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Research paper

# Design and synthesis of diamide-coupled benzophenones as potential anticancer agents

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ABSTRACT

A series of diamide-coupled benzophenone, 2-(4-benzoyl-phenoxy)-N-{2-[2-(4-benzoyl-phenoxy)-acetylamino]-phenyl}-acetamide analogues (**9a-l**) were synthesized by multistep reactions and all compounds were well characterized. Among the series (**9a-l**), compound **9k** with three methyl groups at ortho position in rings A, B, and D and bromo group at the para position in ring E was selected as a lead compound by screening through multiple cancer cell types by *in-vitro* cytotoxic and antiproliferative assay systems. Also, the cytotoxic nature of the compound **9k** resulted the regression of the tumor growth *in-vivo*, which could be due to decreased vascularisation in the peritoneum lining of the mice which regress the tumor growth. The results were reconfirmed *in-vivo* chorioallantoic membrane model which indicates a scope of developing **9k** into potent anticancer drug in near future.



## 1. Introduction

Cancer is one of the deadliest diseases affecting mankind. Although a number of chemotherapeutic agents are available, most of them also kill the normal cells that divide rapidly and cause several side effects such as immune suppression, inflammation of the digestive tract lining and hair loss [1]. Angiogenesis is a biological process where new blood vessels branch out from the existing vasculature [2]. This process is tightly controlled for normal physiologies such as reproduction, development and wound repair. However, it becomes out of control when it is implicated in diseases such as cancer, age-related or diabetic retinopathy and so on [3]. Tumor cells, in general, proliferate very fast and the demand for essential nutrients, oxygen, etc. is always high. The immediate environment of cancers increasing in size, however, often becomes heterogeneous and some regions of large cancers often possess micro environmental niches, which exhibit a significant gradient of critical metabolites including oxygen, glucose, other nutrients, and growth factors [4]. Thus, many cancer cells get the critical metabolites by randomly recruiting new blood vessels, a phenomenon commonly known as angiogenesis, to survive under such severe conditions. The literature survey reveals that benzophenone and its derivatives are an emerging class of molecules with multiple pharmacokinetic properties. New molecules with benzophenone moiety emerging day by day with potent biological activity in recent times [5–8]. Several analogues of benzophenone are well known for their antitumor and antiangiogenic potentials which are under clinical trials [9,10].

Being very much focused on this aspect by our research group, a series of benzophenone have been synthesized with special emphasis given to the anticancer activity with the establishment of the mechanism of action [11–14]. In this connection, several molecules have been identified with potentiality in inhibiting angiogenesis, which plays a very important role in tumor establishment, prognosis of cancer [15–17] and identification of its molecular target [18,19]. Such identification of novel molecular target for cancer therapy has led to a paradigm shift in the drug development process which can effectively inhibit the signaling pathways involved in cancer development and Prognosis [20,21]. As a continued approach of screening for novel drug, a series of diamide-coupled benzophenones, 2-(4-benzoyl-phenoxy)-N-{2-[2-(4-benzoyl-

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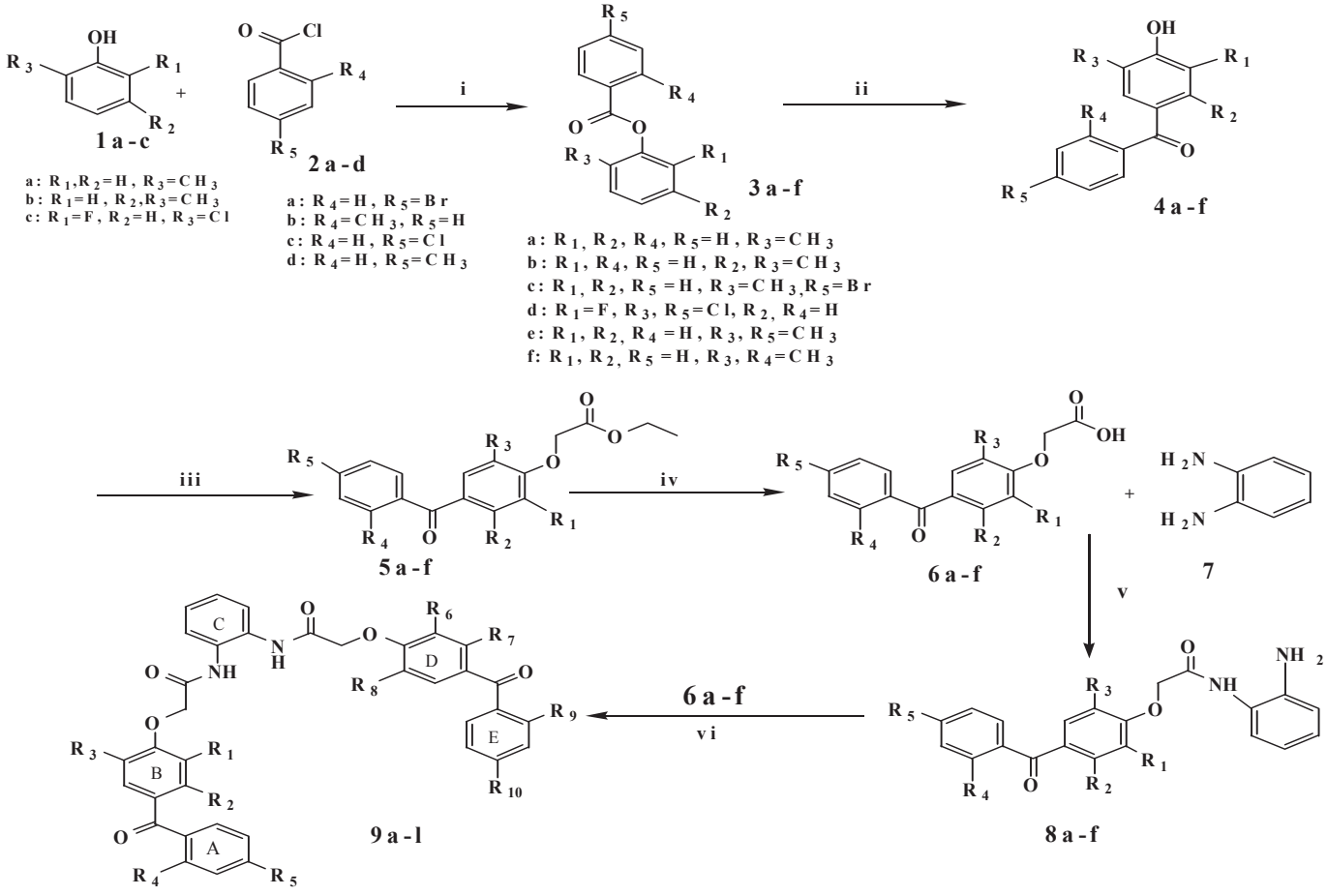
phenoxy)-acetylamino]-phenyl}-acetamides **(9a-l)** were synthesized. The synthesis of amides is one of the most fundamental methods in organic chemistry used to obtain potent compounds [22,23]. Hence we considered it worthwhile to pursue further modifications on the substituted benzophenone part by appending diamide subunit and screened against multiple cancer cell lines, such as lung carcinoma (A-549), breast cancer (MCF-7) and lymphoma (DLA) *in-vitro*. Then, antiproliferative efficacy was verified *in-vivo* in the Daltons lymphoma murine model and mechanism of tumor inhibition.

## 2. Result and discussion

### 2.1. Chemistry

The synthesis of the title compounds **9a**–**l** was accomplished by a synthetic procedure as shown in Scheme 1. All the synthesized compounds were established by IR, proton NMR and mass spectral data. First, the benzoylated products **3a**–**f** were synthesized by the benzoylation of substituted phenols **1a**–**c** with substituted benzoyl chlorides **2a-d** under low temperature and the structures were confirmed by the appearance of the carbonyl stretching band for




9a. $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$ = H; $R_3,R_8$ = $CH_3$
9b. $R_1,R_4,R_5,R_6,R_9,R_{10}$ = H; $R_2,R_3,R_7,R_8$ = $CH_3$
9c. $R_1,R_2,R_4,R_6,R_7,R_9$ = H; $R_3,R_8$ = $CH_3$; $R_5,R_{10}$ = Br
9d. $R_1,R_2,R_4,R_5,R_6,R_9,R_{10}$ = H; $R_3,R_7,R_8$ = $CH_3$
9e. $R_1$=F; $R_2,R_4,R_6,R_7,R_9,R_{10}$ = H; $R_3,R_5$ = Cl; $R_8$ = $CH_3$
9f. $R_1,R_2,R_5,R_6,R_7,R_9,R_{10}$ = H; $R_3,R_4,R_8$ = $CH_3$
9g. $R_1,R_2,R_4,R_6,R_7,R_9,R_{10}$ = H; $R_3,R_5,R_8$ = $CH_3$
9h. $R_1,R_2,R_4,R_5,R_6,R_7,R_9$ = H; $R_3,R_8$ = $CH_3$; $R_{10}$ = Br
9i. $R_1,R_4,R_5,R_6,R_7,R_9$ = H; $R_2,R_3,R_8$ = $CH_3$; $R_{10}$ = Br
9j. $R_1$=F; $R_2,R_4,R_6,R_7,R_9$ = H; $R_3,R_5$ = Cl; $R_8$ = $CH_3$; $R_{10}$ = Br
9k. $R_1,R_2,R_5,R_6,R_7,R_9$ = H; $R_3,R_4,R_8$ = $CH_3$; $R_{10}$ = Br
9l. $R_1,R_2,R_4,R_6,R_7,R_9$, = H; $R_3,R_5,R_8$ = $CH_3$; $R_{10}$ = Br

**Scheme 1.** Synthesis of diamide-coupled benzophenone 2-(4-benzoyl-phenoxy)-N-{2-[2-(4-benzoyl-phenoxy)-acetylamino]-phenyl}-acetamide analogues (**9a-l**). Reaction conditions and yield: (i) Aq. NaOH, stirring 0–5 °C for 2–3 h, yield: 80–90%, (ii) Anhy. $AlCl_3$, 150–170 °C for 2–3 h, yield: 75–85%, (iii) $ClCH_2COOC_2H_5$/Dry Acetone, $K_2CO_3$, Reflux, 60 °C for 8–10 h, yield: 80–90%, (iv) Aq. NaOH/Ethanol, Reflux, for 5–6 h, yield: 85–95%, (v) TBTU/Lutidine, Dry DCM, Stirring 0–5 °C for 30 min then overnight at RT, yield: 80–90%, (vi) TBTU/Lutidine, Dry DCM, Stirring 0–5 °C for 30 min then, overnight at RT, yield: 75–85%.