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RESUMO

New steroidal aromatase inhibitors: biological effects in hormone-dependent breast cancer cell models

Aromatase inhibitors (AIs) are currently used as a first-line therapeutic approach for hormone-dependent (ER+) breast tumors in postmenopausal women, the most common type of cancer diagnosed among women, in which estrogen plays a key role. Aromatase is the enzyme responsible for estrogen biosynthesis, so its inhibition results in estrogen suppression, avoiding tumor growth. However, the existence of side-effects with the current AIs used in clinic, such as development of therapy resistance and bone loss, justifies the search for new AIs. In the past few years, several steroidal compounds have been synthesized with structural modifications in androstenedione, the aromatase substrate, in order to achieve maximum inhibitory effects on aromatase. The present work aims to continue this research line, so newly synthesized steroidal compounds (49, 50, 51 and 52) with structural modifications on A-, B- and D-rings are under biological evaluation, using different human breast cancer cell lines, an ER+ aromatase overexpressing breast cancer cell line (MCF-7aro), an ER- breast cancer cell line (SK-BR-3) and a late stage of acquired endocrine resistance cell line (LTEDaro). Results have shown that all the compounds are potent aromatase inhibitors that induce antiproliferative effects both on hormone-sensitive cell line MCF-7aro and on resistant cell line LTEDaro, being 52 the most effective compound. The effects were dose-dependent and, for compound 52, were also time-dependent. However, steroid 49 was shown to be the only aromatase-

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dependent compound. All the compounds act by an ER-independent manner, suggesting that other mechanisms might be involved. None of the compounds had cytotoxic properties on the non-cancerous fibroblast cell line, HFF-1. In summary, all the studied compounds are capable of acting on sensitive and resistant cell lines. AI 49 is the only compound that viability loss is also dependent on aromatase inhibition. The aromatase inhibitor 52 is the most potent one in sensitive and resistant cancer cells. We believe that this work will contribute to the design of new potent and specific AIs that can inhibit tumor growth and overcome endocrine resistance.

PALAVRAS-CHAVE: breast cancer, estrogens, aromatase inhibitors, endocrine therapy