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Cytotoxic Evaluation of (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-one Derivatives

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ABSTRACT

A series of (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-one derivatives were synthesized and *in vitro* cytotoxic activity of the compounds were evaluated against Hep-2 cell line by MTT assay. The structure activity relationship based on the type of substituent on C-3 propenones was explored.

Keywords: Cytotoxic activity; MTT assay; Hep-2 cell line; Difluorobiphenyl chalcone.

INTRODUCTION

Although there is a rapid development in diagnosing and treating cancer, it remains a major threat to the patients. It is a challenge for the chemists to develop new anticancer drugs with high selectivity and absorptivity than the existing drugs. To overcome the side effects emerging from the presently available drugs, there is a need to develop better cytotoxic agents to prevent such a problem[1].

Chalcones possess wide range of therapeutic and pharmacological activities due to the presence of methylene and carbonyl moieties in their structure. They present in many naturally occurring vascular plants not only in their terrestrial parts but also in roots, flakes and seeds. A large variety chalcone based derivatives were reported and identified as better anticancer agent. These compounds exhibits a wide variety of pharmacological activities which includes anticancer, antiinflammatory, immunomodulatory, antibacterial, and immunosuppressive, as well as antiprotozoan activity, including trypanocidal, leishmanicidal, and antimalarial[2-8]. The biphenyl moiety is also found in many natural products that exhibits a wide variety of biological activities such as anti-cancer[9-12], anti-angiogenic[9,11], anti-viral[13] and have the ability to display enhanced fluorescence[14]. We recently reported the synthesis, characterization, *in vitro* antimicrobial activity against various microbes and *in silico* docking studies against cancer protein 4LRH[15]. From the molecular docking studies it was concluded that the

synthesized difluorobiphenyl chalcones was found to be exhibit anticancer activity against the tested ligand. With the aim to evaluate the *in vitro* cytotoxic activity of the synthesized analogues, in the present study the cytotoxic activity was tested against Hep-2 cell line.

EXPERIMENTAL

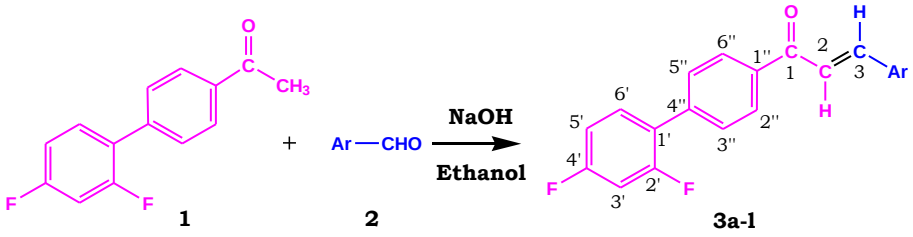
The cytotoxicity of the synthesized compounds were tested against Hep-2 cell lines using the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay[16]. The cells were seeded into a 96-well plate at a density of 1.5×10^4 cells/well and incubated at 37 °C, 5 % CO_2, for 24 h to allow the cells to attach. Cells were incubated with 10 µM of synthesized compounds into designated wells. After 48 h of incubation at 37 °C, 20 µL of MTT solution (4 mg/mL) was added to each well. The plates were further incubated for 4 h at 37 °C, allowing viable cells to change the yellow-colored MTT into dark-blue formazan crystals. Consequently, without disturbing the cells the MTT medium was removed from each well, and 100 µL of DMSO was added into each well. Plates were placed on a shaking table to thoroughly mix the formazan into the solvent. Finally, the absorbance was determined at 570 nm by microplate reader (Tecan infinite M200 pro multimode reader, Austria). The MTT assays were performed four times independently, and each independent experiment was done in triplicate. The percentage of survival was calculated using the formula:

% Survival = [live cell number (test)/live cell number (control)] × 100

Cytotoxicity (%) = 100 – % survival

RESULTS AND DISCUSSION

Various (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones (**3a-l**) were prepared with excellent yield by Claisen-Schimidt condensation of 1-(2',4'-difluorobiphenyl-4-yl)ethanone (**1**) with various substituted aldehydes (**2a-l)** under basic condition as displayed in **Table 1** (**Scheme 1**).



Scheme 1

Table 1 Synthesis of (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones

Compound	Ar	Compound	Ar
3a	C_6H_5	**3g**	4-BrC_6H_4
3b	4-$CH_3C_6H_4$	**3h**	3-$NO_2C_6H_4$
3c	4-FC_6H_4	**3i**	2-furyl
3d	3-$OCH_3C_6H_4$	**3j**	2-thiophenyl
3e	2-$OCH_3C_6H_4$	**3k**	2-naphthyl
3f	4-ClC_6H_4	**3l**	$CH{=}CHC_6H_5$

The *in vitro* cytotoxic activity of the compounds **3a-l** was evaluated against Hep-2 cell line which is derived from laryngeal carcinoma cells by MTT assay. The percentage of the cell viability was determined and cytotoxicity percentage was calculated (**Table 2**). The graphical representation was displayed in **Fig. 1**. On critically analyzing the results, all the compounds exhibit moderate to potent activities. From the cytotoxicity data it was noticed that the conjugates **3d** and **3e** with methoxy substitution (3-OCH_3 and 2-OCH_3) have higher cytotoxicity of 56.7 and 45.5 % respectively. The results were in concord with the reported literature that the electron donating groups on aryl substituted chalcones exhibit relatively higher cytotoxicity than the electron withdrawing group[17]. The compounds **3a**, **3b**, **3f**, **3g** and **3l** with phenyl, 4-methyl, 4-chloro, 4-bromo and cinnamyl substitution displayed moderate activity with 25.5-29.1%. Moreover, the furyl (**3i**), thiophenyl (**3j**) and naphthyl (**3k**) substituted derivatives were found to possess less activity (12.6-15.8%) while the 4-fluoro and 3-nitro derivatives were found to possess very poor cytotoxic activity (5.6-8.4%). Based on the substitution on the phenyl ring, the cytotoxic activity decreases in the order of 2-OCH_3 > 3-OCH_3 > H > 4-Br > cinnamyl > 4-Cl > 4-CH_3 > 2-furyl > 2-thiophenyl > 2-naphthyl > 3-NO_2 > 4-F. From the results it seems that the methoxy group at both ortho and meta position have significant activity against the tested cell line. However, the modifications in the chalcone analogs can explore new cytotoxic agents.

Table 2 Cytotoxicity (%) of the compounds 3a-3l

Compound	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
Cell viability (%)	70.9	74.5	94.4	54.4	43.3	74.2	72.6	91.6	84.2	85.3	87.4	79.2
Cytotoxicity (%)	29.1	25.5	5.6	45.5	56.7	25.8	27.4	8.4	15.8	14.7	12.6	20.8

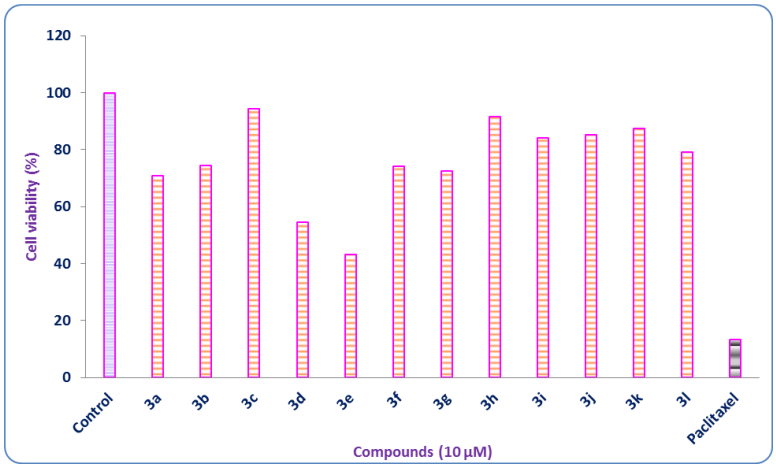


Fig 1. Cell viability of compounds 3a-l

CONCLUSION

In the present work, the efficiently synthesized derivatives were tested against Hep-2 cancer cell line. The 2-methoxy (**3e**) and 3-methoxy (**3d**) substituted compounds displayed

high potency than the other substituted analogues. In conclusion, these findings suggest that the (*E*)-1-(2',4'-difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones exhibit cytotoxic activity and might be developed as an anticancer agent.

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