Effect of vitamin D conformation on interactions and packing in crystal lattice

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Supporting Information (SI)

Content:

FIGURES **3**

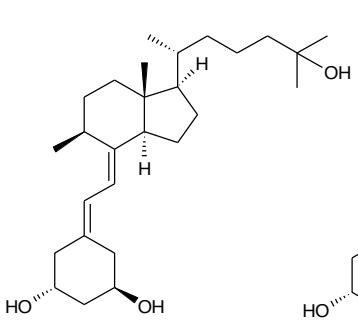
1. 1,25-DIHYDROXYVITAMIN D ANALOGUES 3
2. VITAMIN D ANALOGUES 5
3. HYDROGEN BONDS 5
   3.1. PRI-1730 (1) *5*
   3.2 PRI-1731 (2) *6*
   3.3 PRI-1732 (3) *6*
4. THREE PERPENDICULAR VIEWS OF ANALYZED MOLECULES, VIEW ALONG X,Y AND Z AXIS. 7
   4.1 PRI-1730 (1) *7*
   4.2 PRI-1731 (2) *7*
   4.3 PRI-1732 (3) *7*
   4.4 BNR-1 (4) *8*
5. CRYSTAL PACKING OF THE ANALYZED MOLECULES, VIEW ALONG X,Y AND Z AXIS. 8
   5.1 PRI-1730 (1) *8*
   5.2 PRI-1731 (2) *8*
   5.3 PRI-1732 (3) *9*
   5.4 BNR-1 (4) *9*
6. HYDROGEN BONDS MOTIFS 11
   6.1. Infinitive hydrogen bond motif *9*
   6.2. Discrete hydrogen bond motif *10*
   6.3. R_4^4 ring hydrogen bond motif *10*
   6.4. R_6^6 ring hydrogen bond motif *10*
7. HYDROGEN BONDS WITH SOLVENT 11
8. COULOMB ENERGY FRAMEWORKS 11
   8.1. 1730 (1) *11*
   8.2. 1731 (2) *12*
   8.3. 1732 (3) *12*
   8.4. 1,25D_3 ..... *13*
9. DISPERSION ENERGY FRAMEWORKS 13
   9.1. 1730 (1) *13*
   9.2. 1731 (2) *14*
   9.3. 1732 (3) *15*
   9.4. 1,25D_3 ..... *15*
10. TOTAL ENERGY FRAMEWORKS 16
   10.1. 1730 (1) *16*
   10.2. 1731 (2) *16*
   10.3. 1732 (3) *17*
   10.4. 1,25D_3 ..... *18*

TABLES **18**

1. SUMMARY OF 1,25-DIHYDROXYVITAMIN D ANALOGUES 18
2. LENGTHS OF SELECTED BONDS 19
3. VALUES OF SELECTED ANGLES 19
4. VALUES OF SELECTED TORSION ANGLES 19
5. VALUES OF A/CD-RING ANGLES 19
6. CHARGE OF DONORS AND ACCEPTORS OF HYDROGEN BOND 19
   6.1. 1730 (1) *20*
   6.2. 1731 (2) *20*
   6.3. 1732 (3) *20*
   6.4. 1,25D$_3$ *20*
7. DESCRIPTION OF DIMERS ENERGY ANALYSIS OF 3 20

Figures

1. 1,25-dihydroxyvitamin D analogues



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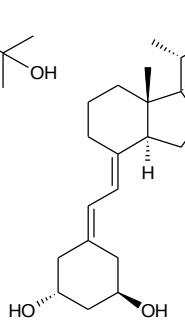

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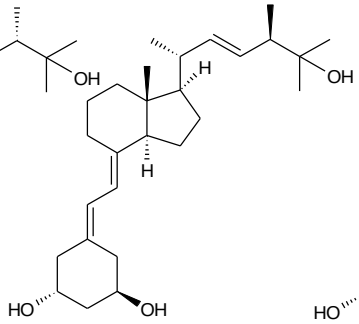

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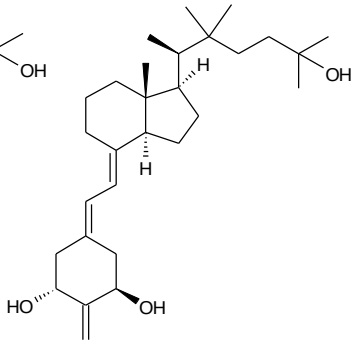

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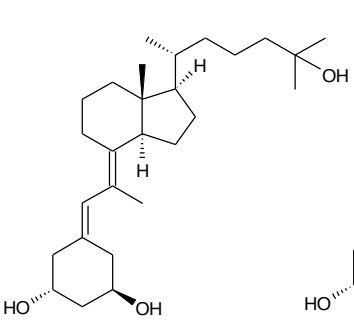

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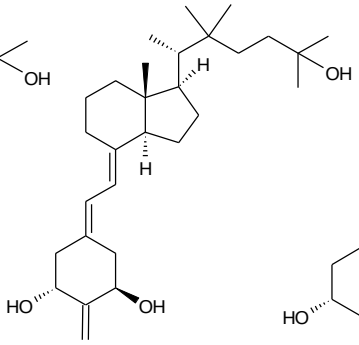

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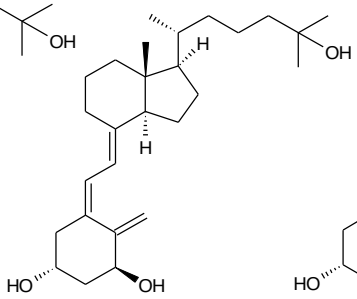

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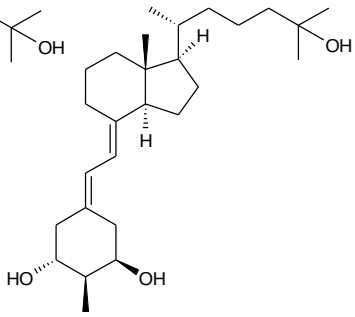

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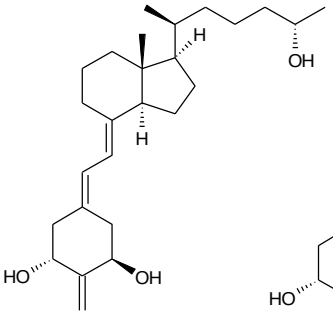

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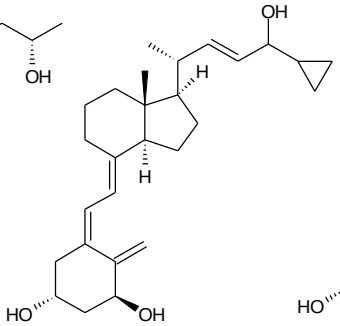

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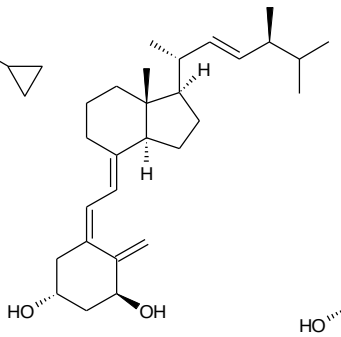

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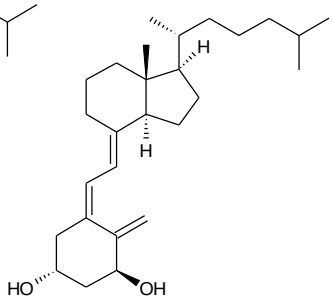

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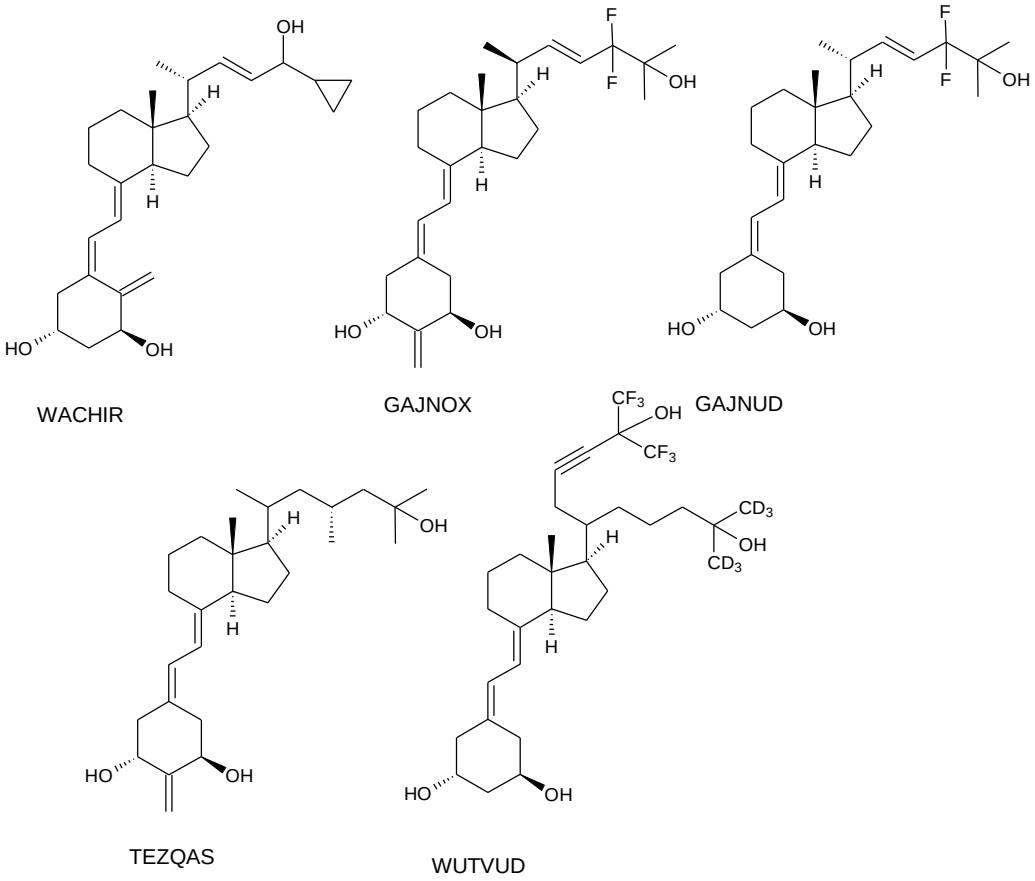


Fig. 1 Structures of 1,25-dihydroxyvitamin D analogues deposited in CSD.

2. Vitamin D analogues

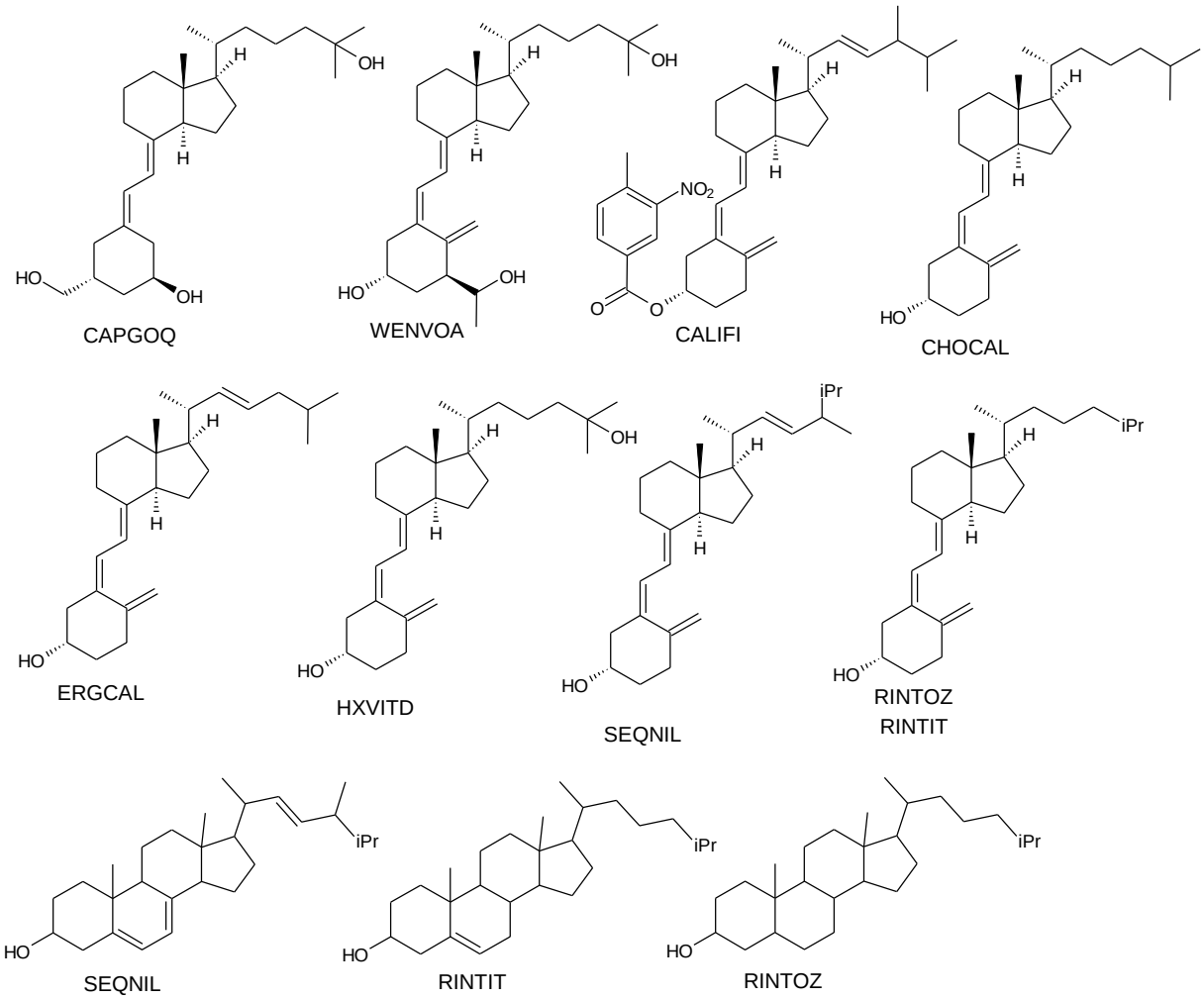


Fig. 2 Structures of 3-hydroxyvitamin D analogues and vitamin D analogues with untypical modification at 1- or 3-hydroxyl deposited in CSD.

3. Hydrogen bonds

3.1. PRI-1730 (1)

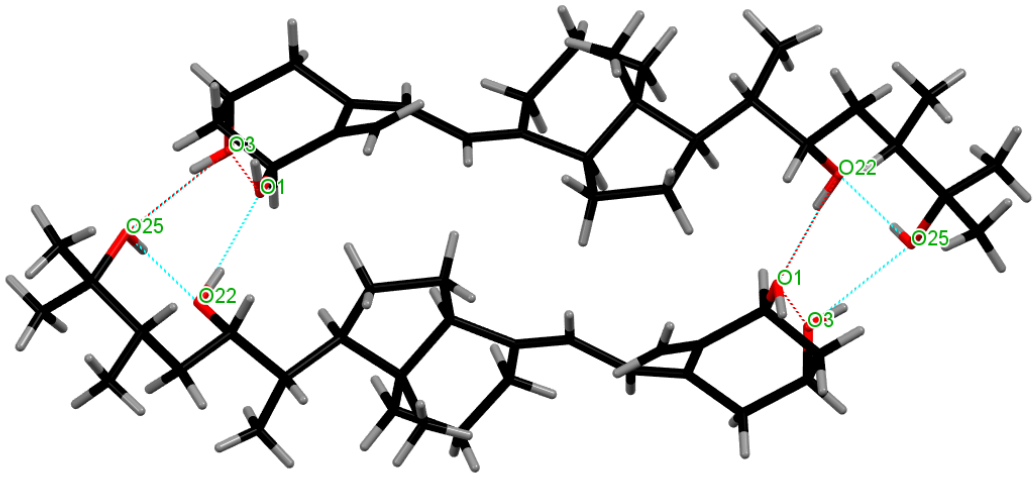


Fig. 3 Hydrogen bonds occur in 1: intramolecular hydrogen bond O25O22 (HB9) and intermolecular hydrogen bonds: O1O3 (HB1), O3O25(HB3) and O1O22(HB7).

3.2 PRI-1731 (2)

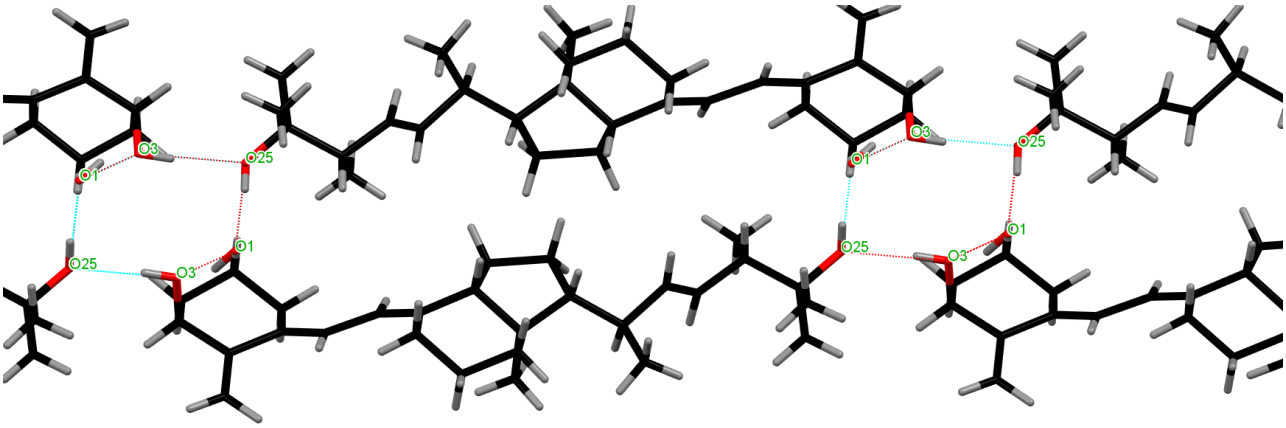


Fig. 4 Intermolecular hydrogen bonds occur in 2: O1O3 (HB1), O1O25 (HB2) and O3O25 (HB3).

3.3 PRI-1732 (3)

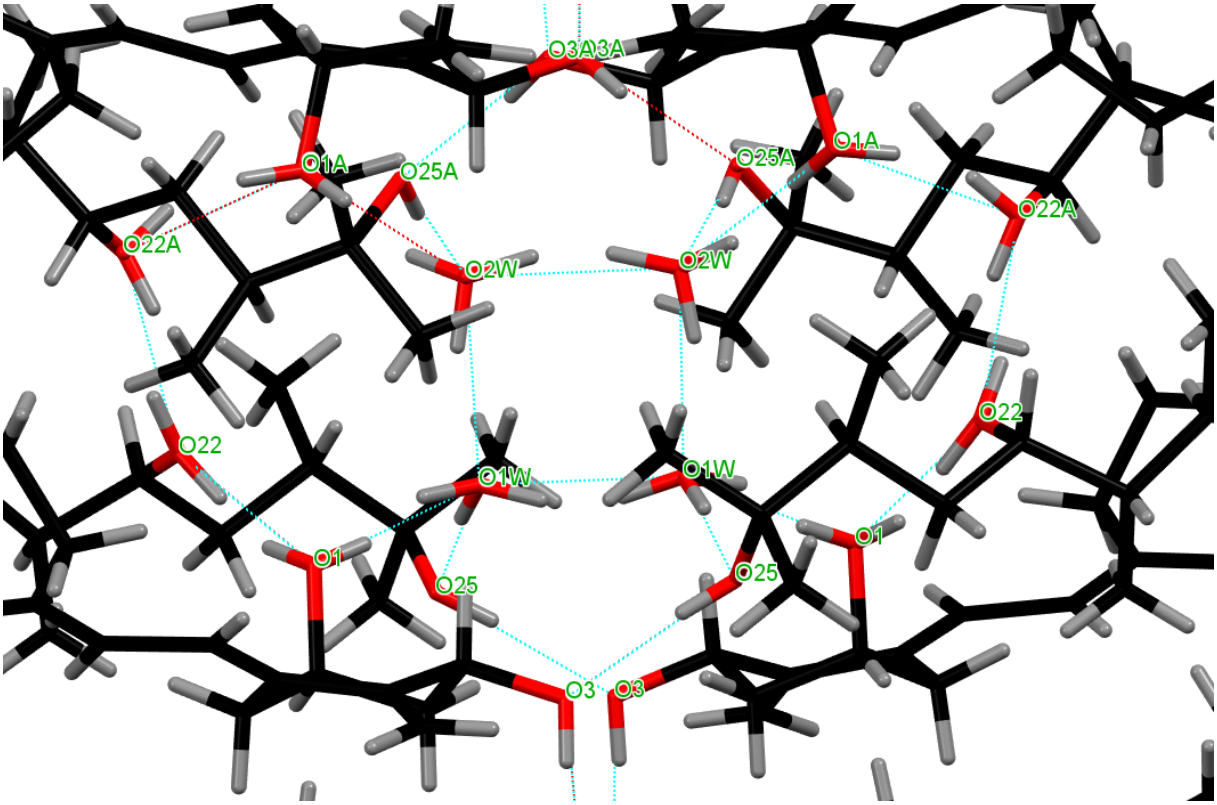
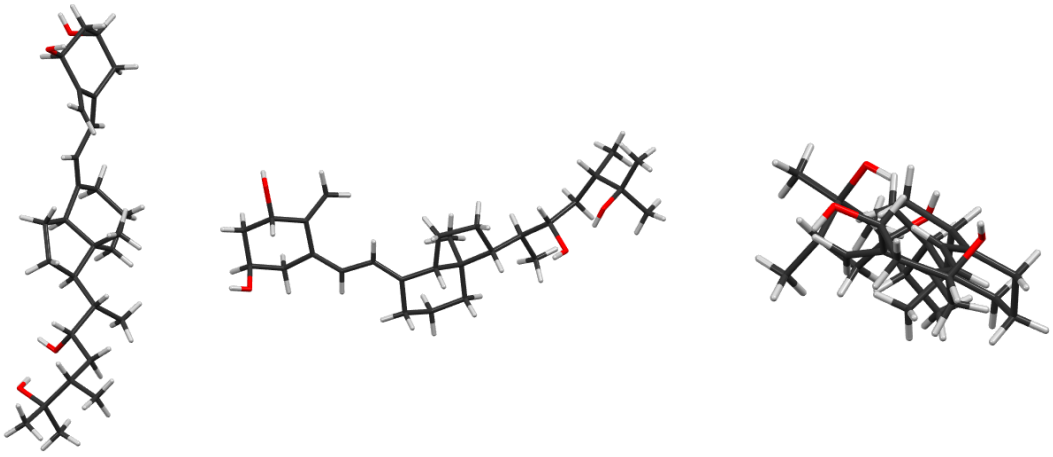


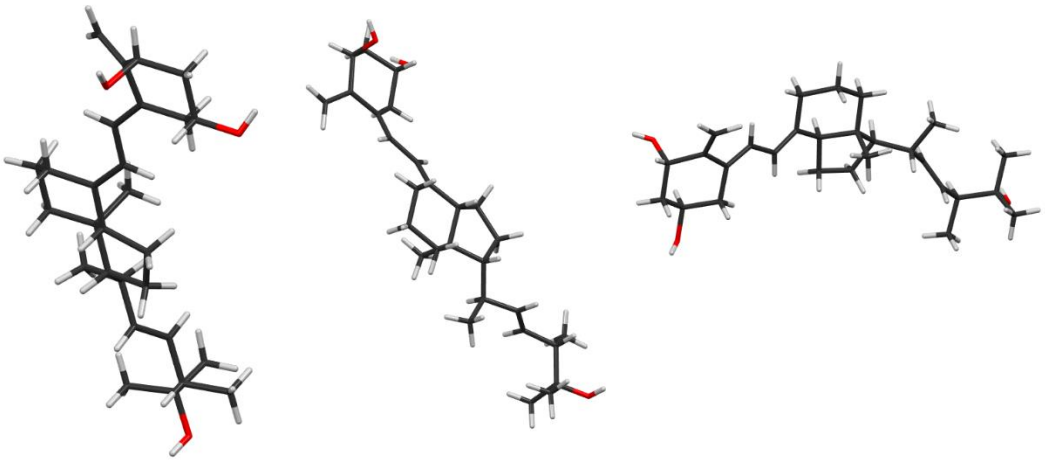
Fig. 5 Hydrogen bonds occur in 3: intermolecular hydrogen bonds O3O25, O3AO25A (HB3), O1O22, O1AO22A (HB7), O3O3A (HB6), O22O22A (HB8); hydrogen bonds between vitamin D and solvent O1O1W, O1AO2W, (HBS(O1)), O25O1W, O25AO2W (HBS(O25)); hydrogen bonds between water molecules O1WO2W (W1W2), O1WO1W (W1W1), O2WO2W (W2W2).

4. Three perpendicular views of analyzed molecules, view along X,Y and Z axis.

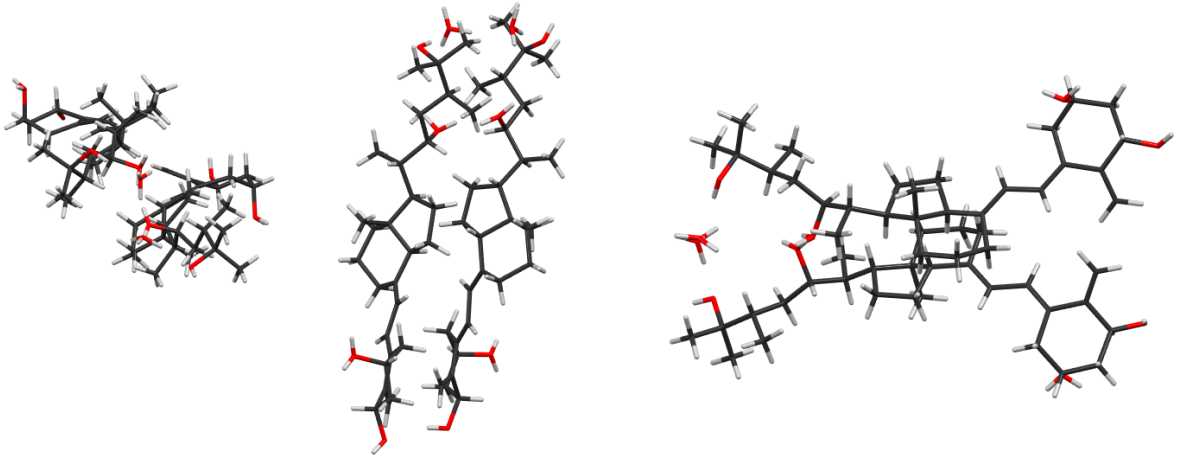
4.1 PRI-1730 (1)



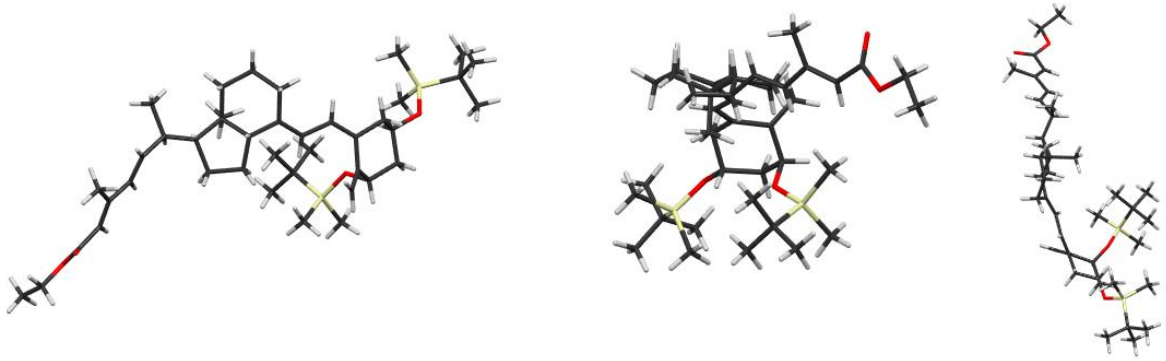
4.2 PRI-1731 (2)



4.3 PRI-1732 (3)

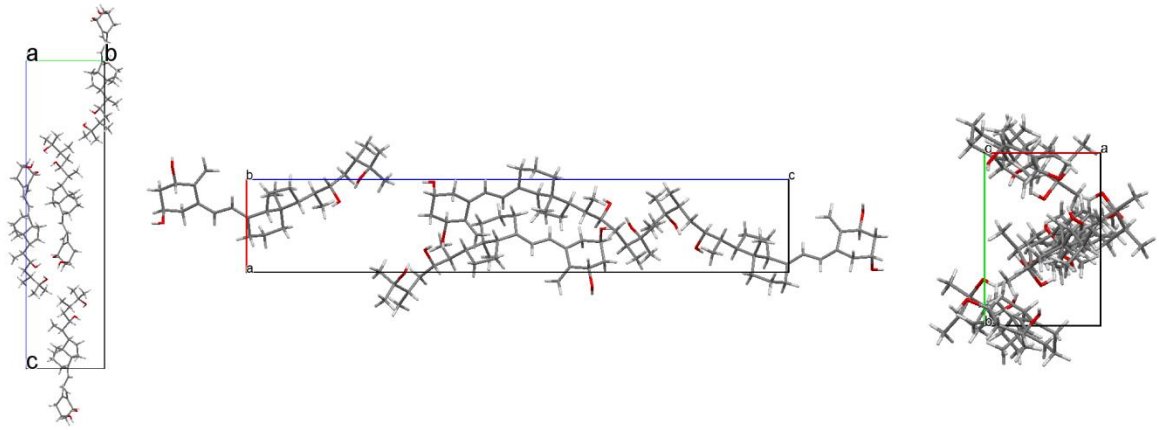


4.4 BNR-1 (4)

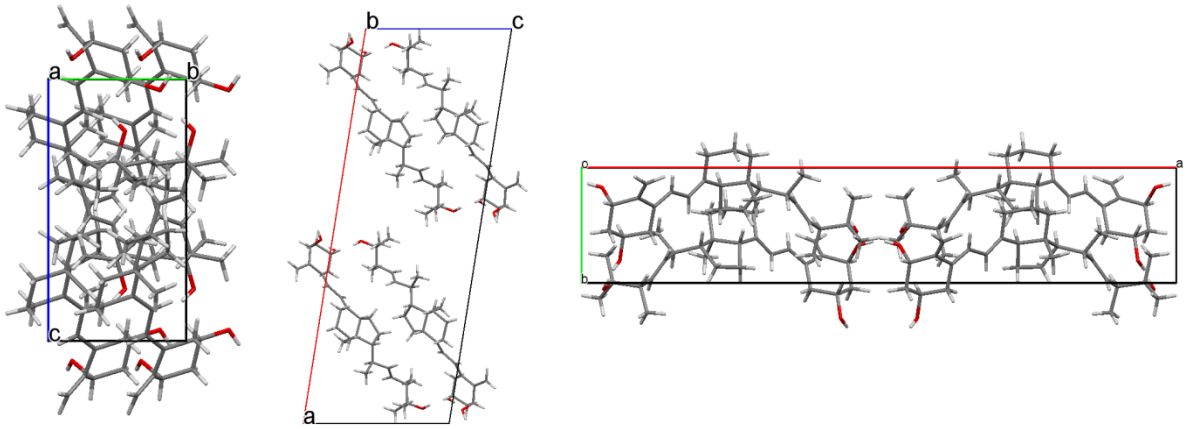


5. Crystal packing of the analyzed molecules, view along X,Y and Z axis.

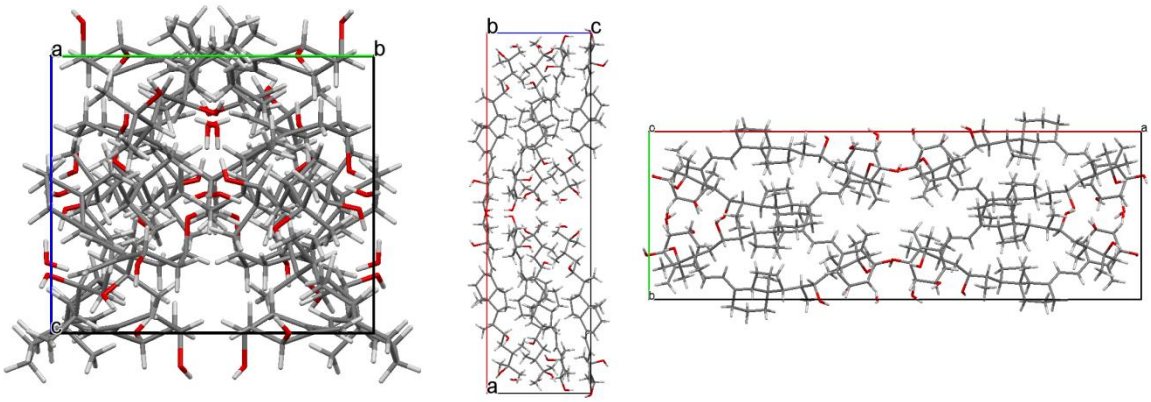
5.1 PRI-1730 (1)



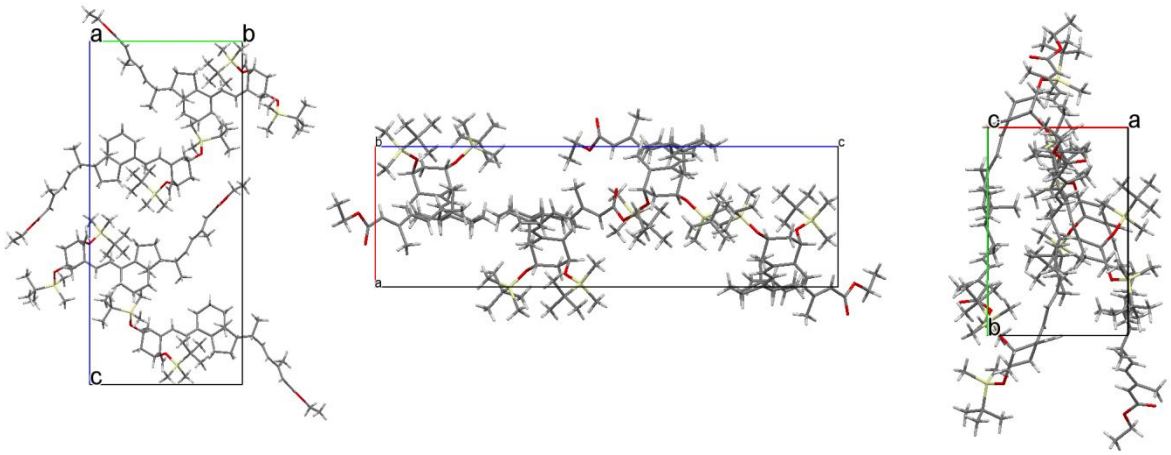
5.2 PRI-1731 (2)



5.3 PRI-1732 (3)

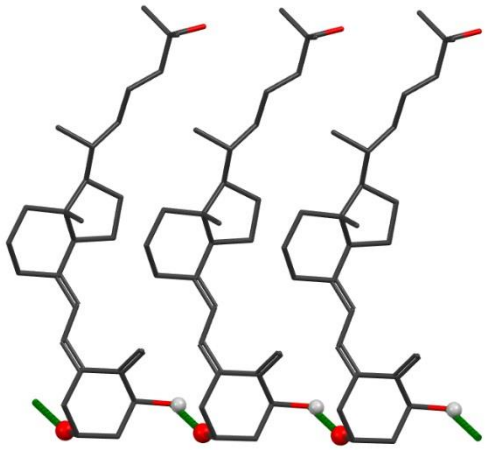


5.4 BNR-1 (4)

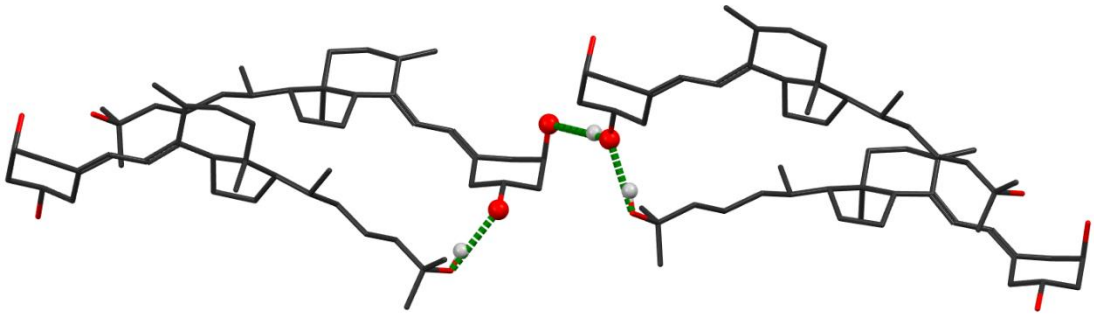


6. Hydrogen bond motifs

6.1. Infinitive hydrogen bond motif



6.2. Discrete hydrogen bond motif



6.3. R_4^4 ring hydrogen bond motif

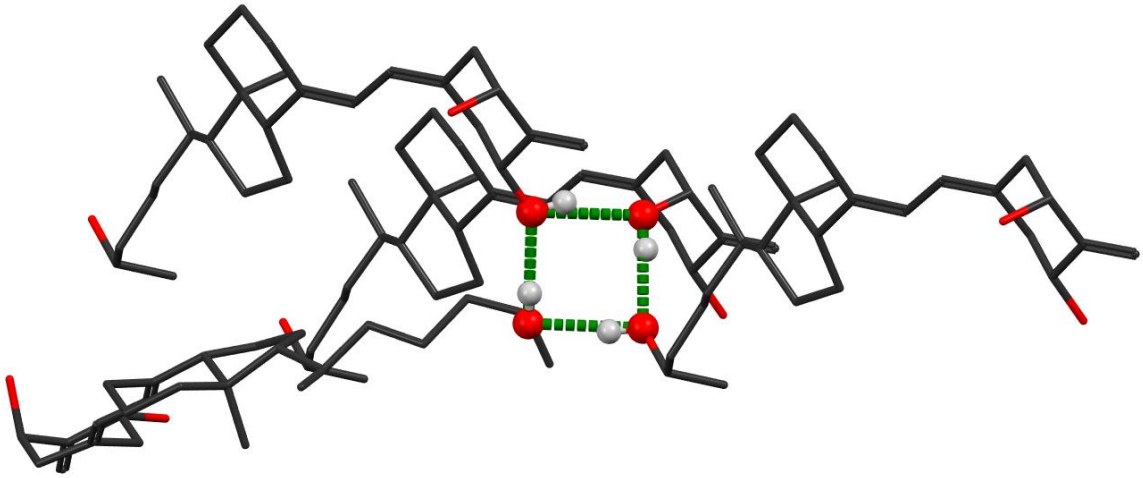


Fig. 6 Hydrogen bond motif containing 4 donors and 4 acceptors.

6.4. R_6^6 ring hydrogen bond motif

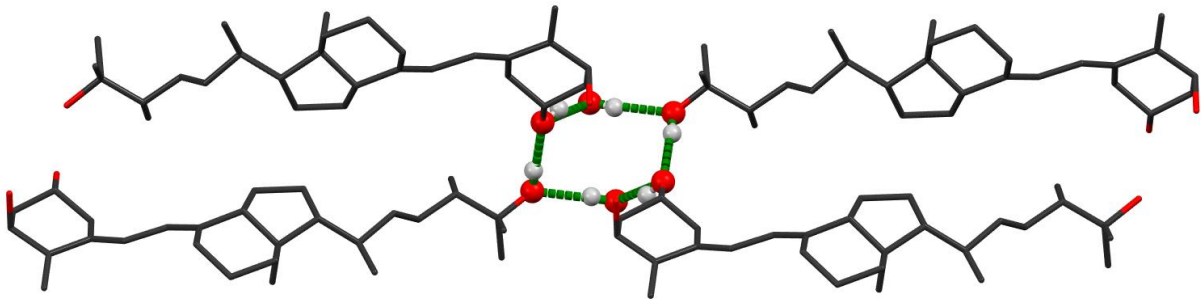


Fig. 7 Hydrogen bond motif containing 6 donors and 6 acceptors.

7. Hydrogen bonds with solvent

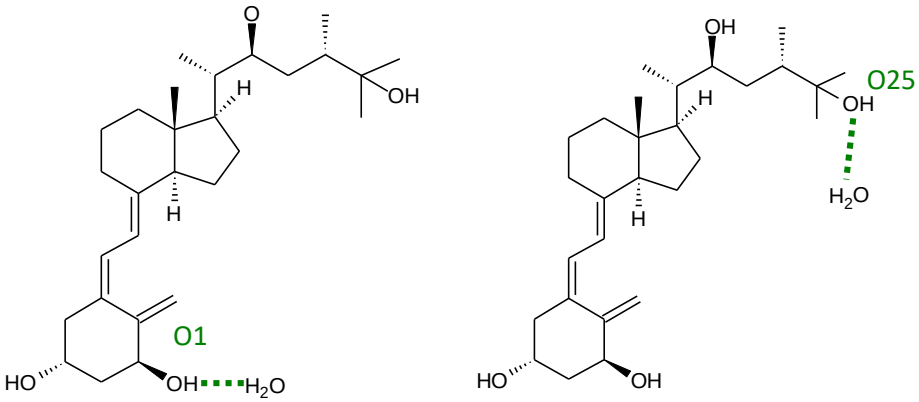


Fig. 8 Scheme of hydrogen bonds between vitamin D analogue and water molecule.

8. Coulomb energy frameworks

Calculations of energy frameworks were performed using Crystal Explorer 3.3 (DFT methods, B3LYP functional, 6-31G(d,p) basis set). Results for all frameworks were presented using scale factor equal 50 and value of energy threshold equal 5 kJ/mol. View along X,Y and Z axis.

8.1. 1730 (1)

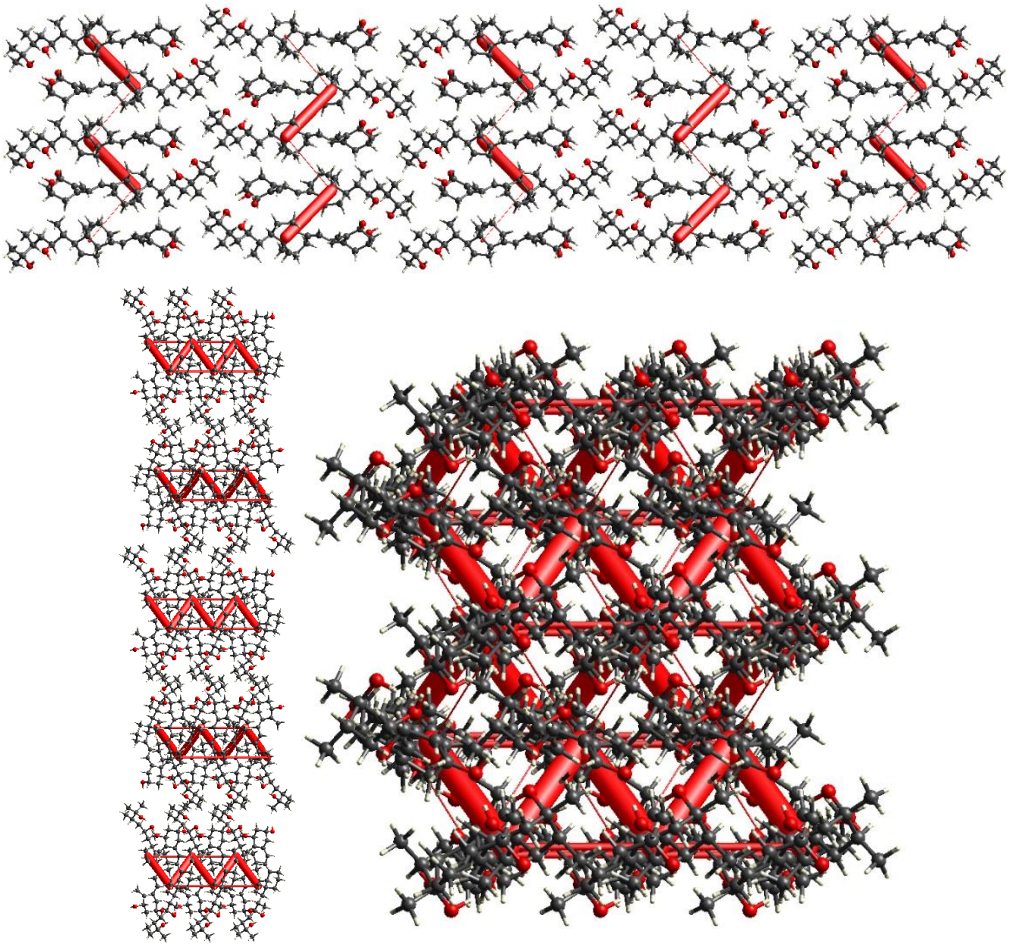


Fig. 9 Coulomb energy frameworks: HB1,HB9 (-31.8 kJ/mol) and HB3, HB7,HB9 (-111.9 kJ/mol)

8.2. 1731 (2)

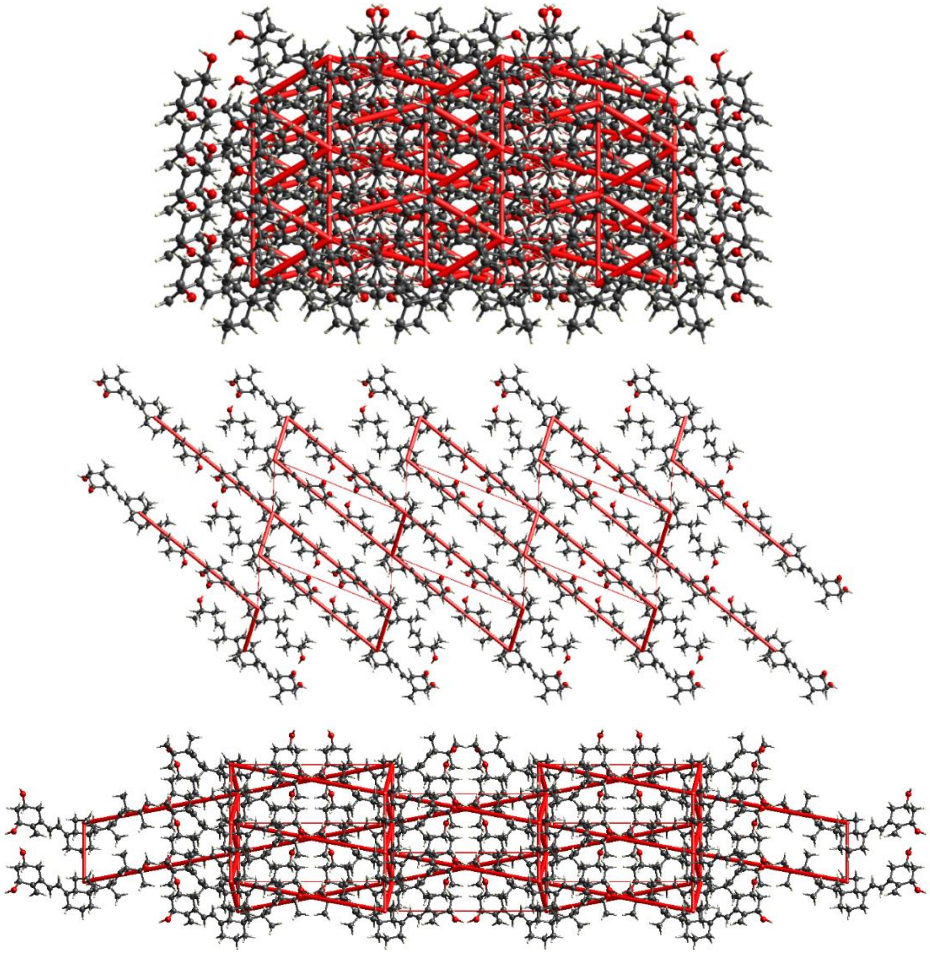


Fig. 10 Coulomb energy frameworks: HB1 (-33.3 kJ/mol), HB2 (-49.4 kJ/mol) and HB3 (-44.3 kJ/mol).

8.3. 1732 (3)

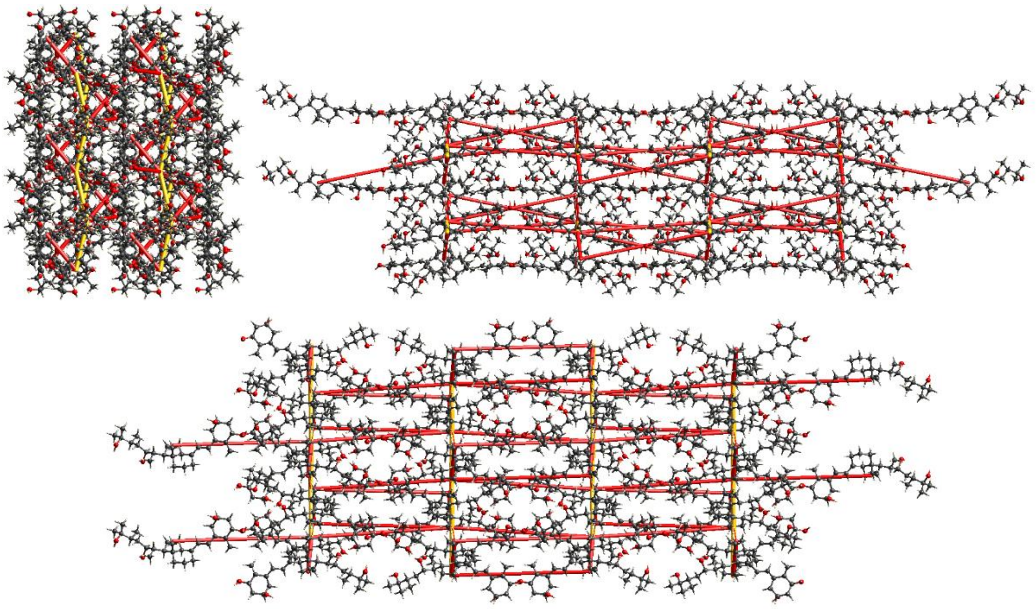


Fig. 11 Coulomb energy frameworks: HB3 (-46.3 kJ/mol), HB6 (-44.6 kJ/mol), HB7 (57.9 kJ/mol) and HB8 (-54.4 kJ/mol). Negative values (HB3, HB6, HB8) are presented using red colour and positive values (HB7) using yellow colour.

8.4. 1,25D$_3$

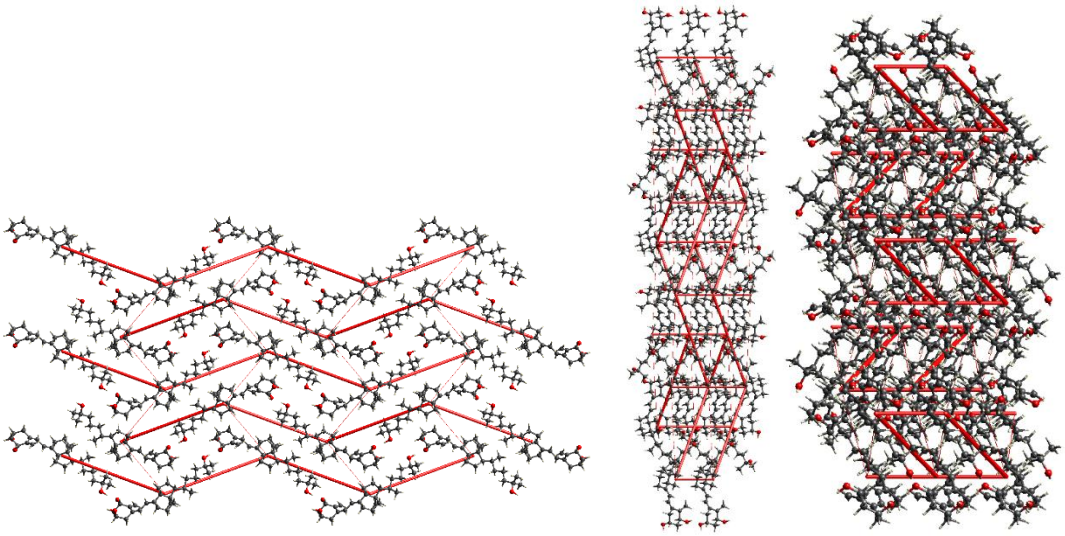


Fig. 12 Coulomb energy frameworks: HB1 (-33.2 kJ/mol) and HB2 (-41.3 kJ/mol).

9. Dispersion energy frameworks

Calculations of energy frameworks were performed using Crystal Explorer 3.3 (DFT methods, B3LYP functional, 6-31G(d,p) basis set). Results for all frameworks were presented using scale factor equal 50 and value of energy threshold equal 5 kJ/mol. View along X,Y and Z axis.

9.1. 1730 (1)

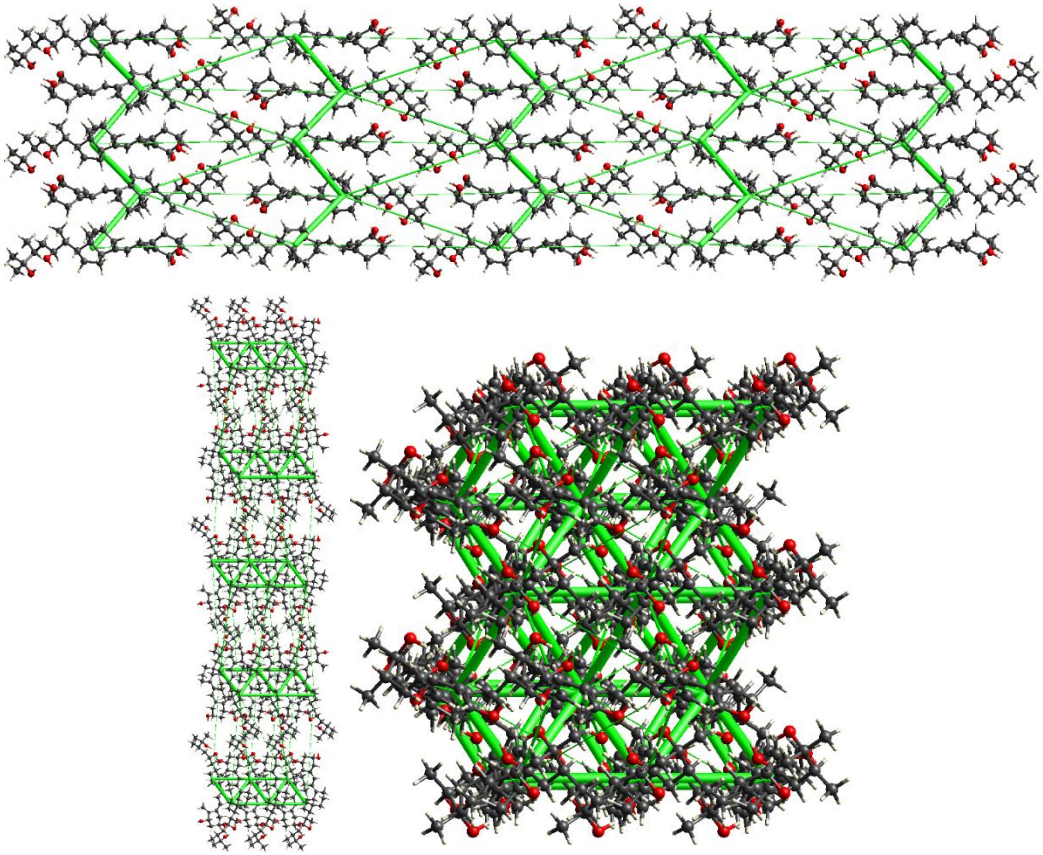


Fig. 13 Dispersion energy frameworks: HB1,HB9 (-63.5 kJ/mol) and HB3,HB7,HB9 (-70.7 kJ/mol).

9.2. 1731 (2)

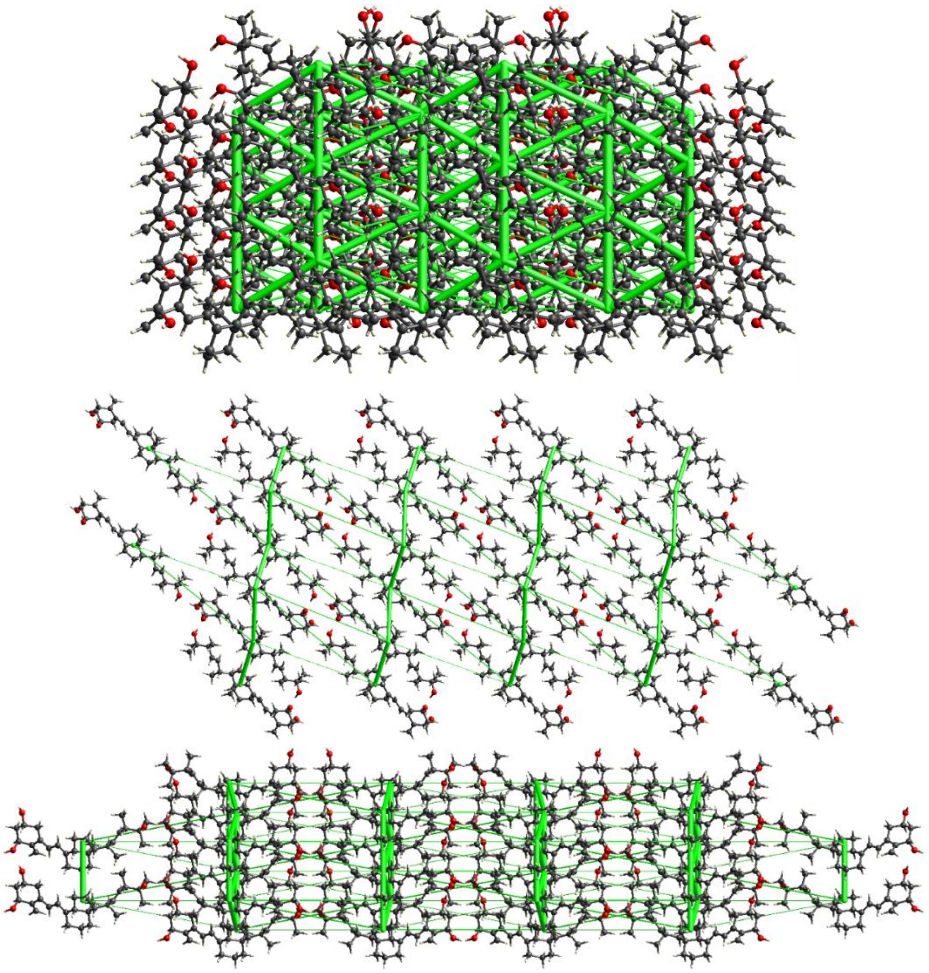


Fig. 14 Dispersion energy frameworks: HB1 (-75.0 kJ/mol), HB2 (-63.1 kJ/mol) and HB3 (-16.3 kJ/mol).

9.3. 1732 (3)

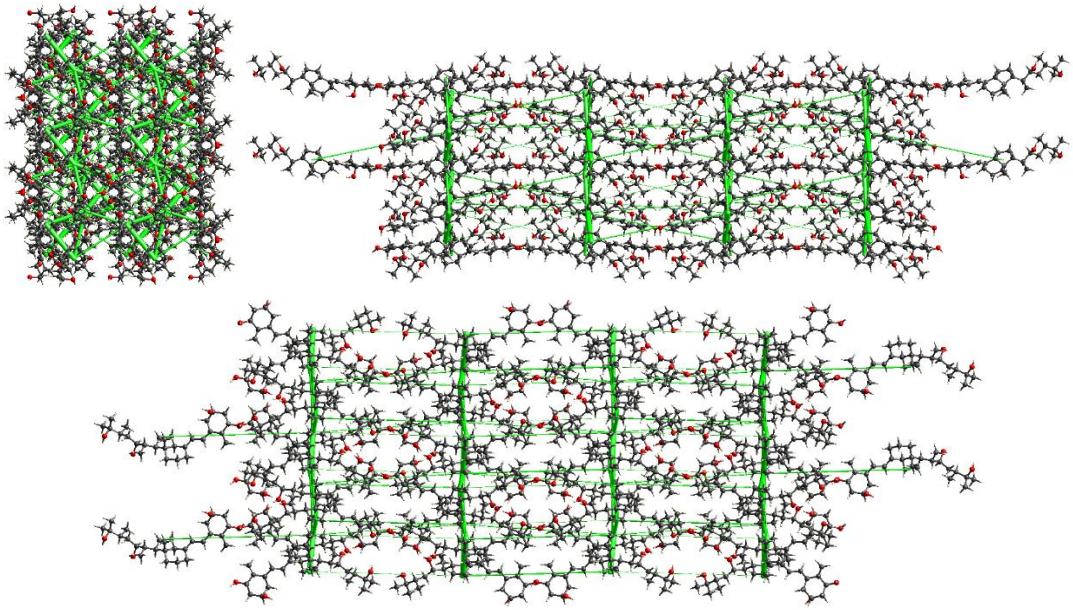


Fig. 15 Dispersion energy frameworks: HB3 (-14.9 kJ/mol), HB6 (-20.6 kJ/mol), HB7 (-63.8 kJ/mol) and HB8 (-86.3 kJ/mol).

9.4. 1,25D$_3$

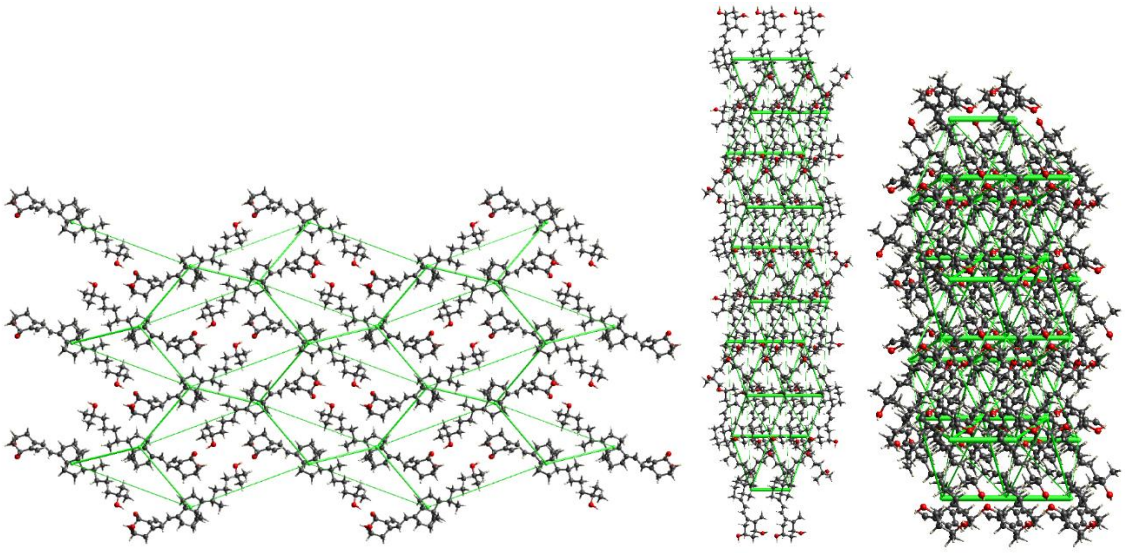


Fig. 16 Dispersion energy frameworks: HB1 (-64.3 kJ/mol) and HB2 (-12.7 kJ/mol).

10. Total energy frameworks

Calculations of energy frameworks were performed using Crystal Explorer 3.3 (DFT methods, B3LYP functional, 6-31G(d,p) basis set). Results for all frameworks were presented using scale factor equal 50 and value of energy threshold equal 5 kJ/mol. View along X,Y and Z axis.

10.1. 1730 (1)

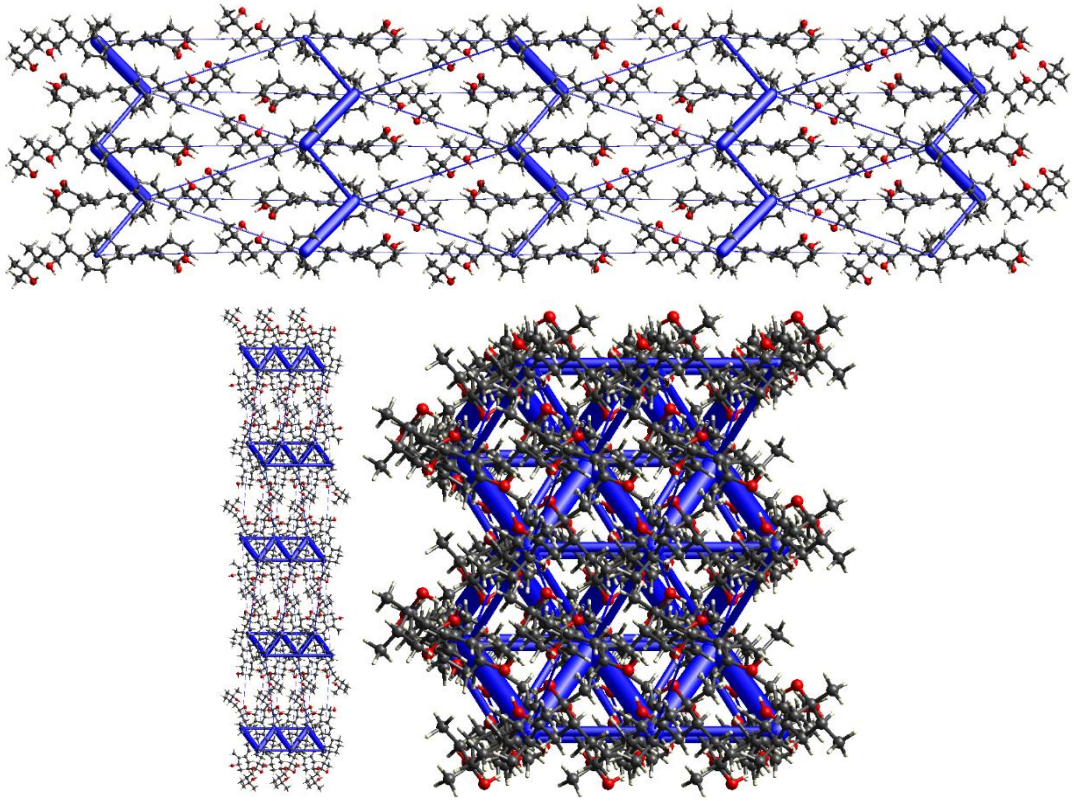


Fig. 17 Total energy frameworks: HB1, HB9 (-55.1 kJ/mol) and HB3,HB7,HB9 (-121.7 kJ/mol).

10.2. 1731 (2)

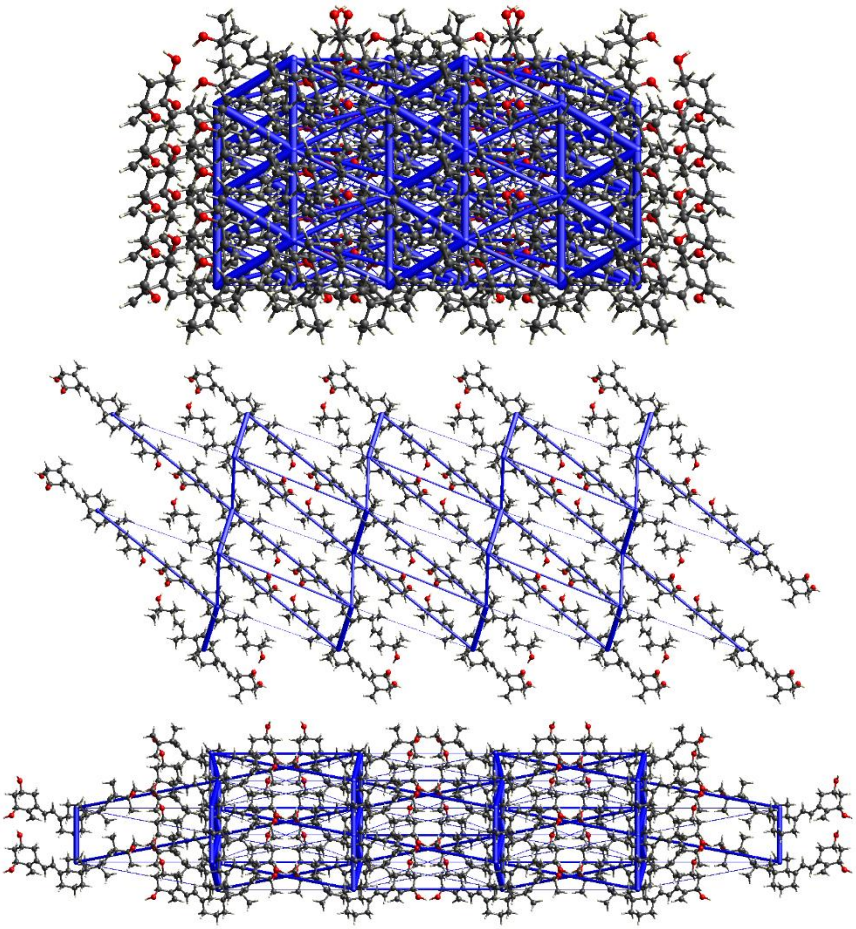


Fig. 18 Total energy frameworks: HB1 (-62.6 kJ/mol), HB2 (-67.5 kJ/mol) and HB3 (-34.1 kJ/mol).

10.3. 1732 (3)

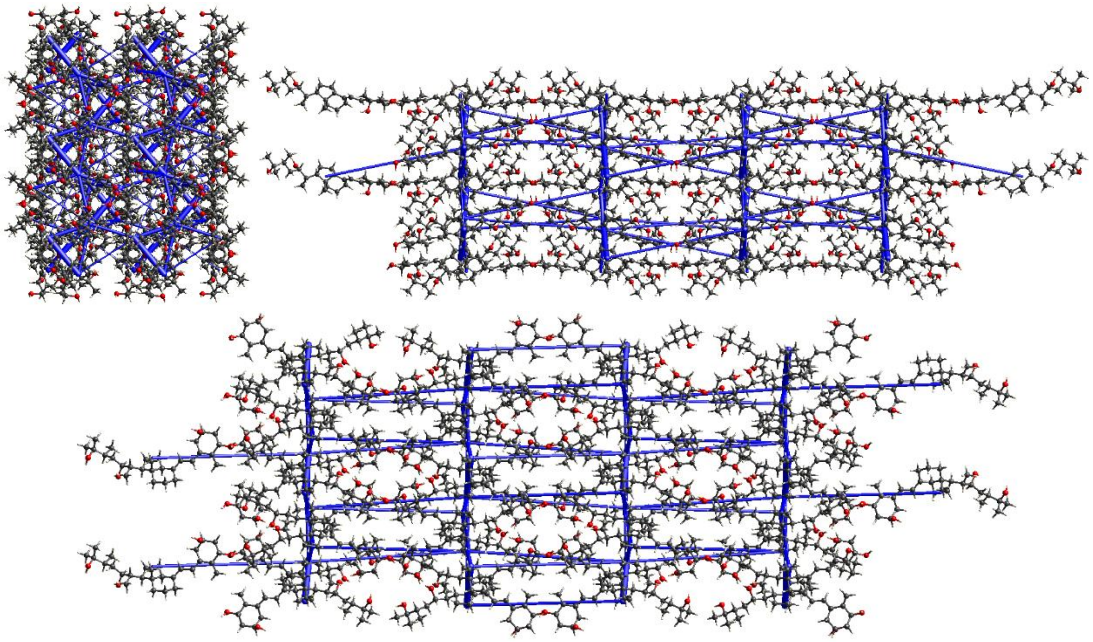


Fig. 19 Total energy frameworks: HB3 (-35.2 kJ/mol), HB6 (-36.0 kJ/mol), HB7 (-48.4 kJ/mol) and HB8 (-80.7 kJ/mol).

10.4. 1,25D₃

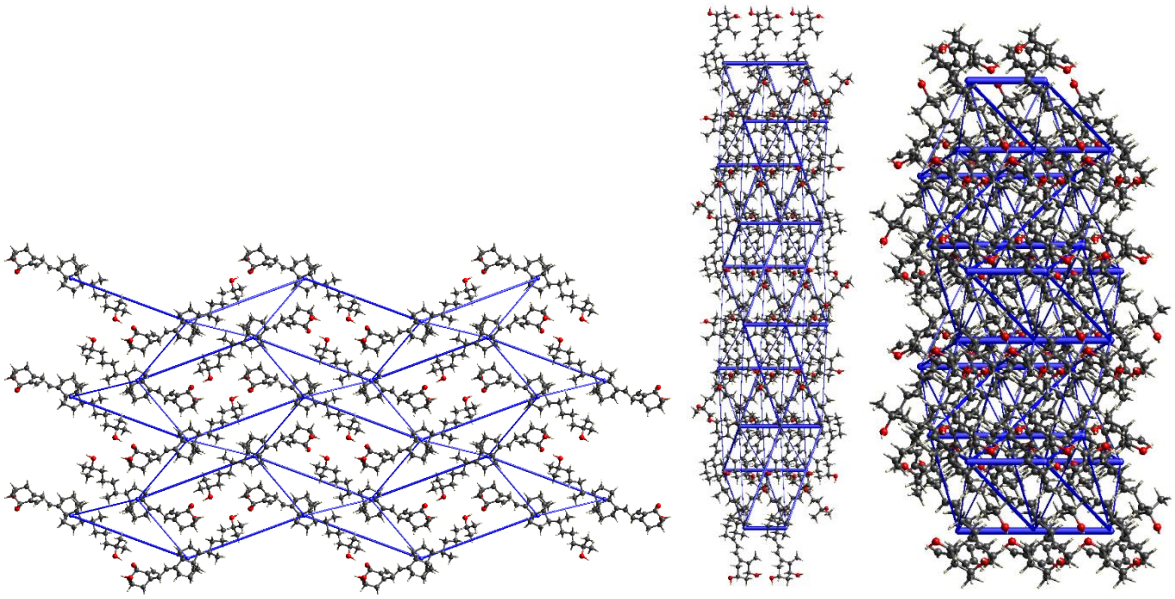


Fig. 20 Total energy frameworks: HB1 (-59.8 kJ/mol) and HB2 (-30.5 kJ/mol).

Tables

1. Summary of 1,25-dihydroxyvitamin D analogues

	Space group	Methylene group	OH-group in side chain	Double bond in side chain	Untypical modification	Solvent	CD-ring	Hydrogen bond motifs
EFEHII	C2	-	25-OH	C22-C23	28C	-	III	Infinitive chains, R_6^6
EFEHOO	$P2_12_12$	-	25-OH	C22-C23	28C	-	IV	Infinitive chains, R_6^6
GAJNOX	C2	C2-C19	25-OH	-	C24-(F)2	-	III	Infinitive, discrete chains
GAJNUD	C2	-	25-OH	-	C24-(F)2	-	III	Infinitive, discrete chains
HIJFAH	$P2_12_12_1$	C10-C19	25-OH	-	-	H_2O	I	Infinitive chains, R_4^4 R_6^6
KAKTOH	P1	C2-C19	25OH	-	-	-	III	Infinitive chains, R_4^4 R_6^6
MIJXUA	C2	C10-C19	24-OH	C22-C23	C24-cyklopropane	-	I	Infinitive, discrete chains, R_4^4
NAJPOE	C2	C10-C19	-	C22-C23	C24-iPr, C28	-	I	Infinitive chains,R_4^4
NAJPUK	$P2_1$	C10-C19	-	-	C24-iPr, C28	-	III	Infinitive chains
QURJUI	$P2_12_12_1$	C10-C19	25-OH	-	C2-CH_3	H_2O	II	Infinitive chains, R_4^4
SUJCUX	I222	-	25-OH	-	C7-CH_3	-	-	Discrete chains, R_4^4
TEZPIZ	C2	C2-C19	25-OH	-	C22-$(CH_3)_2$	iPrOH	IV	Infinitive chains, R_4^4
TEZPOF	$P2_1$	C2-C19	25-OH	-	C22-$(CH_3)_2$	EtOEt	-	Discrete chains
TEZQAS	C2	C2-C19	25-OH	-	C22-C28	iPrOH	II	Infinitive chains, R_4^4
WACHIR	$P2_1$	C10-C19	24-OH	C22-C23	C24-cyklopropane	H_2O	II	Infinitive chains, R_4^4
WUTVUD	$P2_12_12_1$	-	25-OH	-	C21-C≡C-C(OH)$(CF_3)_2$	-	-	Discrete chains
ZUNFUL	$P2_12_12_1$	-	25-OH	-	-	-	-	Discrete chains

2. Lengths of selected bonds

Bond	PRI-1730 (1)	PRI-1731 (2)	PRI-1732 (3)	BNR-1 (4)
C4-C5	1.520(5)	1.488(3)	1.489(3)	1.514(2)
C5-C6	1.347(5)	1.340(3)	1.345(3)	1.342(3)
C5-C10	1.479(5)	1.510(3)	1.509(3)	1.484(3)
C6-C7	1.455(5)	1.453(3)	1.456(3)	1.453(2)
C7-C8	1.342(5)	1.341(3)	1.345(3)	1.340(3)
C8-C9	1.514(5)	1.510(3)	1.510(3)	1.513(2)
C8-C14	1.509(5)	1.507(3)	1.495(2)	1.499(2)
C19-CX	1.327(6)	1.334(4)	1.327(3)	1.332(3)

The bond lengths were analyzed to find how the differences in chair conformation of the A-ring influence the geometry of the triene system. Quite unexpectedly, the A-ring chair conformation influenced mostly the length of the C8-C14 single bond in the CD-ring system. The length of these bonds for the A-ring chair α-conformation was 1.498(2)/1.506(2) Å and 1.499(2) Å for **3** and **4**, respectively. It was shorter than the length of bonds for the chair β-conformation (1.509(5)Å and 1.507(3)Å for **1** and **2**, respectively). The difference between both part of asymmetric unit of **3** is interesting, however the bigger value is still smaller than the values of C8-C14 bond in β-conformation. The location of exocyclic methylene showed much stronger influence on lengths of bonds of the triene system, particularly of C8-C9, C4-C5 and C5-C10 bonds, than the A-ring chair conformation.

3. Values of selected angles

Valence angle [º]	PRI-1730 (1)	PRI-1731 (2)	PRI-1732 (3)	BNR-1 (4)
C5C6C7	130.2(4)	128.0(2)	124.8(2)	126.85(17)
C5C6C10	125.4(3)	124.84(19)	122.31(18)	124.48(18)
C6C7C8	124.3(4)	125.2(2)	127.2(2)	126.31(17)
C7C8C9	124.5(4)	124.5(4)	125.84(18)	124.82(16)
C7C8C14	124.9(3)	124.96(18)	122.45(19)	123.81(16)

The A-ring chair conformation have bigger influence on values of valence angles than for length of bonds. For instance, analogues with the A-ring chair α-conformation (**3** and **4**) have higher C6-C7-C8 valence angles [**3** and **4**: 126.03(17)°/127.18(2) and 126.31(17)°], than those with the chair β-conformation [**1** and **2**: 124.3(4)° and 125.2(2)°, respectively]. Additionally, the C5-C6-C7 and C7-C8-C14 angles of compounds with α-chair conformation are smaller than compounds with β-chair conformation of A-ring.

4. Values of selected torsion angles

Torsion angle [º]	PRI-1730 (1)	PRI-1731 (2)	PRI-1732 (3)	BNR-1 (4)
C5C6C7C8	-173.4(4)	175.3(2)	-176.37070(3)	171.4(2)
C17C20C22C23	-170.8(3)	-135.5(2)	-162.00826(13)	-108.5(2)
C22C23C24C25	69.3(4)	108.7(3)	165.76137(11)	-176.53(18)

As expected, torsion angle of the triene system (C5-C6-C7-C8) was the smallest for **4** [171.4(2)°], due to the presence of TBS groups which obstructed the influence from hydroxyls. Other torsion angles were -173.4(4)° and 175.3(2)°, 177.4(2)°/-176.5(2)° for **1**, **2** and **3**, respectively. For analogues with methylene at C-10 torsion angles were lower than for analogues with methylene at C-4. They were also lower than that for the 19-nor analogues, without C-19 methylene. For the previously described PRI-5100 and PRI-5101 these angles were 177.7(2)° and -175.8(3)°). Torsion angle C22-C23-C24-C25 was extraordinarily small for **1** (69.3(3)°), due to the fold of the side chain which resulted from intramolecular hydrogen bond between C-22 hydroxyl and C-25 hydroxyl. Analogue **3** has the same side chain as **1**, but the side-chain hydroxyls of **3** formed hydrogen bonds with water molecules. Furthermore, presence of unsaturated bond made the angle C22-C23-C24-C25 smaller. Analogue **2**, PRI-5100 and PRI-5101 had this angle smaller, in comparison to **1**, **3** and 1,25D_3 (169.2(7)). The same correlation was also observed for the C17-C20-C22-C23 dihedral angle.

5. Values of A/CD-ring angles

Compound	A/CD angle
PRI-1730 (1)	15.20(12)
PRI-1731 (2)	176.18(7)
PRI-1732 (3)	55.9332(3)
BNR-1 (4)	129.34(6)

6. Charge of donors and acceptors of hydrogen bond

Charges of atoms were fitting to the electrostatic potential for α and β form of **1**, **2**, **3** and 1,25D$_3$ obtained using DFT method, B3LYP functional and 6-311++g(2d,2p) basis set. Calculations were performed for explore Etter's rule which was unconfirmed here.

6.1. 1730 (1)

	β	α
O1	-0,693	-0,669
H22	0,405	0,402
O3	-0,696	-0,706
H1	0,385	0,367
O22	-0,693	-0,672
H25	0,399	0,389
O25	-0,796	-0,777
H3	0,391	0,396

6.2. 1731 (2)

	β	α
O1	-0,701	-0,671
H25	0,36	0,361
O3	-0,666	-0,668
H1	0,392	0,396
O25	-0,68	-0,672
H3	0,398	0,383

6.3. 1732 (3)

	β	α1	α2
O1	-0,678	-0,679	-0,682
H22	0,407	0,389	0,375
O3	-0,710	-0,701	-0,676
H3	0,402	0,384	0,386
O22	-0,672	-0,69	-0,672
H1	0,394	0,395	0,401
O25	-0,772	-0,729	-0,735
H25	0,392	0,384	0,411

6.4. 1,25D$_3$

	β	α
O1	-0,689	-0,643
H25	0,407	0,407
O3	-0,684	-0,683
H1	0,386	0,389
O25	-0,742	-0,751
H3	0,391	0,381

7. Description of dimers energy analysis of 3.

Due to the unexpected value of the positive coulombic energy for HB7 of **3** (equal to 57.9 kJ/mol), compound **3** was investigated in a more detailed manner. The calculations were performed for two molecules of asymmetric unit each with two disordered parts. Due to this, for HB3, HB7 and dimers with solvent (HBS(O1) and HBS(O25), Fig. S7, SI) four equivalent dimers with different energies occurred. For hydrogen bonds in the asymmetric regions (HB6, HB8 and the hydrogen bond between two water molecules W1 and W2) two equivalent dimers with different energy are present. For clarity, results in Table 3 were presented only for one disordered part of each molecule in asymmetric unit. The results of HB3, HB6 and HB8 showed that when equivalent dimers occurred, the energies were similar and differences are equal between 0.1 and 1.9 kJ/mol. Higher differences are result of hydrogen bond formation between different acceptor and donor in equivalent dimers e.g. HB7: O1-H1…O22 and O22-H22…O1. It was observed for one molecule of HB7, HBS(O1) and two molecules of HBS(O25) and energy is equal to 9.6 kJ/mol, 3.2 kJ/mol, 3.3 kJ/mol and 8.5 kJ/mol, respectively. Remaining dimers HB7 and HBS(O1) are unable to form a hydrogen bond due to disorder and forced to form repulsive interactions with close contact between H1…H22, O1…O22 (Δ_E= 44.6 kJ/mol) and O1…O1W, H1W…H1 (Δ_E= 67.6 kJ/mol), respectively. This analysis showed that the higher energy differences occurred between dimers that contain at least one unfavorable interaction: one dimer out of four of HB7, and two dimers out of four HBS(O1), Δ_E=18.5 and Δ_E=86.1 kJ/mol. Moreover, the energies of interaction between equivalent water molecules (W1W1 and W2W2) also have positive values (between 21.4 and 84.7 kJ/mol).