HYDROGEN BONDING AND ACTIVITY ANALYSIS OF CHOLANE CLASS OF STEROID DERIVATIVES

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Keywords: cholane; biological activity, intermolecular hydrogen bonding, bifurcated hydrogen bond, solute-solvent interaction

Most of the crystallographic analysis that follows from structure determination involves interpretation of the molecular geometry and a working knowledge of a variety of intra- and intermolecular interactions based purely on geometrical considerations (distance and angle cut off criteria). In this paper, a total of fifty-nine structures of cholane derivatives have been chosen for the prediction of their biological activities and hydrogen bonding interaction analysis. Intermolecular interactions of the type X-H…A [X=C, O, N; A=O, Cl, N, Br] in all the structures have been computed and discussed primarily on the basis of distance-angle scatter for better understanding of molecular packing in cholane derivatives. In some structures, bifurcated hydrogen bonds have been observed. Solute-solvent/solvent-solute interactions have also been investigated to understand more complicated processes that occur for biomolecules in aqueous solution.

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Introduction

In steroid biochemistry and pharmacology, the carbon skeleton or nucleus consisting of four-ring structure of which three are six-membered cyclohexane rings, one is five-membered cyclopentane ring and a side chain of five carbon atoms located at C17 position of steroid nucleus is regarded as a cholane molecule. Figure1 presents the representative illustration of cholane molecule.[1] The end product of cholesterol metabolism is bile acids which are dihydroxylated and trihydroxylated steroids with 24 carbon atoms i.e., cholane.[2]

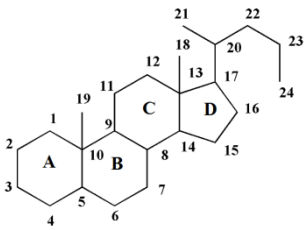


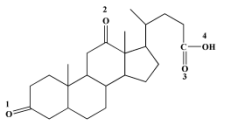
Figure 1. Basic cholane molecule (C24) with standard atomic numbering scheme

Bile acids, their conjugates, and bile salts are natural products that represent the 67% of the soluble components of bile. The most abundant mammalian bile acids are hydroxy derivatives of cholanoic acid and in humans, these consist mainly of cholic acid and chenodeoxycholic acid.[3] The bile acid group also includes conjugates of deoxycholic acid and lithocholic acid, commonly known as secondary bile acids, produced from cholic and chenodeoxycholic acids by intestinal bacteria dehydroxylation.[4] Before excretion into the bile, acids are conjugate either with glycine or taurine to produce the bile salts.[5] These salts enter the small intestine where they facilitate lipid absorption.[6,7] Bile acids are largely reabsorbed from the intestine[8,9] and pass back to the liver in the enterohepatic circulation. Cholic and chenodeoxycholic (and its 7-hydroxy epimer ursodeoxycholic) acids have important pharmaceutical applications related to their ability to dissolve cholesterol gallstones and for the treatment of bile acid deficiency and cholestatic liver diseases.[10,11] Antiviral properties of bile acids have also been investigated.[12] Bile acids have potential medical applications as analgesics,[13] sensitizers of Gram negative bacterial to antibiotics,[14] and radiopharmaceuticals.[15]

The present work provides comprehensive information about biological activity, structural features and packing interactions/hydrogen bonding in cholane derivatives. Here, we have identified a series of fifty-nine derivatives of cholane from the literature (CSD). The chemical structure of each compound and its numbering is presented in Figure 2. The reference code, chemical name, chemical formula, molecular weight and published reference of each structure is presented in Table 1. [16-44]

Biological activity relationship

Biological activity is the result of chemical compound's interaction with biological entity. Any biologically active compound reveals wide spectrum of different effects. Some of them are useful in treatment of definite diseases but the others cause various side and toxic effects. Biological activity spectrum is defined as the "intrinsic" property of compound depending only on its structure and physico-chemical characteristics. Total complex of activities caused by the compound in biological entities is also called as the "biological activity spectrum of the substance".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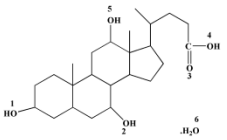
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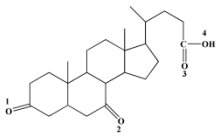
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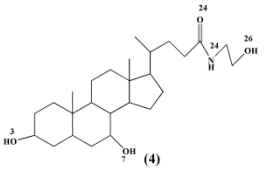
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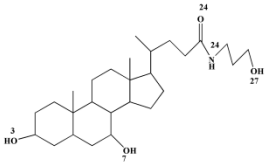
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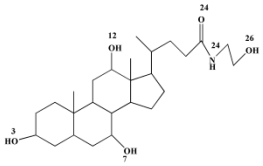
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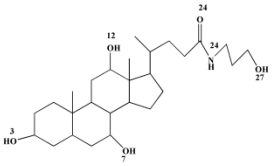
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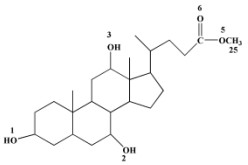
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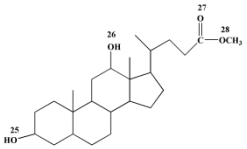
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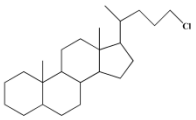
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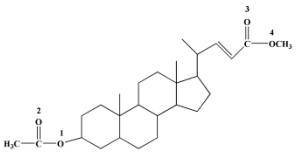
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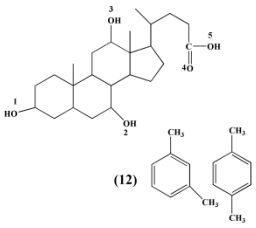
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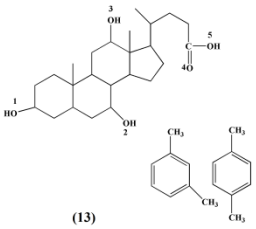
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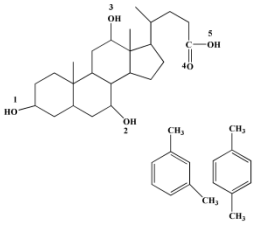
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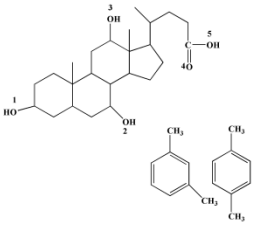
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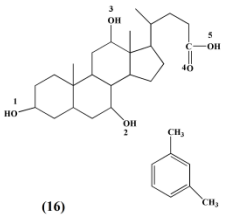
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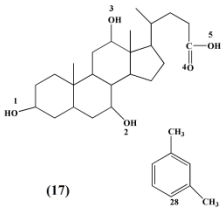
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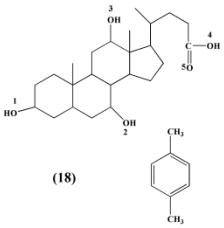
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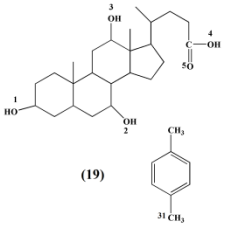
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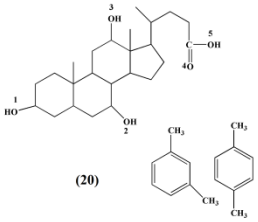
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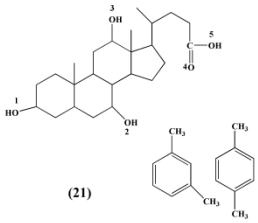
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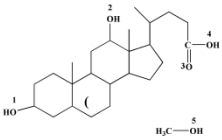
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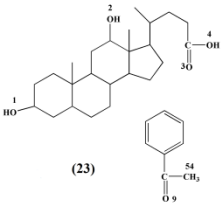
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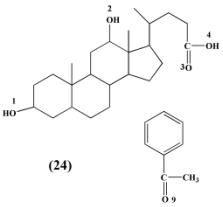
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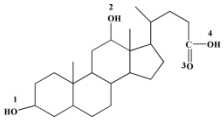
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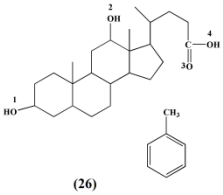
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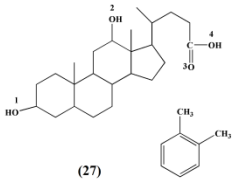
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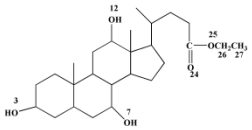
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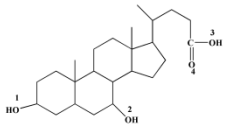
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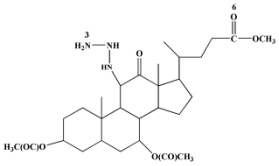
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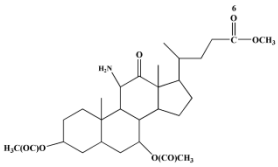
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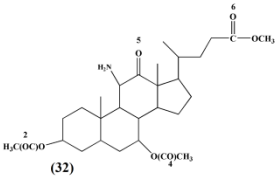
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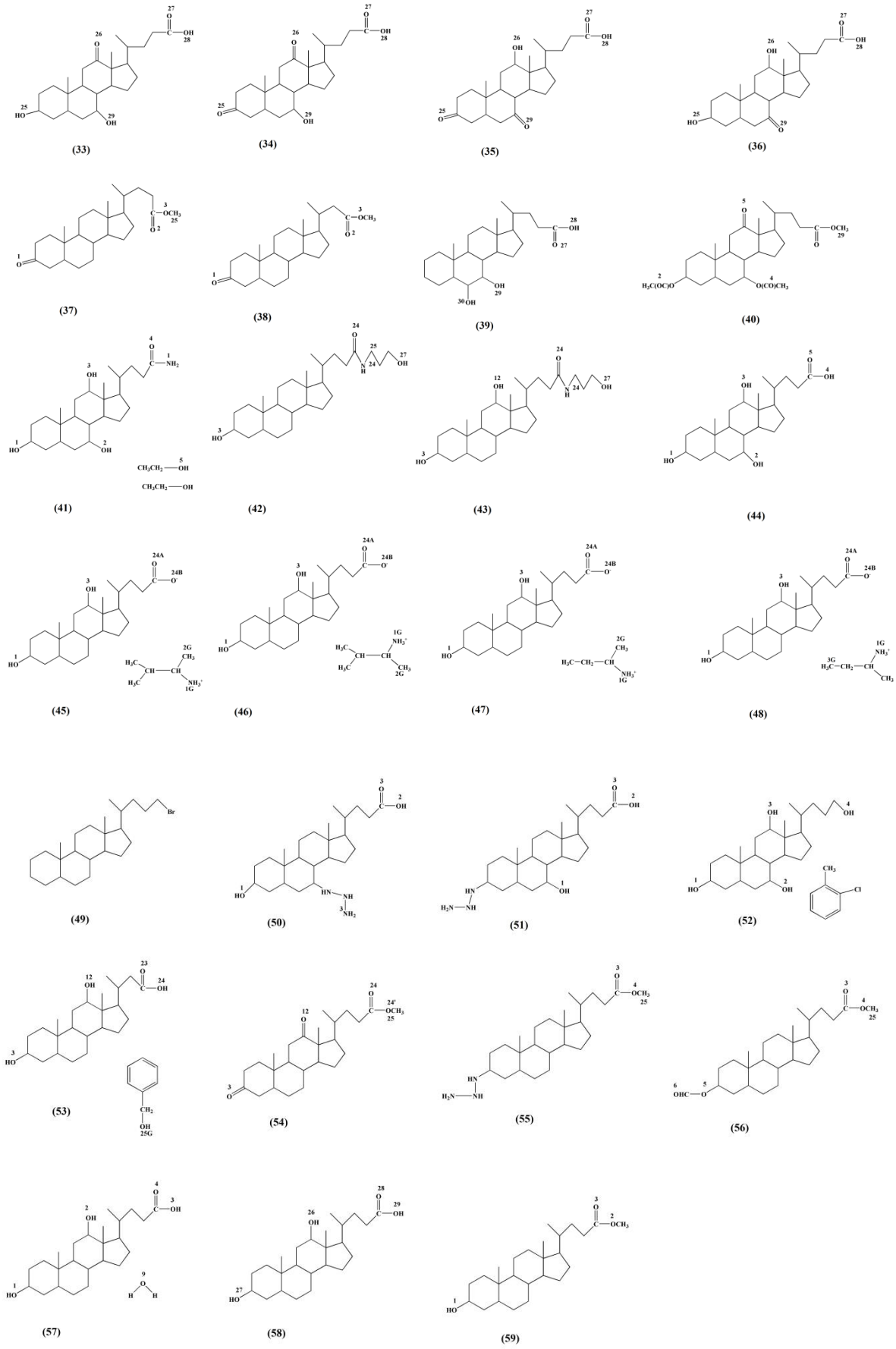

Figure 2. Chemical structures of molecules (**1-59**)

Table 1. CSD code, chemical name, chemical formula, molecular weight. and reference of molecules **1-59**

No.	Reference code	Chemical name	Chemical formula	MW, amu	Ref.,
M-1	ADIMAC	(+)-3,12-Dioxo-5β-cholanic acid	$C_{24}H_{36}O_4$	388.53	16
M-2	BUGJES01	3α,7α,12α-Trihydroxy-5β-cholan-24-oic acid monohydrate clathrate	$C_{24}H_{40}O_5.H_2O$	426.0	17
M-3	CELKOU	(-)-3,7-Dioxo-5β-cholanic acid	$C_2{}^4H_{36}O_4$	388.53	18
M-4	COYYAR	N-(2-Hydroxyethyl)-3α,7β-dihydroxy-5β-cholan-24-amide	$C_{26}H_{45}NO4$	435.63	19
M-5	COYYEV	N-(3-Hydroxypropyl)-3α,7β-dihydroxy-5β-cholan-24-amide	$C_{27}H_{47}NO_4$	449.66	19
M-6	COYYIZ	N-(2-Hydroxyethyl)-3α,7α,12α-trihydroxy-5β-cholan-24-amide	$C_{26}H_{45}NO_5$	451.63	19
M-7	COYYOF	N-(3-Hydroxypropyl)-3α,7α,12α-trihydroxy-5β-cholan-24-amide	$C_{27}H_{47}NO_5$	465.66	19
M-8	COYZIA	Methyl 3α,7α,12α,15β-tetrahydroxy-5β-cholan-24-oate acetonitrile solvate	$C_{25}H_{42}O_6.C_2H_3N$	479.64	20
M-9	DADLEA	3β,12β-Dihydroxy-5β-cholan-24-oic acid	$C_{24}H_{40}O_4$	392.56	21
M-10	EBUYUV	(5S,8R,9R,10R,13S,14S,17R,20R)-5β-Cholan-24-yl chloride	$C_{24}H_{41}Cl$	365.02	22
M-11	EDIGAA	Methyl (20S, 22E)-3-β-acetoxy-5-α-chola-22-enoate	$C_{27}H_{42}O_4$	430.61	23
M-12	ERIMOH02	Cholic acid m-xylene p-xylene clathrate	$C_{24}H_{40}O_5.0.25C_8H_{10}.0.75C_8H_{10}$	514.74	24
M-13	ERIMOH03	Cholic acid m-xylene p-xylene clathrate	$C_{24}H_{40}O_5.0.12C_8H_{10}.0.87C_8H_{10}$	514.74	24
M-14	ERIMOH04	Cholic acid m-xylene p-xylene clathrate	$C_{24}H_{40}O_5.0.17C_8H_{10}.0.82C_8H_{10}$	514.74	24
M-15	ERIMOH05	Cholic acid m-xylene p-xylene clathrate	$C_{24}H_{40}O_5.0.37C_8H_{10}.0.61C_8H_{10}$	730.94	24
M-16	ERIPEA	Cholic acid m-xylene clathrate	$C_{24}H_{40}O_5.C_8H_{10}$	514.74	24
M-17	ERIPEA01(P)	Cholic acid m-xylene clathrate	$C_{24}H_{40}O_5.C_8H_{10}$	514.74	24
M-18	ERIPUQ(P)	Cholic acid p-xylene clathrate	$C_{24}H_{40}O_5.C_8H_{10}$	514.74	24
M-19	ERIPUQ01	Cholic acid p-xylene clathrate	$C_{24}H_{40}O_5.C_8H_{10}$	514.74	24
M-20	ERIQAX	Cholic acid m-xylene p-xylene clathrate	$C_{24}H_{40}O_5,0.56C_8H_{10}.0.45C_8H_{10}$	514.74	24
M-21	ERIQAX01	Cholic acid m-xylene p-xylene clathrate	$C_{24}H_{40}O_5.0.64C_8H_{10}.0.35C_8H_{10}$	514.74	24
M-22	EVUXEY	3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid methanol clathrate	$C_{23}H_{38}O_4.CH_4O$	410.59	25
M-23	EVUZIE	Bis(3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid) acetophenone clathrate	$2C_{23}H_{38}O_4.C_8H_8O$	877.25	25
M-24	EVUZOK	Bis(3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid) 4'-methylacetophenone clathrate	$2C2_3H_{38}O_4.C_9H_{10}O$	891.28	25
M-25	EVUZUQ	3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid	$C_{23}H_{38}O_4$	378.55	25
M-26	EWABAF	3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid toluene clathrate	$C_{23}H_{38}O_4.C_7H_8$	470.69	25
M-27	EWABEJ	3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid o-xylene clathrate	$C_{23}H_{38}O_4.C_8H_{10}$	484.72	25
M-28	FABNUT	Ethyl cholate	$C_{26}H_{44}O_5$	436.0	26
M-29	FEBHUP02	3α,7β-dihydroxy-5β-cholan-24-oic acid	$C_{24}H_{40}O_4$	392.56	27
M-30	FOFCUZ	Methyl 11α-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate	$C_{29}H_{43}N_3O_7$	545.66	28
M-31	FOFDAG	Methyl 11α-amino-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate	$C_{29}H_{45}NO_7$	519.66	28
M-32	FOHQEZ	Methyl 11β-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate	$C_{29}H_{43}N_3O_7$	545.66	28
M-33	FOMPED	3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid	$C_{24}H_{38}O_5$	406.54	29
M-34	FOMPIH	7α-hydroxy-3,12-dioxo-5β-cholan-24-oic acid	$C_{24}H_{36}O_5$	404.53	29
M-35	FOMPON	12α-hydroxy-3,7-dioxo-5β-cholan-24-oic acid	$C_{24}H_{36}O_5$	404.53	29
M-36	FONQEF	3α,12α-dihydroxy-7-oxo-5β-cholan-24-oic acid	$C_{24}H_{38}O_5$	406.54	29
M-37	GABGEW	Methyl 3-oxo-5β-cholan-24-oate	$C_{25}H_{40}O_3$	388.57	30

M-38	GIMRAW	(5R,8R,9S,10S,13R,14S,17R,20R)-3-oxo-5β-24-norcholanic acid	$C_{23}H_{36}O_3$	360.52	[31]
M-39	GOKCUF	6α,7α-Dihydroxy-5β-cholan-24-oic acid	$C_{24}H_{40}O_4$	392.56	[32]
M-40	GOKDIU01	3α,7α-diacetoxy-12-oxo-5β-cholan-24-oic acid methyl ester	$C_{29}H_{44}O7$	504.64	[33]
M-41	GUXDUY01	3α,7α,12α-Trihydroxy-5β-cholamide bis(ethanol) clathrate	$C_{24}H_{41}NO_4.2C_2H_6O$	499.73	[34]
M-42	HOLVOU	3α-Hydroxy-N-(3-hydroxypropyl)-5β-cholan-24-amide	$C_{27}H_{47}NO_3$	433.66	[35]
M-43	JAQFIR	N-(3-Hydroxypropyl)-3α,12α-dihydroxy-5β-cholan-24-amide	$C_{27}H_{47}NO_4$	449.66	[36]
M-44	JEYDEW01	3α,7α,12α-trihydroxy-5β-cholan-24-oic acid	$C_{24}H_{40}O_5$	408.56	[27]
M-45	KIBRAQ	(S)-3-Methyl-2-butylammonium (+)-deoxycholate	$C_5H_{14}NC_{24}H_{39}O_4$	479.72	[37]
M-46	KIBREU	(R)-3-Methyl-2-butylammonium (+)-deoxycholate	$C_5H_{14}NC_{24}H_{39}O_4^-$	479.72	[37]
M-47	KIBRIY	(S)-2-Butylammonium (+)-deoxycholate	$C_4H_{12}NC_{24}H_{39}O_4$	465.70	[37]
M-48	KIBROE	(R)-2-Butylammonium (+)-deoxycholate	$C_4H_{12}NC_{24}H_{39}O_4$	465.7	[37]
M-49	MOSWUN	(20R)-24-Bromo-5β-cholane	$C_{24}H_{41}Br$	409.48	[38]
M-50	MUTFAJ	7α-Azido-3α-hydroxy-5β-cholan-24-oic acid	$C_{24}H_{39}N_3O_3$	417.58	[39]
M-51	MUTFEN	3β-Azido-7β-hydroxy-5β-cholan-24-oic acid	$C_{24}H_{39}N_3O_3$	417.58	[39]
M-52	PEQKIH	Cholane-3,7,12,24-tetrol 1-chloro-2-methylbenzene solvate	$C_{24}H_{42}O_4.C_7H_7Cl$	521.18	[40]
M-53	SUQBUB01	3α,12α-Dihydroxy-23-nor-5β-cholan-23-oic acid benzyl alcohol clathrate	$C_{23}H_{38}O_4.C_7H_8O$	486.69	[25]
M-54	VIQPOB	(5α,8α,9β,10α,13α,14β,17α,20S)-Methyl 3,12-dioxocholan-24-oate	$C_{25}H_{38}O_4$	402.55	[41]
M-55	VODKEF	Methyl 3β-azido-5β-cholan-24-oate	$C_{25}H_{41}N_3O_2$	415.61	[42]
M-56	VODKIJ	Methyl 3β-formyloxy-5β-cholan-24-oate	$C_{26}H_{42}O_4$	418.60	[42]
M-57	YECPUT	3,12-Dihydroxycholan-24-oic acid hemihydrate	$C_{24}H_{40}O_4.0.5H_2O$	803.14	[43]
M-58	ZZZPNS01	3α,12β-Dihydroxy-5β-cholan-24-oic acid	$C_{24}H_{40}O_4$	392.56	[21]
M-59	ZZZPPO01	Methyl 3α-hydroxy-5β-cholan-24-oate	$C_{25}H_{42}O_3$	390.59	[44]

Table 2. P_a and P_i values for the molecules **1-59**

Molecule	Anticarcinogenic $P_a > P_i$	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 $P_a > P_i$
M-1	0.452>0.024	0.751>0.005	0.408>0.091	0.851>0.010	0.710>0.009	0.858>0.009	0.963>0.001
M-2	0.612>0.012	0.734>0.006	0.569>0.038	0.671>0.043	0.672>0.012	0.862 > 0.008	0.984>0.001
M-3	0.446>0.025	0.800>0.004	0.445>0.075	0.832>0.013	0.580>0.019	0.876 > 0.007	0.971>0.001
M-4	0.496>0.020	0.691>0.008	0.422>0.085	-	0.351>0.073	0.769 > 0.025	0.911>0.002
M-5	0.392>0.032	0.683>0.009	0.413>0.089	-	0.452>0.041	0.759 > 0.028	0.813>0.003
M-6	0.467>0.022	0.653>0.011	0.424>0.084	-	0.392>0.060	0.712 > 0.042	0.920>0.001
M-7	0.369>0.037	0.645>0.012	0.415>0.088	-	0.481>0.034	0.700 > 0.046	0.843>0.002
M-8	0.598>0.013	0.719>0.007	0.715>0.014	0.342 > 0.109	0.583>0.019	0.834 > 0.012	0.943>0.001
M-9	0.560>0.015	0.744>0.005	0.507>0.055	0.796 > 0.020	0.717 > 0.009	0.869 > 0.008	0.971>0.001
M-10	0.416>0.028	0.808>0.004	0.354>0.026	0.631 > 0.050	0.741 > 0.007	0.829 > 0.013	0.607>0.005
M-11	-	0.858>0.004	0.585>0.035	0.649 > 0.047	0.562 > 0.021	0.871 > 0.007	0.621>0.005
M-12	0.612>0.012	0.734>0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-13	0.612>0.012	0.734>0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-14	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-15	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-16	0.612 >0.012	0.734 > 0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-17	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-18	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671>0.043	0.672>0.012	0.862 > 0.008	0.984>0.001
M-19	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671>0.043	0.672>0.012	0.862 > 0.008	0.984>0.001
M-20	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671>0.043	0.672>0.012	0.862 > 0.008	0.984>0.001
M-11	-	0.858 > 0.004	0.585>0.035	0.649>0.047	0.562>0.021	0.871 > 0.007	0.621>0.005
M-21	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-22	0.483>0.021	0.718 > 0.007	0.441>0.076	0.823 > 0.015	0.689 > 0.011	0.857 > 0.009	0.962>0.001
M-23	0.483>0.021	0.718 > 0.007	0.441>0.076	0.823 > 0.015	0.689 > 0.011	0.857 > 0.009	0.962>0.001
M-24	0.483>0.021	0.718 > 0.007	0.441>0.076	0.823 > 0.015	0.689 > 0.011	0.857 > 0.009	0.962>0.001
M-25	0.483>0.021	0.718 > 0.007	0.441>0.076	0.823 > 0.015	0.689 > 0.011	0.857 > 0.009	0.962>0.001

M-26	0.483>0.021	0.718 > 0.007	0.441>0.076	0.823 > 0.015	0.689 > 0.011	0.857 > 0.009	0.962>0.001
M-27	0.483>0.021	0.718 > 0.007	0.441>0.076	0.823 > 0.015	0.689 > 0.011	0.857 > 0.009	0.962>0.001
M-28	0.554>0.015	0.713 > 0.007	0.599>0.032	0.445 > 0.083	0.704 > 0.010	0.865 > 0.008	0.983>0.001
M-29	0.651>0.011	0.768 > 0.005	0.570>0.038	0.724 > 0.033	0.632 > 0.015	0.888 > 0.005	0.980>0.001
M-30	-	0.585 > 0.017	-	-	-	0.735 > 0.034	0.855>0.002
M-31	0.465>0.023	0.616 > 0.014	0.334>0.133	-	0.380 > 0.064	0.764>0.027	0.909>0.002
M-32	-	-	-	-	-	0.735 > 0.034	0.855>0.002
M-33	-	-	-	-	0.617 > 0.016	0.849 > 0.010	0.988>0.001
M-34	-	-	-	-	-	0.838 > 0.011	0.988>0.001
M-35	-	-	0.457>0.071	0.761 > 0.026	-	0.838 > 0.011	0.988>0.001
M-36	0.575>0.014	0.731 > 0.006	0.445>0.075	0.751>0.028	0.612>0.017	0.849>0.010	0.988>0.001
M-37	0.377>0.035	0.799 > 0.004	0.507>0.055	0.813>0.017	0.690>0.011	0.843>0.011	0.922>0.001
M-38	0.392>0.032	0.792 > 0.005	0.438>0.078	0.898>0.004	0.704>0.010	0.872>0.007	0.938>0.001
M-39	0.471>0.022	0.750 > 0.005	0.425>0.083	0.629>0.050	0.515>0.027	0.897>0.005	0.920>0.001
M-40	0.511>0.018	0.687 > 0.009	0.507>0.055	0.520>0.069	0.575>0.020	0.827>0.013	0.971>0.001
M-41	0.401>0.030	0.691 > 0.008	0.457>0.070	0.447>0.083	0.408>0.055	0.744>0.032	0.934>0.001
M-42	0.356>0.040	0.693 > 0.008	0.353>0.121	-	0.499 > 0.030	0.769 > 0.025	0.740>0.003
M-43	0.336>0.046	0.655 > 0.011	0.357>0.118	-	0.536 > 0.024	0.712 > 0.042	0.771>0.003
M-44	0.612>0.012	0.734 > 0.006	0.569>0.038	0.671 > 0.043	0.672 > 0.012	0.862 > 0.008	0.984>0.001
M-45	0.466>0.023	0.759 > 0.005	0.491>0.060	0.792 > 0.021	0.642 > 0.014	0.844 > 0.010	0.934>0.001
M-46	0.466>0.023	0.759 > 0.005	0.491>0.060	0.792 > 0.021	0.642 > 0.014	0.844 > 0.010	0.934>0.001
M-47	0.466>0.023	0.759 > 0.005	0.491>0.060	0.792 > 0.021	0.642 > 0.014	0.844 > 0.010	0.934>0.001
M-48	0.466>0.023	0.759 > 0.005	0.491>0.060	0.792 > 0.021	0.642 > 0.014	0.844 > 0.010	0.934>0.001
M-49	0.338>0.045		-	0.537 > 0.066	-	0.829 > 0.013	0.622>0.005
M-50	0.305>0.056	0.658 > 0.010	-	-	0.304 > 0.089	0.840 > 0.011	0.814>0.003
M-51	-	0.652 > 0.011	0.310>0.152	-	0.327 > 0.081	0.821 > 0.014	0.817>0.003
M-52	0.542>0.016	0.741 > 0.005	0.569>0.039	0.496 > 0.073	0.606 > 0.017	0.793 > 0.020	0.952>0.001
M-53	0.367>0.037	0.741 > 0.005	0.403>0.094	0.784 > 0.022	0.627 > 0.015	0.799 > 0.019	-
M-54	0.367>0.037	0.741 > 0.005	0.403>0.094	0.784 > 0.022	0.627 > 0.015	0.799 > 0.019	0.932>0.001
M-55	-	0.658 > 0.010	-	-	0.345 > 0.075	0.779 > 0.023	0.510>0.008
M-56	-	0.667 > 0.010	-	0.338 > 0.110	0.430 > 0.048	0.819 > 0.015	0.771>0.003
M-57	0.560>0.015	0.744 > 0.005	0.507>0.055	0.796 > 0.020	0.717 > 0.009	0.869 > 0.008	0.971>0.001
M-58	0.560>0.015	0.744 > 0.005	0.507>0.055	0.796 > 0.020	0.717 > 0.009	0.869 > 0.008	0.971>0.001
M-59	0.525>0.017	0.757 > 0.005	0.506>0.055	0.733 > 0.031	0.646 > 0.014	0.861 > 0.008	0.945>0.001

Biological-activity spectrum provides the rationale for predicting biological activity types for different compounds. Any component of this spectrum of a given compound is assumed to be detectable under suitable experimental conditions. By using a qualitative representation of biological activity, it is possible to compare and mix activity data for obtaining robust quantitative models.[45] Multilevel Neighbourhoods of Atoms (MNA) descriptors are helpful in describing the crystal structures.[46] These descriptors are successfully applied for predicting the biological activity in drug-like compounds.[47] The MNA descriptors represent various structure property relationships including many types of biological activity,[48] carcinogenicity,[49] drug-likeness,[50]etc.

The three-dimensional (3D) coordinate data of all the compounds have been selected as an input for the PASS software to predict the bioactivity relationship.[49] The biological activity spectra have been correlated empirically on the basis of structure-activity relationship which provides different P_a (probability of activity) and P_i (probability of inactivity) values. Based on statistics of MNA descriptors for active and inactive compounds, two probabilities have been calculated for each activity: P_a- probability of the compound being active and P_i- probability of the compound being inactive. 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 even neutral. The P_a and P_i values for the molecule (1-59) have been computed by the pass software[52] and are given in Table 2. It is quite interesting to note that most of the cholane derivatives possess high *choleretic, dermatologic, antieczematic, antisecretoric* and *antiseborrheic* activity while *anti-inflammatory* and *anticarcinogenic* activity is not much significant.

Hydrogen Bonding

Carbon forms weak hydrogen bonds like C-H…O which is ubiquitous and occurs in most molecular crystals[53,54] Hydrogen bonding is directional, mostly noncovalent interaction which is fundamental element of chemical structure[55] and reactivity.[56] On the basis of some studies which have been carried out by various workers on hydrogen bonding,[54, 57-58] we got interested in the analysis of various kinds of hydrogen bonded interactions present in cholane derivatives (**1-59**) and the study has been carried out to (i) generate H-bonds by calculating the *d*, *D* and θ values for the compounds which are listed in CCDC data, (ii) know whether C-H…O or O-H…O hydrogen bonding is predominant in this class of steroids, (iii) make a small compendium of hydrogen bonding on a comparative graphical scale. The number of hydrogen donors as well as acceptors and comparative data of intermolecular hydrogen bonds of the type O-H…O, C-H…O, N-H…O, C-H…Cl, C-H…N, C-H…Br in molecule (1-59) are presented in Table 3. Different kind of intermolecular hydrogen bonds viz. O-H…O, C-H…O, N-H…O, C-H…Cl, C-H…N, C-H…Br have been observed.

Table 3. Geometry of C-H...O, O-H...O, N-H…O, C-H…Cl, C-H…N and C-H...Br intermolecular interactions.

Molecule [Number of donors and acceptors]	**Intermolecular interactions, X-H...A**	**H...A(Å) *d***	**X...A(Å) *D***	**X-H...A(Å) *θ***
M-1	O4-H4AC...O3'	1.841	2.672	169.7
ADIMAC	O4'-H4BC...O3	1.814	2.654	179.2
Donors=10	O2-H2AA...O1'	2.704	3.186	110.3
Acceptors =6	C23-H23C...O3'	2.385	3.327	158.8
	C1-H1AA...O1	2.645	3.561	153.8
	C19-H19A...O1	2.527	3.419	151.3
	C6'-H6BB...O2	2.717	3.516	138.0
	C19'-H19E...O2'	2.653	3.632	177.7
	C6'-H6BA...O2'	2.495	3.311	139.5
	C8'-H8BA…O2'	2.604	3.399	136.3

The key structural feature distinguishing the hydrogen bond from the other non-covalent interactions is its preference for linearity.[59] A better way to analyse preferences is to draw *d*-*θ* and *D*-*θ* scatter plots. The plots include all contacts found in molecules (1-59) with *d* < 2.915Å and *D*<3.834 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 3a and 3b. The following observations have been made:

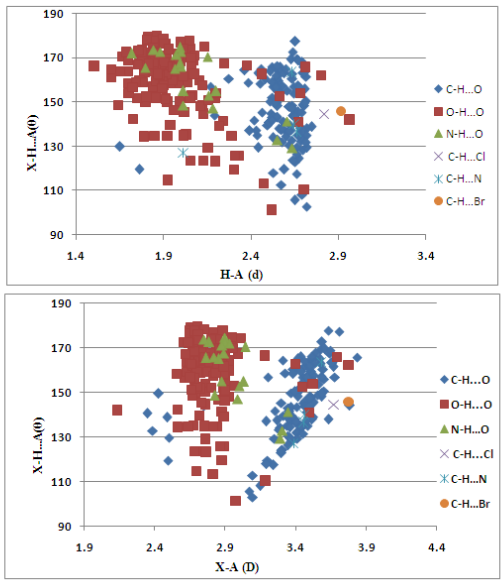

Figure 3 (a) *d*-θ scatter plot for intermolecular C-H...O, O-H...O, N-H...O, C-H...Cl, C-H...N and C-H...Br. (b) *D*-θ scatter plot for intermolecular C-H...O, O-H...O, N-H...O, C-H...Cl, C-H...N and C-H...Br.

The density of spots for *d*(H...A) [= 2.5-2.75 Å] and *D* (X...A) [= 3.30-3.65 Å] is predominant [*θ* (X-H...A) range ~130-170°] in case of C-H...O hydrogen bonds.

The density of spots for O-H...O intermolecular hydrogen bonds is quite high in a given range of values for *d* (H...A) =1.80-2.25 Å and *D* (X...A) =2.60-2.95 Å and *θ* (X-H...A)=150–180°.

The relative frequency of occurrence of various types of O-H...O, C-H...O, N-H…O, C-H…N, C-H…Cl and C-H...Br intermolecular hydrogen bonds is 48.85, 42.95, 6.23, 1.31, 0.32 and 0.32 %, respectively and it is shown in Figure 4.

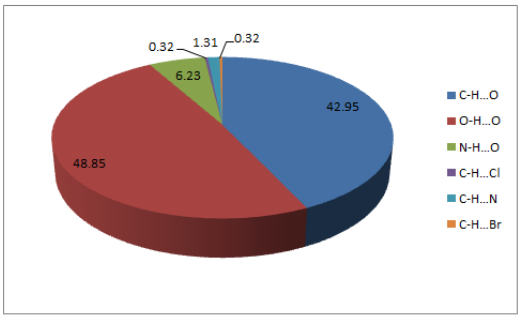

Figure 4. Relative frequency of occurence (in%) for various types of intermolecular hydrogen bonding.

Densely populated clusters 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.[60,61] 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, N, Cl and Br, it has been concluded that H(C) atoms have a statistical preference for contacts to 'O' rather than 'N', 'Cl' or 'Br' atoms. Thus, with oxygen as an acceptor, the frequency of occurrence of C-H...O hydrogen bond becomes very high (42.95 % in the present case). In all the molecules (**1-59**), 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.

Due to long range character of hydrogen bond and a pronounced softness of the angle at H, donors may interact simultaneously with more than one acceptor, thus forming bifurcated hydrogen bond (X-H...(A1,A2)). Here, X atom is referred to as bifurcated donor Sometimes, acceptors may interact simultaneously with more than one donor (X1,

X2-H...A). Atom A here is a bifurcated acceptor. In some cases, an atom can act both as donor as well as acceptor simultaneously. Bifurcated hydrogen bonds are commonly observed in O-H…O and N-H…O hydrogen bonded structures.[62] They are also observed in C-H…O/N patterns. In the present study, bifurcated or trifurcated hydrogen bonds have been observed mostly in C-H…O and O-H…O hydrogen bonded structures and in almost all the structures (with *Z*'=1, 2 and 3), with oxygen acting as a bi or tri or multifurcated hydrogen bond acceptor.

The solute-solvent intermolecular interactions and the effect of solvent on the properties of organic and biological molecules has been successfully described by various workers using different and complementary theoretical models.[63-65] In this direction the investigation as carried out on the solvation mechanism[66] and the specific role of the solute-solvent interactions could be used as a tool for supramolecular structures.[67,68] The specific C-H…O hydrogen bonds between solute and solvent play an important role in solid state chemistry.[69] In the present work we have come across a few cases where solute-solvent interactions have been observed. Some of the prominent solute–solvent interactions as obtained in the present case are: [O2-H38…O6(W), O5-H40…O6(W), C14-H17…O6(W),C9-H13,O6][M-2], [O2'-H75…O9][M-23], [O2-H37…O9][24], [N1-H40…O5][41], and the solvent-solute interactions are: [C31-H31B…O3][M-19], [O5-H42…O2][M-22], [C54-H82…O3][M-23], [NIG-H15…O24A, NIG-H15…O24B][M-45], [NIG-H26…O24A, NIG-H26…O24B][M-46], [NIG-H56…O3, NIG-H54…O24A, NIG-H54…O24B][M-47], [NIG-H143…O3, NIG-H1G1…O24A][M-48], [O25G-H46…O12][M-53] respectively. A representative view of such an interaction in molecule M-2 is shown in Figure 5.

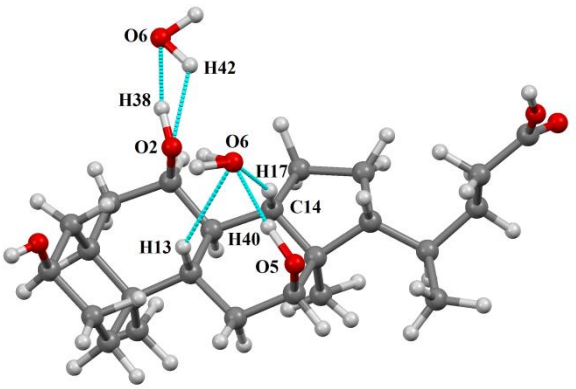

Figure 5. Solute-solvent/solvent-solute interactions in molecule (M-2).

Conclusion

The relationship between X-ray crystallography and structure- activity relationships have high affinity to indicate the drug-likeness and conserved arginine in the binding site for the steroid receptors. The molecules in the unit cell are linked by C-H…O/O-H…O interactions and most of these are associated through the keto and the hydroxyl group located at C3/C12 position of the cholane derivatives. These secondary interactions help in understanding the stacking of molecules in the unit cell as supramolecular entity. It is depicted that unusual substitution with the basic steroid moiety/nucleus may change the biological activity of the molecule.

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