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Comparative Structural Crystallography and Molecular Interaction Analysis of Cholestane class of steroid derivatives

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Abstract: *Cholestane ($C_{27}H_{48}$), the parent compound of all steroids, is obtained by the removal of hydroxyl group (from C3 position) and reduction of double bond (between C5 and C6 atoms) from the basic cholesterol nucleus. A total number of twenty-three structures of cholestane 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. Intermolecular interactions of the type X-H…A [X=C,O, N; A=O, Cl, N, Br, F] have been analysed for a better understanding of molecular packing in cholestane class of steroids and discussed on the basis of distance-angle scatter plots, with the following key questions in the background:(i) Which of the interactions, viz. C-H…O, O-H…O, N-H…O, C-H…Cl, C-H…N, C-H…Br, C-H…F,O-H…N, are dominant in cholestane class of steroids? (ii) Is there any preference of linearity for different hydrogen bonded interactions? (iii) Preparing a small dedicated compendium of crystallographic data, biological activity and hydrogen bonding interactions on a relative scale?*

Keywords: *Bifurcated hydrogen bond, Biological activity, Cholestane, Hydrogen bonding, Intermolecular interactions, Steroids.*

I. Introduction

Crystallographic data on steroids collected in the Atlas of Steroid Structure provide information concerning preferred conformations, relative stabilities and substituent influence of the interactive potential of steroid hormones. Analysis of these data indicates that observed conformational details are intra-molecularly controlled and that the influence of crystal packing forces is not much consequential [1]. In order to revisit the findings of this kind on a crystallography focused analysis of different classes of steroids, we got interested to undertake independent work on various classes of steroid derivatives.

Cholesterol is convertible into a fully saturated compound, cholestane ($C_{27}H_{48}$). A representative illustration of the cholesterol molecule is presented in Fig. 1.Without considering the detail of the reactions or the specific compounds involved, the cholestane skeleton gives rise to some other important steroid classes as shown in Fig.2 [2]. As a part of our research on the comparative crystallographic findings, including biological activity predictions and molecular packing interaction analysis [3, 4 and 5], we identified a series of twenty-three cholestane derivatives [6-24] from Cambridge Structure Database (CSD). The chemical structure of each compound and its numbering is presented in Fig. 3 while the reference code, chemical name, chemical formula, molecular weight and published reference is presented in Table 1.

II. Methodology

1.1 Crystallographic comparison

All the cholestane derivatives as obtained from CSD were analyzed for their precise comparative structural parameters that include the crystal class, space group, the number of molecules per asymmetric unit cell, the final R-factor (Table 2), selected bond distances and bond angles (Table 3). Quantitative description of different ring conformations using asymmetry and pseudorotational parameters and available X-ray structure data gives an impression of the conformational mobility. The ring conformations for each structure were computed and the comprehensive data are presented in Table 4. The CIF for each structure was used as an input to Mercury 3.5 software for the computation of possible hydrogen interactions. The geometrical restrictions placed on the intermolecular H-bonds present in the selected pair are the sum of van der Waals radii for the generation of quality interaction data, ignoring few very weak interactions.

1.2 Biological activity predictions

Biological activity of steroids is one of the most important reasons for their synthesis and structural characterization. It is the result of chemical compound's interaction with biological activity that a total matrix of activities caused by the compound is generated which is generally referred to as the biological activity spectrum of the substance. It is a concept that is crucial to PASS (Prediction of Activity spectra for Substances) software which provides the rationale for predicting many activity types for different compounds[25].The structural formula of a molecule is presented as a mol file and the predictions result is in the form of a table containing the

list of biological activities on a scale of probability ranging from 0-1. 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 the most probable and predicted ones for a given compound. The P_a and P_i values for the molecules (1-23) are presented in Table 5.

1.3 Molecular packing interaction analysis

Hydrogen bonds play a vital role in crystal engineering because of their three peculiar features i.e., strength, directionality and flexibility [26]. Strong hydrogen bonds such as O-H…O and N-H…O are well documented, but weak interactions such as C-H…O , C-H…X (X-halogen atom) and C-H…N have also attracted considerable interest because of their frequent occurrence in organic crystal structures [27, 28]. The knowledge gained about these interactions and through their analysis help to understand the structure of biomolecules with implications for structure-based drug design. Therefore, in the light of some latest research going on in the field of hydrogen bonding [29,30 and 31], we examined hydrogen-bonded interactions of the type, C-H…O, O-H…O, N-H…O, C-H…Cl, C-H…N, C-H…Br, C-H…F,O-H…N, present in cholestane derivatives. The interaction data are presented in Table 6.

III. Results and Discussion

1.4 Comparative crystallographic analysis

Based on the crystallographic data as presented in Table 2-4, the following observations can be made:

1. The most commonly occurring crystal system is monoclinic (73.9%), followed by orthorhombic (26.1%). The most commonly occurring space group is $P2_1$ (65.2%), followed by $P2_12_12_1$ (26%) and C2 (8.7%). This observation is in agreement with the findings of Stout and Jensen [32].
2. A careful analysis of reliability index (R-factor) indicates that a reasonably good level of confidence has been achieved while reporting the crystal structure for each compound (the R-factor range being 0.0264 - 0.0920).
3. The phenomenon of multiple molecules ($Z'=2$), observed in molecules M-1, 4, 6, 8, 14, 18, 20 and 22, respectively, is confined only to 30% of the total number of structures. Reproducible crystallization of such a series of chemically-similar-lookingcompounds might suggest thereasons for cholestanes exhibiting the phenomenon of multiple molecules.
4. The variation in the bond length 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) and bond angle C2-C3-C4(sp^3/sp^2) in all the structures is quite interesting. The value of the bond C2-C3 (sp^3-sp^3) and C3-C4(sp^3-sp^3) in all the molecules except M-6 lies in the range 1.497-1.526Å and 1.497-1.566Å, respectively (average being 1.511Å). The bond angle C2-C3(sp^3)-C4 ranges between 108.9°- 114.39° (the average being 111.68°). However, in M-6 [with Z'=2], both the bond distances are sp^3-sp^2/sp^2-sp^3 hybridised.
5. All the three six- membered rings in twenty- three cholestane molecules adopt chair conformation, except ring B in molecules [M-2, 14(14')] which shows sofa conformation and this may be due to the presence of an epoxy group between C5 and C6. The relative frequency of various types of conformations occurring in six-membered and five-membered rings in molecules (1-23) are as shown in [Fig. 4(a, b)]. The incidence of occurrence of all the six-membered rings in chair conformation is 95.69%, followed by the sofa conformation (4.3%). Similarly, for the five-membered ring in all the twenty-three cholestane derivatives, the incidence of occurrence of envelope and distorted envelope conformation is 35.48%, followed by half-chair and intermediate between half-chair & envelope conformations (35.48 & 29.03% ,respectively).

1.5 Biological activity predictions

On comparing the activities as given in the Table 5, it is quite interesting to note that most of the cholestane derivatives possess high antieczematic, dermatologic, and antipruritic activities. The $P_a > P_i$ indicates that all the molecules except [M10, M-12] show high value of Choleretic activity. There appears to a quite large probability for the molecules M-6,7,9,11,13,14,15 to exhibit anti-inflammatory activity while other molecules are quite low on this aspect. All the molecules show high antisecretoric activity except [M-3, M-7, M-10, M-11, M-16]. Antiseborrheic activity is predicted for almost all the molecules except [M-1, M-7, M-8, M-10, M-13, M-20].

1.6 Molecular packing interactions

Packing interactions include both the intra and intermolecular hydrogen bonds which are directional interactions with a preference for linear geometry [33]. These interactions can be analyzed in a better way by making d-θ and D-θ scatter plots. The plots include all contacts found in molecule (1-23) with d <2.99Å and D <3.86Å at any occurring angle (θ). A graphical projection of d-θ [d(H…A) against θ (X-H…A)] and D-θ

[D(X…A) against θ (X–H…A)] scatter plots is presented in Fig.5(a,b). The following inference can be drawn from the d-θ and D-θ scatter plots:

(i) The scatter spots in the C-H…O hydrogen bond clusters lie in the range of d(H…A) = 2.30-2.72; D(X…A) = 3.3-3.55 and θ (X–H…A) = 130-170°, respectively.

(ii) The density of spots for the O-H…O type of hydrogen bond is maximum [range for d (H…A) =1.8-2.0 Å, D(X…A) =2.6-2.8 Å, θ(X–H…A)=165°-178°]. Most of 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.

(iii) The relative frequency of occurrence of various types 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 intermolecular hydrogen bonds is 48.61, 27.77, 4.16, 4.166, 1.38, 6.94, 1.38 and 5.55%, respectively and is presented in Fig.6,thus making C-H…Oas the most preferred intermolecular interaction in cholestane class of steroids.

(iv) For the overall description of all the intermolecular hydrogen interactions of the type 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,the minimum and maximum values for distance (d and D) and angle (θ) are d(H…A)= 1.73-3.01Å, D=2.45-3.86Å and θ(X–H…A)= 124.2-179.8°, respectively.

(v) The values for the dominant C-H…O and O-H…O hydrogen bonds (Table 7), when compared with the data as reported by Desiraju and Steiner [34], provided us a way for the classification of hydrogen bonding present in cholestane derivatives. The overall D(X-A) and d(H…A) range as obtained in case of C-H…O hydrogen bonds is between 2.45-3.68Å and 2.31-2.71Å, respectively; thus making these interactions fall under the category of "very strong to weak" while the θ(X–H…A) range (119.9-169.2°) suggests these interactions to be weak. However, in case of O-H…O hydrogen bonds, the D(X-A) and d(H…A) range lies between 2.57-3.62Å and 1.73-2.64Å, respectively, indicating these interactions to be "strong to weak" , while the θ(X–H…A) range (129.4-179.4°) in case of O-H…O hydrogen bonds suggests the presence of O-H…O as strong interactions.

Bifurcated hydrogen bonds are observed in O-H…O and N-H…O hydrogen bonded structures [35]. They are also observed in C-H…O/N patterns. In the present study, few bifurcated hydrogen bonds of the type C-H…O and O-H…O have also been observed, besides the presence of a trifurcated hydrogen bond in M-16. In molecule M-1, the asymmetric unit has two independent molecules. Oxygen atom O1and O1' act as a bifurcated hydrogen bond donor forming intermolecular bonds [O1-H1A…N1'and O1-H1A…O1 O1-H1'; O1'-H1B…N1 and O1'-H1B…O1] with bifurcated angle of 292.9° and 279.8°.Oxygen atom O6 of M-3 acts as bifurcated acceptor with bifurcated angle of 314.5° forming [C26-H261…O6 and C1-H2…O6] hydrogen bonds. In M-2(the asymmetric unit having two independent molecules), the oxygen atom O2 of the ketone group acts as a bifurcated acceptor, forming two hydrogen bonds [C17'-H11L…O2 and C19'-H11R…O2], having bifurcated angle of 279.1°. In molecules M-11,14,16, 21,22, the oxygen atoms O4, O1',O3,O2, O6, O1 and O1' act as bifurcated acceptor forming hydrogen bonds [C2-H4…O4 andO1-H46…O4; C4-H4A…O1' and O1-H1…O1'; C6-H6…O3 and O1-H1…O3,O3-H3…O2 and C1-H1B…O2; C6-H6…O6 and O5-H5A…O6; C1-H7AA…O1 and C23'-H23D…O1,C23-H23B…O1' and C1'-H7BA…O1'].In molecule M-20, having two crystallographically independent molecules in the asymmetric unit, the oxygen atoms O1and O1' are involved in bifurcated hydrogen bonding [H1-atom of O1is shared between O1-N2 and O1-O1'], forming two intermolecular H-bonds[O1-H1…N2,O1-H1…O1'] with bifurcated angle of 282.9°and H4-atom of O1' is shared between O1'-N1 and O1'-O1, forming two intermolecular H-bonds[O1'-H4…N1,O1'-H4…O1] with an bifurcated angle of 288.2°, respectively. The oxygen atom O1 acts as a bifurcated acceptor in O1'-H4…O1and C3-H4A…O1 hydrogen bonds, the bifurcated angle being 286.9°. A representative view of bifurcated hydrogen bond formation is shown in Fig. 7.

IV. Figures and Tables

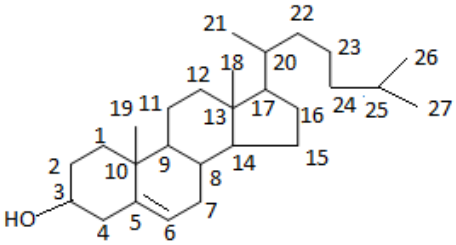
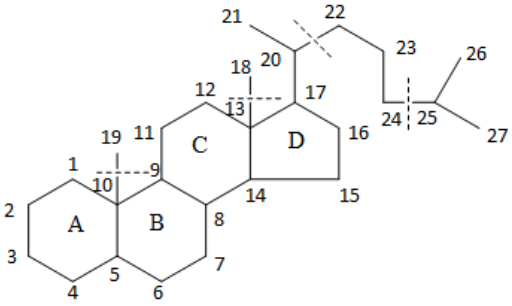
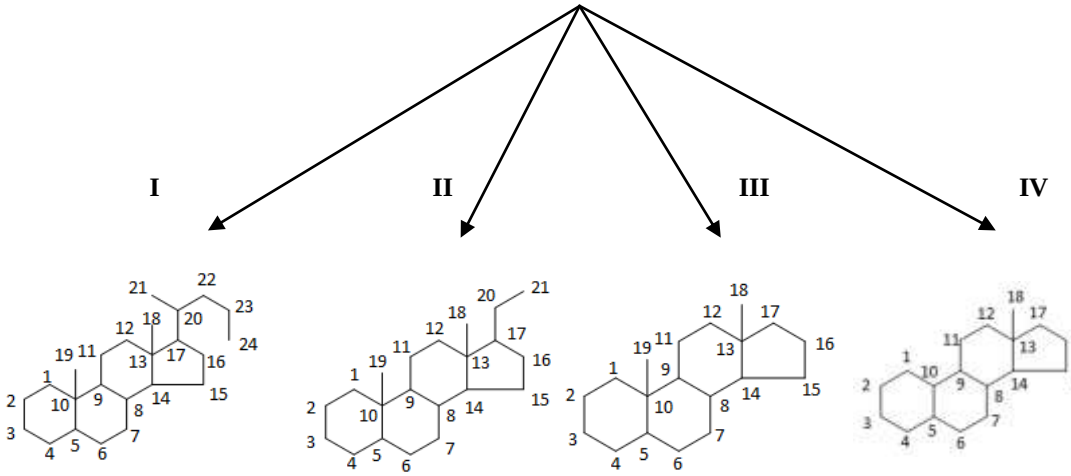


Figure1. The cyclopentanoperhydrophenanthrene nucleus and the numbering scheme of cholesterol.

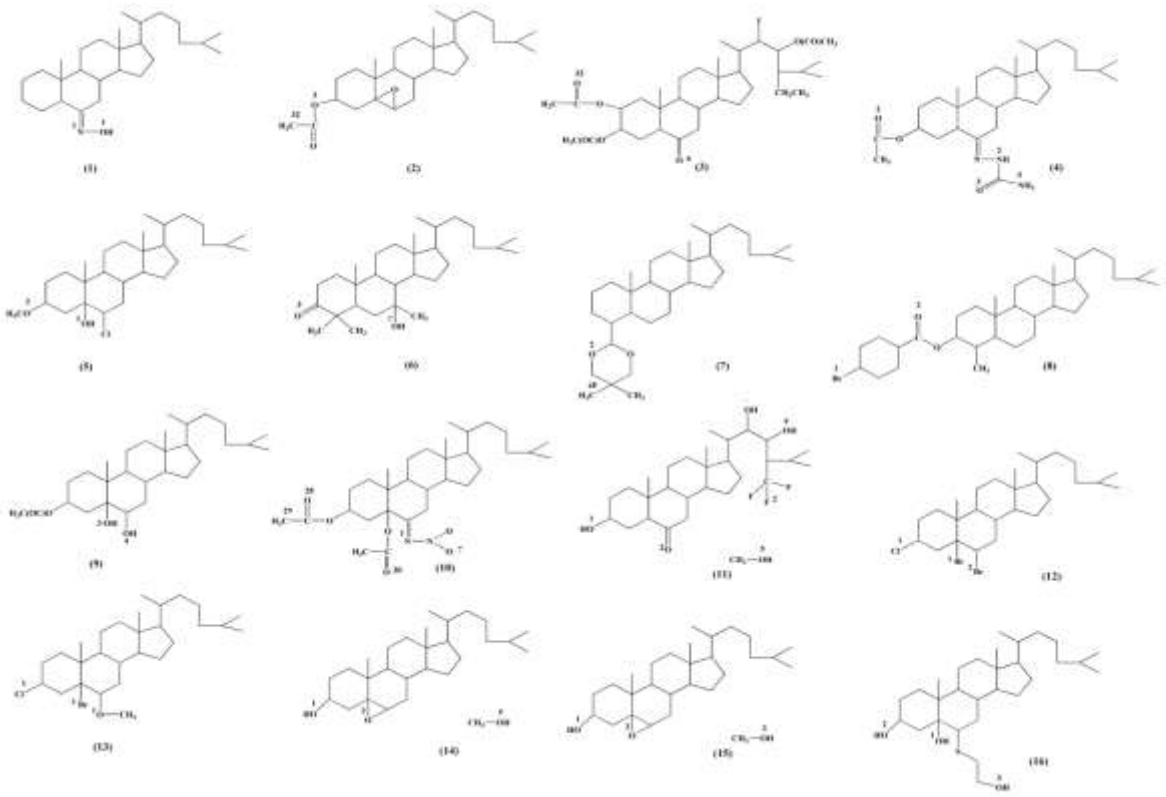


Cholestane (C_{27})



Cholane (C_{24}) **Pregnane (C_{21})** **Androstane (C_{19})** **Estrane (C_{18})**

Figure2. Relationship between various parent steroid hydrocarbon and cholestane.



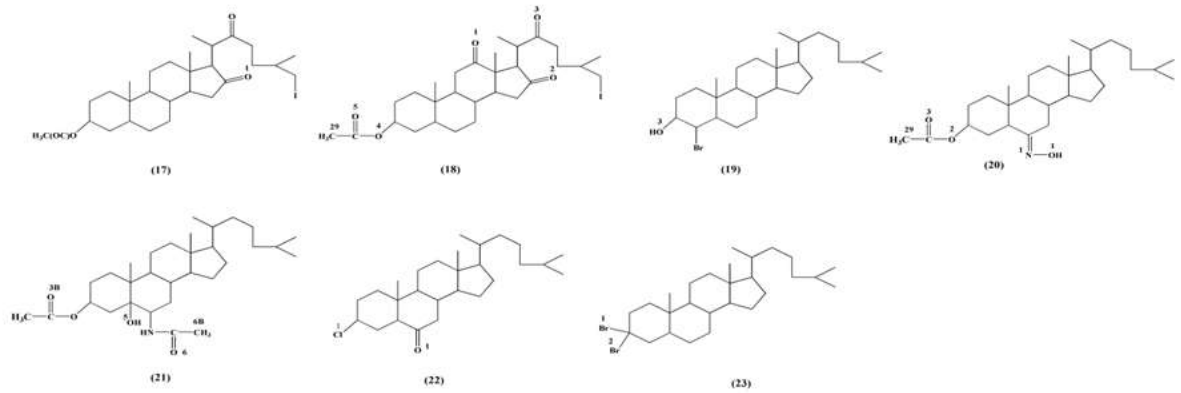
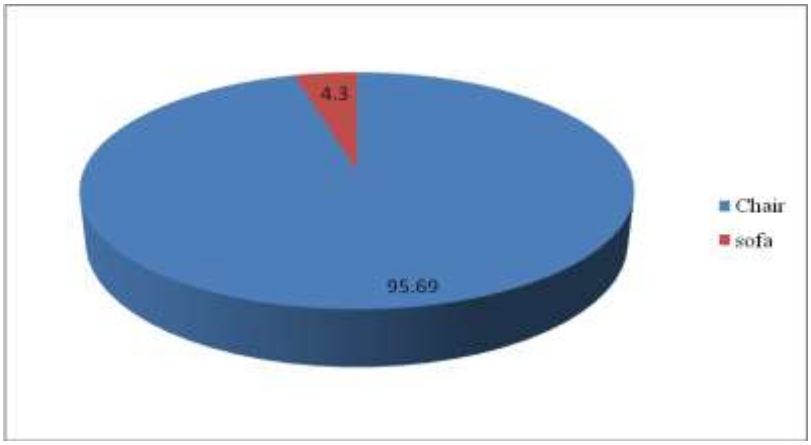
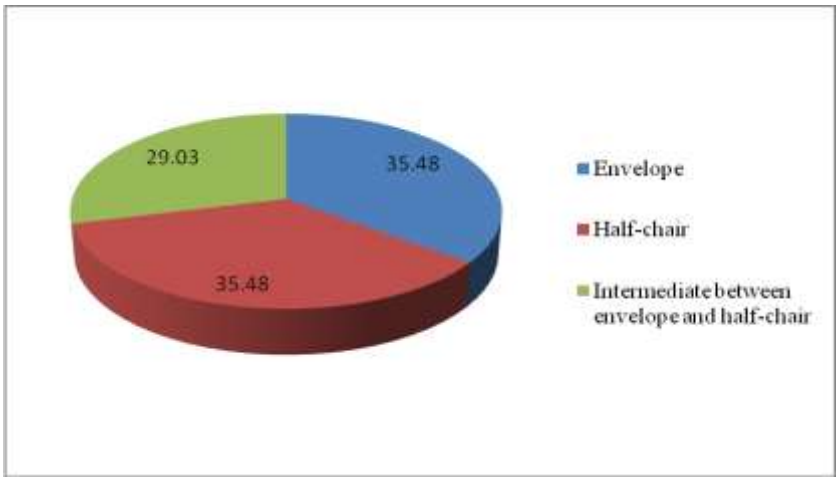


Figure3. Chemical structures of molecules (1-23).

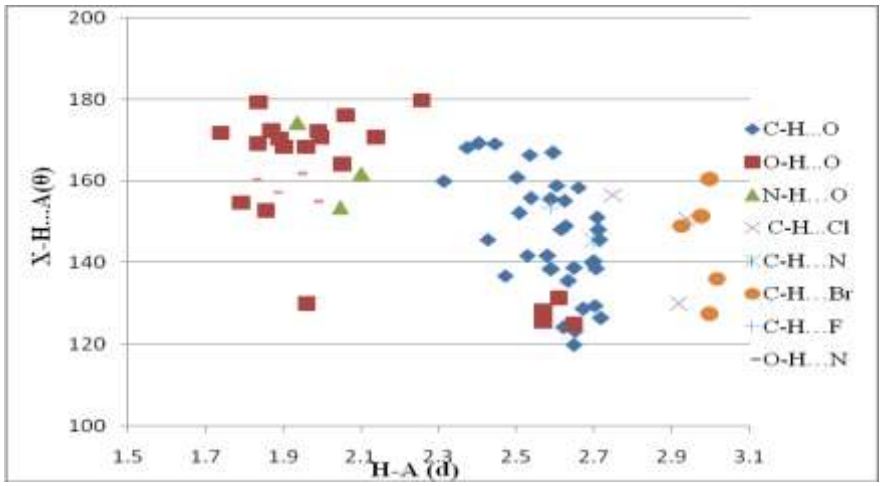


(a)



(b)

Figure4. (a) Relative frequency of occurrence (in %)for various types of conformations in six-memberedrings A, B and C(molecules 1-23).
(b) Relative frequency ofoccurrence (in %) for various types ofconformations in five- membered ringsD(molecules 1-23).



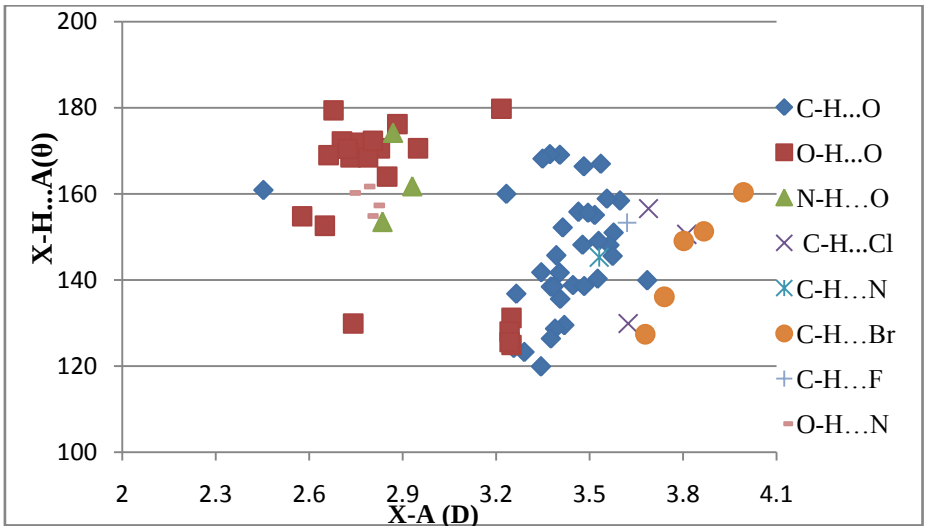


Figure5. (a) d-θ scatter plot for intermolecular C-H...O, O-H...O, N-H...O, C-H...Cl, C-H...N C-H...Br and C-H…F.
(b) D-θ scatter plot for intermolecular C-H...O, O-H...O, N-H...O, C-H...Cl, C-H...N, C-H...Br and C-H…F.

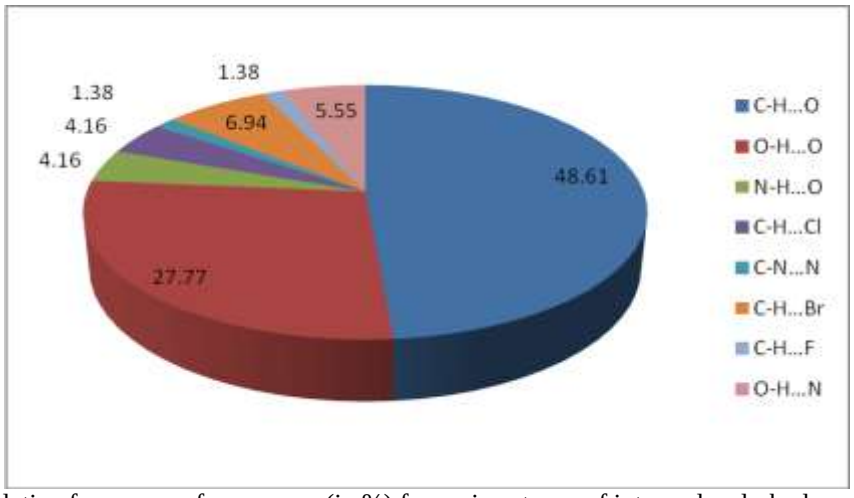


Figure6. Relative frequency of occurence (in %) for various types of intermolecularhydrogen bonding.

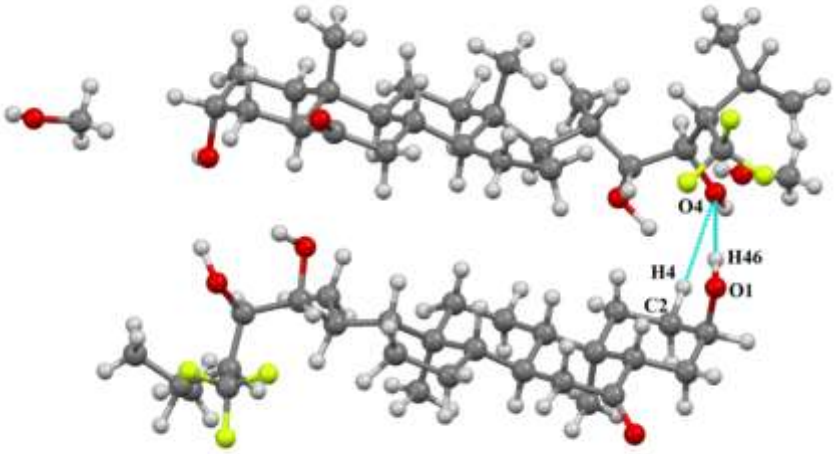


Figure7. Representative view of bifurcated hydrogen bonding in molecule M-11.

Table1. CSD code, chemical name, chemical formula, molecular wt. and reference of Molecule 1-23

Molecule	CSD Code	Chemical Name	Chemical Formula	Molecular Weight (amu)	Reference
M-1	CEHHAA	6-Hydroxyimino-5α-cholestane	$C_{27}H_{47}NO$	401.65	6
M-2	ESIKOG	5,6-Epoxy-3-cholestanyl acetate	$C_{29}H4_8O_3$	444.67	7
M-3	GUXJUE	Triacetoxy-22-iodo-24-ethyl-5-cholestan-6-one	$C_{35}H_{55}IO_7$	714.69	8
M-4	HUNBAT	3β-Acetoxy-5α-cholestan-6-one semicarbazone	$C_{30}H_{51}N_3O_3$	501.00	9
M-5	HUXHEO	(3R,5R,6R,8S,9S,10R,13R,14S,17R,20R)-6β-chloro-5α-hydroxy-3β- Methoxycholestane	$C_{28}H_{49}ClO_2$	453.12	10
M-6	IDIKUB	(5α,7α)-7-Hydroxy-4,4,7-trimethylcholestan-3-one	$C_{30}H_{52}O_2$	444.72	11
M-7	MIVHOP	4α-(5-Dimethyl-1,3-dioxan-2-yl)-5α-H-cholestane	$C_{33}H_{58}O_2$	486.79	12
M-8	NENREE	4α-Methyl-5α-cholestan-3β-yl 4-bromobenzoate	$C_{35}H_{53}BrO_2$	585.68	13
M-9	PIDTAY	5α,6β-Dihydroxycholestan-3β-yl acetate	$C_{29}H_{50}O_4$	462.69	14
M-10	POQTAR	anti-3β,5α-Diacetoxy-6-nitroiminocholestane	$C_{31}H_{50}N_2O_6$	546.73	15
M-11	RAWHIG	(22R,23R,24S)-3α,22,23-Trihydroxy-24-(trifluoromethyl)-5β-cholestan-6-one methanol solvate	$C_{28}H_{45}F_3O_4,CH_4O$	470.0	16
M-12	SEBPAR	5α,6β-Dibromo-3β-chlorocholestane	$C_{27}H_{45}Br_2Cl$	564.90	17
M-13	SEBPEV	5α-Bromo-3β-chloro-6β-methoxycholestane	$C_{28}H_{48}BrClO$	516.02	17
M-14	SEDWOP	5,6α-Epoxycholestan-3-ol methanol solvate	$C_{27}H_{46}O_2,0.5(CH_4O)$	418.66	18
M-15	SEDWUV	5,6β-Epoxycholestan-3-ol methanol solvate	$C_{27}H_{46}O_2,CH_4O$	434.68	18
M-16	SEDXAC	5α-Hydroxy-6β-(2-	$C_{29}H_{52}O_3S$	480.77	18

		hydroxyethylsulfanyl)cholestan-3β-ol			
M-17	SELZAL	(25R)-26-Iodo-3β-acetoxy-5α-cholestane-16,22-dione	$C_{29}H_{45}IO_4$	584.55	19
M-18	SELZEP	(25R)-26-Iodo-3β-acetoxy-5α-cholestane-11,16,22-trione	$C_{29}H_{43}IO_5$	598.53	19
M-19	SUQDUE	4α-Bromo-5α-cholestan-3β-ol	$C_{27}H_{47}BrO$	467.56	20
M-20	UNOZIH	3β-Acetoxy-6-hydroxyiminocholestane	$C_{29}H_{49}NO_3$	459.69	21
M-21	VOJBIG	6β-Acetamido-5α-hydroxycholestan-3β-yl acetate	$C_{31}H_{53}NO_4$	503.74	22
M-22	YAXYAZ	3β-Chloro-5α-cholestan-6-one	$C_{27}H_{45}ClO$	421.08	23
M-23	ZZZQLQ01	3,3-Dibromocholestane	$C_{27}H_{46}Br_2$	530.46	24

Table2. Preliminary crystal data for Molecule 1-23

Molecule	**Crystal system**	**Space group**	**R-factor**	**Z(Z′)**
M-1	Monoclinic	$P2_1$	0.0494	4(2)
M-2	Monoclinic	$P2_1$	0.0759	2
M-3	Monoclinic	C2	0.0397	4
M-4	Orthorhombic	$P2_12_12_1$	0.05	8(2)
M-5	Orthorhombic	$P2_12_12_1$	0.0378	4
M-6	Monoclinic	$P2_1$	0.0650	4(2)
M-7	Monoclinic	$P2_1$	0.0513	2
M-8	Monoclinic	$P2_1$	0.0431	4(2)
M-9	Monoclinic	$P2_1$	0.0512	2
M-10	Orthorhombic	$P2_12_12_1$	0.0711	4
M-11	Monoclinic	$P2_1$	0.05	2
M-12	Orthorhombic	$P2_12_12_1$	0.0264	4
M-13	Monoclinic	$P2_1$	0.0295	2
M-14	Monoclinic	$P2_1$	0.0628	4(2)
M-15	Monoclinic	$P2_1$	0.0546	2
M-16	Orthorhombic	$P2_12_12_1$	0.0372	4
M-17	Orthorhombic	$P2_12_12_1$	0.0689	4
M-18	Monoclinic	$P2_1$	0.0920	4(2)
M-19	Monoclinic	$P2_1$	0.0268	2
M-20	Monoclinic	$P2_1$	0.050	4(2)
M-21	Monoclinic	C2	0.0496	4
M-22	Monoclinic	$P2_1$	0.0666	4(2)
M-23	Monoclinic	$P2_1$	0.0370	2

Table3. Selected bond distances (Å) and bond angles (°) for molecules (1-23)

Molecule	**Bond Distance(Å) [C 2 - C3]**		**Bond Distance(Å) [C 3 - 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	1.511		1.52		110.62	
M-1'	1.526		1.522		110.86	
M-2	1.521		1.566		109.77	
M-3	1.494		1.54		108.99	
M-4	1.498		1.509		111.25	
M-4'	1.519		1.512		112.13	
M-5	1.519		1.533		111.59	
M-6		1.497		1.52		115.99
M-6'		1.493		1.52		116.72
M-7	1.518		1.534		111.82	
M-8	1.502		1.527		112.45	
M- 8'	1.495		1.514		112.84	
M-9	1.512		1.498		112.76	
M-10	1.518		1.519		111.78	
M-11	1.52		1.522		112.59	

M-12	1.514		1.517		112.96	
M-13	1.503		1.52		112.74	
M-14	1.521		1.509		110.89	
M- 14'	1.506		1.537		111.32	
M-15	1.51		1.514		109.9	
M-16	1.523		1.518		110.87	
M-17	1.495		1.499		112.98	
M-18	1.495		1.545		109.31	
M-18'	1.53		1.497		114.39	
M-19	1.509		1.518		110.98	
M-20	1.512		1.511		111.97	
M-20'	1.51		1.514		111.82	
M-21	1.511		1.512		111.74	
M-22	1.515		1.523		112.27	
M- 22'	1.525		1.507		112.2	
M-23	1.491		1.521		113.04	

Table4.Different types of conformations in the individual ring systems for Molecule 1-23

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

Table5. P_a and P_i values for the Molecule 1-23

Molecule	**Dermatologic $P_a > P_i$**	**Antiinflammatory $P_a > P_i$**	**Antiseborrheic $P_a > P_i$**	**Antisecretoric $P_a > P_i$**	**Antieczematic $P_a > P_i$**	**Choleretic $P_a > P_i$**	**Antipruritic $P_a > P_i$**
M-1	0.731 >0.006	-	0.296 >0.125	-	0.777 >0.024	-	0.623 >0.013

M-2	0.673 >0.009	0.282 >0.108	0.540 >0.065	0.776 >0.005	0.785 >0.022	0.408 >0.017	0.782 >0.004
M-3	0.674 >0.009	0.379 >0.015	0.485 >0.075	0.264 >0.109	-	-	0.535 >0.027
M-4	0.655 >0.011	0.251 >0.211	-	-	0.725 >0.037	0.370 >0.021	0.716 >0.007
M-5	0.639 >0.012	0.323 >0.141	0.390 >0.095	-	0.781 >0.023	0.448 >0.013	0.777 >0.004
M-6	0.728 >0.006	0.500 >0.057	0.352 >0.106	0.375 >0.065	0.779 >0.023	0.936 >0.001	0.705 >0.008
M-7	0.782 >0.005	0.544 >0.045	0.221 >0.167	0.244 >0.125	0.803 >0.018	0.644 >0.005	0.734 >0.006
M-8	0.676 >0.009	0.386 >0.103	0.230 >0.160	0.498 >0.030	0.801 >0.018	0.549 >0.007	0.600 >0.016
M-9	0.698 >0.008	0.493 >0.059	0.496 >0.073	0.496 >0.073	0.840 >0.011	0.697 >0.004	0.789 >0.004
M-10	0.683 >0.009	0.289 >0.171	0.194 >0.190	0.195 >0.172	0.803 >0.018	0.254 >0.050	0.612 >0.014
M-11	0.712 >0.007	0.677 >0.019	0.606 >0.054	0.273 >0.104	0.786 >0.022	0.779 >0.003	0.654 >0.011
M-12	0.650 >0.011	-	-	-	0.665 >0.058	0.174 >0.100	0.559 >0.022
M-13	0.694 >0.008	0.466 >0.067	0.237 >0.155	-	0.779 >0.023	0.395 >0.018	0.783 >0.004
M-14	0.704 >0.008	0.430 >0.081	0.432 >0.086	0.680 >0.011	0.810 >0.017	0.644 >0.005	0.790 >0.004
M-15	0.704 >0.008	0.430 >0.081	0.432 >0.086	0.680 >0.011	0.810 >0.017	0.644 >0.005	0.790 >0.004
M-16	0.671 >0.010	0.373 >0.110	0.356>0.104	0.249 >0.121	0.747 >0.031	0.611 >0.005	0.682 >0.009
M-17	0.673 >0.009	-	0.763 >0.026	0.433 >0.047	0.753 >0.030	0.713 >0.004	0.674 >0.009
M-18	0.602 >0.015	-	0.721 >0.034	0.378 >0.065	0.681 >0.052	0.748 >0.003	0.636 >0.012
M-19	0.712 >0.007	-	0.473 >0.077	0.346 >0.074	0.817 >0.015	0.688 >0.004	0.700 >0.008
M-20	0.722 >0.007	0.282 >0.179	0.284 >0.130	-	0.773 >0.024	0.614 >0.005	0.704 >0.008
M-21	0.626 >0.013	-	-	-	0.734 >0.006	0.479 >0.010	0.734 >0.006
M-22	0.765 >0.005	-	0.381 >0.098	-	0.743 >0.032	0.523 >0.008	0.797 >0.004
M-23	0.746 >0.005	-	0.606 >0.054	0.426 >0.049	0.813 >0.016	0.680 >0.004	0.715 >0.007

Table6. 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 Intermolecularinteractions.

Molecule [Number of Donors and Acceptors]	**Intermolecular interactions X-H...A**	**H...A(Å) d**	**X...A(Å) D**	**X-H...A(°) θ**
M-1 CEHHAA Donors=2 Acceptors =4	O1-H1A…N1' O1'-H1B…N1 O1-H1A…O1' O1'-H1B…O1	1.938 1.980 2.608 2.647	2.779 2.790 3.249 3.249	161.7 154.9 131.2 124.9
M-2 ESIKOG Donors=1 Acceptors =1	C32-H323…O3	2.707	3.577	151
M-3 GUXJUE Donors=3 Acceptors =2	C26-H261…O6 C1-H12…O6 C2-H2…O32	2.712 2.533 2.650	3.564 3.482 3.291	148.1 166.4 123.3
M-4 HUNBAT Donors=3 Acceptors =3	N2-H1...O3' N3-H3A...O2 N2'-H2'A...O3	1.936 2.101 2.046	2.869 2.931 2.835	174.2 161.8 153.5
M-5 HUXHEO Donors=2 Acceptors =2	O1-H1…O2 C17-H17…Cl	1.995 2.750	2.827 3.689	170.6 156.6
M-6 IDIKUB Donors=2 Acceptors =2	O7'-H57D…O3 O7-H7D…O3'	2.140 2.062	2.949 2.883	170.6 176.2
M-7 MIVHOP Donors=1 Acceptors =1	C4F-H4F1…O2	2.594	3.536	167
M-8 NENREE Donors=3	C26-H26A…Br1 C17'-H11L…O2 C19'-H11R…O2	2.999 2.699 2.648	3.679 3.526 3.447	127.4 140.3 138.8

Acceptors =2				
M-9 PIDTAY Donors=1 Acceptors =1	O3-H31…O4	2.053	2.85	164
M-10 POQTAR Donors=4 Acceptors =4	C29-H29C…O30 C23-H23B…O28 C16-H16B…O7 C18-H18C…N1	2.314 2.615 2.588 2.699	3.233 3.478 3.376 3.531	160.0 148.2 138.4 145.3
M-11 RAWHIG Donors=6 Acceptors =6	O5-H49…O1 O4-H48…O5 C1-H1…O2 C7-H9…O3 C2-H4…O4 O1-H46…O4 C2-H3…F2	1.737 1.959 2.426 2.647 2.695 2.255 2.589	2.763 2.741 3.393 3.344 3.685 3.217 3.620	171.9 129.9 145.7 119.9 139.9 179.8 153.3
M-12 SEBPAR Donors=2 Acceptors =2	C21-H21A…Cl1 C1-H1A…Br1	2.937 2.927	3.812 3.802	150.6 149.1
M-13 SEBPEV Donors=2 Acceptors =2	C23-H3…O1 C15-H15B…Br1	2.659 2.978	3.598 3.867	158.4 151.3
M-14 SEDWOP Donors=4 Acceptors =3	O5-H5…O1 O1'-H3…O5 C4-H4A…O1' O1-H1…O1'	1.854 1.870 2.702 1.904	2.650 2.705 3.419 2.733	152.6 172.2 129.5 168.5
M-15 SEDWUV Donors=3 Acceptors =3	O3-H3A…O1 C7-H7B…O2 O1-H1…O3	1.792 2.537 1.833	2.577 3.464 2.662	154.8 155.8 169.0
M-16 SEDXAC Donors=6 Acceptors =3	C6-H6…O3 O1-H1…O3 O3-H3…O2 C1-H1B…O2 O2-H2…O1 C3-H3B…O2	2.673 1.891 1.837 2.713 1.961 2.626	3.389 2.723 2.678 3.574 2.789 3.529	128.7 170.5 179.4 145.6 168.5 149.1
M-17 SELZAL Donors=1 Acceptors =1	C27-H27A…O1	2.446	3.405	169.1
M-18 SELZEP Donors=6 Acceptors =6	C29-H29…O4' C29'-H58C…O5 C15-H15B…O3' C18-H18A…O2 C8'-H37…O1 C27-H27A…O5'	2.623 2.717 2.528 2.705 2.634 2.589	3.517 3.376 3.345 3.483 3.406 3.495	155.1 126.4 141.8 138.6 135.6 155.6
M-19 SUQDUE Donors=1 Acceptors =1	C2-H2A…Br	2.998	3.994	160.4
M-20 UNOZIH Donors=5 Acceptors =6	O1'-H4…N1 O1'-H4…O1 O1-H1…N2 O1-H1…O1' C29-H9C…O3' C29'-H37C…O3 C3-H4A…O1	1.821 2.571 1.877 2.570 2.580 2.404 2.604	2.733 3.243 2.810 3.243 3.404 3.373 3.556	160.2 128.0 157.3 125.6 141.7 169.2 158.9
M-21 VOJBIG Donors=3 Acceptors =2	C6BH6BA…O3B C6-H6…O6 O5-H5A…O6	2.620 2.588 1.989	3.257 3.385 2.804	124.2 138.5 172.3
M-22 YAXYAZ Donors=5 Acceptors =3	C1-H7AA…O1 C23'-H23D…O1 C23-H23B…O1' C1'-H7BA…O1' C26-H26E…Cl1'	2.374 2.502 2.507 2.471 2.917	3.349 2.453 3.414 3.265 3.624	168.2 160.9 152.2 136.8 129.9
M-23 ZZZQLQ01 Donors=1	C6-H6A…Br2	3.015	3.74	136.1

Acceptors =1				

' indicates second crystallographically independent molecule;

Table7. Geometrical parameters for very strong, strong and weak 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	2.45-3.68	2.57-3.62
d(H…A) range (Å)	1.2 -1.5	1.5 - 2.2	2. 0 - 3.0	2.31-2.71	1.73- 2.64
θ(X-H…A) range(^{0})	175 - 180	130 -180	90 - 180	119.9- 169.2	124.9- 179.4

V. Conclusion

1. The cholestane class of steroids have been analysed in the present work for their crystallographic comparison, biological activity predictions and molecular packing interactions.
2. Some general but useful inferences have been drawn about the crystal structures of the identified series of cholestane derivatives.
3. The biological activity predictions have been made on the basis of a probability scale (P_a and P_i) generated through PASS software.
4. The nature of the substituent at C3 position of the cholestane nucleus makes these molecules very interesting candidates for hydrogen bonding analysis. In most of the cases, the substituent at C3 position is primarily responsible for the occurrence of intermolecular hydrogen bonding in cholestanes. These substitutions are linked by intermolecular hydrogen bonding which in turn help to understand the dynamics of stacking interactions in supramolecular structures.
5. A careful examination of the entire interaction data reveals that the C-H…O hydrogen bonding is quite predominant in cholestane derivatives. Almost all the O-H…O contacts belongs to the category of strong hydrogen bonds while majority of C-H…O contacts belongs to weak interactions.
6. A small compendium containing information about the comparative crystallography, biological activity prediction and detailed hydrogen bonding analysis of cholestane derivatives is thus presented in the form of this report. It is expected that these findings shall form the basis for the contemplation of further work on different classes of steroid derivatives.

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