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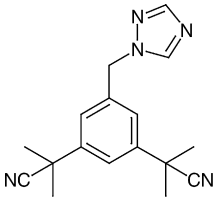
MOLECULES

New aromatase inhibitors with potential in breast cancer treatment

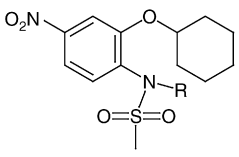
Estrogen-dependent (ER+) breast cancer accounts for approximately one-third of all breast cancer patients, and two-thirds of cases of postmenopausal breast cancer. Two approaches towards hormonal therapy in breast cancer, through either blocking estrogen action by selective estrogen receptor modulators (SERMS) or inhibiting estrogen biosynthesis using aromatase inhibitors (AIs), have been pursued with some considerable success. In particular the anti-estrogen tamoxifen has had a very significant impact in ER+ breast cancer, despite the fact that drug resistance and increased susceptibility to uterine and endometrial cancers limit its clinical utility.

More-recent reports have demonstrated that the third generation of nonsteroidal aromatase inhibitors, such as arimidex (anastrozole) **(i)** have shown considerable efficacy for the treatment of hormone-dependent breast cancer, and are clinically more effective than tamoxifen [1]. The observation that aromatase inhibitors (AIs) could adversely affect sites where estrogen is required for normal function (e.g. bone and brain) has prompted further investigation to develop agents that can decrease aromatase activity in a tissue-selective manner.

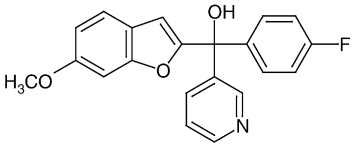
Expression of aromatase (cytochrome P450 19; CYP19) is regulated in a tissue-specific manner by the alternative use of eight promoters, and prostaglandin E_2 (PGE_2) is a major regulator driving aromatase expression from promoter I.3 and II in ER+ breast cancer. Recent data have demonstrated that aromatase activity in SK-BR-3 breast cancer cells can be reduced by the use of cyclooxygenase (COX)-1 and COX-2 inhibitors, such as the selective COX-2 inhibitor NS-398 **(ii)** [2]. Su and co-workers [3] have synthesized and evaluated a series of sulfonanilide analogues for their effects on aromatase enzyme activity and COX-2 inhibition. Structure–activity analysis found no correlation between aromatase and COX-2 inhibition in SK-BR-3 cells, and sulfonanilide analogues such as compound **(iii)** were found to decrease aromatase gene expression independently of COX-2 inhibition. Further analysis of potential molecular targets of these compounds in breast cancer cells, and future drug development is anticipated.



(i) Arimidex



(ii) R = H (NS-398)
(iii) R = Me



(iv)

A further series of potent aromatase inhibitors has been reported by Saberi and co-workers [4] based on the previously reported inhibitors 1-[(benzofuran-2-yl)phenylmethyl]-imidazoles and -triazoles [5]. In particular the 6-methoxy- and 6-hydroxy-substituted benzofuran derivatives were found to be potent aromatase inhibitors (IC_{50} = 0.01–1.46 μM) with activity comparable or greater than the reference compound arimidex (i), as predicted by molecular modelling studies. *In vitro* cytotoxicity assays using rat liver hepatocytes (cytotoxicity determined from alteration in cell morphology and lactate dehydrogenase enzyme retention) for some of the most potent analogues suggested negligible cytotoxicity and good selectivity for CYP19. The most promising compound from the series (**iv**; IC_{50} = 44 nM; LC_{50} >100 μM) compared favourably with the reference compound arimidex (i; IC_{50} = 600 nM; LC_{50} >200 μM).

1 Baum, M. *et al.* (2002) ATAC trialists group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 359, 2131–2139

2 Díaz-Cruz, E.S. *et al.* (2005) Cyclooxygenase inhibitors suppress aromatase expression and activity in breast cancer cells. *J. Clin. Endocrinol. Metab.* 90, 2563–2570

3 Su, B. *et al.* (2006) Novel sulfonanilide analogues suppress aromatase expression and activity in breast cancer cells independent of COX-2 inhibition. *J. Med. Chem.* 49, 1413–1419

4 Saberi, M.R. *et al.* (2006) Potent CYP19 (aromatase) 1-[benzofuran-2-yl)(phenylmethyl)pyridine, -imidazole, and –triazole inhibitors: synthesis and biological evaluation. *J. Med. Chem.* 49, 1016–1022

5 Vinh, T.K. *et al.* (2001) 1-[(Benzofuran-2-yl)phenylmethyl] triazoles as steroidogenic inhibitors: synthesis and in vitro evaluation of human placental CYP19 aromatase. *Anticancer Drug Des.* 16, 217–225

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