Comparative QSAR Analysis of 5α-Reductase Inhibitors

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I. Introduction

Over the years it has been shown that the male sex hormone, testosterone (T), gets converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase (5AR). The nuclear chromatin of the prostate contains an androgen receptor that retains 5α-DHT selectively, the most potent endogenous androgen for the growth of ventral prostrate of the rat,[1,2] i.e., this androgen receptor is specific for DHT. The prostatic enzyme that catalyzes the reduction of T → DHT needs NADPH as a cofactor. It is a membrane-bound enzyme that delivers the pro-*S*-hydrogen of the cofactor to the less hindered α-face of the substrate, testosterone. The enolate (**I**) so formed is stabilized by the enzyme and subsequently protonated to generate 5α-androstan-17β-ol-3-one, DHT (Figure 1).[3]

Testosterone and its more potent metabolite, DHT, are essential hormones for male phenotype sexual differentiation and maturation through their actions at the androgen receptor.[4−6] Normal growth and development of prostate depends on DHT,[7−10] which suggests the role of DHT, and hence 5AR in prostate diseases. Correlation between prostatic growth and elevated prostatic DHT has been observed in BPH patients.[11] Consistent with the elevated levels associated with BPH, several groups have shown an increase in steroid 5AR activity in tissue from BPH prostates relative to normal prostates.[12−14]

In addition to the role of 5AR in male sexual development, it has been found to play a significant role in other physiological processes also. High levels of activity are observed in the liver and skin. Even tissues of the central nervous system contain 5AR activity. In the liver it is believed to have a catabolic function,[15] the skin activity may mediate androgenic drive in that organ.[16−20] Its role in the brain is not

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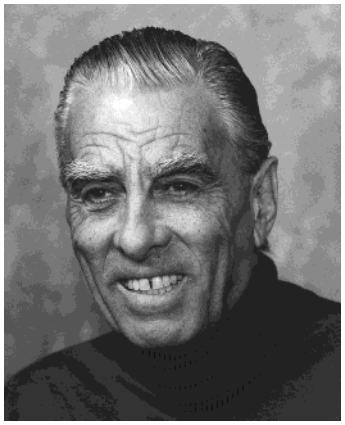
Alka Kurup received her undergraduate degree in Pharmacy in 1981 from Birla Institute of Technology and Science in Pilani, India. In 1988, she received her Masters degree from the College of Pharmacy in Manipal, India. For two years she assumed Inchargeship and Quality Control of the Pharmacy Manufacturing Wing at Kasturba Medical College in Manipal. In 1991, she joined Birla Institute of Technology and Science as a faculty member in the Department of Pharmacy. She completed her Ph.D. degree in 1997 under the supervision of Professor S. P. Gupta with her thesis regarding QSAR studies of anticancer drugs. She joined Professor Hansch's group in July 1998 to pursue postdoctoral research. Currently, she is involved in building the C-QSAR database. Her research interests include QSAR and computer-aided drug design.

Rajni Garg received her M.Sc. degree in Chemistry (1984) from Meerut University and M.Phil. (1988) degree from Delhi University, India. Her M.Phil. dissertation work was on peptide synthesis. She was a faculty member in the Chemistry Department of Birla Institute of Technology and Science, Pilani, India, from 1991 to 1996, where she taught organic and physical chemistry. She received her Ph.D. degree in 1996 under the supervision of Professor S. P. Gupta. Her doctoral work was on QSAR studies on anti-HIV agents. In February 1997, she joined Professor Corwin Hansch as a postdoctoral researcher, and she is currently involved in building a C-QSAR databank. Her research interests include QSAR and computer-assisted drug design.



Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in Organic Chemistry from New York University in 1944. After working with the DuPont Company, first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. In *Current Contents* (1981/41) he was named as one of the 300 most cited scientists out of over one million publishing in all fields of science for the period 1965–1978. In 1986, Hansch was cited in *Current Contents* as being one of the 250 most cited primary authors for 1984. He is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.

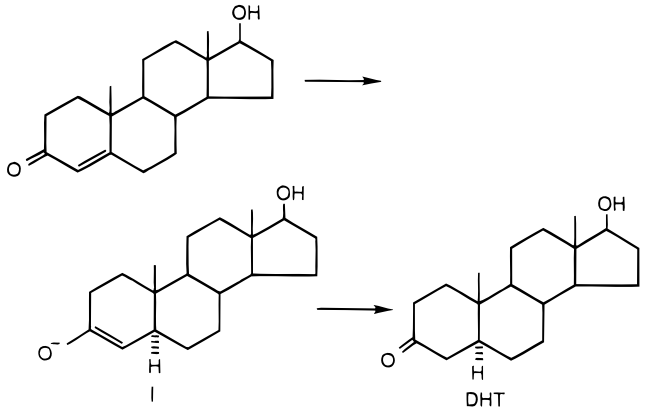


Figure 1.

well understood. The distribution of 5AR activity throughout the central nervous system and the lack of sexual dimorphism in its expression are particularly intriguing.[21−23] Recent evidence suggests that 5α-reduced metabolites of progesterone alter $GABA_A$ receptor function and play a part in sexual differentiation.[24]

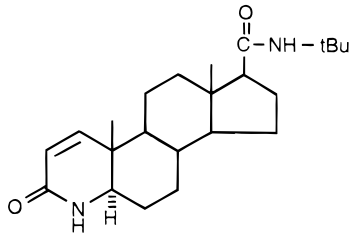
The quantity of the enzyme and its product, DHT, is elevated in the affected tissue of conditions such as benign prostatic hypertrophy,[11,25] acne, certain forms of hirsutism (excessive hair growth of normal or abnormal distribution), and male pattern baldness.[16] Thus, conversion of T → DHT is related to the development of many endocrine diseases[26] such as BPH,[27] prostatic cancer,[28] male pattern baldness,[29] acne,[30] hirsutism in women,[31] etc.

5α-Reductase is a system of two isozymes:[32] 5α-reductase Type 1 and 5α-reductase Type 2. The genetics, biochemistry, tissue distribution, and ontogeny of Type-1 and 2 5AR have been reviewed recently by Russel.[15] Selective inhibition of 5α-reductase has recently made possible a new therapeutic approach to the pharmacological treatment of these prevalent diseases.

A large number of steroidal and nonsteroidal inhibitors have been developed and tested in vitro toward human 5AR.[33,34] Many of these are based on the structure of testosterone itself. Frye, in his review of inhibitors of 5AR,[33] has listed the structure of 190 compounds with qualitative comments about their relative potency. He notes that since the data for these have been collected in a number of laboratories over a period of 3 decades from a variety of tissue

sources of 5AR from the expression of individual clones of Type 1 and 2 enzyme, it is very difficult to draw sharp conclusions.

Only one drug Finasteride (**II**),[35] a member of the 4-azasteroid family, has found its way to the market.



II
Finasteride

Finasteride has been clinically proven to be somewhat less effective in treating BPH than originally expected.[36] Further, Finasteride is a slow-acting potent inhibitor of 5α-reductase Type 2.[37] Dual inhibitors of Types 1 and 2 5AR should be more effective in reducing the circulating DHT in humans than selective type 2 inhibitors such as Finasteride.

Inhibition of one other enzyme that plays a critical role in steroid biosynthesis,[38] adrenal 3β-hydroxy-Δ^5-steroid dehydrogenase/3-keto-Δ^5-steroid isomerase (3BHSD),[53−55] also serves as an important selectivity assay for discovering drugs to treat the above diseases.

To provide a rational basis to design potent 5AR and 3BHSD inhibitors, a comparative quantitative structure−activity relationship (QSAR) study has been carried out. QSAR studies have been based on the premise that parameters from model systems can be used to account for variation in the steric, hydrophobic, and electronic properties of the major differences in the members of a set of congeners. By means of the numerical parameters, statistically valid equations can be formulated to better understand the structure−activity relationship of bioactive chemicals. More important, equations based on different sets of congeners can be used to laterally validate each other.

II. Materials and Methods

The inhibitory activities of the three enzymes 5α-reductase Type 1, Type 2, and 3BHSD have been collected from the literature (see individual data for detailed references). The type of isozymes, as mentioned in each case, is unequivocal if the source is recombinant enzyme but prostatic-derived 5AR activity is assumed to represent Type 25AR activity.[33] All the physicochemical parameters are auto-loaded from our C-QSAR database, and the QSAR regression analysis was executed with the C-QSAR program. The utility of the QSAR program in correlation analysis has been discussed.[39,40] The program includes all the commonly used substituent parameters.[41]

K_i is the enzyme inhibition constant, and IC_{50} is the minimum molar concentration leading to 50% inhibition of the enzyme, n is the number of data points, r^2 is the square of correlation coefficient, q^2 is a measure of the quality of fit, and s is the standard deviation.

The different parameters used have been discussed along with their applications.[42] However, in brief, Clog P is the calculated[43] octanol/water partition coefficient. E_S is the classical Taft steric parameter. It is most useful for intramolecular steric effects but with relatively small substituents sometimes accounts for intermolecular interactions. B1, B5, and L are Verloop's sterimol parameters. B1 is a measure of the width of the first atom of a substituent, B5 is an attempt to define the overall volume, and L is the length of the substituent moiety. The electronic parameters σ, σ^+, σ^- apply to substituent effects on aromatic systems, σ* applies to an aliphatic system and σ_I is the measure of the field/inductive effect.

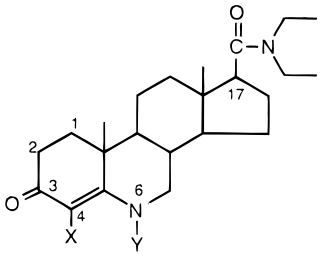
Molar refractivity is calculated as MR = $(n^2 - 1/n^2 + 2)$(MW/d), where n is the refractive index, MW is the molecular weight, and d is the density of the substance. As there is little variation in n, MR is largely a measure of volume with a small correction for polarizability. MR can be used for the substituent or the whole molecule. MR values are calculated, and we have scaled the values by 0.1. All of these parameters and applications have been discussed.[42]

III. Results and Discussions

1. Inhibitors for Human 5α-Reductase Type 1

A. K_i Data of 4-X-N-Y-6-Azaandrost-4-en-3-ones for Inhibition of Human Recombinant Type 1

(Table 1)[44]



$$\log 1/K_i = -1.58(\pm 0.48)L_Y + 1.81(\pm 0.70)\log(\beta \times 10^{LY}) - 1.10(\pm 0.50)L_X + 14.07(\pm 2.80)$$

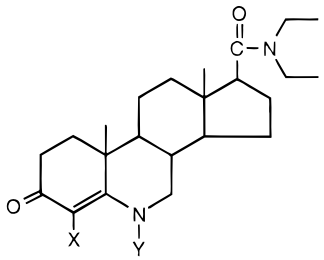
$$n = 15,\ r^2 = 0.872,\ q^2 = 0.698,\ s = 0.417 \quad (1)$$

$$(L_Y)_0 = 5.47(\pm 0.680),\ \log \beta = -4.63$$

Outliers: X = H, Y = COMe; X = C_2H_5, Y = H

Frye et al.[44] reported the inhibition activity of human 5α-reductase Type 1. We obtained eq 1 from their data. Both the substituents 4-X and 6-Y appear to create steric hindrance in binding of the molecule to the receptor. However, the length of the substituent at the sixth position is detrimental to the activity initially (as shown by its negative coefficient in the equation) up to an optimum length and then favorable in a bilinear fashion, a marginal effect −1.58 +

Table 1. K_i Data of 4-X-*N*-Y-6-Azaandrost-4-en-3-ones[44]



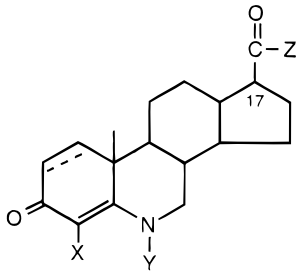
	substituents		log $1/K_i$				
no	X	Y	obsd	calcd (eq 1)	Δ	L_Y	L_X
1	H	COMe[a]	4.40	12.75	−8.35	4.06	2.06
2	H	CN	5.08	5.38	−0.30	4.23	2.06
3	H	CH_2COOH	5.00	4.96	0.04	4.74	2.06
4	H	Me	6.75	7.29	−0.54	2.87	2.06
5	H	C_2H_5	5.89	5.52	0.37	4.11	2.06
6	H	$(CH_2)_2CH_3$	4.62	4.87	−0.25	4.92	2.06
7	H	$CHMe_2$	5.47	5.52	−0.05	4.11	2.06
8	H	$(CH_2)_3CH_3$	5.11	4.86	0.25	6.17	2.06
9	H	$(CH_2)_5CH_3$	5.23	5.31	−0.08	8.22	2.06
10	H	$CH_2C_6H_5$	5.00	5.04	−0.04	4.62	2.06
11	Cl	H	7.29	6.96	0.33	2.06	3.52
12	Br	H	7.01	6.63	0.38	2.06	3.82
13	I	H	6.16	6.18	−0.02	2.06	4.23
14	CH_2NMe_2	H	5.00	5.53	−0.53	2.06	4.83
15	Me	H	7.40	7.67	−0.27	2.06	2.87
16	C_2H_5	H[a]	5.39	10.05	−4.66	2.06	4.11
17	Me	Me	7.09	6.40	0.69	2.87	2.87

[a] Data points not included in deriving equation.

1.81 = 0.23 occurs. It is of interest that no hydrophobic term is seen.

B. K_i Data of 4-X-N-Y-6-Azaandrost-17-CO-Z-4-en-3-ones for Inhibition of Human Recombinant Type 1

(Table 2)[44]



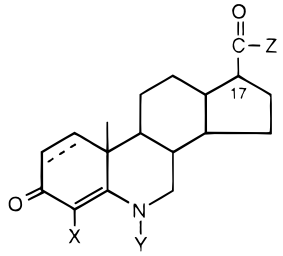
$$\log 1/K_i = 0.42(\pm 0.22)\text{Clog } P - 1.47(\pm 0.43)I - 0.32(\pm 0.30)L_Y + 6.88(\pm 0.13)$$

$$n = 21,\ r^2 = 0.829,\ q^2 = 0.745,\ s = 0.406 \quad (2)$$

Outliers: X = H, Y = H, Z = $NHCMe_3$; X = Me, Y = H, Z = CH_2CHMe_2

This series of compounds was also tested by Frye et al.[44] The dotted line in the structure is to show the

Table 2. K_i Data of 4-X-*N*-Y-6-Azaandrost-17-CO-Z-4-en-3-ones[44]



	substituents				log $1/K_i$					
no.	X	Y	Z	other[a]	obsd	calcd (eq 2)	Δ	Clog *P*	*I*	L_Y
1	H	H	$NHCMe_3$[b]		6.09	7.49	−1.40	3.07	0	2.06
2	H	H	$NHCMe_3$	Δ^1	5.62	6.16	−0.54	3.40	1	2.06
3	H	Me	$NHCMe_3$		7.06	7.29	−0.23	3.22	0	2.87
4	H	Me	$NHCMe_3$	Δ^1	5.85	5.91	−0.06	3.45	1	2.87
5	Me	H	$NHCMe_3$		7.92	7.70	0.22	3.59	0	2.06
6	Me	Me	$NHCMe_3$		7.22	7.50	−0.28	3.74	0	2.87
7	H	H	CH_2CHMe_2		8.05	7.94	0.11	4.16	0	2.06
8	H	Me	CH_2CHMe_2		8.51	7.74	0.77	4.31	0	2.87
9	Br	H	CH_2CHMe_2		8.50	8.30	0.20	5.03	0	2.06
10	Me	H	CH_2CHMe_2[b]		9.40	8.15	1.24	4.68	0	2.06
11	H	H	NH-1-adam[c]		7.96	8.08	−0.12	4.50	0	2.06
12	H	H	NH-1-adam	Δ^1	7.13	6.75	0.39	4.82	1	2.06
13	H	Me	NH-1-adam		8.07	7.88	0.19	4.64	0	2.87
14	H	Me	NH-1-adam	Δ^1	6.55	6.50	0.05	4.87	1	2.87
15	Br	H	NH-1-adam		8.35	8.43	−0.09	5.36	0	2.06
16	Me	H	NH-1-adam		8.96	8.29	0.67	5.01	0	2.06
17	Br	Me	NH-1-adam		8.07	8.23	−0.17	5.51	0	2.87
18	Me	Me	NH-1-adam		8.21	8.09	0.12	5.16	0	2.87
19	H	H	$NHCH(C_6H_5)_2$		7.52	8.37	−0.85	5.21	0	2.06
20	H	H	$NHCH(C_6H_5)_2$	Δ^1	7.32	7.04	0.28	5.54	1	2.06
21	H	Me	$NHCH(C_6H_5)_2$		8.19	8.59	−0.40	5.73	0	2.06
22	H	$(CH_2)_2CH_3$	$NHCH(C_6H_5)_2$	Δ^1	6.47	6.58	−0.11	6.64	1	4.92
23	Me	H	$NHCH(C_6H_5)_2$		8.44	8.59	−0.15	5.73	0	2.06

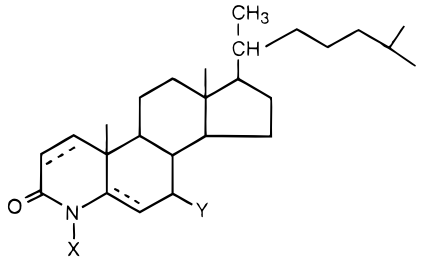
[a] Unsaturation. [b] Data points not included in deriving equation. [c] NH-1-adamantyl.

double bond present in some of the molecules (see Table 2). Equation 2 was obtained by us. In this equation, the indicator variable $I = 1$ is for compounds having a double bond at the C-1 position. In contrast to eq 1, it is evident from this equation that the hydrophobicity of the molecules is important for better activity. The steric effect of the 6-Y substituent is detrimental to the activity. The high negative coefficient of I shows that the presence of a double bond at the 1 carbon is highly detrimental to the activity. The negative effect of L_Y is much like that of eq 1 except that no positive result is seen with the longest substituents.

The Z-substituent at C-20 of the C-17 side chain does not seem to have much effect, but it appears that NH-1-adamantyl is well tolerated; in fact, it improves the activity somewhat.

C. IC_{50} Data of 4-X-7-Y-4-Azacholestan-3-ones for Inhibition of Human Recombinant Type 1

(Table 3)[45]



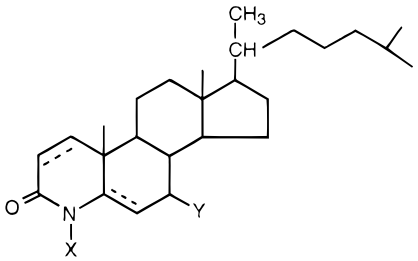
$$\log 1/C = -0.80(\pm 0.18)B5_Y - 2.09(\pm 0.64)\sigma^*_Y - 6.24(\pm 6.17)\sigma_{I,X} + 10.26(\pm 0.47)$$

$$n = 19,\ r^2 = 0.88,\ q^2 = 0.754,\ s = 0.24 \quad (3)$$

Outliers: X = Y = H, Δ^5; X = H, Y = C_2H_5; X = CH_2−CH=CH_2, Y = Me

This series was developed by Bakshi et al.[45] from whose data we derived eq 3. The negative coefficient of B5-sterimol for 7-Y substituents indicates that large groups at this position also lower the activity. Also, the electron-donating groups at this position enhance the activity as evident by a negative coefficient with σ^*_Y. The groups at 4-X appear to be

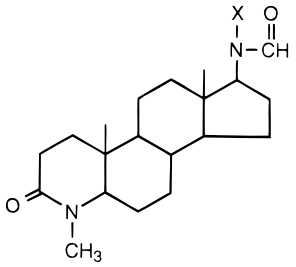
Table 3. IC_{50} Data of 4-X-7-Y-4-Azacholestan-3-ones[45]



	substituents			log 1/*C*					
no.	X	Y	other[a]	obsd	calcd (eq 3)	Δ	$B5_Y$	σ^*_Y	$\sigma_{I,X}$
1	H	H[b]	Δ^5	7.72	8.43	−0.71	1.00	0.49	0.00
2	H	Me	Δ^5	8.60	8.62	−0.02	2.04	0.00	0.00
3	H	C_2H_5	Δ^5	8.07	7.92	0.15	3.17	−0.10	0.00
4	H	$(CH_2)_2CH_3$	Δ^5	7.24	7.71	−0.47	3.49	−0.12	0.00
5	H	H		8.59	8.43	0.16	1.00	0.49	0.00
6	H	Me		8.59	8.62	−0.03	2.04	0.00	0.00
7	H	C_2H_5[b]		8.57	7.92	0.65	3.17	−0.10	0.00
8	H	$(CH_2)_2CH_3$		8.02	7.71	0.32	3.49	−0.12	0.00
9	Me	H		8.77	8.68	0.09	1.00	0.49	−0.04
10	Me	Me		9.05	8.87	0.18	2.04	0.00	−0.04
11	C_2H_5	Me		8.48	8.68	−0.20	2.04	0.00	−0.01
12	$CH_2CH{=}CH_2$	Me[b]		7.38	8.49	−1.12	2.04	0.00	0.02
13	Me	C_2H_5		8.24	8.17	0.08	3.17	−0.10	−0.04
14	Me	$(CH_2)_2CH_3$		7.70	7.95	−0.26	3.49	−0.12	−0.04
15	Me	C_6H_5		6.87	6.76	0.12	3.11	0.60	−0.04
16	Me	H	Δ^5	8.37	8.68	−0.31	1.00	0.49	−0.04
17	Me	Me	Δ^5	9.22	8.87	0.35	2.04	0.00	−0.04
18	Me	C_2H_5	Δ^5	8.02	8.17	−0.15	3.17	−0.10	−0.04
19	Me	$(CH_2)_2CH_3$	Δ^5	8.08	7.95	0.12	3.49	−0.12	−0.04
20	H	H	Δ^1	8.30	8.43	−0.13	1.00	0.49	0.00
21	H	Me	Δ^1	8.80	8.62	0.18	2.04	0.00	0.00
22	Me	Me	Δ^1	8.70	8.87	−0.17	2.04	0.00	−0.04

[a] Unsaturation. [b] Data points not included in deriving equation.

Table 4. IC_{50} Data of 17-β-[*N*-Alkyl(X)formamido]-4-CH_3-4-aza-5α-androstan-3-ones[46]



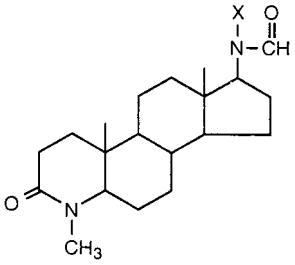
	substituents	log 1/*C*			
no.	X	obsd	calcd (eq 4)	Δ	L_X
1	$(CH_2)_2CH_3$	8.29	8.25	0.05	4.92
2	$(CH_2)_3CH_3$	8.52	8.56	−0.04	6.17
3	$(CH_2)_4CH_3$[a]	9.04	4.60	4.44	6.97
4	$(CH_2)_5CH_3$	8.14	8.24	−0.10	8.22
5	$(CH_2)_6CH_3$	8.02	8.03	−0.02	9.03
6	$(CH_2)_7CH_3$	7.77	7.72	0.05	10.27
7	$CHMe_2$	8.02	7.94	0.08	4.11
8	CH_2CHMe_2	8.14	8.25	−0.11	4.92
9	$(CH_2)_2CHMe_2$	8.66	8.56	0.10	6.17
10	$(CH_2)_2CMe_3$	8.63	8.56	0.07	6.17
11	$CH(CH_2CH_3)_2$	7.98	8.17	−0.20	4.72
12	$CH(CH_2)_2$	7.95	7.96	−0.04	4.14
13	$CH(CH_2)_5$[a]	7.92	4.80	3.13	6.17
14	$CH_2C_6H_5$	8.25	8.14	0.11	4.62

[a] Data points not included in deriving equation.

conducive to the activity, helped by the field/inductive effect.

D. IC_{50} Data of 17-β-[N-Alkyl(X)formamido]-4-CH_3-4-aza-5α-androstan-3-ones for Inhibition of Type 1 in DU-145 Cells

(Table 4)[46]



$$\log 1/C = 0.39(\pm 0.13)L_X - 0.64(\pm 0.19)\log(\beta \times 10^{L,X}) + 6.35(\pm 0.66)$$

$$n = 12,\ r^2 = 0.884,\ q^2 = 0.8,\ s = 0.113 \quad (4)$$

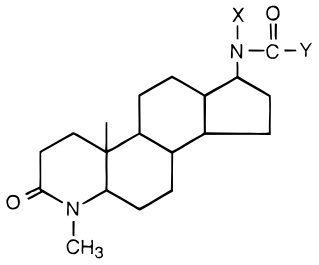
$$(L_X)_0 = 6.37\ (\pm 0.587),\ \log \beta = -6.18$$

Outliers: $X = (CH_2)_4CH_3$; $X = CH(CH_2)_5$

As reported by Li et al.,[46] these compounds have different groups attached to the formamide group at C-17. The bilinear relationship with L-sterimol gave the best correlation. The equation shows that the length of substituent X is favorable to the activity up to $L = 6.37$ and then shows a negative effect, $0.39 - 0.64 = -0.25$. The overall range in activity on which eq 4 is based is rather small.

E. IC_{50} Data of 17-β-[N–(X)CO–Y]-4-CH_3-4-aza-5α-androstan-3-ones for Inhibition of Type 1 in DU-145 Cells

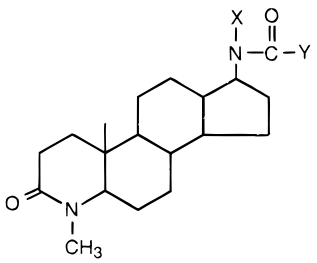
Table 5. IC_{50} Data of 17-β-[N-(X)CO-Y]-4-CH_3-4-Aza-5α-androstan-3-ones[46]



	substituents		log 1/*C*				
no.	X	Y	obsd	calcd (eq 5)	Δ	CMR	L_Y
1	$(CH_2)_3CH_3$	Me	7.93	8.04	−0.11	11.62	2.87
2	$(CH_2)_4CH_3$	C_2H_5	8.34	8.22	0.12	12.55	4.11
3	$(CH_2)_4CH_3$	$(CH_2)_2CH_3$	8.48	8.42	0.07	13.01	4.92
4	$(CH_2)_4CH_3$	$(CH_2)_3CH_3$	8.75	8.85	−0.10	13.48	6.17
5	$(CH_2)_4CH_3$	C_6H_5	8.49	8.56	−0.07	14.13	6.28
6	C_6H_5	C_6H_5	8.53	8.46	0.08	14.33	6.28
7	4-OMe-C_6H_4	C_6H_5[a]	8.68	8.13	0.55	14.94	6.28
8	C_6H_5	$CHMe_2$	7.98	7.87	0.11	13.21	4.11
9	4-OMe-C_6H_4	$CHMe_2$[a]	8.26	7.54	0.73	13.82	4.11
10	4-OMe-C_6H_4	$CHMe_2$	7.48	7.54	−0.05	13.82	4.11
11	3-CF_3,4-NO_2-C_6H_3	$CHMe_2$	7.22	7.26	−0.04	14.33	4.11

[a] Data points not included in deriving equation.

(Table 5)[46]



$$\log 1/C = -0.54(\pm 0.14)\mathrm{CMR} + 0.55(\pm 0.10)L_Y + 12.71(\pm 1.54)$$

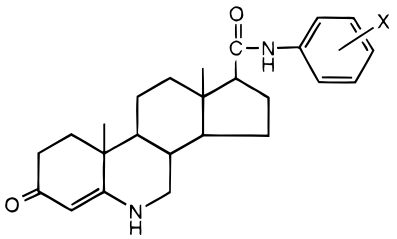
$$n = 9,\ r^2 = 0.968,\ q^2 = 0.913,\ s = 0.107 \quad (5)$$

Outliers: X = 4-OMe−C_6H_4, Y = C_6H_5; X = 4-OMe−C_6H_4, Y = $CHMe_2$

Equation 5, derived from the results of Li et al.,[46] is not a very satisfying result; however, it does provide information for further study. The variation is brought about by various groups such as X and Y substituents on the −NCO group attached to C-17. CMR applies to the whole molecule. The negative coefficient of CMR shows that the increase in size of the molecule decreases activity. Here since size change is by X and/or Y groups, the bigger groups increase the molar refractivity which in turn reduces the activity. But the positive coefficient of L-sterimol for Y-substituents shows positive steric effects in terms of the length of the Y groups attached. The two derivatives are outliers probably because of the *p*-methoxy group on the phenyl ring attached to N of −NCO−. This may be because of the electron-donating effect of OMe as the phenyl groups with electron-withdrawing groups such as NO_2 and CF_3 are well fit. In this study *L* does not exceed the limit of 6.37 set by eq 4.

F. K_i Data of 17β-[N-(X-Substituted phenyl)carbamoyl]-6-azaandrost-4-en-3-ones for Inhibition of Human Recombinant Type 1

(Table 6)[47]



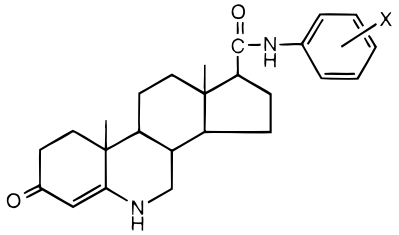
$$\log 1/K_i = 0.35(\pm 0.09)\mathrm{Clog}\ P + 0.26(\pm 0.11)B5_2 + 5.08(\pm 0.58)$$

$$n = 12,\ r^2 = 0.942,\ q^2 = 0.891,\ s = 0.154 \quad (6)$$

Outlier: 2,5-di-CF_3

Frye et al.[47] studied this series of compounds, where the variation in the molecules is brought about by different X groups at different positions of the phenyl ring attached to the CONH group at C-17.

Table 6. K_i Data of 17β-[N-(X-Substituted phenyl)carbamoyl]-6-azaandrost-4-en−3-ones[47]



	substituents	log 1/K_i				
no.	X	obsd	calcd (eq 6)	Δ	Clog *P*	$B5_2$
1	H	6.62	6.74	−0.12	4.08	1.00
2	2-CMe_3	7.57	7.71	−0.14	5.25	3.17
3	2-CMe_3, 5-Cl	8.13	8.04	0.09	6.22	3.17
4	2-CMe_3, 5-Br	8.38	8.09	0.29	6.37	3.17
5	2-CMe_3, 4-Br	8.28	8.09	0.18	6.37	3.17
6	2,5-di-CMe_3	8.30	8.34	−0.03	7.08	3.17
7	2-CMe_3, 5-C_6H_5	8.34	8.36	−0.02	7.14	3.17
8	2-CMe_3, 5-CF_3	8.06	8.17	−0.11	6.59	3.17
9	2-CMe_3, 5-(4-Cl-C_6H_4)	8.47	8.62	−0.15	7.90	3.17
10	2-CMe_3, 5-(4-$CMe_3C_6H_4$)	8.89	8.99	−0.10	8.97	3.17
11	2,5-di-CF_3[a]	8.40	7.47	0.93	4.98	2.61
12	3,5-di-CF_3	7.59	7.56	0.03	6.43	1.00
13	3,4-di-CMe_3	8.10	8.00	0.09	7.73	1.00

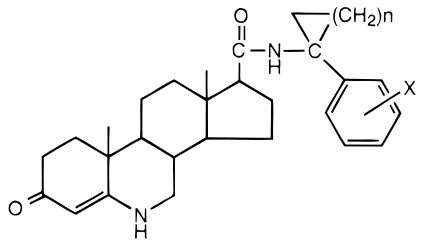
[a] Data point not included in deriving equation.

Here again from eq 6 it is evident that the inhibitory activity is improved by the increased hydrophobicity of the molecule as observed in eq 2. Also, ortho substituents on the phenyl ring have a positive steric interaction. The X -substituents at the ortho position probably twist the phenyl ring out of plane. There must be a hydrophobic site on the receptor to accommodate this phenyl ring along with its substituent.

G. K_i Data of 17β-[N-(1-Substituted phenyl cycloalkyl)-carbamoyl]-6-azaandrost-4-en-3-ones for Inhibition of Human Recombinant Type 1

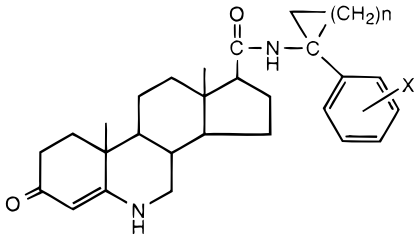
(Table 7)[47]

Table 7. K_i Data of 17β-[*N*-(1-Substituted phenyl cycloalkyl)carbamoyl]-6-azaandrost-4-en-3-ones[47]



	substituents		log 1/K_i			
no.	*n*	X	obsd	calcd (eq 7)	Δ	Clog *P*
1	3	4-Cl	8.17	8.25	−0.09	6.04
2	4	4-Cl	8.51	8.43	0.08	6.60
3	1	2,4-di-Cl	8.17	8.12	0.05	5.63
4	2	4-CMe_3	8.52	8.61	−0.08	7.15
5	4	4-CMe_3	8.82	8.78	0.04	7.11
6	5	4-CMe_3[a]	8.44	8.96	−0.52	8.27

[a] Data point not included in deriving equation.



$$\log 1/K_i = 0.32(\pm 0.17)\text{Clog } P + 6.34(\pm 1.15)$$

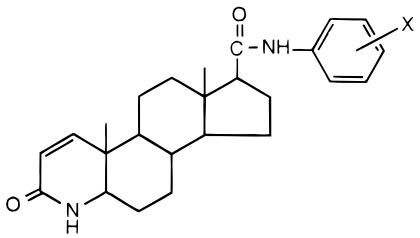
$$n = 5,\ r^2 = 0.920,\ q^2 = 0.791,\ s = 0.090 \quad (7)$$

Outlier: $n = 5$, X = 4-CMe_3

Frye et al.[47] reported K_i data for this series, for which we obtained eq 7. Once again, it is evident that the hydrophobicity of the molecules is conducive to the activity of the compounds. The outlier may be because of the size of the cycloalkyl ring between the amide and phenyl groups. As there were not many data points, this set could not be studied in detail to find roles for other physicochemical properties affecting activity. It is surprising that the cyclic hydrocarbon ring attached to NH shows no significant steric effects.

H. IC_{50} Data of 4-Aza-3-oxo-5α-androst-1-ene-17β-N-(X-aryl)carboxamides for Inhibition of Human Recombinant Type 1

(Table 8)[48]



$$\log 1/C = 1.36(\pm 0.57)\text{Clog } P - 0.13(\pm 0.06)(\text{Clog } P)^2 + 0.14(\pm 0.13)\sigma^+ - 0.18(\pm 0.07)E_{S,O} + 4.27(\pm 1.25)$$

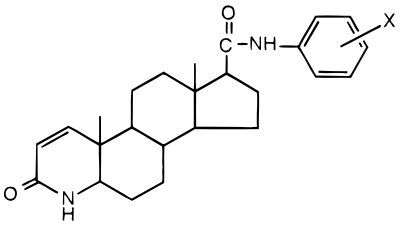
$$n = 25,\ r^2 = 0.899,\ q^2 = 0.832,\ s = 0.122 \quad (8)$$

$$\log P_0 = 5.08(4.76-5.76)$$

Outliers: 2-F; 4-Cl; 2-OMe; 2-C_6H_5; 2-OH

Bakshi et al.[48] reported K_i data for this series, for which we derived eq 8. Hydrophobicity plays an important positive role up to a Clog P of about 5. With a further increase in the hydrophobicity of the compounds, the activity decreases. A very marginal electronic influence of the substituents on the phenyl is shown by σ^+. Since all the substituents except H ($E_S = 0$) have negative E_S values, the negative coefficient with E_S for ortho substituents implies a positive steric effect. The bulky groups at the ortho positions tend to increase the activity, as shown by the negative $E_{S,O}$ term in the equation. It confirms the observation made earlier from eq 6.

Table 8. IC_{50} Data of 4-Aza-3-oxo-5α-androst-1-ene-17β-N(X-aryl)-carboxamides[48]



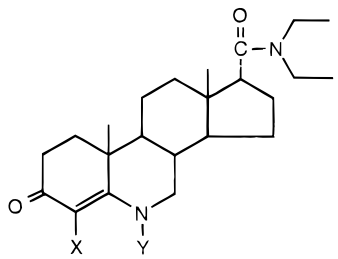
no.	substituents X	log 1/C obsd	log 1/C calcd (eq 8)	Δ	Clog P	σ^+	$E_{S,O}$
1	H	7.70	7.59	0.11	4.02	0.0	0.0
2	2-F[a]	8.10	7.61	0.49	3.82	−0.07	−0.55
3	3-F	7.64	7.73	−0.09	4.42	0.34	0.0
4	4-F	7.65	7.67	−0.02	4.42	−0.07	0.00
5	2-CF_3	8.25	8.07	0.18	3.90	0.61	−2.40
6	3-CF_3	7.90	7.79	0.11	5.35	0.43	0.0
7	4-CF_3	7.68	7.82	−0.14	5.35	0.61	0.0
8	2,5-di-CF_3	8.24	8.32	−0.08	4.92	1.04	−2.40
9	2-Cl	7.84	7.81	0.03	4.14	0.11	−0.97
10	3-Cl	7.74	7.79	−0.05	4.99	0.37	0.0
11	4-Cl[a]	8.17	7.75	0.42	4.99	0.11	0.0
12	3-Br	7.69	7.79	−0.10	5.14	0.39	0.0
13	2-Me	7.52	7.72	−0.20	3.86	−0.31	−1.24
14	3-Me	7.61	7.69	−0.08	4.51	−0.07	0.0
15	4-Me	7.76	7.65	0.11	4.51	−0.31	0.0
16	2,6-di-Me	7.85	7.85	0.01	3.71	−0.62	−2.48
17	2-OMe[a]	7.96	7.39	0.57	3.50	−0.78	−0.55
18	3-OMe	7.72	7.62	0.10	4.09	0.12	0.0
19	4-OMe	7.59	7.50	0.09	4.09	−0.78	0.0
20	2-C_6H_5[a]	7.42	7.89	−0.47	4.87	−0.18	−1.01
21	3-C_6H_5	7.85	7.66	0.20	5.90	0.06	0.0
22	4-C_6H_5	7.46	7.62	−0.17	5.90	−0.18	0.0
23	2-OH[a]	7.89	7.40	0.49	3.58	−0.92	−0.55
24	3-OH	7.28	7.35	−0.07	3.35	0.12	0.0
25	4-OH	7.13	7.20	−0.07	3.35	−0.92	0.0
26	2-NH_2	6.89	6.96	−0.07	2.79	−1.30	−0.61
27	3-NH_2	7.03	7.01	0.02	2.79	−0.16	0.0
28	4-NH_2	6.92	6.85	0.07	2.79	−1.30	0.0
29	3-COC_6H_5	7.92	7.76	0.16	5.52	0.34	0.0
30	4-COC_6H_5	7.72	7.79	−0.06	5.52	0.51	0.0

[a] Data points not included in deriving equation.

2. Inhibitors for Human 5α-Reductase Type 2

A. K_i Data of 4-X-N-Y-6-Azaandrost-4-en-3-ones for Inhibition of Human Recombinant Type 2

(Table 9)[44]



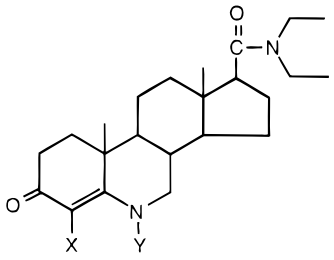
$$\log 1/K_i = -0.95(\pm 0.30)L_Y - 0.95(\pm 0.45)L_X + 1.80(\pm 0.51)\text{Clog } P + 6.86(\pm 1.75)$$

$$n = 14,\ r^2 = 0.868,\ q^2 = 0.710,\ s = 0.436 \quad (9)$$

Outliers: X = H, Y = $CH_2C_6H_5$; X = C_2H_5, Y = H

These compounds have also been tested for their

Table 9. K_i Data of 4-X-N-Y-6-Azaandrost-4-en-3-ones[44]



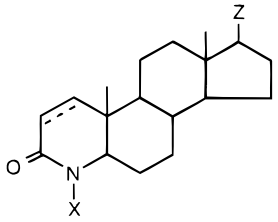
no.	substituents X	substituents Y	log 1/K_i obsd	log 1/K_i calcd (eq 9)	Δ	L_Y	L_X	Clog P
1	H	COMe	5.52	6.33	−0.81	4.06	2.06	2.93
2	H	CH_2COOH	5.82	5.64	0.18	4.74	2.06	2.91
3	H	Me	8.64	8.16	0.49	2.87	2.06	3.32
4	H	C_2H_5	8.46	7.92	0.53	4.11	2.06	3.85
5	H	$(CH_2)_2CH_3$	8.38	8.11	0.27	4.92	2.06	4.38
6	H	$CHMe_2$	8.31	8.48	−0.17	4.11	2.06	4.16
7	H	$(CH_2)_3CH_3$	7.54	7.87	−0.34	6.17	2.06	4.90
8	H	C_6H_{13}	7.92	7.83	0.09	8.22	2.06	5.96
9	H	$CH_2C_6H_5$[a]	7.40	9.30	−1.91	4.62	2.06	4.89
10	Cl	H	8.72	8.65	0.07	2.06	3.52	3.94
11	Br	H	8.68	8.53	0.15	2.06	3.82	4.03
12	I	H	8.22	8.64	−0.42	2.06	4.23	4.31
13	CH_2NMe_2	H	6.77	6.48	0.30	2.06	4.83	3.42
14	Me	H	8.41	8.81	−0.40	2.06	2.87	3.69
15	C_2H_5	H[a]	6.75	8.59	−1.84	2.06	4.11	4.22
16	Me	Me	8.35	8.31	0.04	2.87	2.87	3.84

[a] Data points not included in deriving equation.

activity against 5α-reductase Type 1. As observed in eq 1, here also the 4-X-substituent shows steric interactions which reduce activity. However, it is not clear why the ethyl derivative is an outlier when the derivative with X = CH_2NMe_2 fits well, the N in this group is partially charged at pH 7.4. Hydrophobicity is conducive to the activity, but the large coefficient with log P is out of the normally expected range.[49] The 6-Y-substituents again lower the activity because of steric interactions.

B. IC_{50} Data of 17β-N-X-4-Azasteroids for Inhibition of Human Prostate Enzyme

(Table 10)[50]



$$\log 1/C = 0.26(\pm 0.14)\text{Clog } P - 1.36(\pm 0.43)I_1 + 0.66(\pm 0.39)I_{17} + 6.62(\pm 0.55)$$

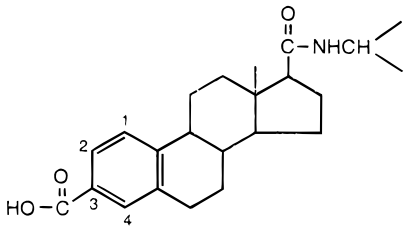
$$n = 16,\ r^2 = 0.841,\ q^2 = 0.654,\ s = 0.354 \qquad (10)$$

Outliers: X = H, Z = 17-$CON(CHMe_2)_2$, Δ^1; X = H, Z = 17-$CONHCMe_3$, Δ^1; X = H, Z = 17-$COCH(Me)CH_2CH_3$; X = H, Z = 17-$COCH(Me)CH_2CH_3$, Δ^1

Liang et al.[50] investigated this series of compounds for action against human prostatic 5α-reductase Type 2. In eq 10, $I_1 = 1$ for the presence of a double bond at position 1, $I_{17} = 1$ for the presence of the CON group at C-17. Once again, eq 10 confirms that the hydrophobicity in the neighborhood of position C-17 enhances the activity as observed in eq 9. The only variation at the 4-X position is the presence of Me/H, and no contribution toward lowering of the activity is observed as seen earlier. Probably small substituents such as CH_3 are well tolerated. The high negative coefficient of I_1 indicates that the presence of a double bond between the first and second carbon of the ring A is highly detrimental to the activity. The positive coefficient of I_{17} shows that the presence of −CON − at C-17 has a positive effect on the activity.

C. K_i Data of X-17-β-CONHCH$(CH_3)_2$-1,3,5-Estratrien-3-carboxylic Acids for Inhibition of Human Prostate Enzyme

(Table 11)[51]



$$\log 1/K_i = -0.97(\pm 0.60)MR_2 - 2.15(\pm 0.75)MR_4 + 8.13(\pm 0.40)$$

$$n = 9,\ r^2 = 0.891,\ q^2 = 0.749,\ s = 0.174 \qquad (11)$$

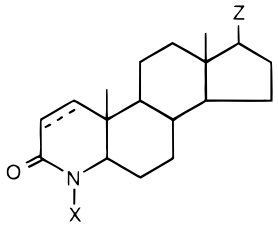
Outliers: 4-Br; 2-COOH

Holt et al.[51] reported the inhibition activity of steroidal A ring aryl carboxylic acids.

The compounds in this series have a variety of substituents at different positions of the ring A. The best equation obtained was with MR for X-substituents at positions 2 and 4. The negative coefficient for both MR_2 and MR_4 shows that substituents at these positions show steric hindrance. Of the two positions, the bigger coefficient of MR_4 indicates that the fourth position seems to show a greater effect. This also suggests why the 4-Br derivative is a misfit (MR = 0.888, highest among all the substituents).

D. IC_{50} Data of 17β-N-X-4-Azasteroids for Inhibition of Rat Prostate Enzyme

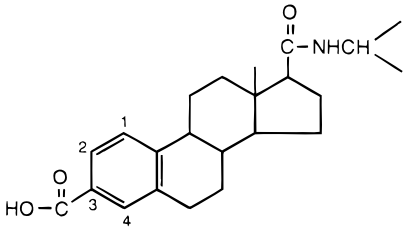
Table 10. IC_{50} Data of 17β-*N*-X-4-Azasteroids[50]



	substituents			log 1/*C*					
no.	X	Z	other[a]	obsd	calcd (eq 10)	Δ	Clog *P*	I_1	I_{17}
1	4-Me	17-CON$(CH_2CH_3)_2$		8.07	8.19	−0.12	3.54	0	1
2	H	17-CON$(CH_2CH_3)_2$		8.00	8.13	−0.13	3.29	0	1
3	4-Me	17-CON$(CH_2CH_3)_2$	Δ^1	6.75	6.93	−0.19	3.95	1	1
4	H	17-CON$(CH_2CH_3)_2$	Δ^1	7.10	6.72	0.39	3.11	1	1
5	4-Me	17-CON$(CHMe_2)_2$		8.66	8.35	0.31	4.16	0	1
6	H	17-CON$(CHMe_2)_2$		8.22	8.28	−0.06	3.91	0	1
7	4-Me	17-CON$(CHMe_2)_2$	Δ^1	6.89	7.09	−0.20	4.56	1	1
8	H	17-CON$(CHMe_2)_2$[b]	Δ^1	7.85	6.88	0.98	3.73	1	1
9	4-Me	17-CONHCMe_3		7.96	7.59	0.37	3.77	0	0
10	H	17-CONHCMe_3		7.40	7.44	−0.04	3.20	0	0
11	4-Me	17-CONHCMe_3	Δ^1	6.50	6.24	0.25	3.85	1	0
12	H	17-CONHCMe_3[b]	Δ^1	8.00	6.03	1.97	3.01	1	0
13	4-Me	17-COCH(Me)CH_2CH_3		7.86	7.76	0.10	4.44	0	0
14	H	17-COCH(Me)CH_2CH_3[b]		9.10	7.70	1.40	4.20	0	0
15	4-Me	17-COCH(Me)CH_2CH_3	Δ^1	6.25	6.50	−0.25	4.85	1	0
16	H	17-COCH(Me)CH_2CH_3[b]	Δ^1	7.30	6.29	1.02	4.01	1	0
17	4-Me	17-CONH$(CH_2)_7CH_3$		8.26	8.14	0.13	5.91	0	0
18	H	17-CONH$(CH_2)_7CH_3$		7.89	8.07	−0.19	5.66	0	0
19	4-Me	17-CH(Me)COO-		7.03	6.62	0.41	0.02	0	0
20	4-Me	17-CH(Me)$(CH_2)_2$COO-		6.13	6.92	−0.78	1.17	0	0

[a] Unsaturation. [a] Data points not included in deriving eq.

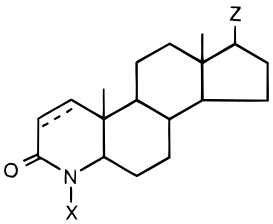
Table 11. K_i Data of X-17-β-CONHCH-$(CH_3)_2$-1,3,5-Estratrien-3-carboxylic Acids[51]



	substituents	log 1/K_i				
no.	X	obsd	calcd (eq 11)	Δ	MR_2	MR_4
1	H	7.70	7.81	−0.11	0.10	0.10
2	4-F	8.00	7.83	0.17	0.10	0.09
3	2-Cl	7.46	7.32	0.13	0.60	0.10
4	4-Cl	6.92	6.73	0.19	0.10	0.60
5	2-Br	7.12	7.05	0.07	0.89	0.10
6	4-Br[a]	6.67	6.12	0.55	0.10	0.89
7	2-CN	7.19	7.30	−0.11	0.63	0.10
8	4-CN	6.70	6.67	0.03	0.10	0.63
9	2-COOH[a]	5.30	7.24	−1.94	0.69	0.10
10	2-Me	7.22	7.36	−0.14	0.57	0.10
11	4-Me	6.59	6.82	−0.23	0.10	0.57

[a] Data points not included in deriving equation.

(Table 12)[50]



These compounds have been also tested for their inhibitory activity against rat prostatic 5α-reductase. The best correlations obtained are given by eqs 12a and 12b.

$$\log 1/C = -1.31(\pm 0.36)I_1 - 1.20(\pm 0.37)I_{CON} + 0.41(\pm 0.23)MR_{17} + 7.88(\pm 0.71)$$

$$n = 19,\ r^2 = 0.904,\ q^2 = 0.851,\ s = 0.352 \quad (12a)$$

Outlier: X = H, Z = 17-CONHCMe_3

$$\log 1/C = -1.43(\pm 0.31)I_1 - 0.61(\pm 0.37)I_{CON} + 0.89(\pm 0.41)I_{CONH} + 8.66(\pm 0.29)$$

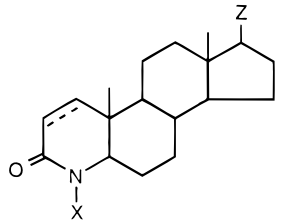
$$n = 19,\ r^2 = 0.923,\ q^2 = 0.880,\ s = 0.314 \quad (12b)$$

Outlier: X = H, Z =17-CONHCMe_3

In the equations, 12a and 12b I_1=1 for the presence of double bond at C-1, I_{CON} = 1 for the presence of −CON and I_{CONH} = 1 for −CONH group at C-17 position, respectively.

It is evident from the negative term of I_1 that the presence of a double bond at C-1- C-2 has a lowering effect on activity. Although MR of the C-17 substituent makes a positive contribution, it is interesting to note that presence of CON group has a detrimental effect on the activity while that of CONH is important as shown by its positive coefficient in eq 12b. Possibly there is hydrogen bond formation which helps in binding to the receptor.

Table 12. IC_{50} Data of 17β-*N*-X-4-Azasteroids[50]

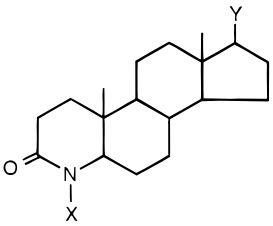


		substituents		log 1/*C*								
no.	X	Z	other[a]	obsd	calcd (eq 12a)	Δ	calcd (eq 12b)	Δ	MR_{17}	I_1	I_{CONH}	I_{CON}
1	4-Me	17-CON(C_2H_5)$_2$		8.00	7.80	0.20	8.05	−0.05	2.72	0	0	1
2	H	17-CON(C_2H_5)$_2$		7.39	7.80	−0.41	8.05	−0.66	2.72	0	0	1
3	4-Me	17-CON(C_2H_5)$_2$	Δ^1	6.54	6.49	0.05	6.62	−0.08	2.72	1	0	1
4	H	17-CON(C_2H_5)$_2$	Δ^1	6.85	6.49	0.37	6.62	0.24	2.72	1	0	1
5	4-Me	17-CON($CHMe_2$)$_2$		8.46	8.18	0.28	8.05	0.41	3.65	0	0	1
6	H	17-CON($CHMe_2$)$_2$		7.96	8.18	−0.22	8.05	−0.09	3.65	0	0	1
7	4-Me	17-CON($CHMe_2$)$_2$	Δ^1	6.37	6.87	−0.50	6.62	−0.25	3.65	1	0	1
8	H	17-CON($CHMe_2$)$_2$	Δ^1	7.10	6.87	0.24	6.62	0.49	3.65	1	0	1
9	4-Me	17-CONHCMe_3		9.25	9.00	0.26	9.55	−0.30	2.72	0	1	0
10	H	17-CONHCMe_3[b]		8.20	9.00	−0.79	9.55	−1.35	2.72	0	1	0
11	4-Me	17-CONHCMe_3	Δ^1	7.89	7.68	0.20	8.11	−0.23	2.72	1	1	0
12	H	17-CONHCMe_3	Δ^1	8.17	7.68	0.48	8.11	0.05	2.72	1	1	0
13	4-Me	17-COCH(Me)CH_2CH_3		8.72	8.84	−0.12	8.66	0.06	2.36	0	0	0
14	H	17-COCH(Me)CH_2CH_3		8.92	8.80	0.11	8.66	0.26	2.25	0	0	0
15	4-Me	17-COCH(Me)CH_2CH_3	Δ^1	6.92	7.53	−0.61	7.22	−0.30	2.35	1	0	0
16	H	17-COCH(Me)CH_2CH_3	Δ^1	7.30	7.53	−0.23	7.22	0.08	2.35	1	0	0
17	4-Me	17-CONH-$(CH_2)_7CH_3$		9.68	9.76	−0.08	9.55	0.13	4.58	0	1	0
18	H	17-CONH-$(CH_2)_7CH_3$		9.89	9.75	0.13	9.55	0.34	4.58	0	1	0
19	4-Me	17-CH(Me)-COO-		8.77	8.49	0.28	8.66	0.11	1.49	0	0	0
20	4-Me	17CH(Me)-$(CH_2)_{2COO-}$		8.44	8.87	−0.43	8.66	−0.21	2.42	0	0	0

[a] Unsaturation. [b] Data point not included in deriving equation.

E. IC_{50} Data of 4-X-17-Y-4-Azaandrost-3-ones for Inhibition of Rat Prostate Enzyme

(Table 13)[52]



$$\log 1/C = 1.08(\pm 0.16)\text{Clog } P - 1.41(\pm 0.22)\log(\beta \times 10^{\text{ClogP}}) + 0.95(\pm 0.24)I_{\text{CONH}} + 4.06(\pm 0.56)$$

$$n = 36,\ r^2 = 0.873,\ q^2 = 0.831,\ s = 0.289 \quad (13)$$

$$\log P_0 = 5.10(\pm 0.467),\ \log \beta = -4.58$$

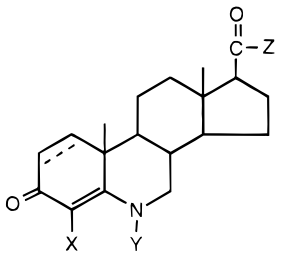
Outliers: X = Me,Y = $CONHCH_2CH(OMe)_2$; X = Me, Y = CHMeCOOMe

Rasmusson et al.[52] studied this series of compounds. The best correlation obtained is given by eq 13. In the equation, $I_{CONH} = 1$ for the presence of CONH group in 17-Y substituents. As evident from the equation, hydrophobicity is important for the action, i.e., compounds with very low or very high hydrophobic value are not good. The optimum value of logP is 5.10. Once again the positive coefficient of I_{CONH} shows that presence of CONH group in the C-17 substituents is significant for improving the activity as observed in eq 12b. It is also observed here that CON group is not conducive to the activity as it has a negative effect.

3. Inhibitors of Human Adrenal 3β-Hydroxy-Δ^5-steroid Dehydrogenase/ 3-Keto-Δ^5-steroid Isomerase (3BHSD)

A. K_i Data of 4-X-N-Y-6-Azaandrost-17-CO-Z-4-en-3-ones for Inhibition of Enzyme from Human Adrenal Tissue

(Table 14)[44]



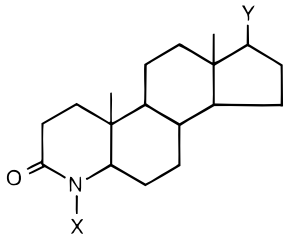
$$\log 1/K_i = 0.69(\pm 0.39)\text{Clog } P - 1.24(\pm 0.49)I - 0.46(\pm 0.23)MR_Z + 6.41(\pm 1.25)$$

$$n = 22,\ r^2 = 0.763,\ q^2 = 0.615,\ s = 0.477 \quad (14)$$

Outliers: X = H, Y = Me, Z = NH-1-adamantyl

Frye et al.[44] reported the K_i data of these compounds

Table 13. IC_{50} Data of 4-X-17-Y-4-Azaandrost-3-ones[52]



		substituents	log1/C				
no.	X	Y	obsd	calcd (eq 13)	Δ	Clog *P*	I_{CONH}
1	H	OH	6.60	6.51	0.09	2.27	0
2	Me	OH	6.82	7.13	−0.30	2.85	0
3	H	COMe	7.30	7.11	0.19	2.83	0
4	Me	COMe	7.64	7.70	−0.06	3.41	0
5	H	CHOHMe	7.35	7.49	−0.15	3.20	0
6	Me	CHOHMe	7.72	7.74	−0.02	3.45	0
7	Me	$CH(Me)CH_2OH$	8.42	8.29	0.13	4.07	0
8	H	COO-	7.60	7.12	0.48	2.84	0
9	Me	COO-	7.43	7.71	−0.28	3.42	0
10	Me	COOMe	8.12	7.76	0.36	3.47	0
11	Me	$CONH_2$	7.77	7.71	0.06	2.50	1
12	Me	CONHMe	7.42	7.39	0.03	2.21	1
13	Me	$CONHC_2H_5$	7.92	7.96	−0.04	2.74	1
14	H	$CONHCMe_3$	8.20	8.44	−0.24	3.20	1
15	Me	$CONHCMe_3$	9.25	9.00	0.25	3.77	1
16	H	$CONH(CH_2)_7Me$	9.89	9.56	0.33	5.66	1
17	Me	$CONH(CH_2)_7Me$	9.68	9.49	0.18	5.91	1
18	Me	$CONH(CH_2)_8CH{=}CH(CH_2)_7Me$	7.70	7.93	−0.23	10.72	1
19	Me	$CONH(CH_2)_2OH$	7.03	7.39	−0.36	2.21	1
20	Me	$CONHCH_2CH(OMe)_2$[a]	8.34	4.33	4.00	2.04	1
21	H	$CON(C_2H_5)_2$	7.39	7.59	−0.20	3.29	0
22	Me	$CON(C_2H_5)_2$	7.96	7.83	0.13	3.54	0
23	H	$CON(CHMe_2)_2$	7.96	8.17	−0.21	3.91	0
24	Me	$CON(CHMe_2)_2$	8.46	8.36	0.10	4.16	0
25	Me	$CON(C_8H_{17})_2$	7.48	7.25	0.23	9.89	0
26	Me	CO-morpholino	7.57	7.07	0.49	2.80	0
27	Me	$CH_2COOC_2H_5$	8.17	8.60	−0.43	4.61	0
28	Me	$CH_2CON(C_2H_5)_2$	8.10	8.36	−0.25	4.16	0
29	Me	$=CHCON(C_2H_5)_2$	8.60	8.58	0.02	4.57	0
30	Me	CHMeCOO-	8.77	8.41	0.36	4.24	0
31	Me	CHMeCOOMe[a]	7.66	2.53	5.13	4.61	0
32	Me	$CHMeCON(C_2H_5)_2$	7.89	8.54	−0.65	4.47	0
33	Me	$CHMe(CH_2)_2COO$-	8.44	8.68	−0.23	5.17	0
34	Me	$CHMe(CH_2)_2CON(C_2H_5)_2$	8.47	8.61	−0.15	5.62	0
35	Me	CHMeCN	8.12	8.09	0.03	3.82	0
36	H	$COCHMeC_2H_5$	8.92	8.51	0.41	4.42	0
37	Me	$COCHMeC_2H_5$	8.72	8.61	0.11	4.66	0
38	Me	NHCOMe	6.57	6.79	−0.22	2.54	0

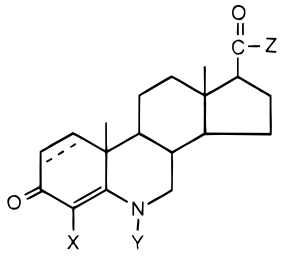
[a] Data points not included in deriving the equation.

for 3BHSD. The best correlation we could find is given by eq 14. In this equation the indicator variable $I = 1$ is for the presence of a double bond at the C-1 position. This group of compounds has also been tested for their activity to inhibit 5α-reductase Type 1 (eq 2). As observed for isozyme 1, the positive coefficient of Clog *P* indicates that hydrophobicity is important even toward 3BHSD. The presence of the double bond at C-1 is responsible for lowering the activity, but unlike isozyme 1, here the size of the Z groups attached to −CO− at C-17 has a negative effect.

B. K_i Data of 4-X-N-Y-6-Azandrost-4-en-3-ones for Inhibition of Enzyme from Human Adrenal Tissue

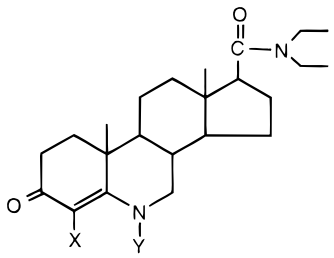
(Table 15)[44]

Table 14. K_i Data of 4-X-*N*-Y-6-Azaandrost-17-CO-Z-4-en-3-ones[44]



	substituents				log 1/K_i					
no.	X	Y	Z	other[a]	obsd	calcd (eq 14)	Δ	Clog *P*	*I*	MR_Z
1	H	H	$NHCMe_3$		6.82	7.47	−0.64	3.07	0	2.31
2	H	H	$NHCMe_3$	Δ^1	5.66	6.45	−0.79	3.40	1	2.31
3	H	Me	$NHCMe_3$		8.10	7.57	0.61	3.22	0	2.31
4	H	Me	$NHCMe_3$	Δ^1	7.21	6.48	0.73	3.45	1	2.31
5	Me	H	$NHCMe_3$		8.04	7.83	0.21	3.59	0	2.31
6	Me	Me	$NHCMe_3$		7.64	7.93	−0.29	3.74	0	2.31
7	H	H	CH_2CHMe_2		8.00	8.38	−0.38	4.16	0	1.96
8	H	Me	CH_2CHMe_2		8.96	8.48	0.48	4.31	0	1.96
9	Br	H	CH_2CHMe_2		8.64	8.98	−0.34	5.03	0	1.96
10	Me	H	CH_2CHMe_2		8.92	8.74	0.18	4.68	0	1.96
11	H	H	NH-1-adam[b]		7.11	7.32	−0.21	4.50	0	4.77
12	H	H	NH-1-adam	Δ^1	6.00	6.30	−0.30	4.82	1	4.77
13	H	Me	NH-1-adam[c]		8.57	7.42	1.15	4.64	0	4.77
14	H	Me	NH-1-adam	Δ^1	7.21	6.33	0.88	4.87	1	4.77
15	Br	H	NH-1-adam		7.89	7.91	−0.02	5.36	0	4.77
16	Me	H	NH-1-adam		8.05	7.67	0.37	5.01	0	4.77
17	Br	Me	NH-1-adam		8.08	8.01	0.07	5.51	0	4.77
18	Me	Me	NH-1-adama		7.75	7.77	−0.03	5.16	0	4.77
19	H	H	$NHCH(C_6H_5)_2$		6.82	7.27	−0.45	5.21	0	5.94
20	H	H	$NHCH(C_6H_5)_2$	Δ^1	6.00	6.25	−0.25	5.54	1	5.94
21	H	Me	$NHCH(C_6H_5)_2$		7.96	7.63	0.33	5.73	0	5.94
22	H	$(CH_2)_2CH_3$	$NHCH(C_6H_5)_2$	Δ^1	6.75	7.02	−0.27	6.64	1	5.94
23	Me	H	$NHCH(C_6H_5)_2$		7.75	7.63	0.11	5.73	0	5.94

[a] Unsaturation. [b] NH-1-adamantyl. [c] Data point not included in deriving equation.



$$\log 1/K_i = -0.67(\pm 0.19)B5_Y - 4.27(\pm 2.09)\sigma_{I,Y} + 8.61(\pm 0.62)$$

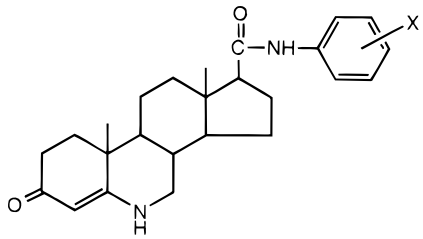
$$n = 15,\ r^2 = 0.846,\ q^2 = 0.632,\ s = 0.562 \qquad (15)$$

Outliers: X = H, Y = CH_2COOH; X = CH_2NMe_2, Y = H

These compounds have been tested by Frye et al.[44] for which we obtained eq 15. The negative coefficient of $B5_Y$ for 6-Y substituents indicates that large groups at this position create a steric interaction and decrease the activity. Electron-attracting substituents have a negative effect on activity shown by $\sigma_{I,Y}$. Although the 4-X substituent's contribution is not observed in the equation, the outlier for X = CH_2-NMe_2 suggests a negative effect.

C. K_i Data of 17β-[N-(X-Substituted phenyl)carbamoyl]-6-azaandrost-4-en-3-ones for Inhibition of Enzyme from Human Adrenal Tissue

(Table 16)[47]



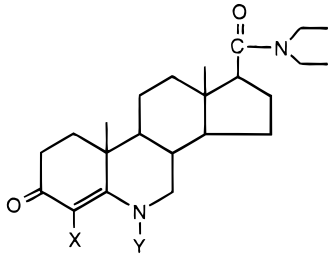
$$\log 1/K_i = -1.00(\pm 0.56)\sigma - 0.95(\pm 0.26)MR_2 + 8.07(\pm 0.44)$$

$$n = 12,\ r^2 = 0.884,\ q^2 = 0.83,\ s = 0.297 \qquad (16)$$

Outliers: 2-CMe_3, 5-[4-CMe_3-C_6H_4]; 2-[4-CMe_3-C_6H_4], 5-CF_3

Reported by Frye et al.,[47] in this series different

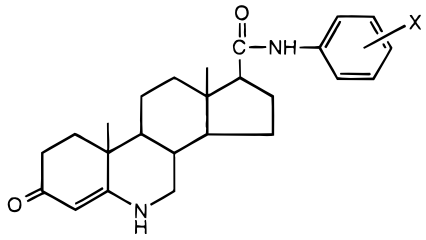
Table 15. K_i Data for 4-X-*N*-Y-6-Azaandrost-4-en-3-ones[44]



no.	substituents X	Y	log 1/K_i obsd	calcd (eq 15)	Δ	B5$_Y$	$\sigma_{I,Y}$
1	H	COMe	4.47	5.24	−0.77	3.13	0.30
2	H	CN	5.82	5.28	0.55	1.60	0.53
3	H	CH_2COOH[a]	6.75	5.61	1.13	3.78	0.11
4	H	Me	8.44	7.42	1.03	2.04	−0.04
5	H	C_2H_5	7.31	6.53	0.78	3.17	−0.01
6	H	$(CH_2)_2CH_3$	6.28	6.32	−0.03	3.49	−0.01
7	H	$CHMe_2$	5.96	6.45	−0.49	3.17	0.01
8	H	$(CH_2)_3CH_3$	5.44	5.74	0.30	4.54	−0.04
9	H	$(CH_2)_5CH_3$	4.96	4.79	0.17	5.96	−0.04
10	H	$CH_2C_6H_5$	4.80	4.92	−0.13	6.02	−0.08
11	Cl	H	7.57	7.94	−0.37	1	0
12	Br	H	7.89	7.94	−0.05	1	0
13	I	H	7.82	7.94	−0.12	1	0
14	CH_2NMe_2	H[a]	5.92	7.94	−2.02	1	0
15	Me	H	7.75	7.94	−0.20	1	0
16	C_2H_5	H	7.33	7.94	−0.61	1	0
17	Me	Me	7.96	7.42	0.54	2.04	−0.04

[a] Data points not included in deriving equation.

Table 16. K_i Data for 17β-[*N*-(X-Substituted phenyl)carbamoyl-6-azaandrost-4-en-3-ones[47]



no.	substituents X	log 1/K_i obsd	calcd (eq 16)	Δ	σ	MR_2
1	H	8.00	7.98	0.02	0.00	0.10
2	2-CMe_3	7.07	6.41	0.66	−0.20	1.96
3	2-CMe_3, 5-Cl	6.12	6.04	0.08	0.17	1.96
4	2-CMe_3, 5-Br	6.09	6.02	0.07	0.19	1.96
5	2-CMe_3, 4-Br	6.41	6.18	0.23	0.03	1.96
6	2,5-di-CMe_3	6.30	6.51	−0.21	−0.30	1.96
7	2-CMe_3, 5-C_6H_5	6.09	6.35	−0.27	−0.14	1.96
8	2-CMe_3, 5-CF_3	5.80	5.98	−0.19	0.23	1.96
9	2-CMe_3, 5-(4-Cl-C_6H_4)	5.92	6.26	−0.34	−0.05	1.96
10	2-CMe_3, 5-(4-$CMe_3C_6H_4$)[a]	5.05	6.34	−1.29	−0.13	1.96
11	2,5-di-CF_3	6.52	6.62	−0.10	0.97	0.50
12	2-(4-CMe_3-C_6H_4), 5-CF_3[a]	7.72	3.46	4.26	0.44	4.40
13	3,5-di-CF_3	7.24	7.11	0.12	0.86	0.10
14	3,4-di-CMe_3	8.11	8.18	−0.07	−0.20	0.10

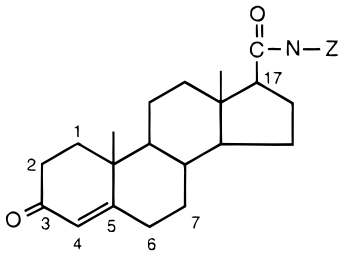
[a] Data points not included in deriving equation.

compounds have varying groups on the phenyl ring attached to the amide at C-17. The electron-donating groups enhance the activity, but the substituents at the second position of the phenyl ring have a negative MR effect.

IV. Summary

To summarize, 5α-reductase exists as two isozymes. Both cause reduction of testosterone to dihydroxytestosterone. To inhibit this reduction, it is necessary to inhibit both of the isozymes. Although action of both of the isozymes is the same on testosterone, they differ in tissue distribution and also there is some difference in the amino acid sequence at the binding sites. 3BHSD is a potent enzyme involved in the biosynthesis of steroids. In addition to the potency versus both isozymes of 5AR, selectivity versus human adrenal 3BHSD has been determined since inhibition of this enzyme would block a major steroid pathway.[38,53−55] The similarity in the transition states catalyzed by 5AR and 3BHSD make this an important selectivity criteria for most 5AR inhibitors.[33,54]

From our analysis of the quantitative structure−activity relationship of various structures toward binding affinity to these enzymes, we can draw some generalizations:



(1) Four or six azasteroids are suitable molecules to inhibit all three types of enzymes, as all the molecules except estrien-3-carboxylic acids are azasteroids, showing inhibitory activity.

(2) From eqs 2, 6, 7, 8, and 10, obtained for the inhibition of both of the isozymes, it appears that there is a hydrophobic region where C-17 substituents interact while it is mostly steric interaction at the other positions. It is observed that Clog *P* appears to be important for the activity in all those series of compounds where variation is introduced in the derivatives by different groups attached to C-17. This again confirms that the presence of a lipophilic group at C-17 is very useful.[56,57]

(3) For inhibiting human 5α-reductase Types 1 and 2, the α−β unsaturated ketone, especially with the ketonic group at C-3 and unsaturation at C-4, have a positive contribution, consistent with the observations made earlier,[51,56,57] whereby a conjugated system at C-3, -4, -5 shows good activity. A double bond at C-1 in addition to C-4 seems to be highly detrimental to the activity as shown by eqs 2 and 10. It may be further noted that compounds having a double bond at C-1 are reported to be irreversible inhibitors of the enzyme.[37,58] The kinetic isotope studies are consistent with addition of an enzyme-based or associated nucleophile to the $\Delta^{1,2}$ bond in an irreversible step.[59] This is further confirmed by Bull et al.[60] in their study carried out for mechanism-based inhibition of human steroid 5α-reductase by finasteride.

(4) Any substituent at C-4 appears to cause steric hindrance in binding to the receptor by virtue of its

length as shown by eqs 1 and 9. However, less bulky groups seem to be well tolerated as indicated by eqs 3−5 and 10 where the compounds with substituents such as Me, Cl, and Br at the 4 position show good activity.

(5) For Type 1 enzyme, substituents at C-6 cause steric hindrance and show a bilinear influence by the Verloop sterimol parameter, eq 1. Substituents at this position also show detrimental effects on the activity indicated by the negative coefficients of the Verloop L_Y sterimol parameter in eq 2. Groups at C-7 also seem to be having a linear steric hindrance in binding to the receptor. It is again the B5 sterimol parameter which means substituents lower the activity with an increase in the volume and length, eq 3. There appears to be a small electronic effect due to groups at 4-N-X and 7-Y as exhibited by eq 3. Electron-donating groups via field/inductive effects seem to be favorable to activity.

For Type 2, any substituent at C-6 decreases the activity. The effect of substituents at C-7 for Type 2 could not be predicted because of the nonavailability of data.

(6) The presence of the −CON− group at C-17 is useful as shown by the positive coefficient of I_{17} in eq 10. In addition, an aryl group attached to CON− potentiates the activity as shown by eqs 6−8. The aryl ring probably binds in the hydrophobic site of the enzyme, and this binding is positively influenced by the presence of substituents at the ortho position of the aryl ring, eqs 6 and 8.

(7) Rat 5α-reductase is different from human 5α-reductase, as is evident from eqs 12a, 12b, and 13, where the presence of the −CON− group causes a decrease in the activity unlike 5 AR, eq 10. But presence of the CONH group is significant in enhancing the activity. The hydrophobicity is also important with an optimum value of 5.10. Here also the presence of a double bond at C-1 appears to be detrimental to the activity as shown by eqs 12a and 12b.

(8) In the case of 3BHSD, the major difference is observed with respect to substituents at C-17. Bulky groups at C-17 create steric hindrance to the binding, eq 14. Unlike 5α-reductase, the substituents at the ortho position of the phenyl ring attached to −CONH at C-17 have a negative effect on the activity, as seen by the negative coefficient of MR_2 that suggests molar refractivity lowers the activity, eq 16. However, like 5AR, less bulky groups such as Me and Cl at the 4 position seem to be well tolerated, as observed in eqs 14 and 15, and the presence of a double bond at C-1 is detrimental to the activity, eq 14.

None of the data sets have been ideally developed for QSAR analysis, but there are salient features that have been pointed out that could be taken advantage of in extending the present studies.

The important problem that remains to be defined is what the ideal log *P* value should be for using a drug for humans. The one commercial product Finasteride has a log *P* of 3.03 (measured), 3.01 (calculated). It lacks substituents in the 4 or 6 positions as we would expect from our QSAR studies. The *tert*-butyl group in this substance may be primarily for adjusting log *P*, as suggested by eqs 2, 6−8, 13, and 14.

Only in eqs 8 and 13 have log *P* values been established as about 5.1. The agreement between these values is interesting. This could set an upper limit on log *P* as far as the receptor goes. However, this might be too high for the best in vivo results. The log *P* value of Finasteride as mentioned above may be in line with the principle of minimal hydrophobicity in drug design.[61] That is, one should make compounds as hydrophilic as possible commensurate with efficacy. The catch in this statement is what does commensurate mean. Three aspects of a drug molecule are involved: (1) its affinity for a receptor; (2) its optimum log *P* for the random walk about the body to locate the receptor; and (3) its resistance to metabolism. For neutral molecules, log P_0 for the random walk seems to be 2.[61] However, this says little about what the optimum log *P* or π would be for the receptor. For Finasteride, the only drug for comparison, log *P* is 3, much lower than the value of 5 that we have found via our QSAR study. Testosterone has a measured value of 3.12 and a Clog *P* value of 3.22. Hence, this could seem, in a way, to be ideal. However, possibly making Finasteride more hydrophilic so that it could better displace testosterone from the receptor could be advantageous. While having a *tert*-butyl or phenyl group at C-17 does highlight a hydrophobic binding region, using a cyclohexyl or possibly an adamantyl group could increase the hydrophobicity without adverse steric effects. The measured log *P* for benzene is 2.13, and that for cyclohexyl is 3.44. Of course to offset this additional hydrophobicity one needs to attach polar substituents to another position on the drug to bring log *P* closer to 2. For instance, using cyclohexyl in the amide, 11-OH, 4-N-Me, 7-Me, the calculated log *P* is 2.72. We believe that the lower log *P* should provide better bioavailability, of course we are assuming no negative effect from the 11-OH.

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