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Zabiulla, H.G. Shamanth Neralagundi, A. Bushra Begum, B.T. Prabhakar, Shaukath Ara Khanum

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Graphical Abstract

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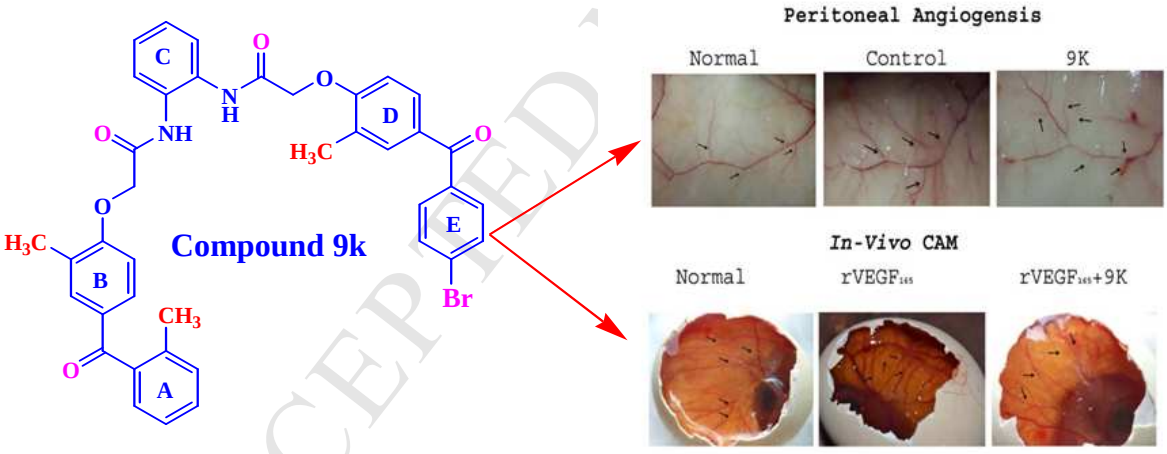
Zabiulla[a], Shamanth Neralagundi HG[b], Bushra Begum A[a], Prabhakar B.T[b] and Shaukath Ara Khanum[a]*

[a]Department of Chemistry, Yuvaraja's College (Autonomous), University of Mysore, Karnataka, India.

[b]Molecular Biomedicine Laboratory, Postgraduate Department of Studies and Research in Biotechnology, Sahyadri Science College (Autonomous), Kuvempu University, Karnataka, India.



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

Zabiulla[a], Shamanth Neralagundi HG[b], Bushra Begum A[a], Prabhakar B.T[b] and Shaukath Ara Khanum[a]*

[a]Department of Chemistry, Yuvaraja's College (Autonomous), University of Mysore, Karnataka, India.

[b]Molecular Biomedicine Laboratory, Postgraduate Department of Studies and Research in Biotechnology, Sahyadri Science College (Autonomous), Kuvempu University, Karnataka, India.

*Correspondence Author:

Dr. Shaukath Ara Khanum

Associate Professor, Department of Chemistry

Yuvaraja's College

University of Mysore, Mysore.

Phone: +91 - 99018 88755Fax: +821- 2419239

Email: shaukathara@yahoo.co.in

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.

Key words: Benzophenone-diamide, Antiproliferation, Antiangiogenesis.

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-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 the ester group in the IR spectra and the disappearance of broad singlet of the OH proton of substituted phenols **1a**–**c** in proton NMR spectra. Fries rearrangement of compounds **3a**–**f** using anhydrous aluminium chloride as a catalyst under neat condition afforded hydroxy benzophenones **4a**–**f**, and these compounds were established by the disappearance of the carbonyl stretching band of the ester group and appearance of the OH stretching band in IR spectra and also, the appearance of broad singlet for OH proton and decrease in one aromatic proton in proton NMR spectra. Compounds **4a**–**f** on etherification with chloro ethyl acetate using dry acetone as a solvent gave

substituted (4-benzoyl phenoxy)-acetic acid ethyl esters **5a**–**f**, which were confirmed by the disappearance of the OH stretching of compounds **4a**–**f** and appearance of carbonyl stretching band for the ester group in the IR absorption spectra. The proton NMR observations of these compounds revealed that, broad singlet for the OH proton of compounds **4a**–**f** disappeared and a triplet and quartet for CH_3 and CH_2 protons respectively appeared [9]. The compounds **5a**–**f** on refluxing with aqueous sodium hydroxide in ethanol gave (4-benzoyl-phenoxy)-acetic acids **6a**–**f**, which was clearly evident with the appearance of carbonyl group stretching band of carboxylic acid and disappearance of carbonyl stretching of ester group for compounds **5a**–**f** in the IR spectra. In proton NMR, the appearance of COOH proton and disappearance of triplet and quartet peaks for CH_3 and CH_2 protons, respectively has confirmed the formation of the compounds **6a**–**f** [24]. Compounds **8a-f** were obtained by treating compounds **6a-f** with 1, 2 diaminobenzene**7** in the presence of 2,6 lutidine and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluoroborate (TBTU) as a coupling agent and dichloromethane (DCM) as a solvent. The structures were confirmed by the disappearance of the carbonyl stretching band of a carboxylic acid in the IR spectra and in proton NMR, the appearance of NH_2 and NH protons, besides, an increase in four aromatic protons. Finally, all the substituted compounds **6a**–**f**, on treatment with **8a-f (**N-(2-amino-phenyl)-2-(4-benzoyl-phenoxy)-acetamides) using lutidine and TBTU as a catalyst, afforded the expected title compounds **9a**–**l** in a good yield (70–90%). This was supported by the disappearance of NH_2 and COOH stretching of the compounds **8a**–**f** and **6a**–**f** respectively in the IR spectra. Also, it is confirmed by the disappearance of COOH of **6a**–**f** and NH_2 of **8a**–**f** proton and appearance of two CONH protons in the NMR spectra.

2.2. Biology

*2.2.1. Compound **9k** has potent cytotoxic and antiprolifertive effect against multiple cancer types*

In a course of drug development process it has always been suggested to screen against multiple cancer cell types with different origin for better assessment strategies of the drug. In the current investigation, the cytotoxic and antiproliferative effects of compounds **9a-l** on multiple cancer cells with different origin A549, MCF-7 and DLA were investigated following 48 h of exposure using three independent assay systems (trypan blue, MTT and LDH release). These methods are the preliminary screening methods to eliminate those analogues that do not show any cytotoxic and antiproliferative effects. The cells were treated with increasing concentrations of the compounds (0, 10, 20, 50 and 100 μM in DMSO and vehicle alone). The results inferred that among the series **9a-l,** the compound **9k** alone has shown significant cytotoxic and antiproliferative activities against all the three cancer cell lines and it was chosen as a lead compound (Fig 1A, 1B and 1C). Thus, our studies using three cell lines of different origin suggest that irrespective of the cancer type, compound **9k** could induce cytotoxicity, as shown by three independent assay study methods and antitumor activity *in-vivo* was further investigated.

2.2.2. Structure activity Relationship (SAR)

The benzophenone derivatives are known to be pharmacologically active molecules against various pathological conditions including cancer [25]. The current investigation involves the multistep synthesis of diamide-coupled benzophenone compounds. Structurally, the title compounds are having a basic backbone of benzophenone with acetamide link and terminal bromo group. The IC_{50} values for compounds as depicted in Fig 1A, 1B and 1C, which suggest that the 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 showed IC_{50} value ~20, 23 and 23μM on A549, MCF-7 and DLA cells respectively as verified by trypan blue, MTT and LDH release assay. The results illustrated that, the compounds **9a**, **9b**, **9d**, **9e**, **9f** and **9g** do not have bromo group and compound **9c** has two bromo groups at the para position in rings A and E. It reveals that the compound **9k** is

important for biological activity. While the other compounds with different substituents have not shown significant cytotoxicity. In this connection, the compound **9k** was selected as a lead compound based on its significant structure activity relationship compared with other analogues and it was further evaluated.

*2.2.3. Compound **9k** regresses tumor growth*

It is a rational and a hierarchical approach beginning with toxicology and pharmacology studies, progressing to primary tumors to identify therapeutic targets and models of metastatic disease to compare drugs using rigorous, clinically relevant outcome parameters [26, 27]. Ascites tumor models of mouse origin is an appropriate model system for preliminary pilot screening and it plays a decisive role in the drug development process [28] because ascites secreting cell implantation induces typical tumor microenvironment by inducing local inflammation, increased vascular permeability and an intense edema formation, cellular migration and invasion. Accumulated fluid serves as a nutritional source for tumor cells and thereby establishing the tumor growth. Hence, decrease in ascites fluids accounts for the suppression of tumor growth [29]. In the present study, we have chosen murine DLA *in-vivo* model system to study the preliminary antitumor property of the chosen lead compound **9k** to evaluate the antitumor effect.The compound **9k** was administered at the concentration of 75 mg/kg body weight i.p. (intraperitoneally), on every alternative day starting from 4^{th} day of the tumor implantation as determined by LD_{50} assay. Results referred that, upon treatment of **9k** compound there was a decrease in tumor growth as assessed by visible tumor morphology (Fig 2A) and dose dependent decrease in tumor establishment and it accounts for ~80% inhibition after the final dose of treatment (Fig 2B). The ascites secretion responsible for establishment of tumor was also low when compared to the untreated mice (Fig 2C) and cell number (Fig. 2D). The regressed tumor expanded andsurivality of the mouse was increased upto 2.5 fold time where mice survived 37

days. Treatment was discontinued for test animals after the 10th day to monitor the survivality (Fig. 2E).

*2.2.4. Compound **9k** inhibits neovascularisation*

Measurement of micro visual density (MVD) is a widely used surrogate measure in pathological specimens and tumor models to assess disease progression. Extensive neovascularization has a direct correlation with tumor progression and its inhibition results in regression of tumor growth [30, 31]. Earlier, our group showed that benzophenone derivatives conjugated with various substituents are potent antiangiogenic compounds that inhibit neovascularization and tumor growth in mice [32]. Treatment with compound **9k** effectively reduced the tumor growth and we verified whether the mechanism of inhibition is linked to neovascularization since angiogenesis is evident in the inner peritoneal lining of EAC-bearing mice and thus, mouse peritoneum is a reliable model for angiogenesis [33]. Hence, the peritoneal lining of mice treated with compound **9k** was examined to gauge the effects on peritoneal angiogenesis. Supporting our hypothesis Tumor-bearing mice treated with **9k** compound showed decreased peritoneal angiogenesis compared to the massive angiogenesis in untreated mice (Fig.3A). Quantification of the neovessel using angioquant software revealed more than 50% reduction in MVD after treatment.

To reconfirm and authenticate our results we approached non tumorigenic model and better validative model fertilized egg CAM [34] where we used recombinant vascular endothelial growth factor 165 ($rVEGF_{165}$, 10mg/embryo) as a potent angiogenic factor [35] to induce neovascularization. Simultaneous treatment with **9k** induced a vascular zone in the developing embryos. Notably, newly formed microvessels regressed around the area of the implanted disk (Fig. 3B). This indicates that the compound **9k** primarily acts to inhibit angiogenesis.

Angiogenesis plays an important role in tumor growth [36, 37] and our compound **9k** inhibits angiogenesis and it also inhibits tumor growth as well as the accumulation of ascites fluid in mice, which is angiogenesis dependent (Fig. 2). Since the ascites fluid nutritional requirement for tumor [38] depletion in ascites fluid accounts for suppression of tumor growth. The results confirm the effect of compound **9k** after i.p. injection was a reduction in the formation of ascites, which directly impacts the growth of the tumor (Fig. 2). This suggests that the target-specific action of compound **9k** corresponds. Hence, novel studies of our compound **9k** have antiproliferative effects against multiple cancer cell lines and angioprevention mediated tumor growth.

3. Conclusion

Summarizing the current investigation, a new series of diamide-coupled benzophenone molecules **(9a-l)** was synthesized and evaluated for cytotoxic and antiproliferative activity against multiple cancer cells with different origin. From the current investigation, structural activity relationship of these compounds suggests that the position and the type of subsituents on the aromatic ring in **9a-l** are important for the activity. Compound **9k** with three methyl groups at the ortho position in rings A, B and D and bromo group at the para position in ring E has been selected as lead compound. The cytotoxic nature of compound **9k** further verified against tumor regressing activity and against murine ascities model DLA resulting in antitumor potency. The mechanism of antitumor activity is a result of the regressed neovessel formation both in tumorigenic and non tumorigenic model system. This highlights that the compound **9k** is a promising anticancer molecule with target specific action which could be further adopted into the drug development process.

4. Materials and methods

4.1 Experimental section

All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt Ltd. TLC was performed on aluminum-backed silica plates and visualized by UV-light. Melting points (M.P) were determined on an electrically heated VMP-III melting point apparatus. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 elemental analyzer. The results of elemental analyses were within ±0.4% of the theoretical values. The FT-IR spectra were recorded using KBr discs and Nujol on FT-IR Jasco 4100 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer in $CDCl_3$ and the chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded on LC-MS (API-4000) mass spectrometer. MTT was purchased from Sigma Aldrich, USA and CD31 antibodies were procured from Santa Cruz, USA.

4.2. Chemistry

*4.2.1. General procedure for the synthesis of phenyl benzoates **3a-f***

The starting substituted benzoates **3a-f** were synthesized by benzoylation of subsituted phenols **1a-c** with substituted benzoyl chlorides (**2a-d**, 1:1) in the presence of 10% sodium hydroxide solution. The reaction mass was stirred for 2-3 hours at 0-5 ^{o}C. The reaction was monitored by thin layer chromatography (TLC) using 4:1 n-hexane: ethyl acetate solvent mixture. After completion of the reaction, the oily product was extracted with ether layer (20 mL × 3). Ether layer was washed with 10% sodium hydroxide solution (40 mL x 3) followed by water (30 mL × 3) and then dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to afford compounds **3a-f**.

*4.2.1.1. Benzoic acid o-tolyl ester **3a***. Yield: 93%. M.P.: 52-54 °C. IR (KBr) ν_{max} (cm^{-1}): 1715 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.45 (s, 3H, CH_3), 7.11-8.25 (m, 9H, Ar-H).

LC-MS m/z 213 (M+1). Anal. Cal. for $C_{14}H_{12}O_2$ (212): C, 79.22; H, 5.70. Found: C, 79.20; H, 5.76%.

4.2.1.2. Benzoic acid 2,5-dimethyl-phenyl ester ***3b***. Yield: 80%. M.P.: 65-67 °C. IR (KBr) ν_{max} (cm^{-1}): 1715 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.41 (s, 6H, CH_3), 7.21-8.26 (m, 8H, Ar-H). LC-MS m/z 227 (M+1). Anal. Cal. for $C_{15}H_{14}O_2$ (227): C, C, 79.62; H, 6.24. Found: C, 79.60; H, 6.19%.

4.2.1.3. 4-Bromo-benzoic acid o-tolyl ester ***3c***. Yield: 91%. M.P.: 60-62 °C. IR (KBr) ν_{max} (cm^{-1}): 1715 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.45 (s, 3H, CH_3), 7.11-8.25 (m, 8H, Ar-H). LC-MS m/z 292 (M+1). Anal. Cal. for $C_{14}H_{11}BrO_2$ (291): C, 57.76; H, 3.81. Found: C, 57.71; H, 3.75%.

4.2.1.4. 4-Chloro-benzoic acid 2-chloro-6-fluoro-phenyl ester ***3d***. Yield: 85%. M.P.: 52-54 °C. IR (KBr) ν_{max} (cm^{-1}): 1715 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.37 (s, 3H, CH_3), 7.01-8.18 (m, 7H, Ar-H). LC-MS m/z 286 (M+1). Anal. Cal. for $C_{13}H_7Cl_2FO_2$ (285): C, 54.77; H, 2.47. Found: C, 54.72; H, 2.41%.

4.2.1.5. 4-Methyl-benzoic acid o-tolyl ester ***3e***. Yield: 90%. M.P.: 54-56 °C. IR (KBr) ν_{max} (cm^{-1}): 1715 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 6H, CH_3), 7.15-8.30 (m, 8H, Ar-H). LC-MS m/z 227 (M+1). Anal. Cal. for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.52; H, 6.15%.

4.2.1.6. 2-Methyl-benzoic acid o-tolyl ester ***3f***. Yield: 83%. M.P.: 59-61 °C. IR (KBr) ν_{max} (cm^{-1}): 1715 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.45 (s, 6H, CH_3), 7.11-8.25 (m, 8H, Ar-H). LC-MS m/z 227 (M+1). Anal. Cal. for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.58; H, 6.20%.

*4.2.2. General procedure for the synthesis of (4-hydroxy phenyl) phenyl methanones **4a-f***

Substituted (4-hydroxy phenyl) phenyl methanone commonly known as hydroxy benzophenones **4a-f** were synthesized by Fries rearrangement. Compounds **3a-f** (0.001 mol) and aluminium chloride (0.002 mol) were blended and the mixture was heated upto 150-170 °C without using solvent condition for about 2-3 hours. Then the reaction mixture was cooled to 0°C and quenched with 6N hydrochloric acid in the presence of ice water. The reaction mixture was stirred for about 2-3 hours. The solid was filtered and recrystallized with ethanol to obtain compounds **4a-f.**

*4.2.2.1. (4-Hydroxy-3-methyl-phenyl)-phenyl-methanone **4a***. Yield: 75%; M.P.: 110-112 °C: IR (KBr) ν_{max} (cm^{-1}): 1640 (C=O), 3510-3600 cm-1 (OH); ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 3H, CH_3), 6.73-7.68 (m, 8H, Ar-H), 12.0 (bs, 1H, OH). LC-MS m/z 213 (M+1). Anal. Cal. data for $C_{14}H_{12}O_2$ (212): C, 79.22; H, 5.70. Found: C, 79.18; H, 5.69%.

*4.2.2.2. (4-Hydroxy-2,5-dimethyl-phenyl)-phenyl-methanone **4b***. Yield: 82%; M.P.: 120-122 °C: IR (KBr) ν_{max} (cm^{-1}): 1660 (C=O), 3515-3600 cm-1 (OH); ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 3H, CH_3), 6.61-7.70 (m, 8H, Ar-H), 11.80 (bs, 1H, OH). LC-MS m/z 227 (M+1). Anal. Cal. data for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.57; H, 6.20%.

*4.2.2.3. (4-Bromo-phenyl)-(4-hydroxy-3-methyl-phenyl)-methanone **4c***. Yield: 85%; M.P.: 153-156 °C: IR (KBr) ν_{max} (cm^{-1}): 1645 (C=O), 3510-3600 cm-1 (OH); ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 3H, CH_3), 6.51-7.60 (m, 7H, Ar-H), 12.0 (bs, 1H, OH). LC-MS m/z 292 (M+1). Anal. Cal. data for $C_{14}H_{11}BrO_2$ (291): C, 57.76; H, 3.81. Found: C, 57.71; H, 3.72%.

*4.2.2.4. (3-Chloro-5-fluoro-4-hydroxy-phenyl)-(4-chloro-phenyl)-methanone **4d***. Yield: 78%; M.P.: 147-149 °C: IR (KBr) ν_{max} (cm^{-1}): 1640 (C=O), 3510-3615 cm-1 (OH); ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 6.71-7.70 (m, 6H, Ar-H), 11.90 (bs, 1H, OH). LC-MS m/z 286 (M+1). Anal. Cal. data for $C_{13}H_7Cl_2FO_2$ (285): C, 54.77; H, 2.47. Found: C, 54.67; H, 2.38%.

*4.2.2.5. (4-Hydroxy-3-methyl-phenyl)-p-tolyl-methanone **4e***. Yield: 80%; M.P.: 150-153 °C: IR (KBr) ν_{max} (cm^{-1}): 1650 (C=O), 3520-3620 cm-1 (OH); ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 6H, CH_3), 7.10-7.70 (m, 7H, Ar-H), 12.20 (bs, 1H, OH). LC-MS m/z 227 (M+1). Anal. Cal. data for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.60; H, 6.17%.

*4.2.2.6. (4-Hydroxy-3-methyl-phenyl)-o-tolyl-methanone **4f***. Yield: 72%; M.P.: 125-128 °C: IR (KBr) ν_{max} (cm^{-1}): 1640 (C=O), 3510-3600 cm-1 (OH); ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 6H, CH_3), 6.73-7.60 (m, 7H, Ar-H), 11.60 (bs, 1H, OH). LC-MS m/z 227 (M+1). Anal. Cal. data for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.59; H, 6.18%.

*4.2.3. General procedure for the synthesis of (4-benzoyl phenoxy)-acetic acid ethyl ester **5a-f***

Compounds **5a-f** were obtained by refluxing a mixture of compounds **4a-f** (0.013 mol) and ethyl chloroacetate (0.026 mol) in dry acetone (50 mL) and anhydrous potassium carbonate (0.019 mol) for 8-10 hours. The reaction mixture was cooled and the solvent was removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate and extracted with ether (50 mL × 3). The ether layer was washed with 10% sodium hydroxide solution (50 mL × 3) followed by water (30 mL × 3) and then dried over anhydrous sodium sulfate and evaporated to dryness to obtain crude solid, which when recrystallised with ethanol, afforded compounds **5a-f.**

*4.2.3.1. (4-Benzoyl-2-methyl-phenoxy)-acetic acid ethyl ester **5a***. Yield: 92%. M.P.: 49-51 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1664 (C=O), 1760 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 1.2 (t, 3H, CH_3 of ester), 2.3 (s, 3H, CH_3), 4.1 (q, 2H, CH_2 of ester), 4.5 (s, 2H, OCH_2), 7.1-7.7 (m, 8H, Ar-H). LC-MS m/z 299 (M+1). Anal. Cal. for $C_{18}H_{18}O_4$ (298): C, 72.48; H, 6.04. Found: C, 72.46; H, 6.02%.

*4.2.3.2. (4-Benzoyl-2,5-dimethyl-phenoxy)-acetic acid ethyl ester **5b***. Yield: 83%. M.P.: 53-55 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1664 (C=O), 1760 (ester, C=O). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm):

1.2 (t, 3H, CH_3 of ester), 2.3 (s, 6H, CH_3), 4.3 (q, 2H, CH_2 of ester), 4.5 (s, 2H, OCH_2), 6.9-7.8 (m, 7H, Ar-H). LC-MS m/z 313 (M+1). Anal. Cal. for $C_{19}H_{20}O_4$ (312): C, 73.06; H, 6.45. Found: C, 73.02; H, 6.41%.

4.2.3.3. [4-(4-Bromo-benzoyl)-2-methyl-phenoxy]-acetic acid ethyl ester ***5c***. Yield: 92%. M.P.: 47-49 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1664 (C=O), 1760 (ester, C=O). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 1.2 (t, 3H, CH_3 of ester), 2.3 (s, 3H, CH_3), 4.4 (q, 2H, CH_2 of ester), 4.5 (s, 2H, OCH_2), 6.7-7.7 (m, 7H, Ar-H). LC-MS m/z 378 (M+1). Anal. Cal. for $C_{18}H_{17}BrO_4$ (377): C, 57.31; H, 4.54. Found: C, 57.27; H, 4.49%.

4.2.3.4. [2-Chloro-4-(4-chloro-benzoyl)-6-fluoro-phenoxy]-acetic acid ethyl ester ***5d***. Yield: 90%. M.P.: 55-57 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1664 (C=O), 1760 (ester, C=O). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 1.3 (t, 3H, CH_3 of ester), 4.1 (q, 2H, CH_2 of ester), 4.8 (s, 2H, OCH_2), 7.1-7.7 (m, 6H, Ar-H). LC-MS m/z 372 (M+1). Anal. Cal. for $C_{17}H_{13}Cl_2FO_4$ (371): C, 55.01; H, 3.53. Found: C, 54.95; H, 3.48%.

4.2.3.5. [2-Chloro-4-(4-chloro-benzoyl)-6-fluoro-phenoxy]-acetic acid ethyl ester ***5e***. Yield: 91%. M.P.: 47-49 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1664 (C=O), 1760 (ester, C=O). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 1.2 (t, 3H, CH_3 of ester), 2.4 (s, 6H, CH_3), 4.1 (q, 2H, CH_2 of ester), 4.5 (s, 2H, OCH_2), 7.1-7.7 (m, 7H, Ar-H). LC-MS m/z 313 (M+1). Anal. Cal. for $C_{19}H_{20}O_4$ (312): C, 73.06; H, 6.45. Found: C, 73.01; H, 6.39%.

4.2.3.6. [2-Methyl-4-(2-methyl-benzoyl)-phenoxy]-acetic acid ethyl ester ***5f***. Yield: 89%. M.P.: 50-52 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1664 (C=O), 1760 (ester, C=O). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 1.3 (t, 3H, CH_3 of ester), 2.3 (s, 6H, CH_3), 4.2 (q, 2H, CH_2 of ester), 4.9 (s, 2H, OCH_2), 6.8-7.6 (m, 7H, Ar-H). LC-MS m/z 313 (M+1). Anal. Cal. for $C_{19}H_{20}O_4$ (312): C, 73.06; H, 6.45. Found: C, 73.02; H, 6.52%.

*4.2.4. General procedure for the synthesis of (4-benzoyl phenoxy)-acetic acid **6a-f***

Compounds **5a-f** (6.0 mmol) were dissolved in ethanol (15 mL) and treated with a solution of sodium hydroxide (15 mmol) in water (5 mL). The reaction mixture was refluxed for 5-6 h, cooled and acidified with 1N hydrochloric acid. The precipiatae was filtered, washed with water and recrystallised with methanol to afford compounds **6a-f** in a good yield.

*4.2.4.1. (4-Benzoyl-2-methyl-phenoxy)-acetic acid **6a***. Yield: 82%. M.P.: 130-132 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (acid, C=O), 3400-3500(acid OH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 4.61 (s, 2H, OCH_2), 7.2-7.7 (m, 8H, Ar-H), 9.5 (s, 1H, COOH). LC-MS m/z 271 (M+1). Anal. Cal. for $C_{16}H_{14}O_4$ (270): C, 71.10; H, 5.22. Found: C, 71.06; H, 5.20%.

*4.2.4.2. (4-Benzoyl-2,5-dimethyl-phenoxy)-acetic acid **6b***. Yield: 88%. M.P.: 153-155 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1660 (C=O), 1738 (acid, C=O), 3410-3540(acid OH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.4 (s, 6H, CH_3), 4.53 (s, 2H, OCH_2), 7.1-7.6 (m, 8H, Ar-H), 9.4 (s, 1H, COOH). LC-MS m/z 285 (M+1). Anal. Cal. for $C_{17}H_{16}O_4$ (284): C, 71.82; H, 5.67. Found: C, 71.78; H, 5.62%.

*4.2.4.3. [4-(4-Bromo-benzoyl)-2-methyl-phenoxy]-acetic acid **6c***. Yield: 93%. M.P.: 141-143 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1615 (C=O), 1760 (acid, C=O), 3465-3575(acid OH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.2 (s, 3H, CH_3), 4.41 (s, 2H, OCH_2), 7.1-7.8 (m, 7H, Ar-H), 9.7 (s, 1H, COOH). LC-MS m/z 350 (M+1). Anal. Cal. for $C_{16}H_{13}BrO_4$ (349): C, 55.04; H, 3.75. Found: C, 55.01; H, 3.73%.

*4.2.4.4. [2-Chloro-4-(4-chloro-benzoyl)-6-fluoro-phenoxy]-acetic acid **6d***. Yield: 89%. M.P.: 137-139 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1640 (C=O), 1750 (acid, C=O), 3480-3585(acid OH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 4.46 (s, 2H, OCH_2), 6.9-7.7 (m, 8H, Ar-H),

9.5 (s, 1H, COOH). LC-MS m/z 344 (M+1). Anal. Cal. for $C_{16}H_{14}Cl_2FO_4$ (343): C, 52.50; H, 2.64. Found: C, 52.47; H, 2.61%.

4.2.4.5. [2-Methyl-4-(4-methyl-benzoyl)-phenoxy]-acetic acid ***6e***. Yield: 90%. M.P.: 119-121 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1665 (C=O), 1735 (acid, C=O), 3470-3580(acid OH). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.3 (s, 6H, CH_3), 4.39 (s, 2H, OCH_2), 6.8-7.5 (m, 7H, Ar-H), 9.7 (s, 1H, COOH). LC-MS m/z 285 (M+1). Anal. Cal. for $C_{17}H_{16}O_4$ (284): C, 71.82; H, 5.67. Found: C, 71.79; H, 5.64%.

4.2.4.6. [2-Methyl-4-(2-methyl-benzoyl)-phenoxy]-acetic acid ***6f***. Yield: 85%. M.P.: 124-126 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1630 (C=O), 1755 (acid, C=O), 3470-3575(acid OH). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.5 (s, 6H, CH_3), 4.40 (s, 2H, OCH_2), 6.9-7.7 (m, 7H, Ar-H), 9.6 (s, 1H, COOH). LC-MS m/z 285 (M+1). Anal. Cal. for $C_{17}H_{16}O_4$ (284): C, 71.82; H, 5.67. Found: C, 71.80; H, 5.63%.

4.2.5. General procedure for the synthesis of N-(2-amino-phenyl)-2-(4-benzoyl-phenoxy)-acetamide ***8a-f***

To compounds **6a-f** (0.0037 mol) in dry dichloromethane (15 mL), lutidine (1.2 vol.) was added at 25-30^oC , followed by the addition of 1,2 diaminobenzene (**7,** 0.0037 mol). The reaction mixture was stirred at 25-30^o C for 30 min. The reaction was cooled to 0-5 ^{o} C, TBTU (0.0037 mol) was added over a period of 30 min while maintaining the temperature below 5^o C. The reaction was strirred overnight and monitored by TLC using hexane and ethyl acetate (4:1). The reaction mixture was diluted with 20 mL of dichloromethane and treated with 1.5 N HCl solution (20 mL). The organic layer was washed with water (25 mL × 3) and brine (25 mL × 3). Finally, the organic layer was dried over anhydrous sodium sulfate and concentrated to afford compounds **8a-f**.

4.2.5.1. N-(2-amino-phenyl)-2-(4-benzoyl-2-methyl-phenoxy)-acetamide ***8a***. Yield: 92%. M.P.: 190-192 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.2 (s, 3H, CH_3), 4.74 (s, 2H, NH_2), 4.91 (s, 2H, OCH_2), 6.5-7.6 (m, 12H, Ar-H), 9.2 (s, 1H, NH). LC-MS m/z 361 (M+1). Anal. Cal. for $C_{22}H_{20}N_2O_3$ (360): C, 73.32; H, 5.59. Found: C, 73.26; H, 5.48%.

4.2.5.2. N-(2-amino-phenyl)-2-(4-benzoyl-2,5-dimethyl-phenoxy)-acetamide ***8b***. Yield: 73%. M.P.: 148-150 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 6H, CH_3), 4.6 (s, 2H, NH_2), 4.88 (s, 2H, OCH_2), 6.7-7.5 (m, 11H, Ar-H), 9.1 (s, 1H, NH). LC-MS m/z 375(M+1). Anal. Cal. for $C_{23}H_{22}N_2O_3$ (374): C, 73.78; H, 5.92. Found: C, 73.68; H, 5.75%.

4.2.5.3. N-(2-amino-phenyl)-2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetamide ***8c***. Yield: 95%. M.P.: 185-187 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.3 (s, 3H, CH_3), 4.7 (s, 2H, NH_2), 4.93 (s, 2H, OCH_2), 6.6-7.8 (m, 11H, Ar-H), 9.2 (s, 1H, NH). LC-MS m/z 440 (M+1 Anal. Cal. for $C_{22}H_{19}BrN_2O_3$ (439): C, 60.15; H, 4.36. Found: C, 60.07; H, 4.28%.

4.2.5.4. N-(2-amino-phenyl)-2-[2-chloro-4-(4-chloro-benzoyl)-6-fluoro-phenoxy]-acetamide ***8d***. Yield: 67%. M.P.: 154-156 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.4 (s, 3H, CH_3), 4.6 (s, 2H, NH_2), 4.9 (s, 2H, OCH_2), 6.7-7.9 (m, 12H, Ar-H), 9.6 (s, 1H, NH). LC-MS m/z 434 (M+1). Anal. Cal. for $C_{21}H_{15}Cl_2FN_2O_3$ (433): C, 58.22; H, 3.49. Found: C, 58.17; H, 3.48%.

4.2.5.5. N-(2-amino-phenyl)-2-[2-methyl-4-(4-methyl-benzoyl)-phenoxy]-acetamide ***8e***. Yield: 89%. M.P.: 180-182 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.5 (s, 6H, CH_3), 4.4 (s, 2H, NH_2), 4.7

(s, 2H, OCH_2), 6.7-7.8 (m, 11H, Ar-H), 9.5 (s, 1H, NH). LC-MS m/z 375 (M+1) Anal. Cal. for $C_{23}H_{22}N_2O_3$ (374): C, 73.78; H, 5.92. Found: C, 73.76; H, 5.89%.

4.2.5.6. N-(2-amino-phenyl)-2-[2-methyl-4-(2-methyl-benzoyl)-phenoxy]-acetamide ***8f***. Yield: 93%. M.P.: 187-189 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1670 (C=O), 1740 (amide, C=O), 3130-3230 (amide CO-NH). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.3 (s, 6H, CH_3), 4.5 (s, 2H, NH_2), 4.8 (s, 2H, OCH_2), 6.6-7.5 (m, 11H, Ar-H), 9.3 (s, 1H, NH). LC-MS m/z 375 (M+1). Anal. Cal. for $C_{23}H_{22}N_2O_3$ (374): C, 73.78; H, 5.92. Found: C, 73.75; H, 5.84%.

4.2.6. General procedure for the synthesis of 2-(4-benzoyl-phenoxy)-N-{2-[2-(4-benzoyl-phenoxy)-acetylamino]-phenyl}-acetamide ***9a-l.***

To compounds **8a-f** (0.001 mol) in dry dichloromethane (15 mL), substituted (4-benzoyl-phenoxy)-acetic acids **6a-f** were added at 25-30 ^oC, followed by the addition of lutidine (0.001 mol). The reaction mixture was stirred at 25-30 ^oC for 30 min. The reaction was cooled to 0-5 ^oC, TBTU (0.001 mol) was added over a period of 30 min while maintaining the temperature below 5 ^oC. The reaction was strirred overnight and monitored by TLC using hexane and ethyl acetate (4:1). The reaction mixture was diluted with 20 mL of dichloromethane and treated with 10% sodium bicarbonate solution (20 mL × 3). The organic layer was washed with water (25 mL × 3), dried over anhydrous sodium sulfate and concentrated to yield compounds **9a-l.**

4.2.6.1. 2-(4-Benzoyl-2-methyl-phenoxy)-N-{2-[2-(4-benzoyl-2-methyl-phenoxy)-acetylamino]-phenyl}-acetamide ***9a***. Yield: 82%. M.P.: 90-92^o C; IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.27 (s, 6H, CH_3), 4.78 (s, 4H, OCH_2), 6.9-7.6 (m, 20H, Ar-H), 9.6 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.8, 167.0, 159.7, 138.2, 132.5, 132.4, 130.7, 130.4, 130.1, 129.7, 129.6, 128.8, 128.7, 127.0, 126.3, 126.0, 111.2, 67.5, 16.5. LC-MS m/z 613 (M+1). Anal. Cal. for $C_{38}H_{32}N_2O_6$ (612): C, 74.49; H, 5.26; N, 4.57. Found: C, 74.37; H, 5.19; N, 4.40%.

4.2.6.2. 2-(4-Benzoyl-2,5-dimethyl-phenoxy)-N-{2-[2-(4-benzoyl-2,5-dimethyl-phenoxy)-acetylamino]-phenyl}-acetamide ***9b***. Yield: 56%. M.P.: 93-95 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH).^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 12H, CH_3), 4.78 (s, 4H, OCH_2), 6.5-7.6 (m, 18H, Ar-H), 9.3 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.6, 165.6, 162.8, 139.5, 138.5, 135.2, 132.4, 131.5, 129.7, 128.6, 124.5, 122.3, 117.8, 68.4, 19.2, 16.6. LC-MS m/z 641 (M+1). Anal. Cal. for $C_{40}H_{36}N_2O_6$ (640): C, 74.49; H, 5.26; N, 4.57. Found: C, 74.40; H, 5.21; N, 4.49%.

4.2.6.3. 2-[4-(4-Bromo-benzoyl)-2-methyl-phenoxy]-N-(2-{2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetylamino}-phenyl)-acetamide ***9c***. Yield: 58%. M.P.: 86-88 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.32 (s, 6H, CH_3), 4.82 (s, 4H, OCH_2), 6.7-7.8 (m, 18H, Ar-H), 9.5 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.3, 165.8, 162.5, 139.7, 134.2, 132.3, 130.0, 129.5, 128.3, 128.1, 126.8, 124.5, 121.9, 116.8, 65.8, 15.9. LC-MS m/z 771 (M+1). Anal. Cal. for $C_{38}H_{30}Br_2N_2O_6$ (770): C, 59.24; H, 3.92; N, 3.64. Found: C, 59.20; H, 3.81; N, 3.53%.

4.2.6.4. N-{2-[2-(4-benzoyl-2,5-dimethyl-phenoxy)-acetylamino]-phenyl}-2-(4-benzoyl-2-methyl-phenoxy)-acetamide ***9d***. Yield: 79%. M.P.: 94-96^{o} C. IR (KBr) ν_{max} cm^{-1}1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.44 (s, 9H, CH_3), 4.76 (s, 4H, OCH_2), 6.8-7.6 (m, 19H, Ar-H), 9.6 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.2, 165.3, 162.3, 161.2, 139.5, 138.7, 136.5, 135.2, 134.8, 132.7, 131.9, 131.2, 128.7, 126.5, 124.3, 123.3, 122.8, 121.5, 120.7, 118.6, 114.2, 73.2, 20.1, 16.3. LC-MS m/z 627 (M+1). Anal. Cal. for $C_{39}H_{34}N_2O_6$ (626): C, 74.74; H, 5.47; N, 4.47; O. Found: C, 74.40; H, 5.21; N, 4.49%.

4.2.6.5. N-{2-[2-(4-benzoyl-2-methyl-phenoxy)-acetylamino]-phenyl}-2-[2-chloro-4-(4-chloro-benzoyl)-6-fluoro-phenoxy]-acetamide ***9e***. Yield: 68%. M.P.: 83-85^{o} C. IR (KBr) ν_{max} (cm^{-1}):

1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.41 (s, 3H, CH_3), 4.82 (s, 4H, OCH_2), 6.7-7.7 (m, 18H, Ar-H), 9.5 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.7, 164.9, 163.3, 152.6, 145.8, 137.5, 136.2, 135.4, 133.9, 133.5, 132.4, 131.7, 130.4, 129.8, 128.5, 127.7, 126.2, 124.2, 123.5, 122.9, 121.5, 120.2, 119.8, 117.3, 116.4, 65.2, 62.8, 15.9. LC-MS m/z 686 (M+1). Anal. Cal. for $C_{37}H_{27}Cl_2FN_2O_6$ (685): C, 68.83; H, 3.97; N, 4.09. Found: C, 68.75; H, 3.87; N, 4.02%.

4.2.6.6. N-{2-[2-(4-benzoyl-2-methyl-phenoxy)-acetylamino]-phenyl}-2-[2-methyl-4-(2-methyl-benzoyl)-phenoxy]-acetamide ***9f***. Yield: 90%. M.P.: 95-97^{o} C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.35 (s, 9H, CH_3), 4.69 (s, 4H, OCH_2), 6.5-7.7 (m, 19H, Ar-H), 9.6 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 193.7, 168.7, 165.3, 140.5, 138.3, 137.7, 135.8, 133.2, 132.2, 131.8, 130.9, 129.2, 128.5, 127.5, 127.1, 124.3, 122.8, 121.6, 119.5, 70.5, 19.3, 16.1. LC-MS m/z 627 (M+1). Anal. Cal. for $C_{39}H_{34}N_2O_6$ (626): C, 74.74; H, 5.47; N, 4.47. Found: C, 74.68; H, 5.41; N, 4.39%.

4.2.6.7. N-{2-[2-(4-benzoyl-2-methyl-phenoxy)-acetylamino]-phenyl}-2-[2-methyl-4-(4-methyl-benzoyl)-phenoxy]-acetamide ***9g***. Yield: 62%. M.P.: 89-90^{o} C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.33 (s, 9H, CH_3), 4.84 (s, 4H, OCH_2), 6.7-7.8 (m, 19H, Ar-H), 9.7 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 193.4, 166.5, 161.8, 140.4, 136.5, 133.8, 133.2, 132.1, 131.4, 130.3, 129.6, 128.6, 127.5, 126.9, 123.6, 122.0, 119.7, 113.3, 69.4, 21.3, 16.3. LC-MS m/z 627 (M+1). Anal. Cal. for $C_{39}H_{34}N_2O_6$ (626): C, 74.74; H, 5.47; N, 4.47. Found: C, 74.71; H, 5.35; N, 4.37%.

4.2.6.8. N-{2-[2-(4-benzoyl-3-methyl-phenoxy)-acetylamino]-phenyl}-2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetamide ***9h***. Yield: 59%. M.P.: 87-89 ^{o}C; IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.31 (s,

6H, CH_3), 4.61 (s, 2H, OCH_2), 6.5-7.6 (m, 19H, Ar-H), 9.5 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 193.5, 167.3, 166.8, 139.2, 138.5, 136.3, 135.1, 134.9, 133.5, 132.8, 131.5, 130.4, 129.7, 128.2,126.5, 125.1, 124.8, 123.6, 122.1, 120.3, 119.7, 65.2, 16.7. LC-MS m/z 692 (M+1). Anal. Cal. for $C_{38}H_{31}N_2BrO_6$ (691): C, 66.00; H, 4.52; N, 4.05. Found: C, 65.96; H, 4.21; N, 4.02%.

4.2.6.9. N-{2-[2-(4-benzoyl-2,5-dimethyl-phenoxy)-acetylamino]-phenyl}-2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetamide ***9i***. Yield: 83%. M.P.: 91-93^o C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.45 (s, 9H, CH_3), 4.72 (s, 4H, OCH_2), 6.4-7.5 (m, 18H, Ar-H), 9.7 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.3, 166.2, 165.2, 164.7, 142.9, 140.3, 138.5, 137.3, 136.2, 133.8, 132.1, 131.7, 130.5, 128.2, 127.3, 126.7, 124.2, 123.8, 122.1, 121.5, 120.7, 119.2, 118.5, 115.3, 69.7, 18.2, 15.6. LC-MS m/z 706 (M+1). Anal. Cal. for $C_{39}H_{33}BrN_2O_6$ (705): C, 66.39; H, 4.71; N, 3.97. Found: C, 66.12; H, 4.68; N, 3.82%.

4.2.6.10. N-(2-{2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetylamino}-phenyl)-2-[2-chloro-4-(4-chloro-benzoyl)-6-fluoro-phenoxy]-acetamide ***9j***. Yield: 76%. M.P.: 80-82 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.31 (s, 3H, CH_3), 4.81 (s, 2H, OCH_2), 6.8-7.7 (m, 17H, Ar-H), 9.6 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.8, 168.3, 161.2, 154.2, 147.6, 136.8, 134.2, 133.9, 133.1, 132.5, 132.3, 131.5, 130.7, 130.2, 130.1, 129.6, 128.8, 127.9, 127.0, 126.3, 124.0, 118.7, 115.2, 111.2, 110.5, 68.3, 67.5, 16.5. LC-MS m/z 765(M+1). Anal. Cal. for $C_{37}H_{26}BrCl_2FN_2O_6$ (764): C, 58.14; H, 3.43; N, 3.66. Found: C, 58.08; H, 3.41; N, 3.63%.

4.2.6.11. N-(2-{2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetylamino}-phenyl)-2-[2-methyl-4-(2-methyl-benzoyl)-phenoxy]-acetamide ***9k***. Yield: 85%. M.P.: 94-96 ^{o}C. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.44 (s, 9H, CH_3), 4.79 (s, 4H, OCH_2), 6.8-7.7 (m, 18H, Ar-H), 9.7 (s, 2H, NH). ^{13}C

NMR (DMSO-d_6) δ: 194.6, 166.3, 164.2, 155.6, 150.3, 143.5, 138.4, 136.9, 134.2, 133.5, 132.1, 131.3, 130.7, 129.9, 128.2, 128.6, 125.3, 124.2, 122.7, 121.6, 120.5, 119.8, 117.5, 116.3, 67.9, 66.3, 16.3. LC-MS m/z 706 (M+1). Anal. Cal. for $C_{39}H_{33}BrN_2O_6$ (705): C, 66.39; H, 4.71; N, 3.97. Found: C, 66.32; H, 4.63; N, 3.86%.

4.2.6.12. N-(2-{2-[4-(4-bromo-benzoyl)-2-methyl-phenoxy]-acetylamino}-phenyl)-2-[2-methyl-4-(4-methyl-benzoyl)-phenoxy]-acetamide ***9l***. Yield: 56%. M.P.:102-104 ^oC. IR (KBr) ν_{max} (cm^{-1}): 1675 (C=O), 1730 (amide, C=O), 3120-3220 (amide CO-NH). ^1H NMR (400 MHz) ($CDCl_3$) δ (ppm): 2.42 (s, 9H, CH_3), 4.81 (s, 4H, OCH_2), 6.7-7.6 (m, 18H, Ar-H), 9.7 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ: 194.2, 166.9, 165.3, 138.5, 136.2, 134.4, 133.6, 132.5, 131.4, 130.4, 129.8, 128.5, 127.7, 126.2, 124.1, 122.7, 121.9, 120.2, , 118.3, 116.4, 65.2, 19.5, 15.3.LC-MS m/z 706 (M+1). Anal. Cal. for $C_{39}H_{33}BrN_2O_6$ (705): C, 66.39; H, 4.71; N, 3.97. Found: C, 66.35; H, 4.68; N, 3.93%.

4.3. Biology

4.3.1. Cell culture and in-vitro compound treatment

Three cell lines from different origin, namely, human lung epithelial carcinoma (A549), human epithelial adenocarcinoma (MCF-7) and Murine Daltons lymphoma (DLA) cells were cultured in DMEM (Gibco-Invitrogen, USA), with 10% FBS (In vitrogen, USA), with necessary antibiotic and antimicotic (Sigma-Aldrich, USA) agents, were maintained and subjected to treatment with varying concentrations of compounds **9a–l** (0, 10, 20,50, and 100 µM in DMSO) for various time intervals for 48h for MTT, trypan blue and LDH release assay as reported earlier [12]. An appropriate vehicle and positive control 5-flurouracil all determinations were carried out in triplicate for a minimum of three times independently as described previously.

4.3.2. Animal models and ethics

Swiss albino male mice weighing 25g-28g were housed under standard laboratory conditions with food and water. All procedures for animal experimentation used were approved by the Institutional Animal Ethics Committee, National College of Pharmacy, Shimoga, India, in accordance with the CPCSEA guidelines for laboratory animal facility (NCP/IAEC/CL/101/05/2012-13).

*4.3.3. Determining the LD50 compound **9k***

Non-tumor bearing normal swiss albino mice divided into 5 groups (n = 6) were subjected to the acute toxicity studies. The LD50 of compound **9k** was determined by intraperitoneal administration of **9k** as per the standard CPCSEA guidelines [11].

4.3.4. Animal tumor models and treatment

DLA cells were cultured *in-vivo* and after the optimal growth of tumor, the mice were divided into group A and group B. The compound **9k** was dissolved in DMSO and three doses on alternative days were injected i.p.to group A mice at a concentration of 75 mg/kg bodyweight using a 26 gauge needle. Group B was maintained as an appropriate vehicle (DMSO) control. The survivability of the animals (n = 10 each) was also determined.

4.3.5. Chorioallontoic membrane (CAM) assay

The *in-vivo* anti-angiogenic effect induced by $rVEGF_{165}$ was analyzed following treatment with **9k** in 12 days, fertilized egg CAM as described earlier [11] and changes in the MVD was analyzed and photographed using Sony steady shot DSC-W610camera.

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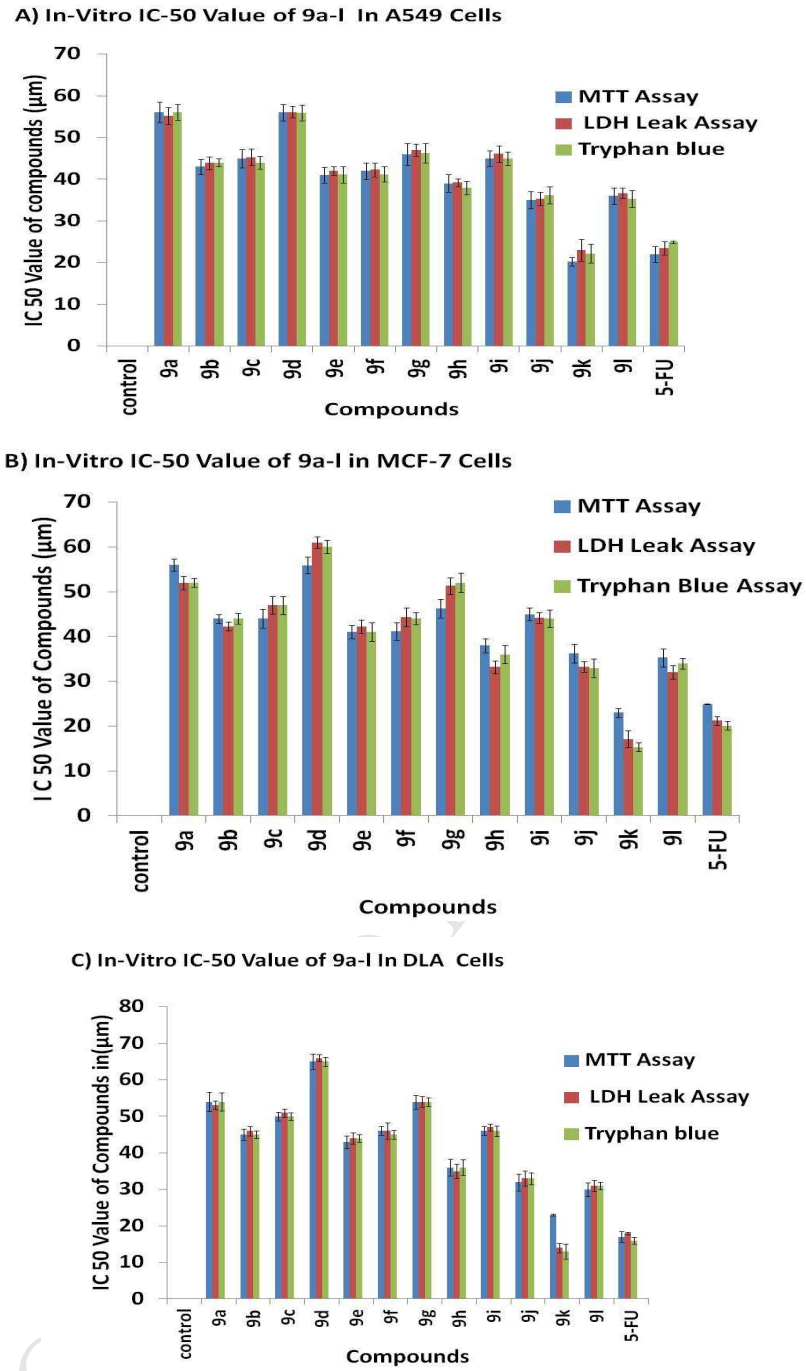
Figure Captions

Figure 1: Screening of potent antiproliferative molecule from 9a-l series in *In-vitro*. IC_{50} values of cytotoxic compounds **9a–l** was determined using various assay methods such as MTT, LDH leak assay and Trypan blue (A) IC_{50} value of **9a-l** in A549 cells (B) In MCF cells. (C) IC_{50} value of **9a-l** in DLA cells.

Figure 2: *In-vivo* tumor inhibitory activity of compound 9k: The compound **9k** was administered i.p. at the concentration of 75mg/Kg body weight after the onset of DLA tumor in mice on every alternate day for three doses. (A) Morphology of tumor bearing mice. (B) Dose dependent decrease in tumor growth. (C) Dose dependent decreased ascites volume (D) Dose dependent decreased cell count (E) Increased in survivality.

Figure 3: Antiangiogenic effect of compound 9k in both tumorigenic and non tumorigenic models: (A) The image showing decreased count of micro vessel density in **9k** treated mice peritoneum compared to the control and normal mice with graphical quantification. (B) CAM images showing a reduction in neovascularisation induced by $rVEGF_{165}$ after **9k** treatment with graphical quantification.



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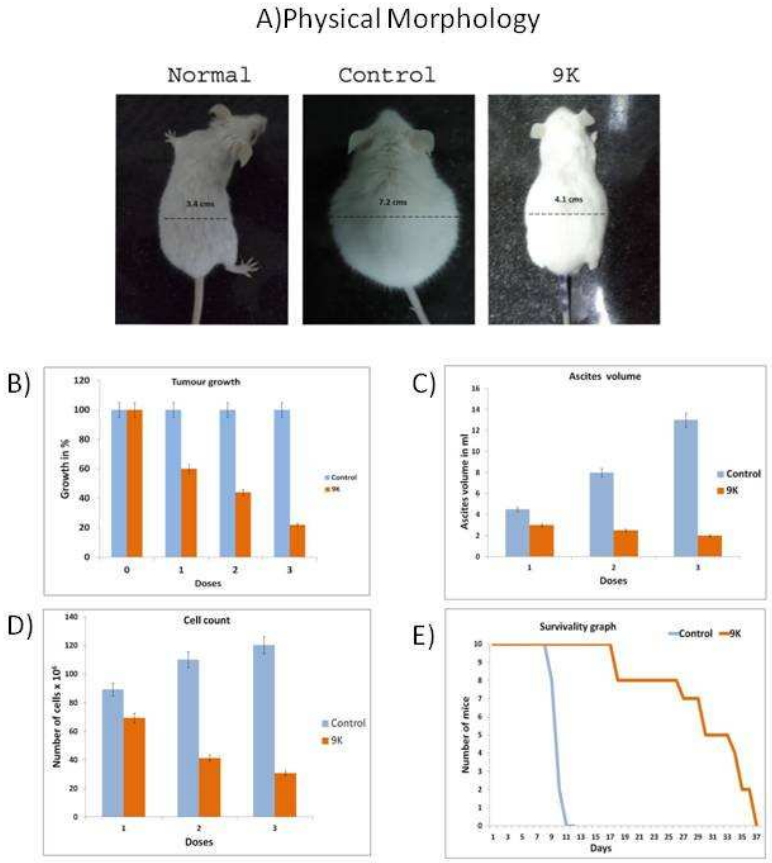

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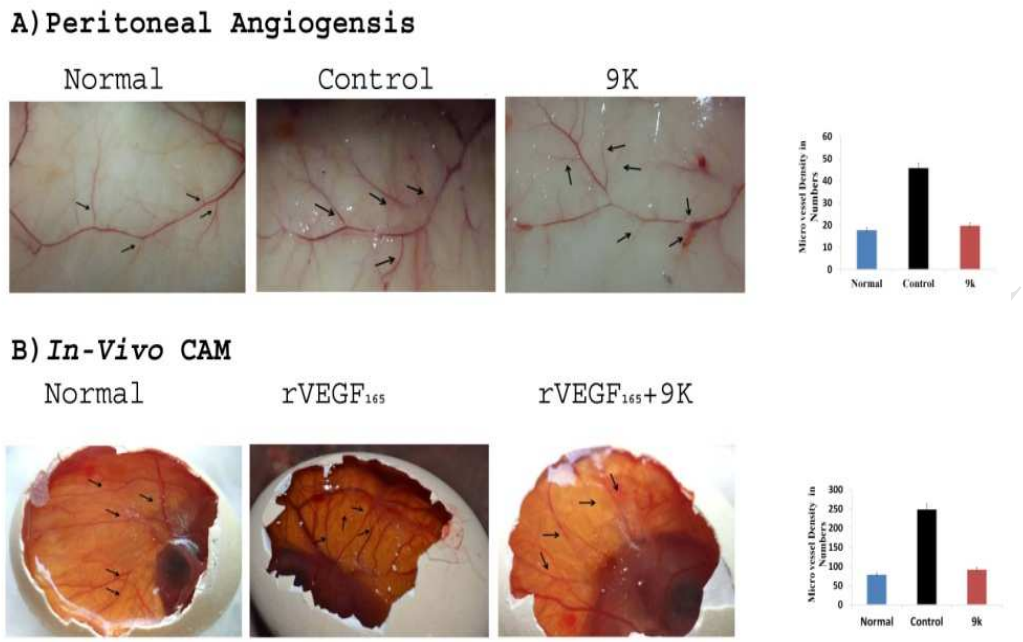

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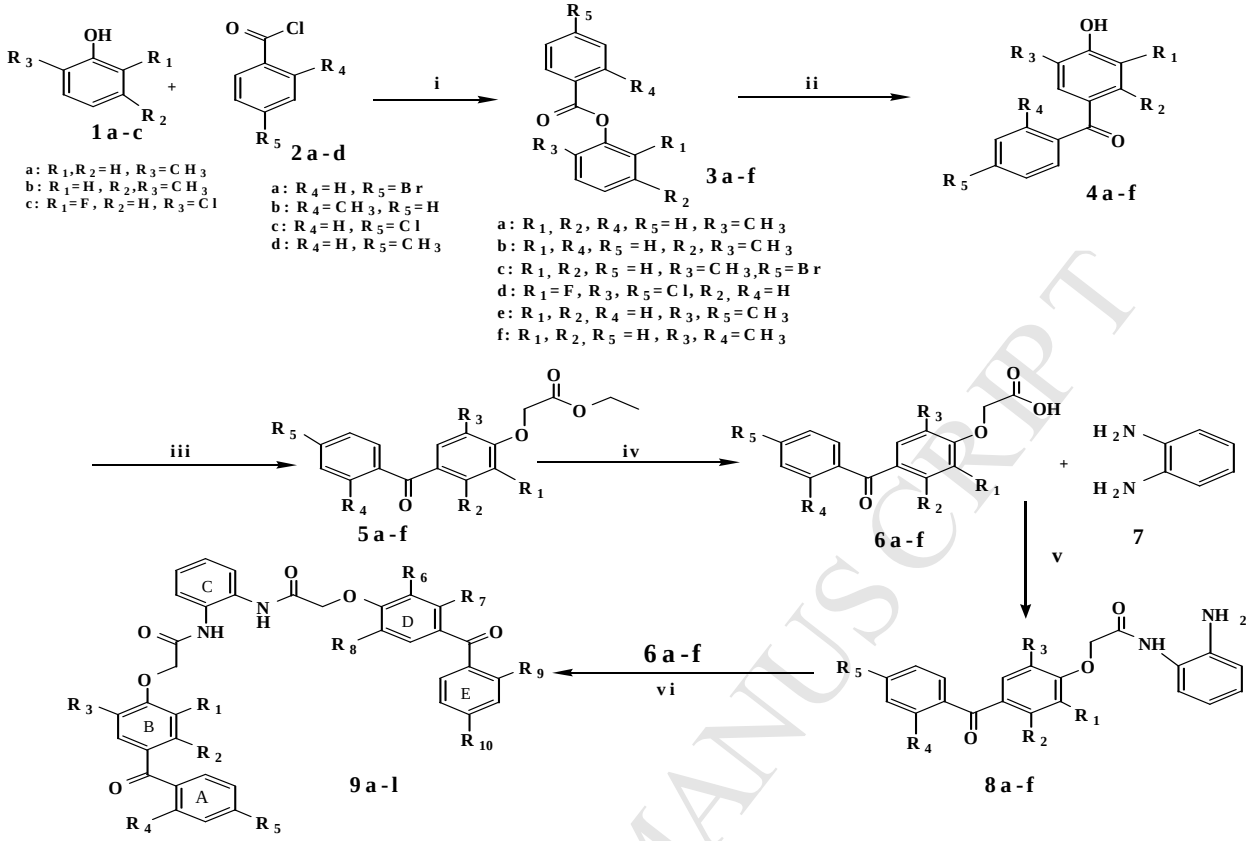

9a. $R_1,R_2,R_4,R_5,R_6,R_7,R_9,R_{10}$ = H; R_3,R_8 = CH_3
9b. $R_1,R_4,R_5,R_6,R_9,R_{10}$ = H; R_2,R_3,R_7,R_8 = CH_3
9c. R_1,R_2,R_4,R_6,R_7,R_9 = H; R_3,R_8 = CH_3; R_5,R_{10} = Br
9d. $R_1,R_2,R_4,R_5,R_6,R_9,R_{10}$ = H; R_3,R_7,R_8 = CH_3
9e. R_1= F; $R_2,R_4,R_6,R_7,R_9,R_{10}$ = H; R_3,R_5 = 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^{o}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 ^{o}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 ^{o}C for 30 min then overnight at RT, yield: 80-90%, (vi) TBTU/Lutidine, Dry DCM, Stirring 0-5 ^{o}C for 30 min then, overnight at RT, yield: 75-85%.

HIGHLIGHTS

- **We have synthesized diamide-coupled benzophenone derivatives.**
- **All the synthesized compounds were tested for potential anticancer agents.**
- **The results were reconfirmed compound 9k as a potent anticancer drug in near future.**