Abstract

Design And Development Of Estrogen-Receptor Based Anticancer Therapeutics

Estrogen and its receptor are classically involved in a majority of cancers of gynecological origin. The estrogen receptor (ER) is expressed in estrogen-responsive organs such as ovary, uterus and mammary glands. Since, the functional expression of the ER is confined to the initial stages of neoplastic transformation; the design of compounds that interfere with ER function is expected to be an effective strategy in preventing these types of cancer. The present work involves, therefore, the exploration of highly potent, ER-selective, anti-breast-cancer oxindole-conjugated bis-phenols, which show highly selective (ER)-mediated anticancer activity at low-nanomolar concentrations in ER (+) breast cancer cells. In comparison with known bis-arylidene drugs, these compounds are at least three orders of magnitude more toxic than tamoxifen and 1.5-4 fold more toxic than 4-hydroxytamoxifen in ER+ MCF-7 cancer cells. These oxindoles inhibit ER-transactivation and their anticancer activities are inhibited in ER-depleted MCF-7 cells. Some of these nonsteroidal molecules also exhibit essential properties of selective ER down-regulation. From the development of two series of bis-arylideneoxindole based compounds, we report a new series of anticancer agents for estrogen-responsive breast cancer.

Cancer treatment needs multi-modal strategies to restrain its aggressive malignancy. Strategies that include simultaneous detection/sensing and treatment should be specific for cancer to avoid any unwanted side-effects. Among tumour-detecting molecular probes, intrinsically fluorescent small molecules are preferably and widely employed as they can enter live cells easily and offer screening through visual detection. With intrinsic fluorescence, this bis-arylideneoxindole derivative upon conjugation with known ROS generator betulinic acid, is then further employed for selective detection and killing of cancer cells. Further, it generates ROS, triggers apoptosis and exhibits potent cytotoxicity in cancer cells selectively. The study demonstrates the first example among isatin derivatives, conjugated with natural product betulinic acid, as a new anticancer therapeutic with dual role of selective detection and killing of cancer cells via apoptosis.

Bis-arylidineoxindole is further preceded towards folate receptor targeted chemotherapy. This approach involves the attachment of folic acid to potent chemotherapeutic compounds to form small molecule drug conjugates and then successfully been delivered inside cancer cells via the folate receptor pathway. Biological evaluation is underway to expand our knowledge in optimizing the pharmacophore with improved potential.

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