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Some 2-(1-phenyl-1-(prop-2′-ynyloxy)methyl) benzofurans as irreversible inhibitors of aromatase (P450 AROM)

G. A. KHODARAHMI, G. SAEED, H. J. SMITH AND P. J. NICHOLLS

The Welsh School of Pharmacy, University of Wales Cardiff, Cardiff CF1 3XF

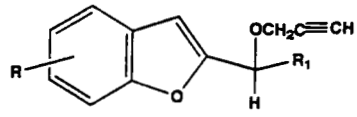
$P450_{AROM}$ converts adrenal androstenedione to oestrone with subsequent production of oestradiol. Aromatase inhibitors are used for post-menopausal women with breast cancer to remove the oestrogen stimulus to metastases growth. Potent non-steroidal inhibitors are known (Miller 1996) as well as the long acting steroidal irreversible inhibitors (mechanism-based enzyme inactivators, MBIs) which require less frequent dosing e.g. formestane, plomestane (Lombardi 1995; Miller 1996). We have reported the first non-steroidal MBIs (Saeed et al 1997) based on 3-(4'-aminophenyl)pyrrolidine-2,5-dione (**1**) with the metabolisable propargyl group of plomestane present and here describe a series of the titled compounds (**2**) similarly based on the potent irreversible inhibitor, 1-[benzofuran-2-yl)phenylmethyl] imidazole (**3**) (Whomsley et al 1993).

Reversible inhibition studies were conducted in the usual manner using human placental microsomes by measurement of ^3H_2O water release from [1β-^{3}H] androstenedione (Thompson & Siiteri 1974). Irreversible inhibition studies followed a similar method except that placental microsomes were pre-incubated with the inhibitor prior to its removal with activated charcoal (Saeed et al 1997). The results are shown in Table 1.

The series of compounds (**2**) were weak reversible inhibitors of the enzyme (4-15%) unlike (**3**) on which they were modelled which demonstrates the importance to binding of the imidazole ligand to the haem- Fe^{3+}. However irreversible inhibition (13-43%) occurred after pre-incubation at 100μM for 1 hour, the most potent compound being the 4-chloro derivative. It would seem that despite weak reversible binding to $P450_{AROM}$ prolonged exposure leads to metabolism of the propargyl function and irreversible inhibition of the enzyme. Similar conclusions were drawn for the propargyloxy derivatives based on (**1**) where the irreversible and reversible inhibition noted in similar experiments was 62-74% and 15-41% respectively.

Miller, W.R. (1996) Endocr. Rev. Lancers 3: 65-79.
Lombardi, P. (1995) Curr. Pharm. Des. 1: 23-50.
Saeed, G. et al (1997) Pharm. Sci. 3: 265-277.
Thompson, E.A., Siiteri, P.K. (1974) J. Biol. Chem. 249: 5373-5378.
Whomsley et al (1993) Steroid Biochem. Molec. Biol. 44: 675-676.

Table 1. Some 2-[1-phenyl (or alkyl)-1-(prop-2'-ynyloxy) methyl] benzofurans as $P450_{AROM}$ inhibitors



R	R_1	% Inhibition* Reversible	Irreversible
H	4-ClC_6H_4	4.1	43.0
H	4-$CH_3C_6H_4$	2.9	13.0
H	cyclo-C_6H_{11}	15.3	26.4
5,7-DiCl	C_3H_7	4.3	16.7
H	C_6H_5	6.3	23.4
H	2-$CH_3C_6H_4$	3.5	25.3
5-Br	C_6H_5	N.D.	30.0
AG		83.0	

* Androstenedione, 1μM; compounds, 100μM. Results are the mean of triplicate determinations where the spread was < 5% of the mean. N.D. = not done.