STRUCTURAL REQUIREMENTS IN NON-STEROIDAL AROMATASE INHIBITORS AS POTENTIAL AGENTS IN OESTROGEN-DEPENDENT BREAST CANCER

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Aminoglutethimide (I,3-(4'-aminophenyl)-3-ethylpiperidine-2,6-dione) a competitive inhibitor of aromatase (K_i = 0.68uM testosterone) is used for the treatment of oestrogen receptor-positive breast cancer in post menopausal women (Santen et al 1982). It is co-administered with a glucocorticoid to supress the resulting reflex-rise in ACTH level due to inhibition of the cholesterol biosynthesis side chain cleavage (CSCC) enzyme in the biosynthetic pathway (Santen et al 1977). Inhibitors with a more specific action in <u>in vitro</u> tests, 3-ethyl-3-(4'-pyridyl) piperidine-2,6-dione (II, K_i = 1.1uM testosterone, Foster et al 1983) and 3-(4'-aminophenyl)-3-ethylpyrrolidine-2,5-dione (III, K_i = 1.0uM testosterone, Daly et al 1986) have recently been developed and other compounds known to inhibit aromatase are cylohexylaniline (IV, K_i = 0.14uM testosterone, Kellis & Vickery 1984) and 1-cyclohexylmethyl -3-(4'-aminophenyl)-1-azabicyclo [3.0.1] -2,6-dioxo-hexane (V, "much more active than (I)", Ciba-Geigy AG 1984). We have found that modification of (III) by (a) alteration of the heterocyclic ring eg 5-(4'-amino-phenyl)-5-ethylimidazolidine-2,4-dione (VI), (b) introduction of a spacer group between the two rings eg 3-(4'-aminophenylmethyl)-pyrrolidine-2,5-dione (VII) and (c) restricting rotation of the phenyl group eg 6-amino-1',2',3',4',-tetrahydron-aphthalene-1,3-pyrrolidine-2,5-dione (VIII) led to either loss of activity (VI and VIII) or reduced inhibitory activity (VII, K_i = 15uM androstenedione, corresponding K_i for (I) = 2.69uM).

Using molecular graphics ('Chemgraf') we have examined the structure-activity requirements within this group of compounds. A successful aromatase inhibitor should possess the following properties (at least): (1) a flat or near flat heterocyclic ring, (2) a 4'-aminophenyl or 4' pyridyl group attached at position 3 and pitched below (above) the plane of the heteroring at a particular angle (Table 1), (3) a torsion angle (C_2-C_3-C_1'-C_2') between the rings within the range -10 to +50° although there may be exceptions to this when the angle of pitch is very shallow, (4) a narrow torsion angle range (vide supra) for the low energy content conformers so that the active conformations are relatively more populated. The separation distances between the aniline nitrogen and the nitrogen and carbonyl oxygens of the imide group are similar in both the active and inactive compounds and thus this parameter alone cannot explain the observed results.

Table 1 Torsion and pitch angles for some Aromatase Inhibitors

Compound	Torsion Angle C_2-C_3-C_1'-C_2'	Pitch Angles C_1'-C_3-ringplane		Bond Angle C_2-C_3-C_1'
I	-1°	100°	117°	113°
III	+10°	71°	63°	113°
V	+91°	34°	33°	122°

Ciba Geigy AG (1984) Eur Patent Application EP114,033
Daly, M J et al (1986) J. Med. Chem. 29, 520-523
Foster, A B et al (1983) J. Med. Chem. 26: 50-54
Kellis, J T, Vickery L E (1984) Endocrinology 114: 2128-2137
Santen, R J et al (1977) J. Cli. Endors. Metab. 45: 469
Santen, R J et al (1982) Breast Cancer Res. 2: 375