A CSD CRYSTALLOGRAPHIC ANALYSIS OF SOME PREGNANE CLASS OF STEROIDS

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The structural diversity of steroids as well as their surpassed biological potential qualify them as challenging targets for chemical synthesis and as lead structures for pharmacological research. A total number of thirty-three structures of pregnane derivatives were obtained from the CSD for a comparative analysis of their crystallographic structures, computation of their possible biological activities and molecular packing interaction analysis. Intra and intermolecular interactions of the type X-H…A [X=C,O, N; A=O, N, S, Cl, F] have been analysed for a better understanding of molecular packing in pregnane class of steroids and discussed on the basis of distance-angle scatter plots. Molecular conformations of all the structures have been computed on the basis of the magnitude of torsion angles present in these structures. Results presented in this paper is a part of our ongoing work on the crystallographic aspects of steroidal derivatives of different classes.

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Introduction

Steroid hormones play a vital role in a wide variety of essential physiological processes including cell growth, sexual development, maintenance of salt balance and sugar metabolism.[1] Pregnane, a crystalline steroid hydrocarbon, is the parent compound of corticosteroids and progesterone. It is a four-ring structure of which three are six-membered cyclohexane rings and one is a five-membered cyclopentane carbon ring. In addition, it has a side chain of two carbon atoms located at C17 position of the steroid nucleus (Figure 1).

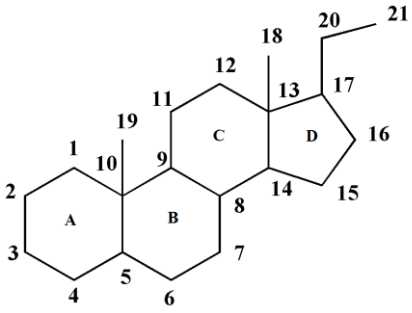

Figure 1. Basic pregnane molecule (C_{21}) with standard atomic numbering scheme.

In the literature on pregnane class of steroids, pregnenolone (3β-hydroxypregn-5-en-20-one) holds a very prominent place and position in the hierarchy of steroid hormones. These are used for addressing various health related issues such as ageing,[2] Alzheimer's disease, depression, mental function,[3,4] fatigue, menopausal symptoms, osteoporosis, Parkinson's disease, rheumatoid arthritis, stress and weight loss,[5] etc. In mammals, like all other steroid hormones, progesterone is essentially the harmone of pregnancy and it is synthesized from pregnenolone. Pregnane and its derivatives have also been reported to possess anti-inflammatory activity, besides anti-asthmatic, cytotoxic, anti-feedant, anti-dyslipidimic and anti-oxidant properties.[6-10] We identified a series of thirty-three pregnane derivatives[11-39] from Cambridge Structure Database (CSD). The chemical structure of each compound and its numbering is presented in Figure 2 while the reference code, chemical name, chemical formula, molecular weight and published reference is presented in Table 1.

Crystallographic comparison

The structures belonging to pregnane series and as obtained from CSD were analyzed for their precise structural parameters which include the crystal class, space group, the number of molecules per asymmetric unit cell, the final R-factor, selected bond distances, bond angles, ring conformations, etc. The information in concise form is presented in Table 2, 3 and 4, respectively. Based on the comparative crystallographic data, the following conclusions can be drawn:

1. The most commonly occurring crystal system is *monoclinic* (57.5%), followed by *orthorhombic* (30.3%), *triclinic* (9.09%) and *trigonal* (3.03%). This observation is in line with the findings of Stout and Jensen.[40]
2. The most frequently occurring space group is $P2_1$ (45.4%), followed by $P2_12_12_1$ (30.3%), C2 (12.1%), P1 (9.09%) and $P3_1$ (3.03%).

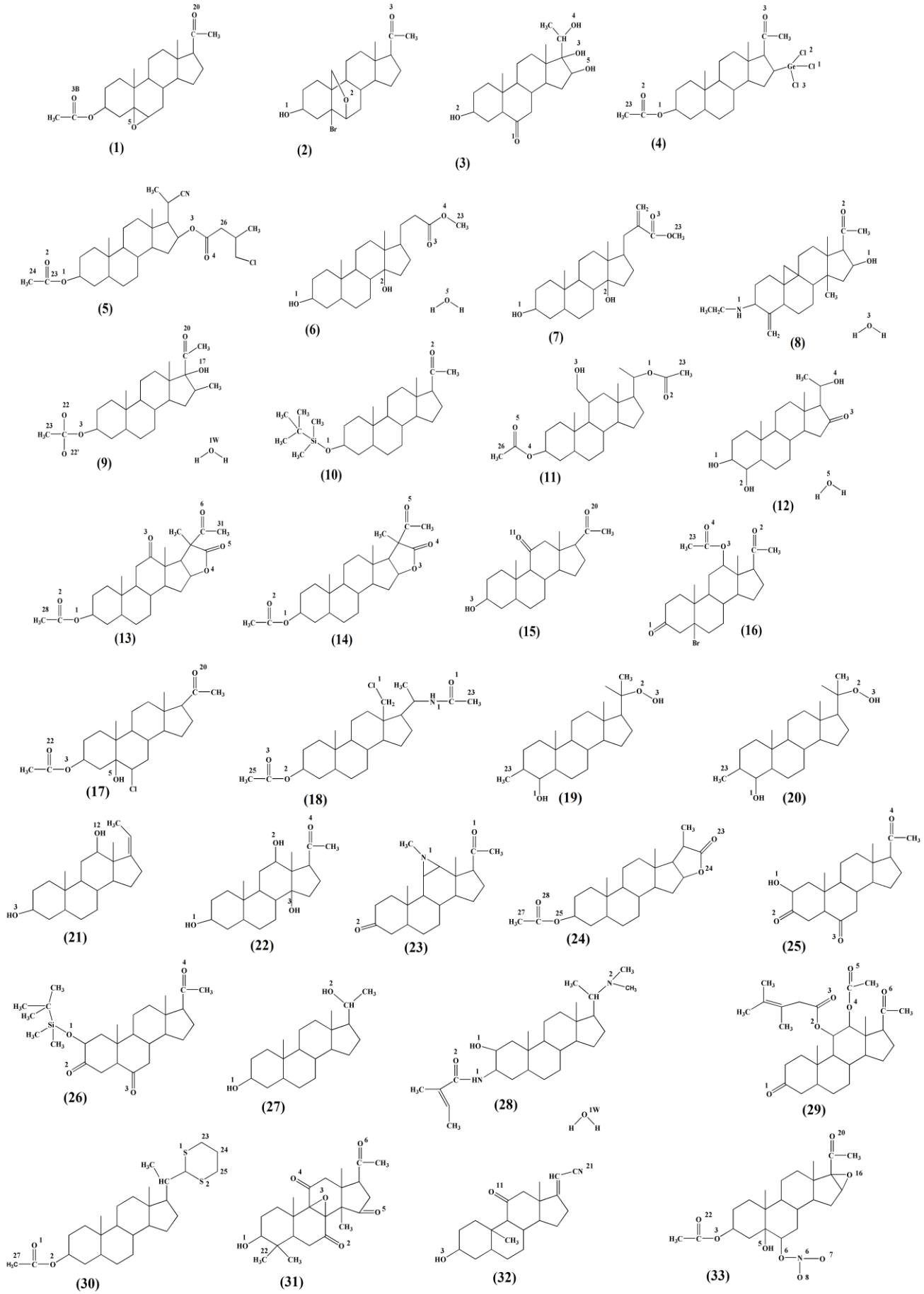

Figure 2. Chemical structure of molecules (**1-33**).

Table 1. CSD code, chemical name/formula, molecular weight and published reference for (M1 - M33)

Mol-ecule	CSD Code	Chemical Name	Chemical formula	MWt. (amu)	Refs.
M-1	BIZPAC	5β,6β-Epoxy-20-oxopregnan-3β-yl acetate	$C_{23}H_{34}O_4$	374.5	[11]
M-2	BOPREO	5α-Bromo-6β,19-oxido-pregnan-3β-ol-20-one	$C_{21}H_{31}BrO_3$	411.0	[12]
M-3	CEQMIU	(-)-(3α,16β,17α,20(S))-3,16,17,20-Tetrahydroxypregnane-6-one	$C_{21}H_{34}O_5$	366.0	[13]
M-4	CIJQOB	β-Acetoxy-16β-trichlorogermyl-5α-pregnan-20-one	$C_{23}H_{35}Cl_3GeO_3$	538.45	[14]
M-5	COYZEW	20(S)-3α-Acetoxy-20-cyano-5β-pregnan-16β-yl (3R)-3-(chloromethyl) butanoate	$C_{29}H_{44}ClNO_4$	506.1	[15]
M-6	CUMYEO	3β,5β,14β,20E)-Methyl 14-hydroxy-pregn-20-ene-21-carboxylate mMonohydrate	$C_{23}H_{36}O_4,H_2O$	394.0	[16]
M-7	CUMYUE	(3β,5β,14β,20E)-Methyl 14-hydroxy-21-methylenepregn-21-carboxylate	$C_{24}H_{38}O_4$	390.0	[16]
M-8	CUZSIZ	3β-(Dimethylamino)-16α-hydroxy-14-methyl-4-methylene-9,19-cyclo-5α-pregnan-20-one monohydrate	$C_{25}H_{39}NO_2,H_2O$	403.59	[17]
M-9	DERHOY	3β-Acetoxy-17α-hydroxy-16α-methylallopregnan-20-one hemihydrate	$C_{24}H_{38}O_4,0.5(H_2O)$	399.55	[18]
M-10	EDIGEE	3β-(t-butyl(dimethyl)silyloxy)-5 α,16α-pregna-20-one	$C2_7H_{48}O_2Si$	432.74	[19]
M-11	FAMYAT	3β,20β-Diacetoxy-11β-hydroxymethyl-5α-pregnane	$C_{26}H_{42}O_5$	434.0	[20]
M-12	GANFUY	3,4,20-Trihydroxypregnan-16-one monohydrate	$C_{21}H_{34}O_4,H_2O$	368.5	[21]
M-13	HOXTEU	7-Acetyl-4α,6α,7-trimethyl-6,8 dioxooctadecahydro-1H naphtho[2',1':4,5]indeno[2,1-β]furan-2-yl acetate	$C_{26}H_{36}O_6$	444.55	[22]
M-14	HOXTIY	7-Acetyl-4α,6α,7-trimethyl-8-oxooctadecahydro-1H-naphtho[2',1':4, 5]indeno[2,1-β]furan-2-yl acetate	$C_{26}H_{38}O_5$	430.56	[22]
M-15	HXPRDO01	(3α-5α)-3-Hydroxypregnane-11,20-dione	$C_{21}H_{32}O_3$	332.47	[23]
M-16	KATXUA	4-Bromo-3,20-dioxopregnan-12-yl acetate	$C_{23}H_{33}BrO_4$	453.4	[24]
M-17	KOFDIT	6β-Chloro-5α-hydroxy-20-oxopregnan-3β-yl acetate	$C_{23}H_{35}ClO_4$	410.96	[25]
M-18	KUTXIH	(20S)-20-Acetamido-18-chloro-5α-pregnan-3β-yl acetate	$C_{25}H_{40}ClNO_3$	438.03	[26]
M-19	LAFCUR	3α,20-Dimethyl-20-hydroperoxy-4β-hydroxy-5β-pregnane	$C_{23}H_{40}O_3$	364.55	[27]
M-20	LAFDAY	4β,20-Dihydroxy-3α,20-dimethyl-5β-pregnane	$C_{23}H_{40}O_2$	348.55	[27]
M-21	LITQUB	(3β,5α,8α,9β,10α,12β,13α,14β,17Z)-pregn-17(20)-ene-3,12-diol	$C_{21}H_{34}O_2$	318.48	[28]
M-22	LOSKAG	3β,12β,14α-Trihydroxypregnan-20-one	$C_{21}H_{34}O_4$	350.48	[29]
M-23	LUVPEX	N-Methyl-11α,12α-aziridino-5β-H-pregnano-3,20-dione	$C_{22}H_{33}NO_2$	343.49	[30]
M-24	OVOQOG	4a,6α,7-Trimethyl-8 oxooctadecahydro-1H naphtho[2',1':4,5]indeno[2,1-β]furan-2-yl acetate	$C_{24}H_{36}O_4$	388.53	[31]
M-25	RAFSAU	2α-hydroxy-5α-pregnane-3,6,20-trione	$C_{21}H_{30}O_4$	346.47	[32]
M-26	RAFSEY	2α-t-butyldimethylsilyloxy-5α-pregnane-3,6,20-trione	$C_{27}H_{44}O_4Si$	460.73	[32]
M-27	ROGNIL	5α-Pregnane-3α,20α-diol	$C_{21}H_{36}O_2$	320.5	[33]
M-28	TUTREG	N-(20-(Dimethylamino)-2-hydroxypregnan-3-yl)-2-methylbut-2-enamide monohydrate	$C_{28}H_{48}N_2O_2,H_2O$	461.69	[34]
M-29	WASCAV	(11α,12β)-12-Acetoxy-11-((3,4-dimethylpent-3-enoyl)oxy)pregnan-3,20-dione	$C_{30}H_{44}O_6$	500.65	[35]
M-30	WETYIE	(20R)-3β-Acetoxy-5α-pregna-20-dithiane	$C_{27}H_{44}O_2S_2$	464.74	[36]
M-31	XOVLUP	8α,9α-Epoxy-4,4,14α-trimethyl-3,7,11,15,20-pentaoxo-5α-pregnane	$C_{24}H_{30}O_6$	414.48	[37]
M-32	YASHOR	3-Hydroxy-11-oxopregn-17-ene-21-nitrile	$C_{21}H_{29}NO_2$	327.45	[38]
M-33	YOTMEA	16α,17α-Epoxy-5α-hydroxy-6β-nitrooxy-20-oxopregnan-3β-yl acetate	$C_{23}H_{33}NO_8$	451.50	[39]

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Table 2. Crystal system, space group, *R*-factor, *Z*(*Z*′) for molecules (**1-33**)

Molecule	Crystal system	Space group	R-factor	Z(Z′)
M-1	Orthorhombic	$P2_12_12_1$	0.0414	4
M-2	Orthorhombic	$P2_12_12_1$	0.065	8(2)
M-3	Monoclinic	$P2_1$	0.054	2
M-4	Triclinic	P1	0.0533	2(2)
M-5	Monoclinic	$P2_1$	0.0589	2
M-6	Orthorhombic	$P2_12_12_1$	0.051	4
M-7	Monoclinic	$P2_1$	0.072	2
M-8	Monoclinic	$P2_1$	0.0585	2
M-9	Monoclinic	C2	0.0419	4
M-10	Orthorhombic	$P2_12_12_1$	0.0737	8(2)
M-11	Monoclinic	$P2_1$	0.048	4(2)
M-12	Orthorhombic	$P2_12_12_1$	0.0922	4
M-13	Monoclinic	P21	0.0407	4(2)
M-14	Orthorhombic	$P2_12_12_1$	0.05	4
M-15	Orthorhombic	$P2_12_12_1$	0.0347	4
M-16	Orthorhombic	$P2_12_12_1$	0.0449	4
M-17	Monoclinic	$P2_1$	0.0423	4(2)
M-18	Monoclinic	$P2_1$	0.057	2
M-19	Monoclinic	$P2_1$	0.0446	4(2)
M-20	Trigonal	$P3_1$	0.0474	6(2)
M-21	Monoclinic	$P2_1$	0.0597	4(2)
M-22	Monoclinic	$P2_1$	0.0481	2
M-23	Monoclinic	$P2_1$	0.0472	2
M-24	Monoclinic	C2	0.0456	8(2)
M-25	Monoclinic	$P2_1$	0.0596	2
M-26	Monoclinic	C2	0.053	4
M-27	Monoclinic	$P2_1$	0.044	2
M-28	Orthorhombic	$P2_12_12_1$	0.0549	4
M-29	Monoclinic	C2	0.0389	4
M-30	Monoclinic	$P2_1$	0.0527	4(2)
M-31	Triclinic	P1	0.0481	1
M-32	Orthorhombic	$P2_12_12_1$	0.0343	4
M-33	Triclinic	P1	0.0431	2(2)

3. A careful analysis of the reliability index (R-factor) indicates better precision in the structure determination of these molecules. This parameter ranges between 0.00347 - 0.065 (except for molecule M-7, 10, 12 for which R- factor is relatively high, i.e., 0.072, 0.073 and 0.0922, respectively).

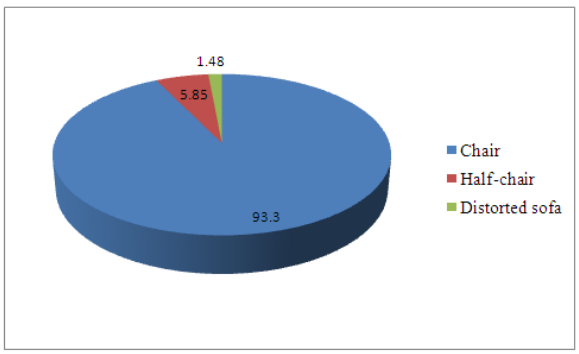
4. The existence of multiple molecules (Z′) phenomenon is quite significant and it exists in molecule M-2, 4, 10, 11, 13, 17, 19-21, 24, 30, 33, respectively.

5. Due to substitution at C3 position of ring A of the steroidal nucleus, there appears a visible change in the bond distances, depending upon whether C2-C3 or C3-C4 is a single or double bond. So, it is of interest to investigate the variation in the C2-C3 (sp^3-sp^3/sp^3-sp^2/sp^2-sp^3) and C3-C4 (sp^3-sp^3/sp^3-sp^2/sp^2-sp^3) bond lengths and C2-C3-C4 (sp^3/sp^2) bond angle in the undertaken structures. The value of the bond C2-C3 (sp^3-sp^3) and C3-C4 (sp^3-sp^3) lies in the range 1.464-1.544Å and 1.485-1.545Å respectively with average value being 1.511Å and 1.516 Å respectively. The bond angle C2-C3(sp^3)-C4 ranges between 108.90°-114.59° having average value 111.38°. However, in structures M-16, 23, 25, 26, 29, 31, both the bond distances C2-C3 and C3-C4 are sp^3-sp^2/sp^2-sp^3 hybridised and lies in the range 1.492-1.528Å and 1.478-1.532Å respectively with average value being 1.508Å and 1.506Å respectively and bond angle (sp^2 hybridised) lies in the range (112.06-116.46°) with average being 114.31°. In M-8, the bond distance C3-C4 is sp^3-sp^2 hybridised having value 1.516 Å.

6. The six- membered rings in all the molecules adopt *chair* conformation with a few exceptions. Like ring B in molecules [M-1] which shows distorted *sofa* conformation and this may be due to the presence of an epoxy group between C5 and C6. Ring B & C in M-8 display *half-chair* conformation, may be due to the presence of a cyclopropane group between C9 and C10; ring A in M-13' &17 show *half-chair* conformation which may be due to the substitution of an acetoxy group at C3; ring A & C in M-23 exhibit *half-chair* conformation due to unusual substitutions at carbon atom C3 and between C11 and C12. Ring B adopts half-chair & ring C distorted *sofa* conformations in M-31which may be due to the presence of an epoxy group between C8 and C9. The relative frequency of various types of conformations occurring in six-membered and five-membered rings in molecules (1-33) are as shown in Figure 3(a, b). The incidence of occurrence of all the six-membered rings in the chair conformation is 93.3%, followed by *half-chair* (5.85%) and distorted *sofa* conformation (1.48%). Similarly, for the five membered rings, the incidence of occurrence of *half-chair* conformation is 44.4%, followed by *envelope* and intermediate between *half-chair* & *envelope* conformations (42.2 & 13.3%), respectively.

Table 3. Selected bond distances (Å) and bond angles (°) for molecules (1-33)

Molecule	Bond distance(Å) [C2-C3]		Bond distance(Å) [C3-C4]		Bond angle(°)	
	sp^3-sp^3	sp^3-sp^2/sp^2-sp^3	sp^3 - sp^3	sp^3 - sp^2/sp^2- sp^3	C3(sp^3)	C3(sp^2)
M-1	1.499		1.512		109.76	
M-2	1.491		1.545		111.51	
M-2'	1.497		1.522		112.9	
M-3	1.519		1.515		111.6	
M-4	1.464		1.531		114.59	
M-4'	1.483		1.504		111.68	
M-5	1.493		1.51		111.41	
M-6	1.499		1.518		110.59	
M-7	1.506		1.524		111.5	
M-8	1.544			1.516	109.22	
M-9	1.498		1.518		111.47	
M-10	1.515		1.519		110.34	
M-10'	1.503		1.51		111.39	
M-11	1.513		1.504		111.16	
M-11'	1.508		1.516		111.12	
M-12	1.518		1.532		110.78	
M-13	1.506		1.515		112.23	
M-13'	1.506		1.509		111.27	
M-14	1.52		1.502		111.61	
M-15	1.527		1.516		111.52	
M-16		1.51		1.515		113.03
M-17	1.511		1.52		112.64	
M-17'	1.52		1.485		113.02	
M-18	1.523		1.521		112.19	
M-19	1.52		1.529		109.86	
M-19'	1.521		1.534		111.25	
M-20	1.521		1.529		108.9	
M-20'	1.511		1.52		109.68	
M-21	1.524		1.509		111.29	
M-21'	1.516		1.518		110.16	
M-22	1.511		1.51		110.52	
M-23		1.498		1.478		112.06
M-24	1.506		1.507		111.22	
M-24'	1.528		1.501		111.49	
M-25		1.528		1.504		116.46
M-26		1.525		1.503		114.52
M-27	1.525		1.506		111.81	
M-28	1.544		1.53		110.11	
M-29		1.496		1.499		114.01
M-30	1.5		1.503		111.33	
M-30'	1.501		1.524		112.4	
M-31		1.492		1.532		115.8
M-32	1.527		1.522		111.1	
M-33	1.508		1.509		111.8	
M-33'	1.503		1.514		112.57	



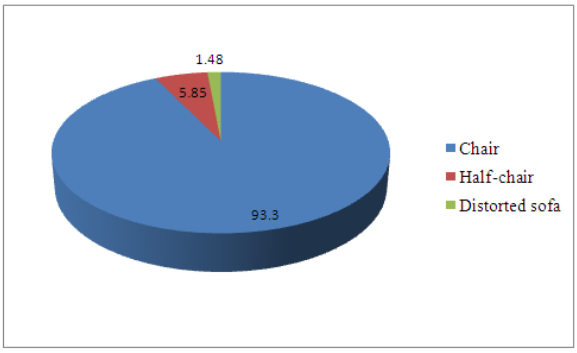


Figure 3. Relative frequency of occurrence (in %) for various types of conformations in (a) six-membered rings A, B and C and (b) five-membered rings D (molecules **1-33**).

Table 4. Computed ring conformations for molecules (1-33)

Molecule	Ring A(conformation)	Ring B(conformation)	Ring C(conformation)	Ring D(conformation)
M-1	Chair	Distorted Sofa	Chair	Half-chair
M-2	Chair	Chair	Chair	Envelope
M-2'	Chair	Chair	Chair	Envelope
M-3	Chair	Chair	Chair	Half-chair
M-4	Chair	Chair	Chair	Half-chair
M-4'	Chair	Chair	Chair	Half-chair
M-5	Chair	Chair	Chair	Half-chair
M-6	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-7	Chair	Chair	Chair	Envelope
M-8	Chair	Half-chair	Half-chair	Half-chair
M-9	Chair	Chair	Chair	Envelope
M-10	Chair	Chair	Chair	Half-chair
M-10'	Chair	Chair	Chair	Half-chair
M-11	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-11'	Chair	Chair	Chair	Envelope
M-12	Chair	Chair	Chair	Envelope
M-13	Chair	Chair	Chair	Half-chair
M-13'	Half-chair	Chair	Chair	Half-chair
M-14	Chair	Chair	Chair	Half-chair
M-15	Chair	Chair	Chair	Envelope
M-16	Chair	Chair	Chair	Half-chair
M-17	Half-chair	Chair	Chair	Envelope
M-17'	Chair	Chair	Chair	Envelope
M-18	Chair	Chair	Chair	Envelope
M-19	Chair	Chair	Chair	Envelope
M-19'	Chair	Chair	Chair	Envelope
M-20	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-20'	Chair	Chair	Chair	Half-chair
M-21	Chair	Chair	Chair	Envelope
M-21'	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-22	Chair	Chair	Chair	Half-chair
M-23	Half-chair	Chair	Half-chair	Half-chair
M-24	Chair	Chair	Chair	Envelope
M-24'	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-25	Chair	Chair	Chair	Half-chair
M-26	Chair	Chair	Chair	Envelope
M-27	Chair	Chair	Chair	Half-chair
M-28	Chair	Chair	Chair	Half-chair
M-29	Chair	Chair	Chair	Half-chair
M-30	Chair	Chair	Chair	Intermediate between envelope and half-chair
M-30'	Chair	Chair	Chair	Half-chair
M-31	Chair	Half-chair	Distorted Sofa	Envelope
M-32	Chair	Chair	Chair	Envelope
M-33	Chair	Chair	Chair	Envelope
M-33'	Chair	Chair	Chair	Envelope

Biological activity predictions

The steroid drug occupies a conspicuous place in the modern therapeutic practice. The broad spectrum of biological activity within the group and the multiplicity of actions displayed by certain individual members make the steroids one of the intriguing classes of biologically active compounds. The biological activity of steroids is related to their chemical structure. PASS (Prediction of Activity spectra for Substances) software[41] emerged as a strong potential tool to predict the biological activity spectrum, is used here to predict the activities of various pregnane related structures. The structural formula of a molecule is presented as a *mol* file to this software and the predictions result in the form of a table containing the list of biological activities. Two values are computed for each activity: P_a -the probability of the compound being active and P_i -the probability of the compound being inactive for a particular activity. Activities with $P_a > P_i$ are retained as possible for a particular compound.

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Table 5. Predicted activities (P_a and P_i) for the molecules (1-33)

Mole-cule	Dermatologic $P_a > P_i$	Antieczematic $P_a > P_i$	Antiprurtic $P_a > P_i$	Antiseborrheic $P_a > P_i$	Choleretic $P_a > P_i$	Antisecre-toric, c$P_a > P_i$	Antiinflam-matory, $P_a > P_i$
M-1	0.674 >0.009	0.716 >0.040	0.683 >0.009	0.694 >0.039	0.380 >0.020	0.678 >0.012	0.508 >0.054
M-2	0.637 >0.012	0.668 >0.057	0.689 >0.009	0.373 >0.100	0.292 >0.036	0.244 >0.125	0.589 >0.034
M-3	0.714 >0.007	0.534 >0.119	0.763 >0.005	0.884 >0.005	0.826 >0.003	0.541 >0.024	0.569 >0.039
M-4	0.598 >0.016	0.721 >0.039	0.615 >0.014	0.816 >0.016	0.466 >0.011	0.408 >0.055	-
M-5	0.511 >0.030	0.672 >0.055	0.503 >0.034	0.239 >0.154	-	0.358 >0.071	-
M-6	0.584 >0.018	0.635 >0.071	0.679 >0.009	0.622 >0.051	0.746 >0.003	0.422 >0.051	-
M-7	0.535 >0.025	0.672 >0.056	0.414 >0.055	0.369 >0.101	0.552 >0.007	-	-
M-8	0.442 >0.044	0.736 >0.034	0.345 >0.080	-	-	0.316 >0.084	0.398 >0.097
M-9	0.787 >0.005	0.698 >0.046	0.540 >0.007	0.907 >0.004	0.540 >0.007	0.766 >0.005	0.893 >0.004
M-10	0.704 >0.008	0.512 >0.130	0.333 >0.087	0.316 >0.117	0.232 >0.060	-	-
M-11	0.770 >0.005	0.642 >0.068	0.587 >0.018	0.652 >0.046	0.735 >0.003	0.439 0.045	0.587 >0.035
M-12	0.679 >0.009	0.853 >0.009	0.703 >0.008	0.828 >0.014	0.720 >0.004	0.521 >0.026	0.332 >0.134
M-13	0.627 >0.013	0.642 >0.068	0.747 >0.005	0.709 >0.036	0.648 >0.005	0.473 >0.035	0.615 >0.028
M-14	0.647 >0.011	0.695 >0.047	0.729 >0.006	0.744 >0.029	0.601 >0.005	0.538 >0.024	0.596 >0.033
M-15	0.765 >0.005	0.721 >0.039	0.729 >0.006	0.802 >0.019	0.765 >0.003	0.433 >0.047	0.655 >0.022
M-16	0.668 >0.010	0.530 >0.121	0.469 >0.041	0.805 >0.018	0.278 >0.041	0.370 >0.067	-
M-17	0.639 >0.012	0.688 >0.050	0.669 >0.010	0.641 >0.048	0.225 >0.063	-	0.457 >0.070
M-18	0.619 >0.014	0.510 >0.131	0.385 >0.064	0.339 >0.110	-	0.406 >0.056	-
M-19	0.673 >0.009	0.683 >0.052	0.338 >0.083	0.644 >0.047	0.291 >0.037	0.239 >0.130	-
M-20	0.790 >0.005	0.762 >0.027	0.566 >0.021	0.814 >0.017	0.579 >0.006	0.376 >0.065	0.569 >0.039
M-21	0.676 >0.009	0.735 >0.034	0.688 >0.009	0.832 >0.013	0.697 >0.004	0.585 >0.019	0.472 >0.065
M-22	0.657 >0.011	0.681 >0.052	0.694 >0.008	0.865 >0.008	0.747 >0.003	0.471 >0.036	0.255 >0.206
M-23	0.692 >0.008	0.515 >0.129	0.591 >0.017	0.876 >0.006	0.346 >0.024	0.723 >0.008	-
M-24	0.615 >0.014	0.772 >0.025	0.706 >0.008	0.763 >0.026	0.373 >0.021	0.553 >0.022	0.735 >0.012
M-25	0.757 >0.005	0.627 >0.074	-	0.904 >0.004	0.524 >0.008	0.718 >0.009	0.530 >0.048
M-26	0.796 >0.004	0.542 >0.114	0.365 >0.070	0.567 >0.060	-	-	0.497 >0.058
M-27	0.772 >0.005	0.765 >0.027	0.715 >0.007	0.830 >0.013	0.863 >0.002	0.535 >0.024	0.399 >0.096
M-28	0.552 >0.022	-	0.419 >0.053	0.214 >0.155	-	0.500 >0.137	0.370 >0.112
M-29	0.655 >0.011	0.495 >0.140	0.638 >0.012	0.751 >0.028	0.439 >0.014	0.649 >0.014	0.604 >0.031
M-30	0.795 >0.004	0.667 >0.057	0.693 >0.008	0.745 >0.029	0.501 >0.009	0.594 >0.018	0.496 >0.058
M-31	0.591 >0.017	0.346 >0.242	0.568 >0.021	0.520 >0.069	0.303 >0.033	0.225 >0.144	0.558 >0.041
M-32	0.731 >0.006	0.628 >0.074	0.689 >0.009	0.657 >0.045	0.456 >0.012	0.320 >0.083	0.559 >0.041
M-33	0.621 >0.014	0.363 >0.227	0.754 >0.005	0.270 >0.137	0.211 >0.071	0.394 >0.060	0.884 >0.005

- indicates the absence of a particular type of activity.

The identified molecules of pregnane have been analyzed for the estimation of various activity types viz. *dermatologic, antieczematic, antipruritic, antiseborrheic choleretic, antisecretoric and antiinflammatory.* The computed values of P_a and P_i for the molecules (1-33) are presented in Table 5.

Based on the data as obtained from the simulation studied on biological activity relationship, it is pertinent that all the molecules possess high probability of *dermatologic* activity. Positive *antieczematic* activity has been shown by all the molecules except M-28 and 33.

All molecules show high value of probability for *antprurtic* activity, while in molecules M-8, 10, 18, 19, 25 and 26, this activity is either absent or show low values. The $P_a > P_i$ indicates that all the molecules except [M- 2, 7, 8, 10, 18, 28 and 33] show high value of *antiseborrheic* activity. It appears that all the molecules exhibits high probability of *choleretic* and *antisecretoric* activities except for molecules [M- 1, 2, 5, 8, 16-19, 24-26, 28, 31, 33 and 2, 5, 7, 10, 16, 17, 19, 20, 26 31-33] respectively for which these activities are either absent or have low values. The *anti-inflammatory* activity is prevalent in almost 50% of the identified molecules.

Table 6. Geometry of C-H...O, O-H...O, N-H…O, C-H…Cl, C-H…N, C-H...Br, C-H…F and O-H…N intra and intermolecular interactions

Molecule [Number of donors andacceptors]	**Intramolecular interactions X-H...A**	**H...A(Å) *d***	**X...A(Å) *D***	**X-H...A(°) *θ***
M-9	O17-H17O…O1W	2.188	3.079	170.9
Donors=1				
Acceptors =1				
M-18	C12H12B…Cl1	2.62	3.076	108
Donors=2	C20-H20…Cl1	2.67	3.349	125
Acceptors =2	C20-H20…O1	2.42	2.812	103
M-22	O2-H2…O4	2.01	2.771	158
Donors=1				
Acceptors =1				
	Intermolecular interactions			
M-1	C7-H7B…O3B	2.673	3.631	169.6
Donors=3	C1-H1B…O5	2.535	3.328	139.0
Acceptors =3	C21-H21C…O20	2.599	3.389	139.6
M-2	C21-H26…O3	2.709	3.304	127.6
Donors=4	C2-H20…O2	2.586	3.194	116.3
Acceptors =4	O1'-H43…O1	1.876	2.770	158.7
	O1-H27…O3'	1.714	2.811	145.5
M-3	C1-H10…O1	2.408	3.396	160.9
Donors=6	O2-H21…O1	2.242	2.974	166.7
Acceptors =4	C15-H17…O3	2.281	3.251	152.8
	C2-H7…O4	2.671	3.644	160.2
	O5-H33…O2	2.026	2.887	158.6
	C4-H5…O4	2.710	3.382	125.2
M-4	C23'-H19F…Cl2	2.931	3.811	151.1
Donors=5	C23-H19A…Cl1	2.883	3.723	146.7
Acceptors =4	C4-H4B…Cl3'	2.909	3.686	137.8
	C12-H12A…O2'	2.566	3.485	158.2
	C17-H17A…O2'	2.720	3.638	156.0
M-5	C15-H15B…Cl	2.899	3.803	155.7
Donors=2	C26-H26A…O4	2.676	3.353	127.2
Acceptors =2				
M-6	O5-H37…O3	2.167	2.926	156.9
Donors=4	C23-H32…O1	2.689	3.673	150.3
Acceptors =4	C1-H2…O5	2.716	3.619	156.9
	O5-H38…O1	1.912	2.855	162.7
	O1-H35…O2	2.135	2.845	162.4
M-7	C23-H34…O1	2.529	3.259	127.6
Donors=3	O1-H37…O3	2.164	2.983	157.1
Acceptors =3	C16-H21…O2	2.498	3.543	163.4
M-8	O3-H31…O2	2.169	2.949	159.4
Donors=2	O3-H32…N1	2.049	2.829	158.9
Acceptors =3	O1-H1…O3 (W)	1.979	2.790	170.7
M-9	C23-H23C…O22'	2.651	3.534	153.2
Donors=4	O1W-H1W…O20	2.032	2.845	144.8
Acceptors =3	C2-H2A…O22'	2.699	3.649	166.8
M-10	C8'-H8'…O2	2.538	3.323	136.9
Donors=1				
Acceptors =1				
M-11	C26'-H78…O3	2.626	3.622	156.2
Donors=5	C6-H11…O2'	2.486	3.352	143.5
Acceptors =5	C26-H36…O3'	2.426	3.231	130.3
	C23'-H72…O5	2.714	3.553	153.5
	O3'-H1…O5	1.980	2.906	157.6
	C26'-H79...O5'	2.382	3.480	174.6

M-12	C4-H4A…O1	2.675	3.535	146.8
Donors=4	O1-H1…O5(W)	2.459	3.103	136.4
Acceptors =3	O4-H4…O5(W)	2.039	2.806	154.0
	C4-H4A…O1	2.675	3.535	146.8
	O2-H2…O4	2.183	2.962	158.8
M-13	C28-H28A…O5	2.619	3.420	141.1
Donors=9	C21'-H71B…O2	2.591	3.416	144.1
Acceptors =6	C31'-H81C…O2	2.707	3.463	136.2
	C3'-H53A…O3	2.595	3.432	143.5
	C5'-H55A…O3	2.637	3.481	144.7
	C16-H16A…O2'	2.519	3.331	140.2
	C5-H5A…O3'	2.514	3.360	144.3
	C16'-H66A…O2	2.542	3.429	150.5
	C6-H6A…O5'	2.669	3.596	160.1
M-14	C8-H8A…O2	2.632	2.560	158.0
Donors=3	C14-H14A…O5	2.531	3.466	159.4
Acceptors =3	C16-H16A…O4	2.410	3.217	139.2
M-15	C21-H21B…O3	2.653	3.401	133.3
Donors=3	O3-H3…O11	2.205	2.948	145.6
Acceptors =3	C2-H2A…O20	2.679	3.578	151.1
M-16	C19-H18A…O1	2.635	3.278	123.5
Donors=3	C23-H23A…O4	2.422	3.397	172.9
Acceptors =3	C21-H20C...O2	2.605	3.535	158.5
M-17	C15-H15B…O22	2.466	3.436	177.4
Donors=5	O5-H5A…O20	1.981	2.794	170.9
Acceptors =5	C16-H16A…O5'	2.649	3.617	176.4
	C15'-H15D…O22'	2.322	3.286	172.9
	O5'-H5B…O20'	1.983	2.782	164.7
M-18	C25-H25C…O1	2.683	3.516	143.0
Donors=4	C23-H23C…O3	2.539	3.488	162.8
Acceptors =3	C2-H2C…Cl1	2.882	3.592	129.4
	N1-H1…O1	2.034	2.893	165.3
M-19	O1-H1X…O3	2.087	2.868	164.7
Donors=4	C23-H23C…O2	2.584	3.562	175.3
Acceptors =5	O3-H3X…O1'	1.862	2.740	162.5
	O1'-H1Y…O2'	2.373	3.179	148.6
	O1'-H1Y…O3'	2.023	2.915	170.3
M-20	O16-H1Y…O2	2.104	2.806	152.9
Donors=4	O2-H2X…O2'	1.954	2.818	162.1
Acceptors =4	O2'-H2Y…O1	1.837	2.716	163.2
	O1-H1X…O1'	1.882	2.743	162.2
M-21	O3-H3…O3'	1.943	2.709	170.4
Donors=3	C16'-H16C…O12'	2.435	3.287	143.9
Acceptors =2	C21-H17F…O3'	2.673	3.600	157.8
M-22	C21-H21A…O1	2.610	3.288	127.9
Donors=3	O3-H3…O4	2.187	2.916	149.8
Acceptors =4	C21-H2A…O3	2.658	3.423	136.8
	O1-H1…O2	2.059	2.928	169.7
M-23	C19-H19C…O1	2.628	3.569	166.8
Donors=3	C5-H5A…N1	2.685	3.615	158.5
Acceptors =3	C18-H18C…O2	2.565	3.472	157.7
M-24	C27-H27C…O28'	2.44	3.36	160.22
Donors=1				
Acceptors =1				

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M-25	C21-H212…O3	2.707	3.629	158.5
Donors=3	C21-H211…O1	2.678	3.291	121.3
Acceptors =4	C7-H71…O4	2.574	3.525	168.3
	C17-H171…O2	2.633	3.215	118.3
M-26	C1-H11…O3	2.492	3.393	153.8
Donors=2	C9-H91…O3	2.661	3.449	138.0
Acceptors =1				
M-27	O1-H1…O2	1.864	2.698	166.8
Donors=3	C21-H19B…O1	2.561	3.271	130.9
Acceptors =2	O2-H2…O1	1.899	2.741	170.8
M-28	C12-H12B…O2	2.715	3.623	156.2
Donors=4	C21-H21B…O2	2.682	3.588	157.9
Acceptors =3	N1-H1…O1W	2.126	2.972	167.8
	O1W-H1WA…O1	1.892	2.745	153.1
M-29	C4-H4B…O1	2.714	3.539	143.1
Donors=3	C9-H9…O3	2.365	3.321	164.8
Acceptors =3	C21-H30A…O5	2.442	3.345	156.5
M-30	C27'-H27E…O1	2.706	3.659	172.1
Donors=4	C25-H25B…S1	2.848	3.558	130.7
Acceptors =4	C4'-H4'B…O2'	2.695	3.419	131.8
	C23'-H23C…S2'	2.822	2.648	148.0
M-31	C6-H6B…O4	2.655	3.231	118.4
Donors=4	C22-H22A…O4	2.572	3.531	177.1
Acceptors =3	C2-H2A…O5	2.712	3.673	171.1
	C12-H12B…O6	2.488	3.362	149.7
M-32	C15-H15B…O3	2.560	3.327	134.2
Donors=4	C16-H16A…O3	2.687	3.378	127.1
Acceptors =3	C15-H15A…O11	2.465	3.358	149.7
	C7-H7B…O11	2.553	3.329	135.2
	O3-H3…N21	2.204	2.949	147.8
M-33	C15'-H15C…O22	2.614	3.482	149.1
Donors=8	C4-H4A1…O20	2.553	3.242	127.9
Acceptors =5	C5-H5A…O20	2.013	2.822	168.3
	C1'-H1B1…O7	2.616	3.326	130.2
	C1-H1A1…O7'	2.582	3.145	117.2
	C4'-H2B1…O20'	2.550	2.297	133.8
	O5'-H5B…O20'	2.107	2.913	167.6
	C15-H15A…O22	2.529	3.429	154.2

' indicates second crystallographically independent molecule;

Molecular packing interaction analysis

Hydrogen bonds play a very vital role in crystal engineering due to their strength, directionality and flexibility.[41] In almost every crystal structure that contains hydrogen bonding functionalities, the packing cannot be understood without taking into account the hydrogen bonding patterns. The strong hydrogen bond of the type O-H…O and N-H…O remains well documented but the concept of weak hydrogen bonds formed between C-H groups and electronegative atoms has received considerable attention of the community involved in the field of crystal design and engineering. Crystallographers regard these interactions as weak but significant "Directional Intermolecular Forces". It is now very well understood that C-H…O interactions (and other types of weak hydrogen bonds) are important as secondary interactions, and in many instances even play dominant roles in determining crystal packing, molecular conformations and in the stability & activity of biological small and macromolecules.[42-44] A close examination of intra and intermolecular interactions, including the bifurcated hydrogen bond, present in pregnane class of steroids leads us to the existence of intra and intermolecular hydrogen bonds of the type C-H…O, O-H…O, N-H…O, C-H…N, C-H…S, O-H…N, C-H…Cl, C-H…F hydrogen bonds as observed in pregnane are presented in Table 6.

Packing interactions include both the intra and intermolecular hydrogen bonds which are directional interactions with a preference for linear geometry.[45] These interactions can be analyzed in a better way by drawing *d*-θ and *D*-θ scatter plots. The plots include all contacts found in molecule (1-33) with d < 2.84Å and D < 3.81Å at any occurring angle θ. The graphical projection of d(H…A) against θ (X-H…A) and D(X…A) against θ (X–H…A) i.e. *d*-θ and *D*-θ scatter plots have been made for intermolecular hydrogen bonds as presented in Figure 4(a, b).

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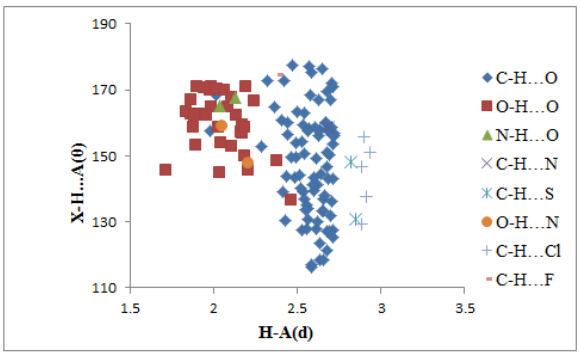
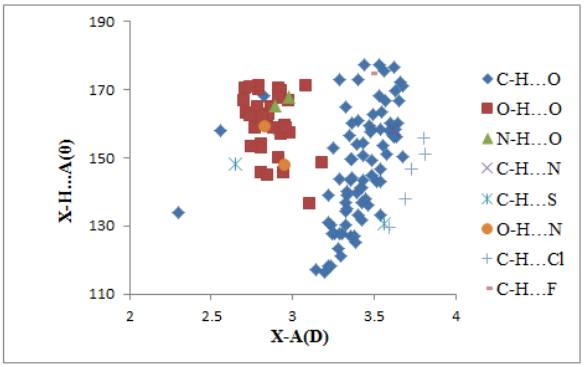


a)



b)

Figure 4. (a) *d*-*θ* scatter plot for intermolecular C-H...O, O-H...O, N-H…O, C-H…N, C-H…S, O-H…N, C-H…Cl and C-H...F. (b) *D*-*θ* scatter plot for intermolecular C-H...O, O-H...O, N-H…O, C-H…N, C-H…S, O-H…N,C-H…Cl and C-H...F.

From *d*-*θ* and *D*-*θ* scatter plots for hydrogen bonds, the following observations have been made:

The scatter spots for C-H…O hydrogen bonds clusters in the range of *d*(H…A) = 2.40-2.75 Å; *D*(X…A) = 3.20-3.70 Å and *θ*(X–H…A) =115-179°.

For the O-H…O type of hydrogen bond, the density of spots is maximum in the *d*(H…A) range of 1.85-2.30 Å, *D*(X…A) range of 2.75-3.1 Å for *θ*(X-H…A) in the range 145-175°.

Almost all the O-H…O contacts belongs to the category of strong H-bonds whereas C-H…O contacts falls in the range of weak interactions.

The relative frequency of occurrence of various types of C-H...O, O-H...O, N-H…O, C-H…N, C-H…S, O-H…N, C-H…Cl and C-H...F intermolecular hydrogen bonds is 64.61, 25.15, 1.53, 0.76, 1.53, 1.53, 3.84 and 0.76%, respectively and it is shown in Figure 5.

Based on the data on hydrogen bonding as presented in Table 6, it is observed that the *d* (H…A) lies between 1.76-2.93Å, *D*(X-A) ranges between 2.29-3.81Å, whereas angular range falls between 116.3-177.4° for all H-bonds. The range for *d* (H…A), *D*(X-A) and angular range *θ*(X–H…A) for C-H…O and O-H…O hydrogen bonds are presented in Table 7 and are compared with the values suggested by Desiraju and Steiner[46] to classify the hydrogen bonds as very strong, strong and weak.

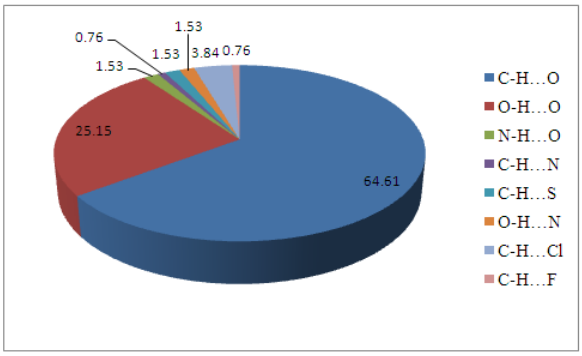


Figure 5. Relative frequency of occurrence (in %) for various types of intermolecular hydrogen bonding.

The overall D(X-A) and d(H…A) range as obtained in case of C-H…O hydrogen bonds comes out to be between 2.56-3.67Å and 1.98-2.72Å respectively, making these interactions fall under the category of "strong to weak" interactions. The angular *θ*(X–H…A) range (116.3-177.4^0) in the present case is tilted more towards the values used to describe weak interactions, hence interactions can be assumed as weak one. However, in case of O-H…O hydrogen bonds, *D*(X-A) and *d*(H…A) range lies between 2.70-3.17Å and 1.71-2.45Å respectively, indicating that the interactions belongs to the category of "strong to weak" inter actions. The angular range (136.4-170.9^0) in case of O-H…O hydrogen bonds lies purely in the range used to describe the interactions as strong one.

The existence of bifurcated hydrogen bonding is the stand out feature of pregnane derivatives. Around 40% of the structures identified for the present work have revealed their existence. In molecule M-1, Oxygen atom O1and O4 act as a bifurcated hydrogen bond acceptor forming intermolecular bonds [C1-H10…O1and O2-H21…O1; C2-H7…O4 and C4-H5…O4] with bifurcated angle of 327.6° and 285.4° respectively. In M-4 (asymmetric unit having two independent molecules), oxygen atom O2' of the acetoxy group acts as bifurcated acceptor forming two hydrogen bonds [C12-H12A…O2' and C17-H17A…O2'] having bifurcated angle of 314.2°. In molecules M-6, oxygen atom O1acts as bifurcated acceptor forming hydrogen bonds [C32-H32…O1 and O5-H38…O1]. In molecule M-12, Oxygen atom O5 of water molecule is involved in bifurcated hydrogen bonding forming bonds [O1-H1…O5 and O4-H4…O5] with a bifurcated angle of 290.4°. In molecule M-13, asymmetric unit is having two independent molecules. Oxygen atom O2 is involved in trifurcated hydrogen bonding forming hydrogen bonds [C21'-H71B…O2, C31'-H81C…O2 and C16'-H66A…O2] and O3 is also acting as bifurcated acceptor in hydrogen bonds C3'-H53A…O3and C5'-H55A…O3 with bifurcated angle of 288.2°. Oxygen atom O1 of M-18 is also acting as bifurcated acceptor with a bifurcated angle of 308.3° in bonds C25-H25C…O1 and N1-H1…O1. Molecule M-19 is having two crystallographically independent molecules in the asymmetric unit. Oxygen atom O1' of second independent molecule is involved in bifurcated hydrogen bonding in which H1Y-atom of O1' is shared between O1'-O2' and O1'-O3' forming two intermolecular H-bonds [O1'-H1Y…O2', O1'-H1…O3'] with bifurcated angle of 318.9°.

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Table 7. Geometrical parameters for very strong, strong and weak intermolecular hydrogen bonds

Property	Very strong	Strong	Weak	Present work	
				C-H…O	O-H…O
D(X-A) range (Å)	2.0 -2.5	2.5 - 3.2	3.0 - 4.0	2.56-3.67	2.70-3.17
d(H…A)range (Å)	1.2 -1.5	1.5 - 2.2	2. 0 - 3.0	1.98-2.72	1.71-2.45
θ(X-H…A) range(^{0})	175 - 180	130 -180	90 - 180	116.3-177.4	136.4-170.9

Oxygen atom O3' of molecule M-21 is acting as a bifurcated acceptor in hydrogen bonds O3-H3…O3' and C21-H21A…O3' with bifurcated angle of 328.2°. Oxygen atom O3 of M-26 acts as bifurcated acceptor with bifurcated angle of 291.8° forming [C1-H11…O3 and C9-H91…O3] hydrogen bonds. In M-32, oxygen atoms O4, O3 and O11act as bifurcated acceptors forming hydrogen bonds [C6-H6B…O4 and C22-H22A…O4; C15-H15B…O3 and C16-H16A…O3; C15-H15A…O11and C7-H7B…O11]. Bifurcated bonds are also observed in molecule M-33 where oxygen atoms O22, O20 and O20' are involved in bifurcated hydrogen bonding. A representative view of bifurcated bond having oxygen atom acting as bifurcated acceptor of M-18 is shown in Figure 6.

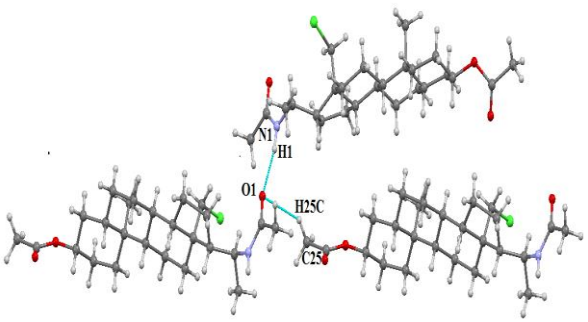

Figure6 Representative view of bifurcated hydrogen bonding in molecule M-18.

Conclusions

The pregnane class of steroids have been analysed in the present work for their crystallographic comparison, biological activity predictions and molecular packing interactions. The molecules in the unit cell are linked by C-H…O/O-H…O/N-H…O interactions and most of these are associated through the acetyl, acetoxy and the hydroxyl group located at different positions of the pregnane derivatives. The biological activity predictions have been made on the basis of a probability scale (P_a and P_i) generated through PASS software. It is depicted that unusual substitution with the basic steroid moiety/nucleus may change the biological activity of the molecule. The nature of the substituent at C3 and C17 positions of the pregnane nucleus makes these molecules very interesting candidates for hydrogen bonding analysis. In most of the cases, the substituent at C3 and C17 positions are primarily responsible for the occurrence of intra and intermolecular hydrogen bonding in pregnanes. Different kind of molecular interactions make up the different crystal structures in the pregnane series. The first and strongest interaction is the O-H...O hydrogen bonds while majority consists of weak C-H…O contacts. We anticipate that the understanding of these interactions in crystal packing will help the chemists /crystallographers to ameliorate a structure to give it desired properties. Hence, the information about the comparative crystallography, biological activity prediction and detailed hydrogen bonding analysis of some pregnane derivatives as presented in the form of a small compendium shall go a log way in understanding the structure and function of steroids.

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