AROMATASE INHIBITION STUDIES WITH SOME DERIVATIVES OF 1,3-DIMETHYL-3-PHENYLPYRROLIDINE-2,5-DIONE

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Inhibition of the aromatase (oestrogen synthetase) enzyme presents a new approach to the therapy of hormone-dependent breast cancer, and aminoglutethimide (1) is a clinically useful, competitive inhibitor of this enzyme (Santen and Brodie 1982). The primary amine moiety of 1 is thought to act as an electron donor at the active site of the aromatase enzyme, although the 4-pyridyl analogue of 1 is also an inhibitor of testosterone aromatisation (Foster et al, 1985). Since aromatic amines have previously been postulated to form weaker ligands than pyridyl or nitrile groups (Uzgiris et al, 1977), we have developed analogues of the structurally related anticonvulsant methsuximide (2, 1,3-dimethyl-3-phenylpyrrolidine-2,5-dione) bearing various electron donating heteroatoms at the 4-phenyl position, to study the effects of such substitution on aromatase inhibition. 2 was nitrated and hydrogenated to the primary amine as described previously (Scoular et al, 1976), diazotised with $NaNO_2$ in HCl, and converted to the desired product by standard procedures. The compounds developed are shown in figure 1.

No.	R
2	H
3	NO_2
4	NH_2
5	OH
6	CN
7	OCH_3

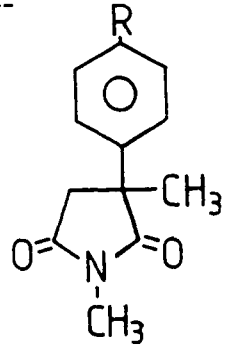

FIGURE 1

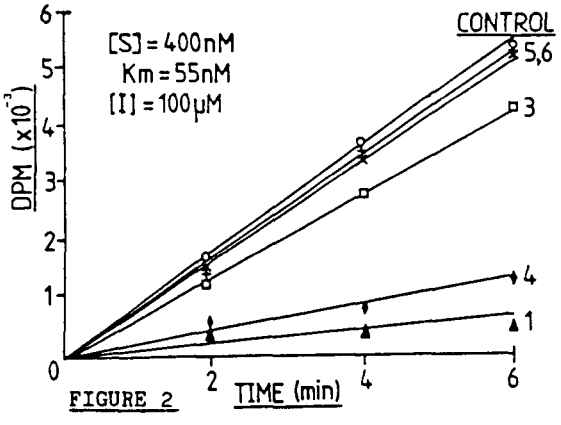

FIGURE 2

These derivatives were tested for their ability to inhibit the aromatisation of [1β,2β -^{3}H]androstenedione, catalysed by human placental aromatase, as described previously (Daly et al, 1984). The results obtained are shown in figure 2, excluding 2, which was totally inactive. The primary amine 4 was a competitive inhibitor of the placental aromatase system, with an apparent Ki (testosterone) of 1.2μM (Ki for 1, 0.68μM). The derivatives prepared lacked potent inhibitory activity, confirming the importance of the primary amine moiety.

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Daly, M.J. et al. (1984)	J.Pharm.Pharmacol.,	36:64P.
Foster, A.B.F. et al. (1985)	J.Med.Chem.,	28:200-204.
Santen, R.J. and Brodie, A.M.H. (1982)	Clin.Oncol.,	1:77-130.
Scoular, I.T. et al. (1976)	Eur.J.Med.Chem.,	11:91-93.
Uzgiris, V.I. et al. (1977)	Biochemistry,	16:593-599.