INTRODUCTION

Estrogens are not only involved in numerous physiological processes including the development and maintenance of the female sexual organs, reproduction, and various neuroendocrine functions, but they are also responsible for the promotion of certain tumors, such as prostatic hyperplasia, prostate, endometrial, and especially breast cancers. In fact, 30-50% of breast cancers are considered to be estrogen-dependent and regression can be achieved by reducing blood and tissue estrogen levels. The highest incidence of breast cancer occurs in postmenopausal women, whose ovarian function and hypophyseal control of estrogen production has ceased. In these women, estrogen biosynthesis occurs mostly in peripheral tissues such as liver, skin, muscle and adipose tissue. For this reason, total blockage of estrogen biosynthesis is easier to achieve by chemical means rather than by surgical therapy.

Tamoxifen, the most well-known Selective Estrogen Receptor Modulator (SERM), has been considered as the gold standard of endocrine therapy in hormone-dependent breast cancer. Nowadays, it is being taken over by aromatase inhibitors (Als) in postmenopausal women, due to their superior efficacy and favorable safety profile. In breast cancer, intratumoral aromatase is the source for local estrogen production and inhibition of this enzyme is an important approach for reducing tumor growth. The two classes of Als include steroidal and nonsteroidal compounds, which cause potent estrogen suppression. The non-steroidal Als are mostly azole type compounds such as the clinically used anastrazole and letrozole, which compete with the substrate for binding to the enzyme active site. Steroidal Als, e.g., exemestane and formestane, mimic the natural substrate androstenedione and are converted by the enzyme in reactive intermediates, which bind irreversibly to the enzyme active site, resulting in inactivation of aromatase. Extensive functionalization of various ring positions of steroid nucleus has resulted in a number of therapeutically useful aromatase inhibitors.
Despite the success of the third-generation steroidal and nonsteroidal AIs, some major side effects, such as musculoskeletal effects (arthritis, arthralgia, and/or myalgia) and bone toxicity still exists. For this reason, it is pertinent to search for more potent and specific molecules with lower side effects.\textsuperscript{12}

Development of hybrid structures, in which pharmacologically crucial structural elements from two molecules are combined to produce a non-identical twin drug, is a rational approach to obtain therapeutically useful molecules. The present work is also aimed towards synthesis of new chemical hybrids of steroidal and non-steroidal aromatase inhibitors. Various azole derived 16-substituted androstene derivatives have been synthesized and evaluated for aromatase inhibitory activity in the current study.