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Structure–activity relationship study of steroidal and non-steroidal inhibitors of the enzyme oestrone sulphatase

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In the treatment of hormone dependent breast cancer, extensive research has been undertaken to produce compounds which are both potent and selective inhibitors of the cytochrome P-450 enzyme aromatase (AR). However, the use of AR inhibitors has not shown the expected decrease in the plasma levels of the female sex hormones (which have been implicated in the initiation/progression of hormone dependent breast cancers). This has been shown to be due to the activity of the enzyme estrone sulfatase (ES), the enzyme responsible for the conversion of the stored (sulfated) form of the estrogens to the active forms (Figure 1).

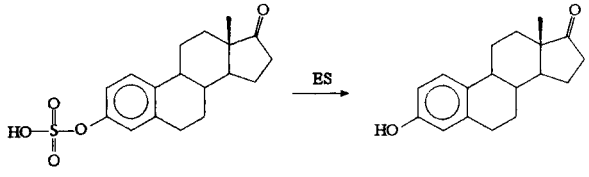

Figure 1. Action of ES on estrone sulfate.

A number of steroidal inhibitors has been investigated as potent inhibitors of this enzyme, including EMATE (IC50=65pM) (Purohit et al 1995), a time and concentration dependent irreversible inhibitor. However, this compound has been shown to possess estrogenic properties, as a result the investigation of non-steroidal inhibitors has intensified. However, very little information exists regarding the active site of this enzyme. As such rational drug design has been difficult.

In an effort to overcome this problem, we have initiated a series of structure-activity relationship (SAR) determination studies involving the consideration of inhibition data available for this enzyme (Purohit et al 1995; Li et al 1996). We therefore present in this report, the initial results of the SAR and molecular modelling studies into the properties of the active site of this enzyme.

The molecular structures (e.g. estrone sulfate and the known steroidal and non-steroidal inhibitors) were all constructed and minimised using the conjugate-gradient algorithm within the molecular modelling software Alchemy III®. Conformational analysis was undertaken within Powersearch.

From the results of the superimpositioning study, we propose that there are no hydrogen bonding groups about the C(17) position of the steroid backbone - this observation is further supported by the consideration of inhibitors which possess significant side chains (without any polar groups) which appear to occupy an extensive area about the C(17)=O position of estrone. Indeed, in some cases, the alkyl chains are observed to extend beyond the C(17)=O position. This is further supported by the consideration of the androgen sulfate compounds which have been shown to be inhibitors of ES. Superimposition of these compounds shows that there is a lack of common overlap between estrone sulfate and the androgen sulfate.

In conclusion, we believe that through the consideration of numerous steroidal and non-steroidal inhibitors, it has been possible to consider the existence of a hydrogen bonding group about the C(17) area of the steroidal backbone.

Purohit, A. et al (1995) Biochemistry 34:11508-11514
Li, P.K. et al (1996) Steroid Biochem. Mol. Biol. 59:41-49