Chapter 4
Ligand- and Structure-Based Drug Design of Non-Steroidal Aromatase Inhibitors (NSAIs) in Breast Cancer

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ABSTRACT

Aromatase is a multienzyme complex overexpressed in breast cancer and responsible for estrogen production. It is the potential target for designing anti-breast cancer drugs. Ligand and Structure-Based Drug Designing approaches (LBDD and SBDD) are involved in development of active and more specific Nonsteroidal Aromatase Inhibitors (NSAIs). Different LBDD and SBDD approaches are presented here to understand their utility in designing novel NSAIs. It is observed that molecules should possess a five or six membered heterocyclic nitrogen containing ring to coordinate with heme portion of aromatase for inhibition. Moreover, one or two hydrogen bond acceptor features, hydrophobicity, and steric factors may play crucial roles for anti-aromatase activity. Electrostatic, van der Waals, and π-π interactions are other important factors that determine binding affinity of inhibitors. HQSAR, LDA-QSAR, GQSAR, CoMFA, and CoMSIA approaches, pharmacophore mapping followed by virtual screening, docking, and dynamic simulation may be effective approaches for designing new potent anti-aromatase molecules.

INTRODUCTION

Breast cancer, one of the commonest form (accounting for 35% of all cancers) among different types of life threatening malignancies in females, is responsible for 20% of all cancer deaths (Bandi, 2010). More than 5,22,000 women across the world died as a result of breast cancer (May, 2014). The maximum incidence of breast cancer is observed in the Western Europe, North America, Australia and New

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Zealand. The incidence of breast cancer is seven fold higher in developing nations. Belgium has the age-standardized highest rate of incidence (more than 110 cases per 1,00,000 women per annum). Apart from that, among top 12 countries, nine belong to Western European, but the Bahamas, Barbados and the United States of America are also in the top ranking. The 12 lowest incidence countries belong to mainly sub-Saharan Africa, South Asia and the far East, those suffer from poverty (May, 2014). The distribution pattern of the age-standardized mortality rate is different across the world. Belgium has the highest mortality followed by the Republic of Ireland with the highest rate of diagnosis but they are outranked by Fiji, Bahamas, Nigeria and Pakistan. Though the mortality is relatively low in low-incidence countries but the mortality rate and probability are higher than the high-incidence countries due to social and cultural influence, stage of presentation and the standards of health care. Due to the high incidence rate, breast cancer ranks top among women's health concerns. Despite the advancement of new preventive strategies against breast cancer consideration, the incidence of breast cancer has remained the same since 2005 (Arumugam *et al*., 2014; Siegel *et al.*, 2012). Breast carcinoma is most frequently diagnosed cancer in women apart from cancer of skin. Approximately 70% of the breast cancers are diagnosed in postmenopausal women (Howlader *et al*., 2014). It ranks second in tumor-related deaths after lung cancer (Muftuoglu & Mustata, 2010). It is predicted that one in eight American women is susceptible to develop invasive breast cancer in their lifetime (American Cancer Society Cancer Facts & Figures, 2013; Brueggemeier, Hackett, & Diaz-Cruz, 2005).

Sex hormones play crucial roles like growth regulation, maturation and reproduction in living animals. Sex hormones are composed of a steroidal cyclopentanoperhydrophenanthrene nucleus. Steroidal hormones are involved in regulation of different physiological effects, like muscle and hair growth, fertility, water retention and dilatation of the capillary vessels as well as sebaceous gland activity (Proteau, 2011; Davis *et al*., 2004; Morales *et al*., 2004). Estrogen is a prominent regulator of cell proliferation in the tumorogenesis of hormone-dependent breast cancer and other tumors. The exact mechanisms of this incidence are still hypothesized. Estrogen metabolites like reactive quinones may directly interact with DNA. It causes mutations that are responsible for these proliferative effects (Miller, 2003). Nearly, two-thirds of breast tumors are hormone-dependent and require estrogens to grow (Brueggemeier, Hackett, & Diaz-Cruz, 2005; Howell, 2005; Muti, Rogan, & Cavalieri, 2006). This phenomenon demands application of an endocrine therapy with a more favorable activity profile and less adverse effects compared to unspecific chemotherapy. More than 100 years ago, Beatson reported that ovariectomy in premenopausal women with breast cancer can induce tumor remission (Beatson, 1896). By knowing the advantage of lowering estrogen level in breast cancer, antihormonal therapy led to the development of new drug candidates. As high serum levels of estrogen is seen in progression of breast cancer, two pharmacological strategies have been employed successfully to control breast cancer (Murthy, Rao, & Sastry, 2004). Drugs either act through estrogen receptor (ER) modulation (Ariazi *et al*., 2006) or interfere with the biosyntheses of steroidal hormones by inhibiting the enzyme controlling the interconversion from androgenic precursors, i.e., aromatase inhibitors (AIs) (Brueggemeier, Hackett, & Diaz-Cruz, 2005). Considerable research work has been devoted to the study of this aromatase enzyme. This helps to develop potent and selective agents that are able to interfere with enzymatic action. Selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) are successfully utilized as therapeutically important weapons in the battle against breast cancer deaths (Pasqualini, 2004). Several classes of steroidal and nonsteroidal aromatase inhibitors are developed (Brodie, Sabnis, & Jelovac, 2006; Neves *et al*., 2009; Colozza *et al*., 2008; Dutta & Pant, 2008; Eisen *et al*., 2008; Gobbi *et al*., 2008; Jackson *et al*., 2008; Osborne & Tripathy, 2005; Osborne & Schiff, 2005; Recanatini & Cavalli, 1998; Recanatini,