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Quantitative structure–activity relationships in a series of endogenous and synthetic steroids exhibiting induction of CYP3A activity and hepatomegaly associated with increased DNA synthesis

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Abstract

The results of a quantitative structure–activity relationship (QSAR) study on a total of 14 steroids exhibiting induction of a CYP3A-associated activity and increase in liver weight/DNA synthesis is reported. It is found that different, but related, structural descriptors correlate with increase in ethylmorphine *N*-demethylase activity ($r = 0.92$) and with the increase in liver weight ($r = 0.78$) and DNA synthesis ($r = 0.78$). Although there is a strong correlation between increase in liver weight and DNA content ($r = 0.999$), neither of these correlated with ethylmorphine *N*-demethylase activity. These findings are discussed in the light of CYP3A induction, substrate specificity and inhibition; a proposed model of human CYP3A4 based on sequence homology with CYP102, a bacterial P450 of known crystal structure, demonstrates the possible mode of interaction between substrates and inhibitors within the putative active site.

Keywords: QSAR; CYP3A; Ethylmorphine *N*-demethylase

1. Introduction

Induction of cytochromes P450 of the CYP3 family by macrolide antibiotics, synthetic steroids and endogenous glucocorticoids has been well established [1–6]. As members of the CYP3 family constitute the major proportion (40–60%) of the human hepatic P450 complement [7] and it is also known that the majority of drugs in clinical use is metabolised by CYP3 (reported to be about 40–50%), studies on substrates and inducers of the enzyme family are of considerable current interest [8,9]. As far as steroidal substrates are concerned, it appears that hydroxylation in the 6β-position of the steroid nucleus is a feature of CYP3-mediated metabolism [1,10] and this suggests that a specific orientation of the steroid substrate within the CYP3A active site tends to lead primarily, to hydroxylation in this position. It is presumed, therefore, that there are specific interactions between key groupings on the steroid nucleus and complementary amino acid residues within the active site region, which direct the course of oxygenation towards the 6β position, as has been indicated previously [11].

In the present study, a possible means of rationalising CYP3A induction of the steroids concerned in terms of molecular structural features has been investigated using QSAR analysis of various structural descriptors relating to molecular shape and electronic structure. Moreover, the use of other biological data, in the form of increase in liver weight per dose concentration and increase in DNA content per dose concentration, enables the formulation of QSARs to describe potency differences within the series of steroids investi-

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gated. It is appreciated that the biological mechanisms of hepatomegaly are both varied and complex, but likely to involve the interaction between ligand-bound steroid receptors (such as the oestrogen receptor, for example) and regulatory elements on specific genes associated with cell growth, together with tissue-specific factors. We have reported earlier a model for the human oestrogen receptor, based on sequence homology and site-directed mutagenesis data, which provides a possible explanation regarding the mode of interaction between hER ligands and the receptor protein [12]. The present study represents an alternative approach to explain the biological potency variations in steroids, including both androgens and estrogens.

2. Methods

Molecular orbital (MO) calculations by the CNDO/2 method [13] were carried out on the 14 steroids listed in Table 1, and the relevant molecular shape parameters, area/depth^2 and length/width, were calculated from the measured molecular dimensions of each structure. The COSMIC molecular modelling package [14] was employed in the production of minimum energy geometries and electronic structural data, as shown in Table 1.

Quantitative structure–activity relationships (QSARs) were generated by stepwise multiple linear regression analysis of the structural descriptors and biological data in the form of percentage increase in ethylmorphine *N*-demethylase activity (A), increase in liver weight/dose and increase in DNA/dose. Expressing the activity data as a percentage of the control values takes into account the experimental variation apparent in the various studies. All of the biological data on the 14 steroids were obtained from previously published studies [15–17]. In this work, CYP3A activity was monitored using the *N*-demethylation of ethylmorphine which, in rat hepatic microsomes, is recognised as a good probe for this P450 subfamily [18].

Molecular interactions of a selected number of the steroids in the series under consideration (namely, dexamethasone, testosterone and ethinylestradiol) within a model of the CYP3A4 active site, obtained by homology modelling [11,19] with the CYP102 crystal structure [20,21] was carried out using the Sybyl molecular modelling software (Tripos Associates, St. Louis, MO,

Table 1
Biological and structural data for 15 steroids[a]

	Compound	Length/width	Area/depth^2	E_{HOMO}	E_{LUMO}	ΔE	μ	log P	log A (Obs.)	log A (Calc.)	I	D
1	Estradiol	1.9	3.8	−11.3	3.7	15.0	2.0	2.69	2.0645	2.0888	0.285	1.45
2	Ethynylestradiol	2.0	2.4	−11.3	2.4	13.7	4.8	3.41	2.2695	2.3258	0.595	3.15
3	Norethynodrel	1.9	1.3	−11.6	2.3	13.9	5.4	3.04	1.8751	2.0150	0.011	0.034
4	Norethisterone acetate	2.0	1.8	−11.6	1.9	13.5	6.8	3.75	2.4533	2.3006	0.0025	0.015
5	Progesterone	1.9	2.4	−11.5	2.3	13.8	5.0	3.87	2.2041	2.2791	–	–
6	Cyproterone acetate	1.5	1.7	−11.1	0.8	11.9	9.1	3.26	3.3617	3.0280	–	–
7	Hydroxycyproterone acetate	1.5	1.5	−11.1	0.8	11.9	10.4	1.98	2.5752	2.9884	0.0036	0.012
8	Spironolactone	1.3	3.3	−11.3	1.9	13.2	1.7	2.78	2.6128	2.7372	0.0046	0.011
9	Medroxyprogesterone acetate	1.6	3.0	−11.5	2.2	13.7	1.5	3.51	2.4983	2.4444	0.012	0.0
10	Cortisol	1.9	2.9	−11.5	2.2	13.7	5.7	1.61	2.3997	2.4246	–	–
11	Dexamethasone	1.8	2.3	−11.2	1.7	12.9	–	1.99	2.8555	2.6796	–	–
12	Testosterone	1.8	2.0	−11.6	2.3	13.9	4.6	3.32	2.1004	2.1533	0.0009	0.008
13	Methyl testosterone	1.7	2.0	−11.6	2.3	13.9	4.6	3.36	2.3464	2.1533	0.0009	0.004
14	Levonorgestrel	1.8	1.9	−11.5	2.3	13.8	7.0	4.09	2.1818	2.1803	0.0077	0.002
15	Gestodene	1.8	2.0	−11.5	2.3	13.8	7.0	3.64	–	–	0.0	0.0

[a] Length/width, ratio of molecular length (Å) to width (Å) using van der Waals radii; area/depth^2, ratio of molecular area (length × width) to depth^2 using van der Waals radii; E_{HOMO}, energy (eV) of the highest occupied molecular orbital; E_{LUMO}, energy (eV) of the lowest unoccupied molecular orbital; ΔE, $E_{LUMO} - E_{HOMO}$; μ, dipole moment (Debyes); log P, logarithm of the octanol/water partition coefficient (c = calculated value); log A (Obs.), common logarithm of the percentage increase in ethylmorphine *N*-demethylase activity; log A (Calc.), calculated value of log A using equation 1 (Table 2); I, increase in liver weight/dose; D, increase in DNA content/dose; –, data not available or not determined. Data for log P were either taken from the literature [30] calculated via the Pallas System (CompuDrug Ltd., Budapest, Hungary).

USA) running on an Evans and Sutherland ESV30 and a Silicon Graphics Indigo 2 IMPACT 1000 Unix workstations. The molecular and electronic structural calculations using the COSMIC package were performed on a MicroVAX II/Sigmex 6130 combination, whereas all statistical calculations were executed on a Hewlett–Packard HP-9000 mainframe at the University of Surrey Computer Centre.

3. Results and discussion

3.1. Steroid interaction with CYP3A4 active site

The techniques involved in generation of the CYP3A4 model have been described previously [11,19,22] and these have been shown to give rise to stable protein geometries that are also consistent with available experimental evidence from metabolism studies. Fig. 1 shows a possible orientation for the steroidal analogue, dexamethasone, within the putative active site of CYP3A4, where key complementary interactions with specific amino acid residues (namely, Asn74 and Ser271) orientate the substrate for hydroxylation at the 6β-position; and we have shown earlier that structurally related steroids like testosterone and dexamethasone appear to become orientated by the enzyme in a similar fashion to enable 6β-oxidation [11,22]. In addition to androgens such as testosterone and androstenedione, certain oestrogenic-type steroids are also able to fit the putative CYP3A4 active site, as evidenced by the interaction between ethynylestradiol and CYP3A4 presented in Fig. 2, where it can be appreciated that somewhat different contacts are involved. In particular, hydrogen-bonded interactions between the substrate and the sidechains of Asn74 and Ser271, which are also involved in binding both dexamethasone and testosterone as mentioned above, form somewhat different orientations, and this is probably due to a π–π stacking interaction between the ethynyl group and the sidechain of Phe78, which is close to the Asn74 residue. In the orientation shown in Fig. 2, the A-ring hydroxyl group of the oestrogen analogue forms a hydrogen bond with Ser271 whereas the D-ring 17β-OH donates a second hydrogen bond to the amide carbonyl oxygen of Asn74. This would explain the fact that 2-hydroxylation is the major CYP3A4-mediated oxidation reaction of ethynyl estradiol, because the aforementioned contacts with complementary amino acid residues ensures that the 2-position lies directly above the haem iron in the enzyme–substrate complex, as shown in Fig. 2. Consequently, the CYP3A-catalyzed metabolism of both types of steroid hormones can be explained in terms of putative active site modelling, where the orientation of steroidal substrates appears to be determined by hydrogen-bonded and hydrophobic interactions within the haem environment. Indeed, the number of hydrogen-bonds formed probably relate to the overall binding affinity of the CYP3A4 substrate itself, as it can be expected that a single hydrogen-bond may contribute on average about 2 kcal mol^{-1} to the binding free energy [23].

3.2. Quantitative structure–activity relationships

Table 1 shows the full dataset for the steroids investigated in this study, including biological activities in the form of CYP3A induction as determined by the percentage increase in ethylmorphine *N*-demethylase activity. In addition, the increases in liver weight relative to dose and DNA content over dose are also shown in Table 1, together with a number of calculated molecular and electronic structural properties and the relevant compound lipophilicities in the form of log *P* values. Linear stepwise multiple regression analysis on these data gave rise to statistically significant quantitative structure–activity relationships with each form of biological activity, and these are presented in Table 2, which indicates those descriptors, which were involved in correlations with biological activity although a greater number of variables was subjected initially to statistical analysis. Moreover, there is a high correlation ($r = 0.999$) between increase in liver weight and increase in DNA content relative to dose, although activities were only available for 11 compounds.

As far as induction of CYP3A-mediated activity ($\log A$) is concerned, there is a good correlation ($r = 0.81$) with ΔE, which is the difference between frontier orbital energies, E_{HOMO} and E_{LUMO}. However, inclusion of the molecular planarity, as determined by the ratio of molecular area and depth-squared, improves the correlation with $\log A$ from 0.81 to 0.87, which is statistically significant at this level. The information shown in Table 2 indicates, moreover, that there is little correlation ($r = 0.47$) between the two independent variables, ΔE and area/depth^2. It is possible to improve the correlation between activity and the combination of ΔE and area/depth^2 further (to $r = 0.89$) by inclusion of compound lipophilicity in the form of log *P* data, although there is some degree of lowering in statistical significance as described by the variance ratio (*F*-value), and this is also presented in Table 2.

For the increase in liver weight and increased DNA content, it is found that the most significant correlations ($r = 0.78$) are obtained with a combination of the molecular rectangularity (length/width ratio) and energy of the highest occupied molecular orbital, E_{HOMO}, as shown in Table 2. The correlation matrix covering these variables indicates that there is very little covariance ($r = 0.37$) between the two independent structural descriptors (Table 2) although the cor-

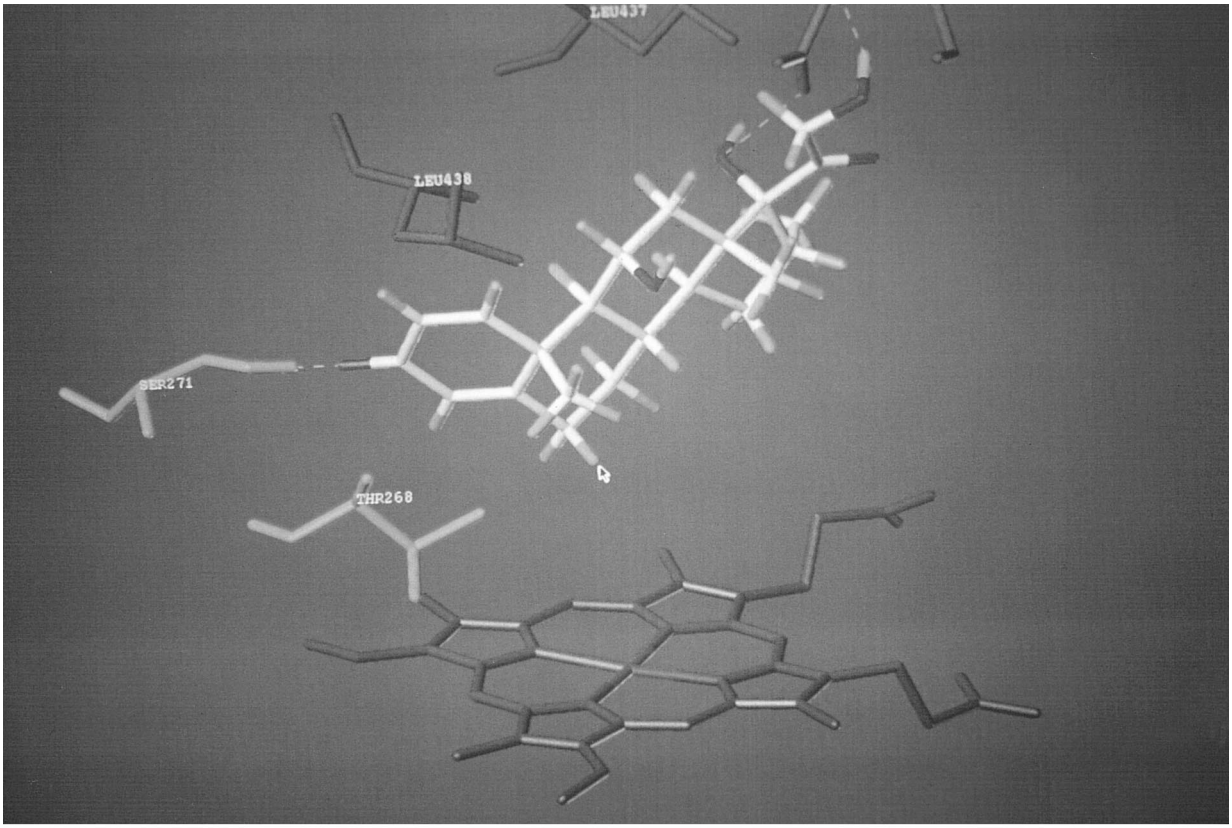

Fig. 1

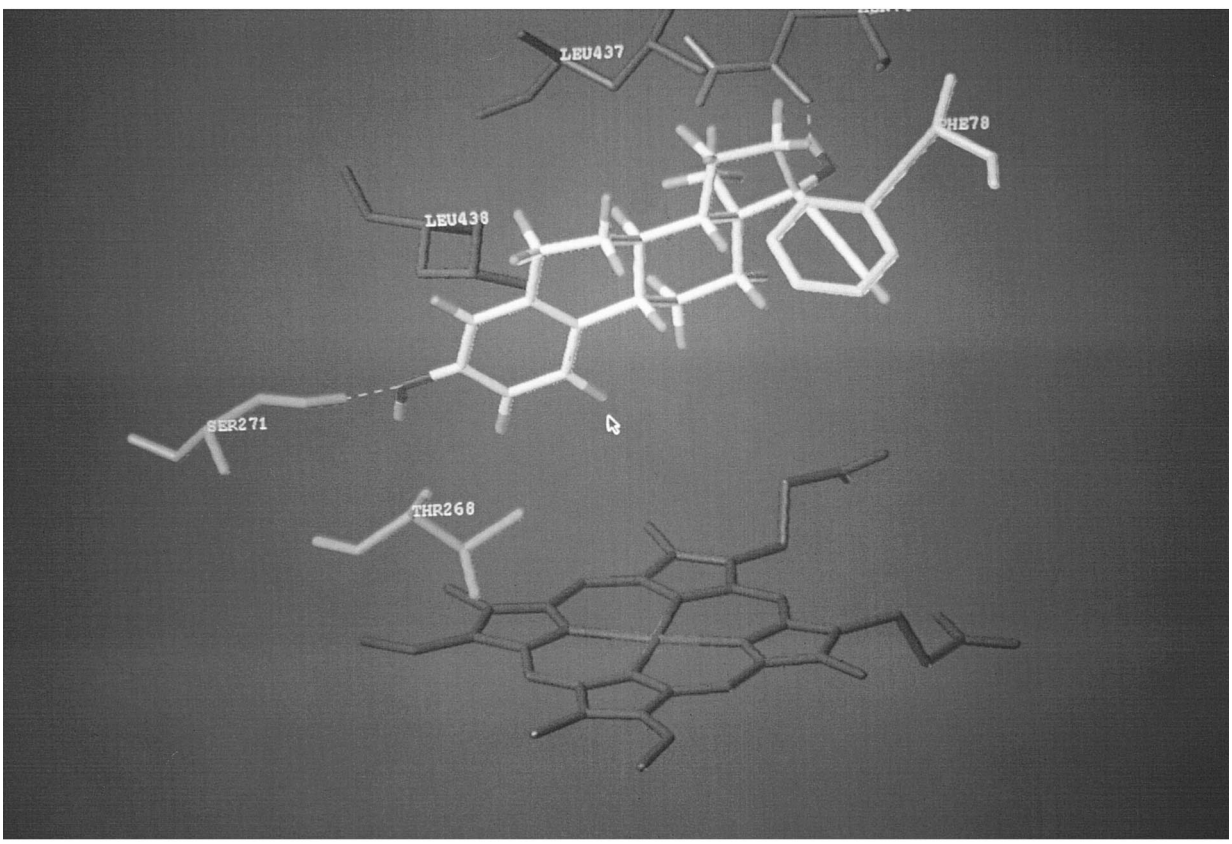

Fig. 2

Fig. 1. Possible orientation of dexamethasone within the putative active site of CYP3A4 which is consistent with 6β-hydroxylation. Specific contacts with Asn74 and Ser271 appear to be involved in hydrogen bond interactions with the substrate.
Fig. 2. Orientation of ethynylestradiol in the CYP3A4 active site showing complementary contacts with amino acid residues, such as Asn74 and Ser271.

Table 2
Quantitative structure-activity relationship for 14 steroids[a]

Relationship	n	s	R	F
$\log A = 0.20\ \underset{(\pm 0.09)}{\text{area/depth}^2} - 0.47\Delta E \underset{(\pm 0.08)}{+ 8.25}$	14	0.196	0.87	17.9
$I = 0.74E_{\text{HOMO}} \underset{(\pm 0.27)}{} + 0.63\ \text{length/width} + 7.48\ (\pm 0.21)$	11	0.133	0.78	6.1
$D = 3.92E_{\text{HOMO}} \underset{(\pm 1.42)}{} + 3.35\ \text{length/width} + 39.40\ (\pm 1.11)$	11	0.706	0.78	6.1
$\log A = 0.25a/d^2 \underset{(\pm 0.10)}{} - 0.50\Delta E \underset{(\pm 0.09)}{} + 0.08 \log P \underset{(\pm 0.08)}{} + 8.27$	14	0.196	0.89	12.3
$\log A = 0.29a/d^2 \underset{(\pm 0.10)}{} - 0.56E_{\text{LUMO}} \underset{(\pm 0.10)}{} + 2.93$	14	0.204	0.86	16.2

Correlation matrix (11 points)

	E_{HOMO}	I/W	I
Length/width	−0.37	1.00	0.47
Increase in liver weight/dose	0.39	0.47	1.00
DNA increase/dose	0.39	0.47	0.999

Correlation matrix (14 points)

	ΔE	Area/depth^2	$\log A$
ΔE	1.00	0.47	−0.81
Area/depth^2	0.47	1.00	−0.08
ELUMO	0.98	0.59	0.74
$\log P$	0.2	0.20	0.23

[a] n, Number of observations; s, standard error; R, correlation coefficient; F, variance ratio.

relations with activity are of lower significance than those exhibited for CYP3A induction.

3.3. Relevance of nuclear receptor binding to CYP3A induction

For percentage increase in CYP3A-mediated activity, the most important descriptor appears to be ΔE, as this is the major component of the QSAR expression, which also includes area/depth^2 (Table 2). It is likely, therefore, that the mechanism of CYP3A induction, which is thought to involve ligand binding to a nuclear receptor such as the glucocorticoid (GR) and/or pregnane-X (PXR) receptors, could be equated with specific interactions between the steroidal ligand molecule and key amino acid residues within the receptor binding site. If this is the case, then structural properties of the steroid molecules will, to some extent, be a measure of certain factors contributing to this overall binding interaction. Presumably, therefore, the ΔE value is a determinant of the steroidal ligand's ability to form frontier orbital-controlled contacts with the relevant nuclear receptor, and it is likely that these comprise hydrogen bond formation and/or charge-transfer interactions.

The binding of endogenous steroids to various proteins is known to involve hydrogen-bonded contacts, as has been shown in the crystal structures of uteroglobin [24], a monoclonal progesterone antibody [25] and the human oestrogen receptor [26], for example. It is probable, therefore, that similar interactions may occur when the steroids considered in this study bind to either the GR [27] or another nuclear receptor associated with CYP3A induction, such as the PXR, for instance [28]. However, the molecular shape of the ligand also appears to be of importance to the strength of interaction leading to both induction of CYP3A and increased DNA synthesis, which gives rise to liver enlargement. This is evidenced by presence of molecular planarity and rectangularity descriptors in the QSARs governing CYP3A induction and increase in liver weight/DNA content, respectively. Furthermore, as E_{HOMO} is a component of ΔE and could relate to hydrogen bond acceptor ability (or an electron donor capacity), it is possible that both the interaction with receptors associated with CYP3A induction, and with macromolecules controlling liver cell growth, involves hydrogen bonding, together with matched hydrophobic interactions probably involving a $\pi-\pi$ stacking component. However, it will be necessary to acquire some information about structural characteristics of the relevant nuclear receptors to develop these indications further, and work is in progress within our own group on the homology modelling of the GR and PXR receptors themselves. In particular, we have recently produced a molecular model of the GR ligand-binding domain (LBD) using the published hERα crystal structure [26]. The putative ligand-binding site permits the occupancy of typical CYP3A inducers, such as dexamethasone, via a combination of key hydrogen bond interactions (Lewis et al., unpublished data). Furthermore, QSAR analysis of a small number of non-steroidal GR ligands, which also exhibit CYP3A4 induction, indicates that similar structural descriptors to those presented in this work are able to explain the variation in induction potency, thus suggesting that there are likely to be related structural factors involved in both GR ligand binding and CYP3A induction (Lewis et al., unpublished findings). As there has been some success in utilising a homology model of the peroxisome proliferator-activated receptor

(PPARα) and QSAR approach for rationalising induction potency variations in certain peroxisome proliferators [29], it is hoped that the application of a similar methodology to other steroid hormone receptor superfamily members will provide further insights into the molecular mechanisms of induction by these chemicals.

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