J. Pharm. Pharmacol. 1998, 50 (Supplement): 207

Enantioselectivity of some 1-(benzofuran-2-yl)-1-(1-H-imidaz-1-yl) alkanes as inhibitors of P450 AROM

G. A. KHODARAHMI, H. J. SMITH, P. J. NICHOLLS AND M. AHMADI

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

$P450_{AROM}$ has been a target for inhibition in the treatment of postmenopausal women with breast cancer, to reduce oestrogen levels and the stimulus to growth of metastases. In aminoglutethimide (AG), used clinically as the racemate, the activity mainly resides in the (+) (*R*) form and in later generation agents inhibitory potency mainly resides in one form (Luscombe et al 1994). However, in the potent 1-[(benzofuran-2-yl) phenylmethyl] imidazoles (**1**) (Whomsley et al 1993) both enantiomers of the 4'-chloro compound had identical potencies (IC_{50}=8.4nM) and the enantiomers of the 4'-fluoro compound were both potent ((+)=5.3nM; (-)=65nM). We have studied the effect on stereoselectivity of replacing the phenyl group in (**1**) with a methyl or ethyl group (**2-7**). The (±)-benzofurans (**2-7**) were resolved as their dibenzoyl-L-(-)-tartaric acid (DLT) or dibenzoyl-D-(+)-tartaric acid salts using ether as solvent with repeated recrystallisation and monitoring using HPLC by the general method of Pepper et al (1995). A Milton Roy LC system was used with a Chiralpak AD column (4.6X250mm) and precolumn (4.6X50mm); solvent system, n-hexane/2-propanol/diethylamine (85:15:0.1); flow rate, 0.45 $mLmin^{-1}$; pressure, 50-60 psi. Purity: (+)-(**2**), 99.28%; (+)-(**3**), 99.0%; (-)-(**3**), 98.5%; (+) and (-) **4**, **6**, and **7** 99.0%.

The compounds (100μM) in ethanol (10μL) were included in the standard assay for $P450_{AROM}$ which depends on the release of ^3H_2O from [1β-^{3}H] androstenedione (Thompson & Siiteri 1974). Control incubations including ethanol (10μL) were run.

The (±)-methyl substituted compounds were 2.36-12 fold more potent than (±)-AG and the more hydrophobic (±)-ethyl compounds were 5.4-33 fold. The 5,7-dichloro compounds (**3, 6**) were the most potent. The DDT salt of the (+) form of the methyl substituted compound was more potent than the DLT salt of the (-) form by 4.8-fold (**3**) and 12.6-fold (**4**). In the ethyl series the (-) salts were more active, the stereoselective ratio being 8.3 (**6**) and 5.2 (**7**). Within the series of 1-(benzofuran-2-yl)-1-(1-H-imidaz-1-yl) alkanes studied the enantioselectivity as inhibitors of $P450_{AROM}$ is less pronounced than previously observed and in accord with that noted by us for the phenyl analogues (**1**).

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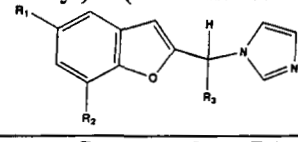
Table 1. **Some substituted 1-(benzofuran-2-yl)-1-(1-H-imidazol-1-yl) ethanes and propanes as inhibitors of $P450_{AROM}$**



Compound	R1	R2	R3	IC_{50} (μM)*	Compound	R1	R2	R3	IC_{50} (μM)
(±)-**2** (HCl)	H	H	CH_3	4.67	(±)-**6** (Base)	Cl	Cl	C_2H_5	0.335
(+)-**2** (DDT)	H	H	CH_3	5.62	(+)-**6** (DDT)	Cl	Cl	C_2H_5	2.32
(±)-**3** (HCl)	Cl	Cl	CH_3	0.905	(-)-**6** (DLT)	Cl	Cl	C_2H_5	0.28
(+)-**3** (DDT)	Cl	Cl	CH_3	0.49	(±)-**7** (Base)	Br	Br	C_2H_5	0.91
(-)-**3** (DLT)	Cl	Cl	CH_3	2.33	(+)-**7** (DDT)	Br	Br	C_2H_5	1.51
(±)-**4** (HCl)	Br	Br	CH_3	1.305	(-)-**7** (DLT	Br	Br	C_2H_5	0.29
(+)-**4** (DDT)	Br	Br	CH_3	0.835	AG				11.0
(-)-**4** (DLT)	Br	Br	CH_3	10.54					
(±)-**5** (Base)	H	H	C_2H_5	2.02					

* androstenedione, 0.6μM. Mean of triplicate estimations <2% of mean.