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Reduced antioestrogenic activity in derivatives of tamoxifen unable to undergo metabolic p-hydroxylation

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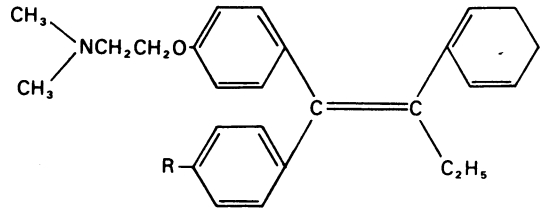
Katzenellenbogen, Katzenellenbogen, Ferguson & Kranthammer (1978) have suggested that nonsteroidal antioestrogens are pro-drugs. In support of this concept the antioestrogen tamoxifen is metabolised in laboratory animals to the more potent monohydroxytamoxifen (Jordan, Collins, Rowsby & Prestwich, 1977). However, tamoxifen inhibits the growth of human breast cancer cells *in vitro* under conditions where metabolic transformation cannot be detected (Horwitz, Koseki & McGuire, 1978).

In the present study we have examined a series of tamoxifen derivatives (see Figure) for oestrogenic and antioestrogenic properties and also their ability to inhibit the binding of oestradiol-17β to the oestrogen receptor. These derivatives were designed with the aim of preventing the para-hydroxylation that occurs with tamoxifen.

In the 3 d uterine wet weight test (8 rats/group, 35–50 g, Alderley Park strain) all compounds investigated were partial oestrogen agonists. Similarly all compounds inhibited increases in uterine wet weight produced by oestradiol benzoate (0.16 µg in 0.1 ml arachis oil daily × 3 s.c.) in a dose related manner. The order of antioestrogenic potency was monohydroxytamoxifen > tamoxifen > *p* fluorotamoxifen ≡ *p* chlorotamoxifen ≡ *p* methyl tamoxifen.

In contrast tamoxifen was approximately equiactive with its *p* methyl, *p*-fluoro and *p*-chloro derivatives in their ability to inhibit [^{3}H]-oestradiol binding to rat uterine oestrogen receptors *in vitro*. Assays were undertaken with a 30 min incubation time at 30°C. The relative binding of tamoxifen and its derivatives



R	
H	tamoxifen
OH	monohydroxytamoxifen
CH_3	*p* methyl tamoxifen
F	*p* fluoro tamoxifen
Cl	*p* chloro tamoxifen

was approximately 0.1% of that observed with oestradiol-17β. Monohydroxytamoxifen was only slightly less active than oestradiol-17β.

In conclusion these results suggest that the biological activity of tamoxifen at low doses is the net result of its own activity and that of its more potent metabolite, monohydroxytamoxifen. However the results also demonstrate that the metabolic transformation of nonsteroidal antioestrogens is only an advantage and not a requirement for antioestrogenic activity.

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