**INTRODUCTION**

The inner most glandular layer of the uterus recognized as endometrium is a dynamic tissue that undergoes a spectrum of alterations during a woman’s reproductive years (Wang et al., 2010; Jabbour et al., 2006). It is prone to various disturbances due to its tissue complexity which in turn depends on a number of factors such as hormonal balance, molecular mechanism, environment, age and others (Kaaks et al., 2002).

Endometrium hyperplasia depicts a spectrum of changes in the endometrium ranging from a slightly disordered pattern which exaggerates the changes seen in the late proliferative phase of the menstrual cycle to irregular, hyperchromatic lesions that are similar to endometrioid adenocarcinoma (Reed et al., 2010). Hyperplasia usually develops in the presence of continuous estrogen stimulation unopposed by progesterone (Rose, 1996). Some other causes like polycystic ovary, Tamoxifen treatment or hormone replacement therapy may also lead to endometrial hyperplasia. Non-invasive hyperplasia can be divided into two basic types- hyperplasia and atypical hyperplasia (Mazur, 2005). About 20% of the women with complex atypical hyperplasia develop endometrial adenocarcinoma compared to 1-2% of those with the other lesions. Among the patients with atypical hyperplasia, postmenopausal status is associated with highest risk of progression to adenocarcinoma (Reed et al., 2010).

Endometrial cancer is the most common invasive gynecologic cancer worldwide, and the fifth most common cancer in women. American Cancer Society (2013) reported approximately 47,130 new endometrial cancer cases and approximately 8,010 women death because of this disease in 2012 in US. Moreover, the incidence is increasing in developing countries because there is a steady increase in longevity and the life style
changes are approaching to that of west. Endometrial cancer is also an estrogen dependent disease, and it can be regarded as a consequence of estrogen-induced alteration in proliferation and morphogenesis (Emons et al., 2000).

The regression of hyperplasia to normal endometrium is the main purpose of any conservative treatment in order to prevent development of adenocarcinoma. Currently, as a mode of treatment for hyperplasia, cyclical progestin therapy is recommended whereas in patients with cellular atypia, hysterectomy is recommended (Reed et al., 2010). Neither progestin treatment, the major hormonal therapy of endometrial cancer, nor cytotoxic chemotherapy showed substantial benefits in the adjuvant settings (Markman et al., 1992; Satyaswaroop et al., 1992; Neijt, 1994). Therefore, future research activities must evaluate new compounds and treatment strategies.

Most of the endometrial malignancies such as endometrial hyperplasia and endometrial cancer are hormone dependent. A high percentage i.e., around 80-90%, of these tumors expresses the estrogen receptors and/or progesterone receptors. One major aspect of estrogen action on uterus is to increase proliferative processes (Zhang et al., 1998; Couse & Korach, 1999). Another important result of chronic estrogen action on the uterus is morphometric alterations that include changes in the type of luminal and glandular epithelia, the number and shape of glands, the gland to stroma ratio, and the morphology of epithelial cells (Martin et al., 1973; Deligdisch, 2000; Silverberg, 2000).

Therefore, targeting estrogen receptor may be a viable approach towards the development of novel treatment strategies for such disease. For the identification of novel potent antiestrogens several triphenylethylene type of antiestrogens have been discovered in the past few decades which have been shown to affect various target sites thus, exhibiting anti-breast cancer, cardio-protective, anti-osteoporotic anti-implantation activity (Mitlak & Cohen, 1999). Among these, clomiphene, tamoxifen, centchroman and raloxifene are known to possess both agonistic and antagonistic activities (Kamboj et al 1977; Nilsson & Koehler 2005). In the quest for the development of novel antiestrogenic agent devoid of estrogenic property, some of the
non-steroidal antiestrogens like, triarylethenes and triarylpropenones were synthesized by various investigator groups. At CDRI, based on structure-activity relationship of a number of estrogen agonist/antagonist having potent anti-implantation activity, a new lead was obtained in Z-1 triarylpropenones (Mittal et al., 1985; Durani et al., 1989) for development of potent antiestrogens devoid of inherent estrogenicity (Sharma et al., 1990). Among this series, 2,3-diaryl-2H-1-benzopyran derivatives virtually devoid of agonistic activity with potent anti-implantation activity were identified.

Thus, future strategy should include agents that could simultaneously target pathways involved in the pathogenesis of estradiol induced endometrial hyperplasia and endometrial cancer. Novel therapeutic agents specifically targeted at the inhibition of ER as well as growth factor receptors and events within the signal transduction pathways constitute an ideal approach for the treatment of endometrial hyperplasia and endometrial cancer patients. In search for better therapeutic agent, we targeted ER, growth factor receptor EGFR and Wnt/β-catenin signaling using small molecule inhibitors. To that end, we screened a series of synthetic compounds consisting of benzopyran derivatives against endometrial hyperplasia and endometrial cancer cells, evaluated the efficacy of the lead molecules and finally validated the molecular targets. The study has been divided into three chapters:

- Inhibition of hyperplasia formation by 2-[piperidinoethoxyphenyl]-3-[4-hydroxyphenyl]-2H-benzo (b) pyran in rat uterus and its mechanism of action.
- Inhibitory effect of 2-(piperidinoethoxyphenyl)-3-(4-hydroxyphenyl) -2H-benzo (b) pyran (K-1) on human primary endometrial hyperplasia cells and its mechanism of action.
- Anti-tumorigenic action of 2-[piperidinoethoxyphenyl]-3-[4-hydroxyphenyl]-2H-benzo(b) pyran and its mechanism of action.