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RESEARCH ARTICLE

An Insight into the Crystallographic Aspects of Androstanes

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Abstract: In this paper, an attempt has been made to carry out a crystallographic comparison of some geometrical and structural features for a series of androstane derivatives of steroids. Selected bond distances and bond angles of interest in a series of forty- five androstane derivatives have been discussed in detail, besides conformations of individual ring systems, their graphical presentation and their frequency of occurrence. Intra- and intermolecular interactions of the type X-H...A [X=C,O; A=O,Cl,Br,F] in androstane derivatives have been computed and discussed primarily on the basis of distance-angle scatter for better understanding of molecular packing in androstane derivatives.

Keywords: Steroids, Intermolecular interactions, Hydrogen bonding, Conformations

Introduction

Androstane molecule comprises of a four ring structure of which three are six- membered cyclohexane rings and one is five-membered cyclopentane ring with angular methyl groups located at C10 and C13 positions, respectively (Figure 1)[1]. The most important class of androstane-based steroids androgens which are primarily responsible for the production of masculinisation characterstics, *i.e*., they maintain the normal structure and function of the prostate gland and seminal vesicle; growth and pigmentation of the scrotum[2]. In addition, they influence the development of secondary male characterstics: hair distribution and deepening of voice. Administration of androgens results in retention of nitrogen, phosphorous and potassium together with a lowering of the respiratory quotient, which implies the use of body fat for protein biosynthesis[3].

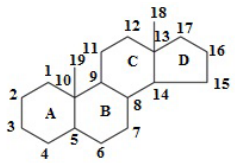
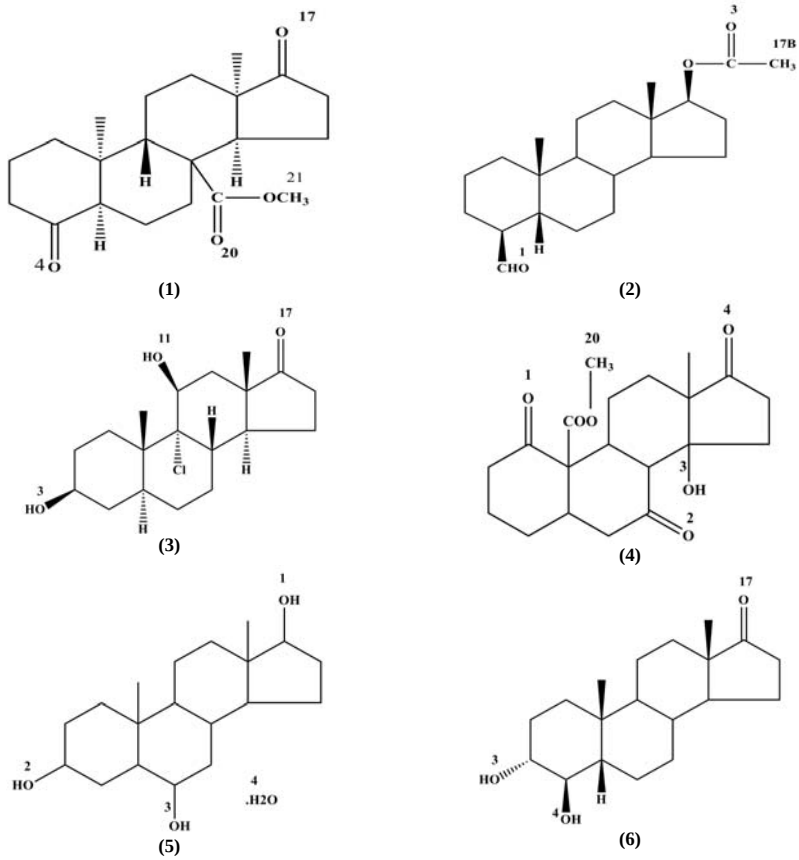
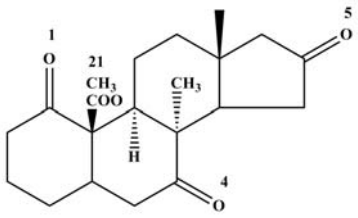


Figure 1. Basic androstane molecule (C19) with atomic numbering scheme

The major naturally occurring compounds that possess androgenic activity are testosterone, 5α-Dihydrotestosterone (5α-DHT) and 4-androstenedione. Structurally, testosterones are characterised by: a double bond at C4 and an oxo group at C3 position (b) a hydroxyl group at C17 (c) The absence of a double bond at C4 and presence of hydrogen atom at cis (C5) position, thus giving rise to 5α-DHT. Therefore, it is possible to correlate the structural features of androgens and their physiological actions as follows: for a C_{19} steroid to be androgen, a 17-oxygen function should be present with, either the 4-en-3-oxo configuration (as in testosterone) or a 3-oxo group and a saturated A- ring (as in 5α-DHT). If the 17-oxygen function is absent, as in 4, 16-androstadien-3-one, androgenic activity is completely lost[4]. If oxidation of the 17β-hydroxyl group occurs to give a 17-oxosteroid, as in the case of testosterone being converted to 4-androstenedione or -DHT to 5α-androstane-3, 17-dione, then androgenecity be reduced or lost completely. The 3-oxo-group is also necessary for androgenecity, even though the 17β-hydroxyl is intact in this case[5].

The present work provides a comprehensive information about biological activity, structural features and packing interactions/hydrogen bonding in androstane derivatives. Here, we have identified a series of forty- five derivatives of androstane from the literature (CCDC). The chemical structure of each molecule (1-45) is shown in Figure 2. The reference code, chemical name, chemical formula, molecular weight and published reference[6-41] of each molecule is presented in Table 1.





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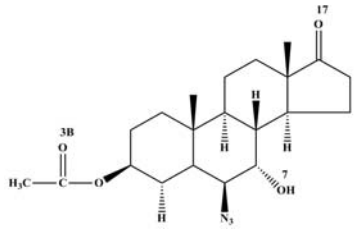

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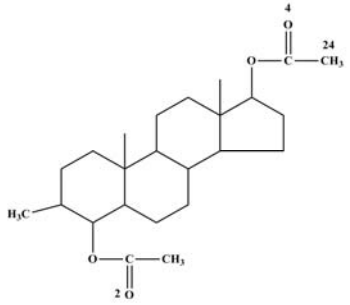

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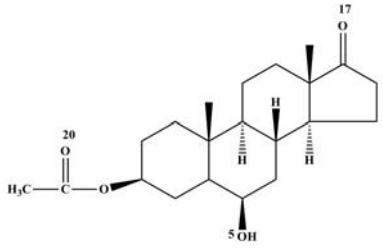

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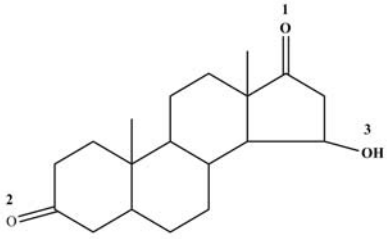

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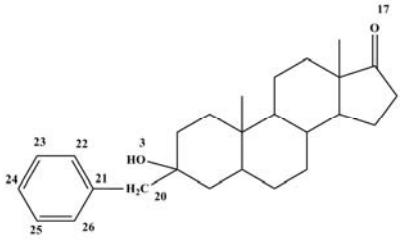

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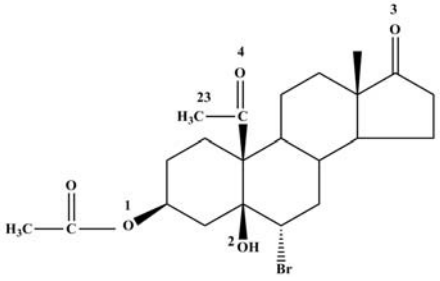

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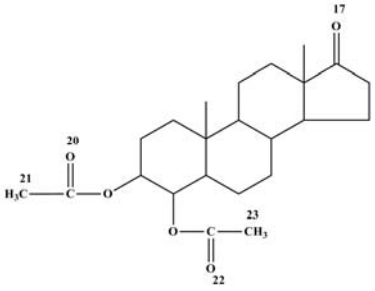

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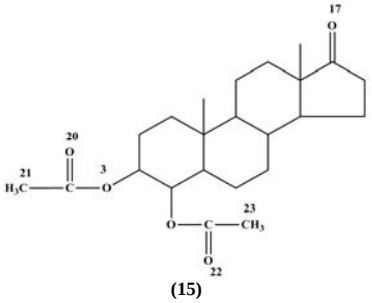

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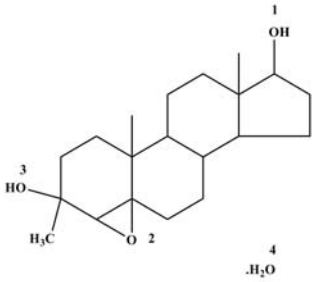

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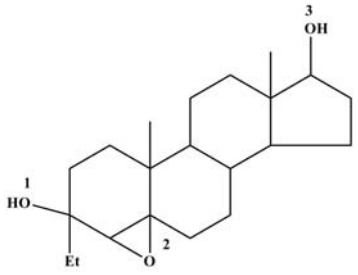

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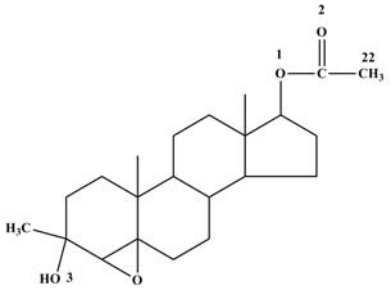

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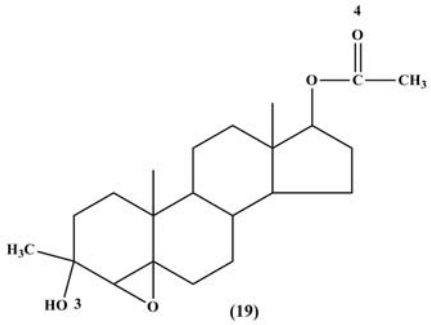

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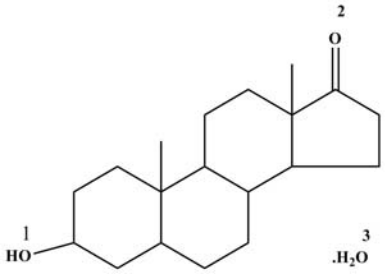

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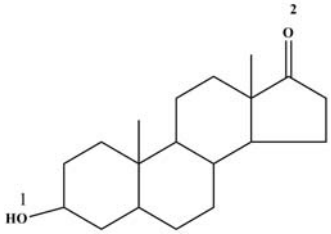

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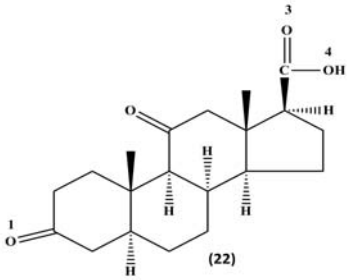

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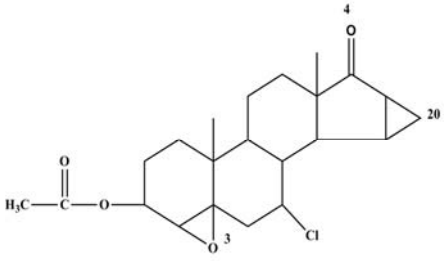

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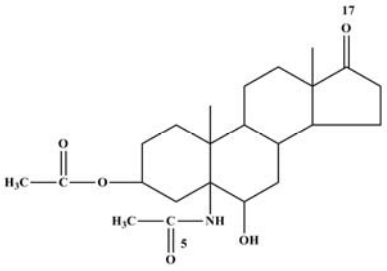

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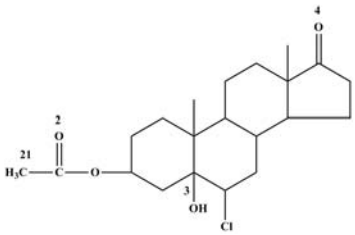

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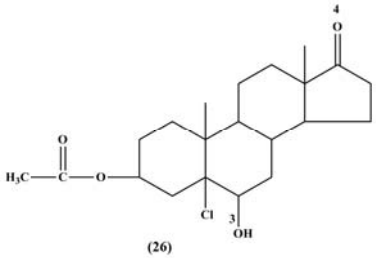

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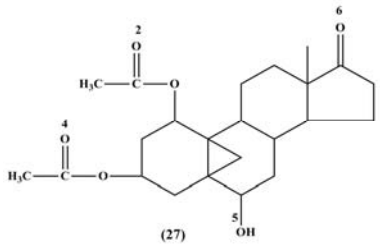

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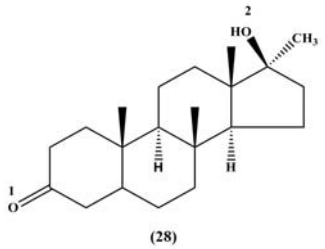

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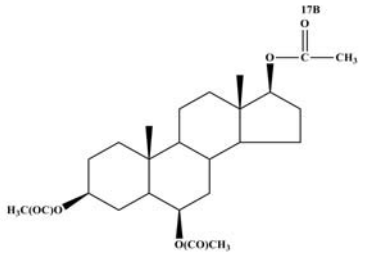

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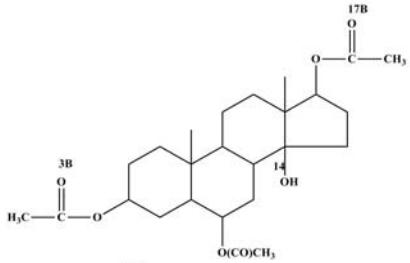

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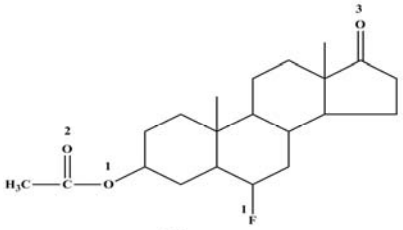

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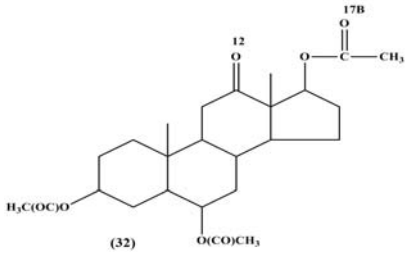

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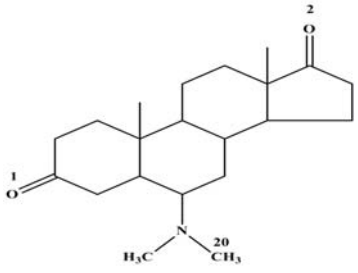

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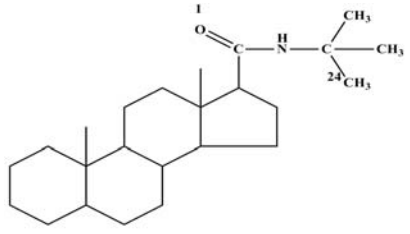

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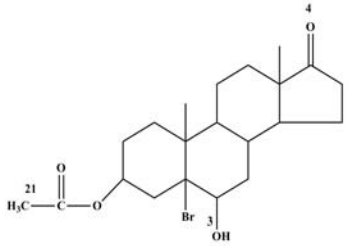

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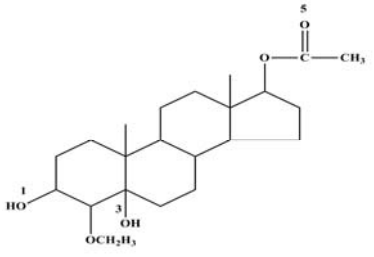

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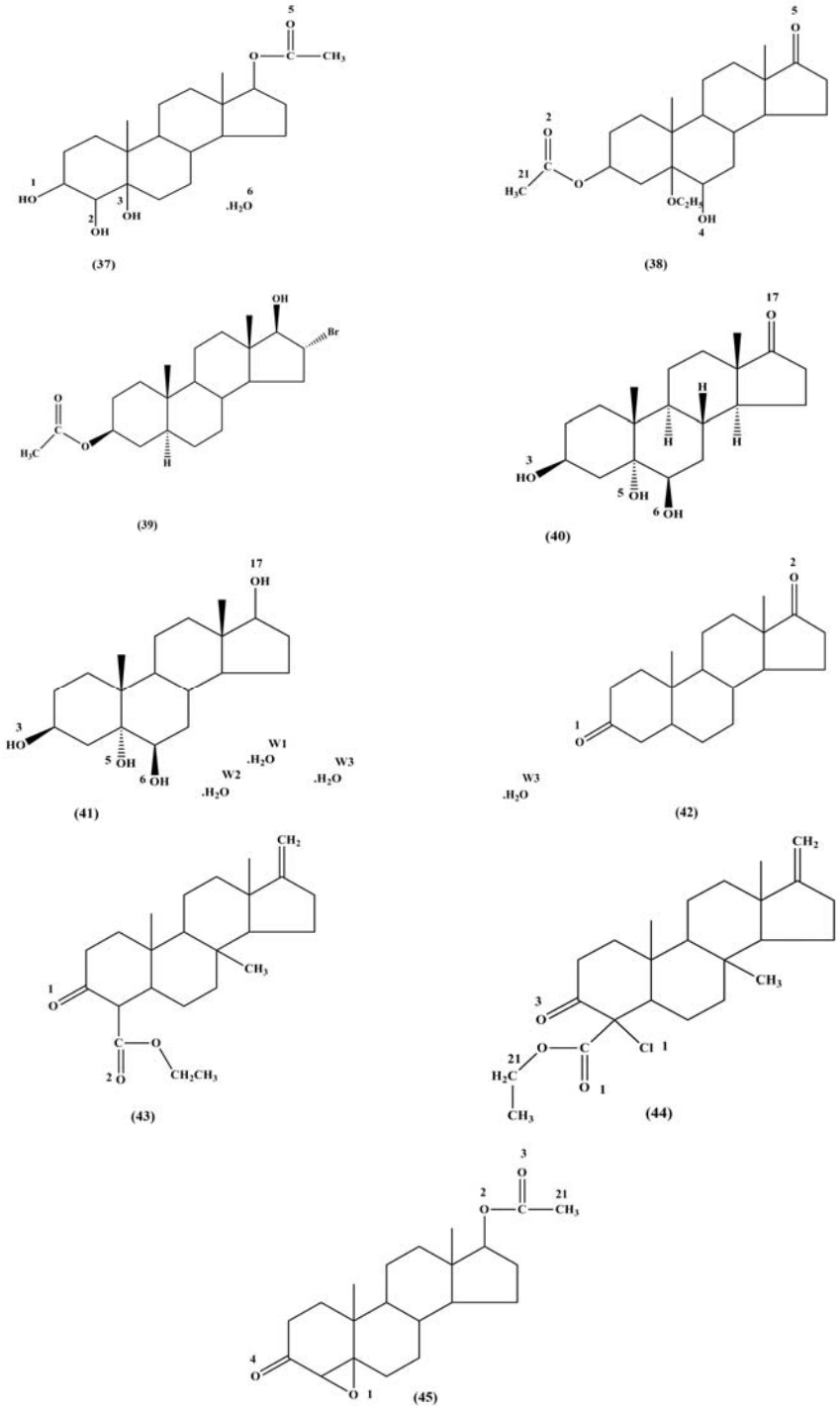

Figure 2. Chemical structures of molecules (1-45)

Table 1. CSD code, chemical name, chemical formula, molecular wt. and reference of molecules (1-45)

Molecule	Reference Code	Chemical Name	Chemical Formula	Molecular Weight (amu)	Reference
M-1	LOSNAI	trans-anti-trans-anti-cis-4,17-Dioxoandrostane-8-carboxylic acid methyl Ester	$C_{21}H_{30}O_4$	346.45	(a)
M-2	MOVFOS	4β–formyl-17β-acetoxy-5β-androstane	$C_{22}H_{34}O_3$	346.49	(b)
M-3	GURFEE	9α-Chloro-3β,11β-dihydroxy-5α-androstan-17-one	$C_{19}H_{29}Cl_1O_3$	340.87	(c)
M-4	MOSYEY	rac-(5β,8α,9α,10β,13α,14α)-Methyl 14-hydroxy-1,7,17-trioxoandrostane-10-carboxylate	$C_{20}H_{26}O_6$	362.41	(d)
M-5	IKIRID	3α,6β,17β-Trihydroxy-5β-androstane monohydrate	$C_{19}H_{32}O_3,H_2O_1$	326.46	(e)
M-6	VADWAZ	3α,4β-Dihydroxy-5β-androstan-17-one	$C_{19}H_{30}O_3$	306.43	(f)
M-7	AKAJUR	methyl 1,8-dimethyl-7,16-dioxoandrostan-19-oate	$C_{21}H_{28}O_5$	360.43	(g)
M-8	IZAXEM	6β-Azido-7α-hydroxy-17-oxo-5α-androstan-3β-yl acetate	$C_{21}H_{31}N_3O_4$	389.49	(i)
M-9	LAFCOL	4β,17β-Diacetoxy-3α-methyl-5β-androstane	$C_{24}H_{38}O_4$	390.54	(j)
M-10	XAMCAQ	17-Oxo-5β-hydroxyandrostan-3β-yl acetate	$C_{21}H_{32}O_4$	348.47	(k)
M-11	XAPXIW	15α-Hydroxy-1α-methyl-5α-androstane-3,17-dione	$C_{20}H_{30}O_3$	318.44	(l)
M-12	KESKAV	3β-hydroxy-3α-phenyl-methyl-5α-androstan-17-one	$C_{26}H_{36}O_2$	380.548	(m)
M-13	LAPRUQ	3β,19-Diacetoxy-6α-bromo-5-hydroxy-17-oxo-5β-androstane	$C_{23}H_{33}Br_1O_6$	485.4	(n)
M-14	FEFKEH	17-Oxo-5α-androstane-3α,4β-diyl diacetate unknown solvate	$C_{23}H_{34}O_5$	390.50	(o)
M-15	FEFROY	17-Oxo-5β-androstane-3α,4β-diyl diacetate	$C_{23}H_{34}O_5$	390.50	(p)
M-16	FIRXOU	3β,17β-Dihydroxy-4α,5α-epoxy-3α-methylandrostane monohydrate	$C_{20}H_{32}O_3,H_2O_1$	338.47	(q)

M-17	FIRXIO	3β,17β-Dihydroxy-4β,5β-epoxy-3α-ethylandrostane	$C_{21}H_{34}O_3$	334.48	(r)
M-18	FIRXUA	17β-Acetoxy-4β,5β-epoxy-3α-hydroxy-3β-methylandrostane	$C_{22}H_{34}O_4$	362.49	(s)
M-19	FIRXUA01	17β-Acetoxy-4β,5β-epoxy-3α-hydroxy-3β-methylandrostane	$C_{22}H_{34}O_4$	362.49	(t)
M-20	ANDOON05	5α-Androstane-3α-ol-17-one hemihydrates	$C_{19}H_{30}O_2$,0.5(H_2O_1)	598.88	(u)
M-21	ANDOON06	5α-Androstane-3α-ol-17-one	$C_{19}H_{30}O_2$	290.43	(v)
M-22	CELKUA	(+)-3,11-Dioxo-5α-androstanecarboxylic acid	$C_{20}H_{28}O_4$	332.42	(w)
M-23	QEXPEP	3β-Acetoxy-7α-chloro-5, 6β-epoxy-15β,16β-methyl-ene-5β-androstan-17-One	$C_{22}H_{29}Cl_1O_4$	392.90	(x)
M-24	MIGTAY	5α-Acetamido-6β-hydroxy-17-oxoandrostan-3β-yl acetate	$C_{23}H_{35}N_1O_5$	405.52	(y)
M-25	XEYTOL	3β-Acetoxy-6α-chloro-5β-hydroxyandrostan-17-one	$C_{21}H_{31}Cl_1O_4$	382.91	(z)
M-26	XIFSIP	3β-Acetoxy-5α-chloro-6β-hydroxyandrostan-17-one	$C_{21}H_{31}Cl_1O_4$	382.91	(aa)
M-27	XIGHOL	5,19-Cyclo-1α,3β-diacetoxy-6β-hydroxyandrostan-17-one	$C_{23}H_{32}O_6$	404.49	(ab)
M-28	YOFWOG	17β-Hydroxy-17α-methyl-5α-androstan-3-one	$C_{20}H_{32}O_2$	304.47	(ac)
M-29	EGAHEA	3β,6α,17β-Triacetoxy-5α-androstane	$C_{25}H_{38}O_6$	434.55	(ad)
M-30	EGAHIE	3β,6α,17β-Triacetoxy-5α-androstan-14α-ol	$C_{25}H_{38}O_7$	450.55	(ae)
M-31	AGAVEK	3β-Acetoxy-6α-fluoro-5α-androstan-17-one	$C_{21}H_{31}F_1O_3$	350.46	(af)
M-32	EHAKAA	3β,6α,17β-Triacetoxy-5α-androstan-12-one	$C_{25}H_{36}O_7$	448.54	(ag)
M-33	YOPYIM	4α-(Dimethylamino)-5α-androstane-3,17-dione	$C_{21}H_{33}N_1O_2$	331.48	(ah)
M-34	EHABUL	(5R,8R,9S,10S,13S,14S,17S) -N-t-Butyl-5α-androstane-17β-Carboxamide	$C_{24}H_{41}N_1O_1$	359.58	(ai)
M-35	LALCEI	3β-Acetoxy-5α-bromo-6β-hydroxyandrostan-17-one	$C_{21}H_{31}Br_1O_4$	427.36	(aj)

M-36	GAFSEN	4β-Ethoxy-3β,5α-dihydroxyandrostan-17β-yl acetate	$C_{23}\ H_{38}\ O_5$	394.53	(ak)
M-37	LAWBIW	3β,4β,5α-Trihydroxyandrostan-17β-yl acetate monohydrate	$C_{21}\ H_{34}\ O_5, H_2\ O_1$	384.5	(al)
M-38	GAFSOX	5α-Ethoxy-6β-hydroxy-17-oxoandrostan-3β-yl acetate	$C_{23}\ H_{36}\ O_5$	392.52	(am)
M-39	KUSNES	16α-Bromo-17β-hydroxy-5α-androstan-3β-yl acetate	$C_{21}\ H_{33}\ Br_1\ O_3$	413.38	(an)
M-40	URAJON	3β,5α,6β-Trihydroxyandrostan-17-one	$C_{19}\ H_{30}\ O_4$	322.43	(ao)
M-41	EVARUP	Androstane-3β,5α,6β,17β-tetrol trihydrate	$C_{19}\ H_{32}\ O_4, 3(H_2\ O_1)$	378.49	(ap)
M-42	CIGQAM	(+)-Androstane-3,17-dione	$C_{19}\ H_{28}\ O_2$	288.41	(aq)
M-43	RETKOS	Ethyl 8-methyl-17-methylene-3-oxoandrostane-4-carboxylate	$C_{24}\ H_{36}\ O_3$	372.53	(ar)
M-44	RETKUY	Ethyl 4-chloro-8-methyl-17-methylene-3-oxoandrostane-4-carboxylate	$C_{24}\ H_{35}\ Cl_1\ O_3$	406.97	(as)
M-45	ZILKEM	17β-acetoxy-4,5-epoxy-5α-androstan-3-one	$C_{21}\ H_{30}\ O_4$	346.45	(at)

Comparative geometrical parameters

Bond distances and bond angles

Most of the molecules in the present study have substituents at the C3, followed by C4 and C6 positions. The substituents at these positions of the steroid nucleus causes significant changes in bond distances in ring A and B, depending upon whether the bond C2-C3/C3-C4, C3-C4/C4-C5, C5-C6/C6-C7 is single or double in nature . Therefore, it is of interest to investigate the bond lengths C2-C3, C3-C4, C4-C5, C5-C6 and C6-C7 and the bond angles C2-C3-C4, C3-C4-C5 and C5-C6-C7, respectively (Table 2). The bond distances $C2(sp^3)$-$C3(sp^3)$ lie in the range 1.492–1.540 Å (average = 1.514 Å) but for the molecules 23 (1.492Å) and 39 (1.495 Å)[39'(1.494 Å)] have values shorter than the standard value of 1.533Å[51]. The bond distances $C3(sp^3)$-$C4(sp^3)$ lie in the range 1.493-1.541 Å (average value 1.516 Å). However, these values in case of molecule 29(1.497 Å) and 35(1.493 Å) are significantly different[42] from the accepted value of 1.533 Å. The deviation of bond distances $C2(sp^3)$-$C3(sp^3)$ and $C3(sp^3)$-$C4(sp^3)$ could be due to the effect of functional groups located at C3 which invariably are involved in C-H...O/O-H...O intra/intermolecular interactions. The $C2(sp^3)$-$C3(sp^2)$/ $C2(sp^2)$-$C3(sp^3)$ bond distances in molecules having substitutions at C3 lie in the range 1.48-1.510 Å (average value 1.495 Å), whereas the bond distances $C3(sp^3)$-$C4(sp^2)$/ $C3(sp^2)$-$C4(sp^3)$ lie in the range 1.482-1.541 Å (average value 1.509 Å). It is probably the involvement of O atom of the keto group in C-H...O/O-H...O intra/intermolecular interactions that causes deviation in the corresponding bond distances. The bond distances $C5(sp^3)$-$C6(sp^3)$ and $C6(sp^3)$-$C7(sp^3)$ lie in the range 1.454-1.548 Å (average value 1.526 Å) and 1.49-1.53 Å (average value 1.51 Å), respectively.

Table 2. C2-C3, C3-C4, C4-C5, C5-C6 and C6-C7 bond distances (Å) and C2-C3-C4, C3-C4-C6 and C5-C6-C7 bond angles (°) for molecules (1-45)

	Bond Distance(Å)								Bond Angle(°)				
Mol.	[C 2 - C3]		[C 3 - C4]		[C4 - C5]		[C5-C6]	[C6-C7]	C3		C4		C6
	sp3-sp3	sp3- sp2/ sp2 - sp3	sp3 - sp3	sp3 - sp2/ sp2- sp3	sp3 - sp3	sp3-sp2/ sp2-sp3	sp3-sp3	sp3-sp3	sp3	sp2	sp3	sp2	sp3
M-1	-	-	-	1.496	-	1.504	-	-	-	-		115	-
M-2	-	-	1.541	-	1.539	-	-	-	-	-	112	-	-
M-3	1.506	-	1.517	-	-	-	-	-	111	-	-	-	-
M-4	-	-	-	-	-	-	-	-	-	-	-	-	-
M-5	1.513	-	1.51	-	-	-	1.527	1.524	111	-	-	-	112
M-6	1.513	-	1.51	-	1.537	-	-	-	112	-	112	-	-
M-7	-	-		-	-	-	-	-	-	-	-	-	-
M-8	1.507	-	1.514	-	-	-	1.522	1.528	112	-	-	-	110.7
M-9	1.532	-	1.518	-	1.53	-	-	-	109	-	115	-	-
M-9'	1.527	-	1.521	-	1.538	-	-	-	109	-	114	-	-
M-10	1.513	-	1.518	-	-	-	-	-	112	-	-	-	-
M-10'	1.509	-	1.514	-	-	-	-	-	113	-	-	-	-
M-11	-	1.488	-	1.487	-	-	-	-	-	116	-	-	-
M-12	1.527	-	1.521	-	-	-	-	-	109	-	-	-	-
M-12'	1.531	-	1.526	-	-	-	-	-	109	-	-	-	-
M-13	1.521	-	1.509	-	-	-	1.545	1.522	112	-	-	-	115.1
M-14	1.511	-	1.52	-	1.523	-	-	-	112	-	113	-	-
M-15	1.502	-	1.505	-	1.529	-	-	-	112	-	113	-	-
M-16	1.54	-	1.522	-	-	-	-	-	112	-	-	-	-
M-17	1.531	-	1.521	-	1.49	-	-	-	111	-	123	-	-
M-17'	1.537	-	1.52	-	1.478	-	-	-	112	-	124	-	-
M-18	1.53	-	1.523	-	-	-	-	-	112	-	-	-	-
M-19	1.507	-	1.514	-	-	-	-	-	112	-	-	-	-
M-20	1.519	-	1.521	-	-	-	-	-	110	-	-	-	-
M-20'	1.521	-	1.515	-	-	-	-	-	111	-	-	-	-
M-21	1.507	-	1.525	-	-	-	-	-	111	-	-	-	-
M-22	-	1.5		1.504	-	-	-	-	-	116	-	-	-
M-23	1.492	-	1.503	-	-	-	1.454	1.49	110	-	-	-	121.2
M-24	1.517	-	1.52	-	-	-	1.548	1.515	113	-	-	-	111.5
M-25	1.51	-	1.509	-	-	-	1.52	1.502	112	-	-	-	114.7
M-26	1.519	-	1.507	-	-	-	1..530	1.515	113	-	-	-	111.7
M-26'	1.509	-	1.515	-	-	-	1.532	1.523	113	-	-	-	111.6
M-27	1.51	-	1.513	-	-	-	1.526	1.524	112	-	-	-	113.8
M-28	-	1.499		1.499	-	-	-	-	-	116		-	-
M-29	1.501	-	1.497	-	-	-	1.519	1.51	112	-	-	-	111.8
M-30	1.506		1.519				1.513	1.511	111				112.1

Contd…

M-31	1.518		1.522				1.524	1.516	112				112.1
M-32	1.508	-	1.514	-	-	-	1.526	1.511	111	-	-	-	111.2
M-33	-	1.5	-	1.533	-	-	-	-	-	116	-	-	-
M-34	-	-	-	-	-	-	-	-	-	-	-	-	-
M-35	1.519	-	1.493	-	-	-	1.541	1.53	114	-	-	-	112.2
M-35'	1.517	-	1.527	-	-	-	1.541	1.494	111	-	-	-	111.5
M-36	1.509	-	1.528	-	1.525	-	-	-	111	-	111	-	-
M-37	1.522	-	1.522	-	1.535	-	-	-	112	-	113	-	-
M-38	1.524	-	1.52	-	-	-	1.54	1.514	112	-	-	-	111.5
M-39	1.495	-	1.514	-	-	-	-	-	112	-	-	-	-
M-39'	1.494	-	1.518	-	-	-	-	-	113	-	-		--
M-40	1.51	-	1.518	-	-	-	1.533	1.522	112	-	-		111
M-41	1.513	-	1.52	-	-	-	1.535	1.52	112	-	-		110.4
M-42	-	1.513	-	1.51	-	-	-	-	-	111	-	-	-
M-43	-	1.5	-	1.534	-	-	-	-	-	115	-	-	-
M-44	-	1.48	-	1.541	1.544	-	-	-	-	114	114	-	-
M-45	-	1.502	-	1.482	1.481	-	-	-	-	119	120	-	-

indicates the absence of a particular bond/angle; ' indicates second independent molecule

The substitution of a group at the C3 position also causes a significant change in the value of bond angle C2-C3-C4 in ring A, depending upon whether C3 is sp^3 or sp^2 hybridized. The bond angle C2-C3-C4 in molecules with a substituent at the C3(sp^3) position varies from 108.89 to 112.95(°) (average being 111.57(°)). The bond angle C2-C3-C4 with C3(sp^3) in all molecules except 3(110.6°), 5(110.73°), 9(108.89°)[9'(109.16°)] 12(109.49°), [12'(109.33°)], 20(110.3°) and 21(110.8°) shows a significant deviation from the tetrahedral value of 109.46°. The deviation in the C2-C3-C4 bond angle in these molecules is caused by O-H...O intermolecular interactions, which are probably due to the presence of different groups at the C3 position. The bond angle C2-C3(sp^2) -C4 in molecules with a substituent at the C3 position varies from 110.73 to 118.52° (average value 115.09°). The bond angle C2-C3(sp^2) -C4 in molecules 42 (110.73°), 43(114.95°), 44(113.6°), shows some deviation from the value of 120.0° for sp^2-type hybridization. The presence of a ketone group makes the C2-C3-C4 bond angle deviate significantly and it also results in the occurrence of C-H...O/O-H...O intra- and intermolecular interactions. The bond angle C5-C6-C7 in molecules with a substituent at the C6(sp^3) position varies from 110.36 to 115.1° (average value 112.55°).

Ring conformations and their graphical representations

Asymmetry parameters (ΔC_2 and ΔC_S)[43] play an important role in describing the conformation of five- and six-membered moieties of steroidal molecules. The asymmetry parameters have been calculated for the individual ring systems of all the molecules (1-45) and their detailed analysis shows the existence of different types of conformations. These conformations as obtained for individual ring systems are presented in Table 3.

The following observations can be made from the different ring conformations as adopted by individual ring systems of molecules (1-45): The incidence of occurrence of a chair conformation in ring A is quite large (83.01%). Ring A in molecule (16), (17)' and (18) occurs in the sofa conformation with asymmetric parameters (ΔC_2 = 23.04, ΔC_S = 4.97), (ΔC_2 = 21.70, ΔC_S = 6.314), (ΔC_2 = 22.50, ΔC_S = 5.81) respectively, although these are saturated rings. This type of behaviour by the saturated rings may be due to the presence of an epoxy

ring between C4 and C5. Ring A and B of molecule (27) adopts half-chair conformation which may be due to the presence of a cyclopropane ring between C5 and C10. In most of the molecules, ring B adopts chair conformation. The incidence of occurrence of a chair conformation in ring C is quite large. Ring D adopts different conformations (envelope, half-chair and intermediate between the two) in different molecules.

Table 3. Different types of conformations in the individual ring systems (molecules 1-45)

Molecule	Ring A *(conformation)*	Ring B *(conformation)*	Ring C *(conformation)*	Ring D *(conformation)*
M-1	Chair	Chair	Distorted Chair	Intermediate between envelope and Half- chair
M-2	Chair	Chair	Chair	Half- chair
M-3	Chair	Chair	Chair	Envelope
M-4	Chair	Chair	Distorted chair	Envelope
M-5	Chair	Chair	Chair	Half-chair
M-6	Chair	Chair	Chair	Half- chair
M-7	Distorted chair	Chair	Distorted chair	Half- chair
M-8	Chair	Chair	Chair	Envelope
M-9	Chair	Chair	Chair	Half- chair
M-9'	Chair	Chair	Chair	Half- chair
M-10	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-10'	Chair	Chair	Chair	Envelope
M-11	Chair	Chair	Chair	Half-chair
M-12	Chair	Chair	Chair	Envelope
M-12'	Chair	Chair	Chair	Envelope
M-13	Chair	Chair	Chair	Envelope
M-14	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-15	Chair	Chair	Chair	Envelope
M-16	Sofa	Chair	Chair	Envelope
M-17	Half-chair	Chair	Chair	Envelope
M-17'	Sofa	Chair	Chair	Envelope
M-18	Sofa	Chair	Chair	Envelope
M-19	Intermediate between envelope and half-chair	Chair	Chair	Envelope
M-20	Chair	Chair	Chair	Envelope
M-20'	Chair	Half-chair	Chair	Envelope
M-21	Chair	Chair	Chair	Half-chair
M-22	Chair	Chair	Chair	Half-chair
M-23	Distorted chair	Sofa	Chair	Envelope
M-24	Chair	Chair	Chair	Envelope
M-25	Chair	Chair	Chair	Distorted Envelope
M-26	Chair	Chair	Chair	Envelope
M-26'	Chair	Chair	Chair	Intermediate between envelope and half-chair

M-27	Half-chair	Half-chair	Chair	Envelope
M-28	Chair	Chair	Chair	Half-chair
M-29	Chair	Chair	Chair	Envelope
M-30	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-31	Chair	Chair	Chair	Envelope
M-32	Chair	Chair	Chair	Envelope
M-33	Chair	Chair	Chair	Envelope
M-34	Chair	Chair	Chair	Half-chair
M-35	Chair	Chair	Chair	Envelope
M-35'	Chair	Chair	Chair	Envelope
M-36	Chair	Chair	Chair	Envelope
M-37	Chair	Chair	Chair	Envelope
M-38	Chair	Chair	Chair	Envelope
M-39	Chair	Chair	Chair	Envelope
M-39'	Chair	Chair	Chair	Envelope
M-40	Chair	Chair	Chair	Envelope
M-41	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-42	Chair	Chair	Chair	Envelope
M-43	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-44	Chair	Chair	Distorted chair	Half-chair
M-45	Half-chair	Chair	Chair	Intermediate between envelope and half-chair

The relative frequency of various types of conformations occurring in six-membered and five-membered rings in molecules (1-45) are shown in Figure 3(a, b). The incidence of occurrence of the three six-membered rings in the chair conformation (normal as well as distorted-chair) is 93.08%, followed by the half-chair and sofa conformations (3.14% and 2.50%, respectively). Similarly, for the five membered rings, the incidence of occurrence of (envelope and distorted envelope) conformation is 62.2%, followed by half-chair and intermediate between half-chair and envelope conformations (22.6 and 15.0%, respectively).

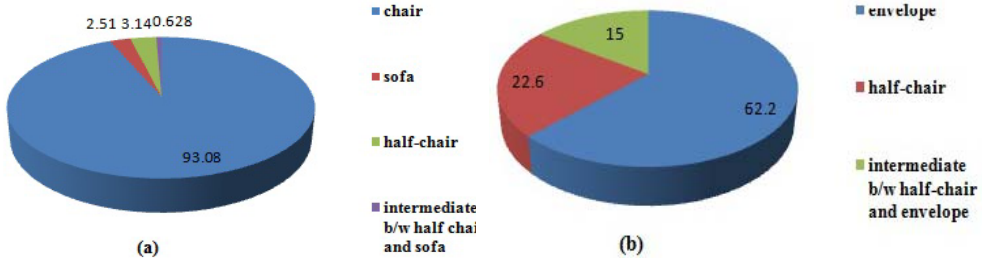

Figure 3. (a) Relative frequency of occurrence (in %) for various types of conformations in six-membered rings A, B and C (molecules 1-45); (b) Relative frequency of occurrence (in %) for various types of conformations in five-membered rings D (molecules 1-45)

Structure activity relationship

The biological activity spectra for substances are correlated on SAR base (Structure-activity relationships data and knowledge base), which provides different P_a and P_i values. Based on MNA(Multilevel Neighbourhood of atoms) descriptors for active and inactive compounds,

the two probabilities have been calculated for each activity: P_a - the probability of compound being active and P_i - the probability of compound being inactive. The influence of these descriptors can be positive (if they are found in compounds with particular activity) or negative (if they are found in compounds without the particular activity) or neutral. The P_a and P_i values for the molecules (1-45) have been computed by the PASS software[44] and are given in the Table 4.

Table 4. Pa and P_i values for the molecules (1-45)

Molecule	Antipruritic	Diuretic	Anticarino-genic	Dermatologic	Antiinflam-matory	Antisebor-rheic	Antisecretoric
	Pa > Pi	Pa > Pi	Pa > Pi	Pa > Pi	Pa > Pi	Pa > Pi	Pa > Pi
M-1	-	-	-	-	-	-	-
M-2	0.388 > 0.016	0.254 > 0.141	0.217 > 0.103	0.775 > 0.005	0.348 > 0.029	0.814 > 0.016	0.333 > 0.079
M-3	0.798 > 0.004	0.281 > 0.103	0.281 > 0.067	0.843 > 0.004	0.937 > 0.004	0.850 > 0.010	0.458 > 0.039
M-4	0.602 > 0.016	0.447 > 0.008	0.284 > 0.065	0.550 > 0.022	0.335 > 0.039	0.841 > 0.012	0.468 > 0.037
M-5	0.691 > 0.009	0.400 > 0.021	0.462 > 0.023	0.723 > 0.006	0.541 > 0045	0.893 > 0.005	0.729 > 0.008
M-6	0.732 > 0.006	0.361 > 0.036	0.443 > 0.025	0.650 > 0.011	0.404 > 0.009	0.889 > 0.005	0.672 > 0.012
M-7	0.580 > 0.019	0.355 > 0.016	0.345 > 0.043	0.627 > 0.013	0.499 > 0.057	0.780 > 0.023	0.529 > 0.025
M-8	0.670 > 0.010	0.239 > 0.057	0.245 > 0.085	0.520 > 0.028	0.308 > 0.067	0.349 > 0.107	0.199 > 0.168
Mol 9	0.661 > 0.010	0.259 > 0.043	0.210 > 0.109	0.843 > 0.004	0.786 > 0.008	0.887 > 0.005	0.546 > 0.023
M-10	0.689 > 0.009	0.305 > 0.023	0.430 > 0.026	0.640 > 0.012	0.429 > 0.007	0.862 > 0.008	0.520 > 0.026
M-11	0.762 > 0.005	0.236 > 0.060	0.312 > 0.054	0.936 > 0.003	0.057 > 0.002	0.932 > 0.003	0.526 > 0.026
M-12	0.698 > 0.008	0.223 > 0.070	0.231 > 0.093	0.735 > 0.006	0.525 > 0.050	0.787 > 0.021	0.440 > 0.045
M-13	0.529 > 0.029	-	0.207 > 0.112	0.737 > 0.006	0.257 > 0.161	0.497 > 0.073	0.253 > 0.118
M-14	0.651 > 0.011	0.189 > 0.106	0.224 > 0.099	0.878 > 0.004	0.780 > 0.008	0.737 > 0.031	0.603 > 0.017
M-15	0.878 > 0.004	0.189 > 0.106	0.224 > 0.099	0.878 > 0.004	0.307 > 0.069	0.737 > 0.031	0.603 > 0.017
M-16	0.642 > 0.007	0.526 > 0.005	0.218 > 0.103	0.773 > 0.005	0.060 > 0.002	0.896 > 0.005	0.769 > 0.005
M-17	0.642 > 0.007	0.526 > 0.005	0.218 > 0.103	0.773 > 0.005	0.060 > 0.002	0.896 > 0.005	0.769 > 0.005
M-18	-	-	-	-	-	-	-
M-19	-	-	-	-	-	-	-
M-20	0.755 > 0.005	0.469 > 0.007	0.568 > 0.014	0.701 > 0.008	0.384 > 0.014	0.904 > 0.004	0.641 > 0.014

M-21	0.755 > 0.005	0.469 > 0.007	0.568 > 0.014	0.701> 0.008	0.384 > 0.014	0..904 > 0.004	0.641> 0.014
M-22	0.431 > 0.010	0.452 > 0.008	0.222 > 0.100	0.812 > 0.004	0.392 > 0.012	0.881> 0.006	0.467 > 0.037
M-23	0.599 > 0.016	0.509 > 0.006	-	0.584 > 0.018	0.613 > 0.029	0.351> 0.106	0.228 > 0.140
M-24	0.751 > 0.005	0.290 > 0.027	0.351 > 0.041	0.629 > 0.013	0.405 > 0.009	0.480 > 0.076	0.449 > 0.042
M-25	0.696 > 0.008	0.346 > 0.017	0.220 > 0.101	0.552 > 0.022	0.300 > 0.079	0.742 > 0.030	-
M-26	0.796 > 0.004	-	0.423 > 0.027	0.747 > 0.005	0.769 > 0.009	0.866 > 0.008	0.374 > 0.066
M-27	0.595 > 0.016	0.268 > 0.037	0.330 > 0.048	0.627 > 0.013	0.397 > 0.097	0.792 > 0.021	0.216 > 0.152
M-28	-	-	-	-	-	-	-
M-29	0.691 > 0.009	0.331 > 0.019	0.211 > 0.109	0.891 > 0.004	0.545 > 0.044	0.871 > 0.007	0.559 > 0.022
M-30	0.601 > 0.016	0.325 > 0.020	-	0.679 > 0.009	0.236 > 0.230	0.809> 0.017	0.329 > 0.080
M-31	0.787 > 0.004	0.173 > 0.129	0.295 > 0.060	0.750 > 0.005	0.625 > 0.027	0.621 > 0.051	0.560 > 0.022
M-32	0.702 > 0.008	0.382 > 0.013	0.222 > 0.099	0.765 > 0.005	0.377 > 0.108	0.884 > 0.005	0.543 > 0.023
M-33	0.506 > 0.033	0.353 > 0.016	0.276 > 0.069	0.577 > 0.019	0.373 > 0.017	0.674 > 0.042	0.438 > 0.046
M-34	0.599 > 0.016	0.540 > 0.005	-	0.812 > 0.004	0.333 > 0.041	0.634 > 0.049	0.528 > 0.025
M-35	0.693 > 0.008	0.281 > 0.031	0.366 > 0.037	0.602 > 0.015	0.430 > 0.081	0.820 > 0.015	0.356 > 0.071
M-36	0.695 > 0.008	0.406 > 0.011	0.237 > 0.090	0.663 > 0.010	0.491> 0.060	0.840 > 0.012	0.339 > 0.077
M-37	0.707> 0.008	0.330 > 0.019	0.277> 0.068	0.754 > 0.005	0.484 > 0.062	0.880 > 0.006	0.344 > 0.075
M-38	0.645 > 0.012	0.336 > 0.018	0.315 > 0.053	0.537 > 0.025	0.453 > 0.072	0.759 > 0.027	0.343 > 0.076
M-39	0.558 > 0.023	-	0.198 > 0.122	0.610 > 0.014	0.349 > 0.029	0.820 > 0.015	0.473 > 0.035
M-40	0.518 > 0.031	0.253 > 0.047	0.363 > 0.038	0.580 > 0.018	0.322 > 0.051	0.768 > 0.025	0.221 > 0.148
M-41	0.552> 0.024	0.303> 0.024	0.372 > 0.036	0.617 > 0.014	0.461 > 0.069	0.868 > 0.007	0.454 > 0.041
M-42	0.687 > 0.009	0.576 > 0.005	0.372 > 0.036	0.770 > 0.005	0.366 > 0.113	0.931 > 0.003	0.650 > 0.014
M-43	0.600 > 0.016	0.262 > 0.040	0.175 > 0.152	0.797 > 0.004	0.471 > 0.066	0.475 > 0.077	0.758 > 0.005
M-44	0.640 > 0.012	0.258> 0.044	-	0.778 > 0.005	0.408 > 0.091	0.576 > 0.059	0.654 > 0.013
M-45	0.671 > 0.010	0.618 > 0.004	0.191 > 0.130	0.703 > 0.008	0.522 >0.050	0.836 > 0.012	0.775 > 0.005

Indicates the absence of a particular type of activity

A majority of the androstane derivatives appear to possess high antiprurtic and antiseborrheic activity while anti-inflammatory activity is not that significant. The diuretic and anticarcinogenic activity in most of the androstane derivatives is found to be significantly low while the dermatological activity is predominantly high.

Hydrogen bonding

Hydrogen bonds have been known since the beginning of this century, but were brought into the common body of knowledge by Pauling in 1939, in his book *The Nature of the Chemical Bond*[45]. Strong and weak hydrogen bonds are discussed by Jeffrey and Saenger, in *Hydrogen Bonding in Biological Structures*[46.47].

Based on the comparative data of intra- and intermolecular interactions of the types C-H...O, O-H...O and C-H...Br as observed in the steroidal molecules (1-45) and presented in Table 5, it has been observed that the O atom is the predominant hydrogen donor and acceptor. The overall d(H...A) range lies between 1.94 and 2.13Å, the D(X...A) range is between 2.71 and 2.86 Å, and the angular range Θ(X-H...A) falls between 156 and 169°. Table 5 presents a range of values for d, D and Θ as exist in case of C-H...O and O-H...O intramolecular interactions.

Table 5. Geometry of C-H...O, O-H...O and C-H...Br/C-H...Cl/C-H...F intra- and intermolecular interactions

Molecule [Number of Donors and Acceptors]	Intramolecular interaction (X-H...A)	H...A(Å) d	X...A(Å) D	X-H...A(°) Θ
M-26 XEYTOL Donors=1 Acceptors=1	O3-H3X...O1	2.13	2.841	156
M-42 EVARUP Donors=3 Acceptors =3	O5-H5...OW1 O17-H17...OW3 OW2-HW21...O17	1.98 1.94 2.05	2.78 2.71 2.86	169 159 168
	Intermolecular interactions			
M-1 Donors =3 Acceptors =3	C2-H2B...O4 C5-H5...O17 C5-H5...O20 C21-H21A...O17	2.662 2.534 2.692 2.376	3.384 3.155 3.634 3.340	128.16 120.01 157.14 167.66
M-2 Donors =3 Acceptors =2	C4-H4...O3 C7-H7A...O3 C17B-H17B...O1	2.714 2.592 2.600	3.688 3.524 3.517	171.71 160.99 169.99
M-3 Donors =3 Acceptors =2	C1-H1A...O3 O3-H3A...O17 O11-H11A...O3	2.666 2.08 2.05	3.625 2.874 2.862	169.80 164 171
M-4 Donors =4 Acceptors =3	C6-H6A...O1 C11-H11A...O4 C20-H20B...O4 O3-H3...O2	2.362 2.432 2.588 2.101	3.311 3.257 3.412 2.787	165.86 142.59 144.72 141.01

M-5 Donors =5 Acceptors =4	O1-H1...O2	1.878	2.672	157.13
	O4(W)-H4C...O1	1.953	2.849	161.60
	O2-H2...O3	1.932	2.744	162.18
	O3-H3...O4(W)	1.910	2.686	153.06
	O4-H4D...O1	2.102	2.869	167.73
	C18-H18B...O4(W)	2.715	3.311	119.61
M-6 Donors =3 Acceptors =3	C16-H16A...O4	2.707	3.462	135.11
	O3-H3...O17	2.035	2.792	149.20
	O4-H4...O3	1.93	2.751	168
M-7 Donors =2 Acceptors =3	C15-H15A...O4	2.573	3.474	153.45
	C15-H15B...O1	2.458	3.397	162.93
	C21-H21A...O5	2.504	3.362	152.02
M-8 Donors =4 Acceptors =3	C6-H6...O3B	2.651	3.413	134.78
	C15-H15A...O17	2.66	3.609	163.70
	C18-H18A...O7	2.630	3.419	134.64
	O7-H7A...O17	2.023	2.825	165.69
M-9 Donors =2 Acceptors =2	C24-H24C...O2	2.690	3.459	134.80
	C15-H15A...O4	2.639	3.590	160.98
M-10 Donors =5 Acceptors =4	C11-H11B...O20	2.713	3.683	177.96
	C19-H19A...O20	2.502	3.366	149.72
	C19-H19C...O5'	2.696	3.382	128.88
	C19'-H19F...O5	2.543	3.361	143.21
	C8'-H8'...O20'	2.648	3.403	134
	C2'-H2'2...O17	2.702	3.652	166.75
	O5-H5...O5'	2.101	2.983	165.51
M-11 Donors =4 Acceptors =2	C2-H2A...O3	2.562	3.319	135.01
	C4-H4C...O3	2.699	3.415	131.10
	C19-H19B...O3	2.627	3.568	178.19
	O3-H3(O3)...O2	1.994	2.813	177.65
M- 12 Donors =4 Acceptors =2	C2'-H2'B...O3	2.613	3.422	140.07
	O3'-H3'(O3')...O3	2.137	2.920	157.13
	C1-H1B...O17'	2.413	3.375	166.72
	C24-H24...O17'	2.494	3.368	154.52
M- 13 Donors =2 Acceptors =2	C9-H9...O3	2.596	3.56	167.05
	C23-H23C...O2	2.516	3.297	138.42
M-14 Donors =3 Acceptors =3	C16-H16A...O20	2.677	3.418	133.54
	C21-H21C...O20	2.688	3.628	166.38
	C23-H23A...O17	2.519	3.322	141.27
	C23-H23B...O22	2.501	3.303	141.01
M-15 Donors =4 Acceptors =4	C2-H2B...O20	2.701	3.604	154.99
	C2-H2A...O22	2.615	3.567	167.28
	C9-H9...O20	2.465	3.418	164.36
	C18-H18C...O17	2.640	3.590	170.21
	C21-H21B...O3	2.453	3.395	167.17

	C12-H12B...O3	2.611	3.473	146.74
M- 16	C19-H19C...O2	2.655	3.465	140.32
Donors =5	O1-H1X...O3	1.952	2.808	163.30
Acceptors =4	O2-H4Y...O4	2.028	2.777	162.44
	O4-H4X...O1	1.678	2.766	171.97
	O3-H3X...O1	2.038	2.903	167.84
	O3'-H3Y...O3	1.879	2.868	170.81
M-17	C19-H19B...O2'	2.438	3.345	153.72
Donors =4	C1'-H1B2...O2	2.624	3.508	147.93
Acceptors =3	O1'-H1Y...O2	1.929	2.822	151.49
	C1-H1B...OI'	2.522	3.465	159.25
	O1-H1X...O1'	2.233	3.318	177.68
	C6'-H6'1...O3'	2.630	3.504	147.19
	C4-H4...O2	2.635	3.444	137.97
M-18	C22-H22E...O3	2.696	3.414	141.02
Donors =3	C22-H22C...O3	2.692	3.414	130.85
Acceptors =2	C22-H22D...O2	2.698	3.656	165.87
	O3-H3X...O2	2.079	2.899	167.35
M-19 Donors =1 Acceptors =1	O3-H3X...O4	2.062	2.976	171.13
	C16'-H16'B...O1	2.509	3.435	154.93
	O1-H1...O3(W)	1.955	2.831	169.47
	C16-H16A...O3(W)	2.542	3.470	167.74
M-20	C15-H15B...O1	2.591	3.375	136.10
Donors =4	O1'-H1O1'...O2	1.938	2.756	178.94
Acceptors =3	C2'-H2'A...O2	2.576	3.335	132.64
	O3(W)-H2O3...O2'	1.707	2.747	157.96
	O3(W)-H1O3...O1'	1.655	2.799	168.88
	C2'-H2'A...O2	2.576	3.335	132.84
M- 21	C15-H15A...O1	2.536	3.347	142.55
Donors =3	C16-H16B...O2	2.653	3.424	136.89
Acceptors =2	O1-H1...O2	2.130	2.956	175.43
	C1-H1A...O4	2.709	3.52	134.36
M-22	C15-H15B...O3	2.719	3.212	111.09
Donors =4	C19-H19A...O3	2.583	3.518	159.48
Acceptors =3	O4-H4...O1	1.944	2.754	161.71
	C1-H1A...O3	2.590	3.479	152.58
M-23	C11-H11A...O3	2.704	3.670	174.04
Donors =4	C18-H18A...O4	2.614	3.518	157.26
Acceptors =2	C20-H20A...O4	2.631	3.451	142.39
	C20-H20B...O4	2.717	3.362	124.46
M- 24	C3B-H3B1...O5	2.611	3.387	138.07
Donors =3	C18-H18A...O17	2.695	3.397	164.07
Acceptors =2	O6-H6A...O17	2.025	2.822	130.49
M-25	C8-H8...O4	2.475	3.352	148.75
Donors =3	C11-H11A...O2	2.681	3.611	160.70
Acceptors =3	C21-H21B...O3	2.715	3.554	146.29

M-26 Donors =6 Acceptors =3	O3-H3X...O4	1.98	2.745	155
	O7-H7X...O8	2.03		160
	C18'-H48A...O3	2.690	2.791	127.14
	C16'-H46A...O4	2.602	3.357	158.74
	C6'-H36...O8	2.635		116.42
	O7-H7X...O8	2.03	3.194	160
	C19-H19A...O4	2.698		130.11
M-27 Donors =2 Acceptors =3	C21-H2A...O4	2.523	3.477	164.22
	C23-H17B...O6	2.512	3.367	148.51
	C23-H7C...O2	2.509	3.326	140.70
	O5-H23...O6	1.966	2.884	155.67
M-28 Donors =2 Acceptors =2	C4-H5...O2	2.483	3.450	169.79
	O2-H32...O1	1.979	2.922	177.04
M-29 Donors =1 Acceptors =1	C15-H15B...O17B	2.704	3.406	129.52
M- 30 Donors =4 Acceptors =3	C3-H9...O3B	2.714	3.621	153.98
	C6B-H6B3...O14	2.452	3.375	161.00
	C15-H15B...O17B	2.712	3.408	129.15
	O14-H14...O3B	2.324	2.980	137.36
M-31 Donors =4 Acceptors =3	C16-H161...O3	2.696	3.444	132.57
	C15-H151...O2	2.389	3.153	133.44
	C2-H212...O3	2.620	3.546	157.59
	C1-H11...F1	2.437	3.373	157.43
M-32 Donors =3 Acceptors =2	C1-H1B...O12	2.571	3.438	148.86
	C3-H3...O12	2.677	3.529	145.53
	C15-H15B...O17B	2.6739	3.424	133.95
M-33 Donors =3 Acceptors =2	C11-H11A...O1	2.699	3.387	128.32
	C16-H16A...O2	2.588	3.436	146.35
	C20-H20C...O2	2.669	3.584	159.63
M-34 Donors =1 Acceptors =1	C24-H24C...O1	2.638	3.567	163.43
M-35 Donors =6 Acceptors =2	O3-H30...O4	2.113	2.842	144.92
	C6-H6...O4	2.495	3.114	119.63
	C12'-H12C...O2	2.704	3.544	142.85
	C11-H11B...O2'	2.682	3.415	131.02
	C16-H16A...O4'	2.627	3.586	163.32
	C21'-H21E...O2	2.716	3.350	122.06
	O3'-H30'...O4'	1.940	2.737	157.97
	C6'-H6'...O4'	2.638	3.174	113.66
	C18-H18C...O3'	2.529	3.361	142.55
	C16'-H16C...O3	2.611	3.424	139.39
M- 36 Donors =3 Acceptors =1	C11-H11A...O5	2.599	3.508	152.62
	O1-H1...O5	2.166	2.984	164.35
	O3-H3A...O5	2.198	2.980	154.88

M- 37 Donors =5 Acceptors =3	C7-H7B...O1	2.464	3.418	161.79
	O1-H1X...O5	2.152	2.984	171.11
	O2-H2X...O6(W)	1.979	2.776	157.99
	O3-H3X...O1	2.134	2.912	153.82
	O6(W)-H6Y...O5	1.883	2.861	168.30
M-38 Donors =3 Acceptors =2	C18-H18B...O5	2.695	3.449	134.08
	C21-H21C...O2	2.500	3.376	148.64
	O4-H4X...O5	2.005	2.792	156.53
M-39 Donors =5 Acceptors =3	O3-H3A...O3'	2.12	2.936	179
	O6-H6...O2'	1.97	2.757	160
	C16-H16...O3'	2.56	3.347	137
	C2'-H22A...Br1	2.92	3.868	166
	C16'-H37...Br1	2.87	3.788	156
	C1'-H22A...Br1	2.919	2.919	166.16
M-40 Donors =3 Acceptors =3	O3-H3...O17	2.112	2.931	174.88
	O5-H5...O3	1.995	2.806	170.43
	O6-H6A...O5	2.393	3.120	148.23
M-41 Donors =7 Acceptors =6	C9-H9...O6	2.511	3.469	165.76
	O3-H3...O17	1.979	2.788	168.59
	O5-H5...O(W1)	2.080	2.891	170.32
	O6-H6...O5	2.260	2.26	149
	O17-H17...O(W3)	1.94	2.718	159
	OW1-HW11...O3	2.152	2.944	170
	OW2-HW21...O17	2.05	2.862	168
	OW3-HW31...OW1	2.05	2.850	169
	OW1-HW12...OW2	2.19	2.977	160
M-42 Donors =4 Acceptors =2	C4-H4B...O2	2.699	3.543	145.77
	C7-H8B...O1	2.706	3.414	130.25
	C19-H9C...O1	2.683	3.529	147.37
	C9-H10...O2	2.632	3.589	165.43
M-43 Donors =2 Acceptors =2	C1-H1...O2	2.611	3.355	131.90
	C21-H27...O2	2.713	3.492	136.76
	C21-H28...O1	2.689	3.506	141.02
M-44 Donors =4 Acceptors =3	C7-H9...O1	2.475	3.455	170.76
	C9-H10...O3	2.509	3.487	165.83
	C15-H17...O1	2.659	3.643	172.08
	C21-H21...Cl	2.903	3.649	132.88
M-45 Donors =4 Acceptors =3	C4-H4...O3	2.615	3.354	130.72
	C8-H8...O3	2.537	3.427	148.11
	C17-H17...O4	2.549	3.457	151.11
	C21-H21...O1	2.460	3.161	128.27

The atom C acts as the most predominant hydrogen donor with frequency of occurrence at 68.8% and the O atom acts as hydrogen acceptor with frequency of occurrence at 98.9%. The range for d(H...A), D(X...A) and angular range Θ(X-H...A) for C-H..O and O-H...O intramolecular hydrogen bonds is presented in Table 6. In the case of intermolecular interactions, it has also been observed that that the C atom acts as the most predominant hydrogen donor with frequency of occurrence 68.8% and the O atom acts as hydrogen acceptor with frequency of occurrence 98.9%. Most of the intermolecular C-H...O hydrogen

bonds are observed in molecules having a keto group. The overall range d(H...A) lies between 1.655 and 2.92 Å , the D(X...A) range is between 2.26 and 3.868 Å and the angular range Θ(X-H...A) falls between 111.09 and 179°. The range for d(H...A), D(X...A) and angular range Θ (X-H...A) for C-H...O, O-H...O and C-H...Br intermolecular hydrogen bonds are presented in Table 6.

Table 6. Range for d(H...A), D(X...A) and Θ(X-H...A) for C-H...O, O-H...O and C-H...Br intra- and intermolecular hydrogen bonds

Type of bond	D(H...A) range(Å)	D(X...A) range(Å)	Θ(X-H...A) range(°)
Intramolecular			
(a) O-H...O	1.94-2.13	2.71-2.86	156-169
Intermolecular			
(a) C-H...O	2.137-2.719	2.920-3.688	111.09-177.96
(b) O-H...O	1.655-2.635	2.26-3.318	130.49-179
(c) C-H...Br	2.87-2.92	3.788-3.868	156-166

On the basis of interaction data, it may be concluded that C-H...O hydrogen bonding is predominant (frequency of occurrence 66.1%) and it agrees well with the conclusions of Steiner & Saenger (1992a)[48]. The C-H...O hydrogen bond is observed mostly in molecules having a keto group as substituent and the O-H...O hydrogen bond is found in molecules having the OH group as substituent.

Graphical presentation of interactions

The key structural feature distinguishing the hydrogen bond from the other non-covalent interactions is its preference for linearity[49]. A better way to analyse preferences is to draw d-Θ and D-Θ scatter plots. The plots include all contacts found in molecules (1-45) with d < 2.9 Å and D < 3.8 Å at any occurring angle. The graphical projections of d- Θ [d(H...A) against Θ (X-H...A)] and D- Θ [D(X...A) against Θ (X-H...A)] scatter plots have been made for intermolecular interactions which are shown in Figure 4(a, b). The following observations have been made:

(i) The density of spots for d(H...A) [= 2.42-2.72 Å] and D(X...A) [= 3.3-3.6 Å] is predominant in the theta [Θ(X-H...A)] range ~120-179° in the case of C-H...O hydrogen bonds.

(ii) The density of spots for O-H...O intermolecular hydrogen bonds is quite high in a given range of values for d(H...A)=1.90-2.15 Å and D(X...A)=2.32-2.90 Å and Θ(X-H...A)=150–179°.

(iii) The relative frequency of occurrence of various types of C-H...O, O-H...O,C-H...Br and C-H...Cl, and C-H...F intermolecular hydrogen bonds is 66.6, 31.18 ,1.61, 0.53 and 0.53%, respectively and it is shown in Figure 5.

Densely populated clusters of data points at short distances and fairly linear angles have been found and each point in these clusters represents a hydrogen bond. Plots analogous to these figures exist in the literature for other kinds of hydrogen bonds, such as O-H...O, C-H...O, *etc*[50]. Similar features (preference for linearity) have been depicted by these plots which indicate that the angular characteristics of all kinds of hydrogen bonds are related. On comparison of the frequency of contacts from H(C) to O, Cl, Br and F, it has been concluded that H(C) atoms have a statistical preference for contacts to 'O' rather than 'Br', 'F'or 'Cl' atoms. Thus, with oxygen as an acceptor, the frequency of occurrence of C-H...O hydrogen

bond becomes very high (97.84% in the present case) In all the molecules (1-45), the C atoms act as donors but not as acceptors in all the bonds. Most of the C-H...O contacts have distance d(H...O) less than 2.7 Å and based on the criterion that the van der Waals distance should be < 2.7 Å, it was regarded as a certain indication of hydrogen bonding.

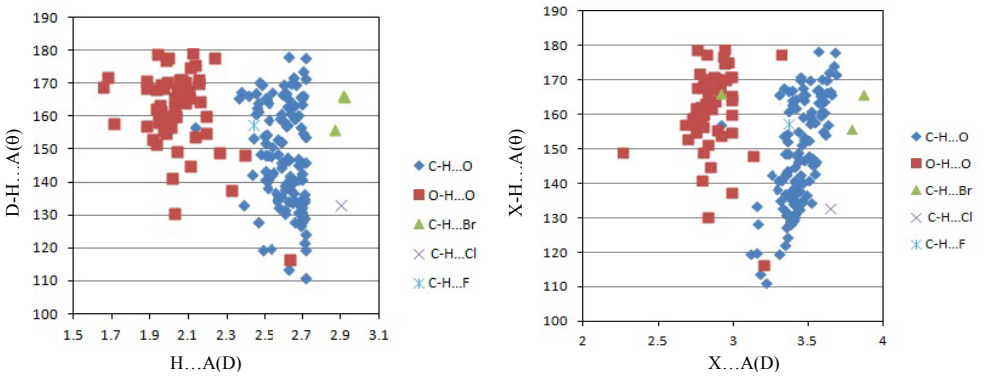

Figure 4. (a) d-θ scatter plot for intermolecular C-H…O, O-H…O, C-H…Br, C-H…CI and C-H…F hydrogen bonds (b) D-θ scatter plot for intermolecular C-H…O, O-H…O, C-H…Br, C-H…CI and C-H…F

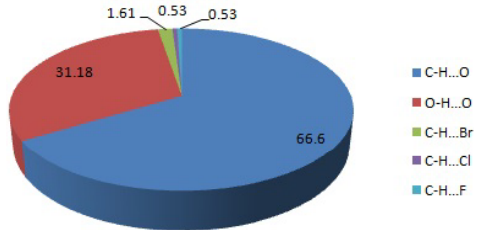

Figure 5. Relative frequency of occurrence (in %) for various types of intermolecular hydrogen bonding

Conclusion

On comparison of some geometrical and structural features of the series of androstane derivatives, it is found that substituents are located mostly at C3, C4 and C6 position of the steroid nucleus. Hydrogen bonding interactions are present in these molecules and the substituents (at the C3, C4 and C6 position) which are involved in these interactions may be responsible for the lengthening and shortening of bond distances C2-C3, C3-C4, C4-C5, C5-C6 and C6-C7. Hydrogen bonding may also be responsible for the deviation of C2-C3-C4, C3-C4-C5 and C5-C6-C7 bond angles from its normal value. The bending in this bond angle typically amounts to only few degrees, which resembles the results shown by Desiraju & Steiner[51]. Stress has been laid to study the hybridization (single/double bond) and ring fusions for the conformation of individual ring systems and stability of androstane molecules.

On comparing the hydrogen bond interactions, it is also concluded that the C-H...O hydrogen bonding is quite predominant in androstane class of steroids and the frequent contacts from H(C) atoms have a statistical preference to 'O' as donor. The design of new molecules/supramolecules with desired properties is the future intention of chemists/crystallographers which requires the understanding of intermolecular interactions in crystal packing. Thus, understanding of intermolecular interactions becomes important.

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