesized by Vilsmeier Haack Arnold reaction [14] of substituted benzosuberones **1a**–**b** in presence of $POCl_3$, dimethylformamide with 84–87% yield. The structures of all the synthesized compounds were confirmed by spectral data analysis (FTIR, ^{1}H NMR, ^{13}C NMR and ESI-MS). In the ^{1}H NMR spectra, the presence of characteristic singlet at δ 10.36 ppm representing one proton provided evidence for the formation of carbaldehyde **2b**. The required starting compounds were synthesized from Fridel-Craft's acylation of aromatic hydrocarbons with glutaric anhydride furnishing aryl butyric acids which on Clemmenson reduction followed by cyclization with excess polyphosphoric acid gave substituted benzosuberones **1a**–**b** (Scheme 1).

2.3. Synthesis of 3-(2-oxo-2-phenylethyl)thiazolidine-2, 4-dione

The synthetic procedure of the thiazolidenone derivatives **3a**–**e** is shown in Scheme 1. Due to the labile hydrogen atom at the 3-