Supporting Information

Naturally occurring FANCF-Hes1 complex inhibitors

from *Wrightia religiosa*

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Supporting Information

General experiment procedures

NMR spectra were recorded on JEOL ECP400 and ECP600 spectrometers in a deuterated solvent whose chemical shift was taken as an internal standard. Mass spectra were obtained using Exactive (Thermo Scientific) and AccuTOF LC-plus JMS-T100LP (JEOL). UV spectra were measured in a SHIMADZU UV mini-1240 spectrometer and

UV-1575 (JASCO). HPLC was carried out on a PU-1580 pump (JACSO), a UV-1575 (JASCO) and a RI-1530 (JASCO). Column chromatography was performed using silica gel PSQ100B, Chromatorex ODS, (Fuji Silysia Chemical Ltd., Kasugai, Japan), silica gel 60N (Kanto Chemical Co., Inc., Tokyo, Japan) and Sephadex LH-20 (GE Healthcare life sciences, Tokyo, Japan). Preparative HPLC was performed using CAPCELL PAK C18 (Shiseido Co., Ltd.), YMC-Pack Pro C18 (YMC, Co., Ltd., Kyoto, Japan), and Develosil C30-UG-5 (Nomura Chemical Co., Ltd., Seto, Japan).

Preparation of a plasmid.

GST fused at N-terminal a human HES1 (full length) was prepared by using pGEX-6p-1 vector (GE Healthcare). A DNA coding HES1 were prepared by digested of pCMVzeo-HA HES1 plasmid (*Eco*RI and *Xho*I). The DNA (855 bp) was purified and ligated with pGEX-6P-1 expression vector digested with *Eco*RI and *Xho*I to generate pGEX-6P-hHES1$_{full}$. GST fused at N-terminal a mouse β-catenin (aa 128-683) was prepared by subcloning pBSSK-β-catenin plasmid (a gift from Prof. Tetsu Akiyama, Tokyo University, Japan) as a template by PCR. The primer for PCR are as follows:

forward primer, 5'-AGGGATCCCCATCACAGATGTTG-3', reverse primer, 5'-AGGTCGACTCAGAAGAGGGAACT-3'. The PCR-amplified DNA fragments were digested with *Bam*HI and *Sal*I and ligated with pGEX-6P-1 vector (GE Healthcare) digested with *Bam*HI and *Sal*I to generate pGEX-mβ-catenin$_{128-683}$ plasmid. GST fused at N-terminal a human TCF4E (aa 1-100) was prepared by subcloning pBSSK-hTCF4E (a gift from Prof. Tetsu Akiyama) as a template by PCR. The primers for PCR are as follows: forward primer, 5'-AGGAATTCATGCCGCAGCTGAAC-3', reverse primer, 5'-AGCTCGAGTCAATACGGTGGCCC-3'. The PCR-amplified DNA fragments were digested with *Eco*RI and *Xho*I and ligated with pGEX-6P-1 vector digested with *Eco*RI and *Xho*I to generate pGEX-hTCF4E$_{1-100}$ plasmid.

Expression and purification of recombinant proteins.

E. Coli strain JM109 (TOYOBO, Osaka, Japan) serves as a host for pGEX-rHes1$_{3-281}$, pGEX-hFANCF$_{full}$, pGEX-6P-hHES1$_{full}$, pGEX-6P-1, pGEX-mβ-catenin$_{128-683}$ and pGEX-hTCF4E$_{1-100}$. An overnight plateau phase culture of JM109 was used to inoculate fresh LB medium containing 100 mg/l ampicillin. Cells were grown at 25 ˚C to a

density of OD_{600} of 0.6 and induced by 0.1 mM IPTG (isopropyl-1-thio-β-D-galactopyranoside) followed by incubation for an additional 3 h at 25 ˚C. The cells were harvested and were lysed by sonication. The lysate was added to Triton X-100 (final conc. 1 % (v/v)) and gently mixed at 4 ˚C for 30 min. The resulting solution was centrifuged at 5000 rpm for 7 min at 4 ˚C. The supernatant was added to pre-washed glutathione sepharose 4B beads (GE Healthcare, Uppsala, Sweden) and gently mixed at 4 ˚C for 60 min. The beads obtained after centrifugation (2000 rpm, 5 min, at 4 ˚C) were washed 5 times (2000 rpm, 1 min, at 4 ˚C) with PBS. The GST was cleaved from recombinant protein (GST-$Hes1_{3\text{-}281}$, GST-6P-$HES1_{full}$ and GST-$hTCF4E_{1\text{-}100}$) by PreScission protease (GE Healthcare, Buckinghamshire, UK) for 4 h at 4 ˚C in cleavage buffer (50 mM Tris-HCl, pH 7.0, 150 mM NaCl, 1 mM EDTA, 1 mM DTT). After centrifuged at 2000 rpm for 1 min at 4 ˚C, the supernatant was then dialyzed against PBS buffer using Slide-A-Lyzer^R Dialysis Cassette (Extra Strength, 10,000 MWCO; Thermo, Rockford, USA). The recombinant GST fused proteins (GST-$FANCF_{full}$ and GST-mβ-$catenin_{128\text{-}683}$) were eluted with 50 mM glutathione buffer (50 mM Tris-HCl, pH 8.8) and then dialyzed against PBS or NET buffer using

Slide-A-Lyzer® Dialysis Cassette (Thermo).

The protein concentration was determined by Micro BCA Protein Assay Kit (Thermo, Rockford, USA). The recombinant proteins were estimated to be greater than 90 % pure by SDS-PAGE. Recombinant proteins were checked by Western blotting analysis by using antibody as follows: rat $Hes1_{3\text{-}281}$; rabbit polyclonal antibody, 1/400, (Merck Millipore, Darmstadt, Germany), human $HES1_{full}$; HES1 antibody (H-20) (Santa Cruz Biotech. Inc., Texas, USA), human $FANCF_{full}$; FANCF (H-310) (Santa Cruz Biotech. Inc., Texas, USA), human $TCF4E_{1\text{-}100}$; TCF-4 (N-20) (Santa Cruz Biotech. Inc., Texas, USA) and β-catenin; Anti-β-catenin Mouse mAb (Merck Millipore, Darmstadt, Germany).

Preparation of Hes1, HES1 and TCF bound microplate.

Typical procedure; Nunc Immobilizer™ Amino 96 well Plate, white (Nalge Nunc Int., NY, USA) was used for immobilizing of rat $Hes1_{3\text{-}281}$, human $HES1_{full}$ and human $TCF4E_{1\text{-}100}$. The micro plate wells were incubated with 100 μl of Hes1 (20 μg/ml in PBS), HES1 (5 μg/ml in PBS) and TCF (5 μg/ml in PBS) overnight at 4 ˚C. The protein

solution was removed, and then each well was washed twice with 200 μl of PBS-Tween buffer (PBST; PBS plus 0.05 % Tween 20). To block remaining activated succinimidyl ester unit on the well, the wells were incubated for 2 h at room temperature with 100 μl of 10 mM ethanolamine (in 100 mM Na_2CO_3 pH 9.6 buffer), then washed 2 times with 200 μl of PBST. Immobilized proteins were detected with anti-body described above and peroxidase-conjugated antibody.

Preparation of Cy dye-labeled proteins.

The Cy dye-labeled human FANCF (rat or human Hes1) was prepared by mixing of protein in PBS solution with Cy3 bisfunctional dye reagents (succinimidyl ester type; GE Healthcare) in DMSO for 1 h at 4 ˚C in the dark. Cy dye solution was made by adding 50 μl DMSO to 1 vial of Cy dye reagent, and stored at -20 ˚C. Typically, 1 μl of DMSO solution was added to 1 ml of protein solution (100 μg/ml) in PBS. After incubation, the mixture was directly dialyzed with NET buffer at 4 ºC to remove excess unreacted dye reagent. After 3 h dialysis, NET buffer was replaced with fresh NET buffer and dialyzed overnight. The ratio of dye/protein was calculated from the

absorption for Cy3 (ε 150000 M^{-1} cm^{-1} at 552 nm). Because it was revealed that 30% reduction of protein concentration after dialysis, concentration of Cy3-Hes1 protein estimated ca. 7 mg/L. The ratio of dye/protein was obtained after the absorption for Cy3 (ε 150000 $M^{-1}cm^{-1}$) was determined at the wavelength 552 (typically the ratio was 0.6-0.8).

HTS assay for inhibitors of FANCF-Hes1, Hes1 dimer and TCF-β-catenin.

The rat Hes1 or human HES1 bound microplate wells were incubated with 50 μl of Cy3-human FANCF (20 μg/ml, 0.3 μM), Cy3-rat Hes1 (16 μg/ml, 0.3 μM) or Cy3-human HES1 (16 μg/ml, 0.3 μM) in NET-N buffer (dye/protein = 0.6~0.8) and samples (1 μl, DMSO solution) for 1 h at rt (After addition of samples, plate was shacked with a microplate mixer for 5 s). After removal of protein solution, each well was washed twice with 200 μl of NET-N buffer (20 mM Tris-HCl pH 7.5, 200 mM NaCl, 1 mM EDTA, 0.05 % Nonidet P-40), then dried under reduced pressure 1 h in the dark. The fluorescence intensity was detected by a microplate reader. The assays were carried out in three individual wells, and the mean value and SD were calculated.

Microplate Reader: Fluoroskan Ascent (Thermo). Cy3; Excitation 544 nm, Emission 590 nm.

HTS assay for inhibitors of TCF/β-catenin complex formation.

This assay was performed by the modified method which was reported (ref. 1). The $hTCF4E_{1-100}$ bound microplate wells were incubated with 50 μl of GST-mβ-catenin (5 μg/L, 60 nM) and samples (1 μl, DMSO solution) for 1 h at rt (After addition of samples, plate was shacked with a microplate mixer for 5 s). After removal of protein solution, each well was washed twice with 200 μl of NET-N buffer, then dried under reduced pressure 1 h in the dark. The fluorescence intensity was detected by a microplate reader. The assays were carried out in three individual wells, and the mean value and SD were calculated. Microplate Reader: Luminoskan Ascent (Thermo). Non-specific interaction was assessed by Cy3-GST (1.48 μg/L, 60 nM).

ref. 1: Lepourcelet, M., Chen, Y. -N. P., France, D. S., Wang, H., Crews, P., Petersen, F., Bruseo, C., Wood, A. W., and Shivdasani, R. A. (2004) Small-molecule antagonists of the oncogenic Tcf/beta-catenin protein complex, *Cancer Cell 5*, 91-102.

Plant Materials.

Wrightia religiosa (Apocynaceae) leaves were collected from Thailand. A voucher specimen (KKP22) was deposited at the Department Natural Products Chemistry, Graduate School of Pharmaceutical Sciences, Chiba University。

Isolation of compounds from *Wrightia religiosa*.

The MeOH extract of *W. religiosa* (leaves) (28.5 g) was partitioned with hexane (500 mL × 3), EtOAc (500 mL × 3), *n*BuOH (500 mL × 3) and H_2O (500 mL × 3). The *n*BuOH-soluble fraction (8.0 g) was subjected to ODS flash column chromatography (40 × 550 mm) and eluted with gradient mixtures of H_2O-MeOH (1/0-0/1) to give eight fractions (frs. 1A-1H). Part (220 mg) of fr. 1D (1.5 g) was subjected to reverse-phase HPLC (YMC-Pack ODS-AM, 10 × 250 mm; eluent, H_2O-MeOH (54/46); flow rate, 1.7 mL/min; detection, UV at 254 nm) to give compound **1** (39.8 mg), compound **2** (29.4 mg), compound **3** (13.2 mg) and compound **4** (13.2 mg). Fr. 2A (64.7 mg) was purified by reverse-phase HPLC (Develosil C30-UG-5, 10 × 250 mm; eluent, H_2O-MeOH (45/55); flow rate, 2.0 mL/min; detection, UV at 254 nm) to give compound **5** (2.2 mg),

compound **6** (25.1 mg) and compound **7** (11.7 mg). The Hexane-soluble fraction (8.8 g) was subjected to Dianion HP-20 column chromatography (70 × 250 mm) and eluted with gradient mixtures of acetone-MeOH (0/1-1/0) to give four fractions (frs. 4A-4D). Fr. 4B (2.5 g) was subjected to silica gel 60N column chromatography (50 × 250 mm) and eluted with gradient mixtures of Hexane-AcOEt-MeOH (9/1/0-0/0/1) to fifteen fractions (frs. 5A-5O). Fr. 5E was purified by to give reverse-phase HPLC (CAPCELL PAK C18, 4.6 × 250 mm; eluent, H_2O-MeOH (18/82); flow rate, 0.7 mL/min; detection, UV at 254 nm) to give compound **8** (0.5 mg).

Colony forming cell assay.

Bone marrow cells were collected from femurs of wild-type and from wild-type (WT) and knockout Fanconi A (FancA) and C (FancC) mice, and stem/progenitors were selected using the StemSep negative selection procedure, according to the manufacturer's protocol (Stem Cell Technology). Two to 5 x 10^3 stem/progenitor cells per ml were seeded in complete methylcellulose medium (Stem Cell Technology), with or without compound **5** (50 μM), and incubated for 10 and 14 days at 37°C in 5% CO_2.

The total number of colonies were counted and presented as colony forming cells (CFC).

Data represent the mean obtained from two experiments performed in triplicate.

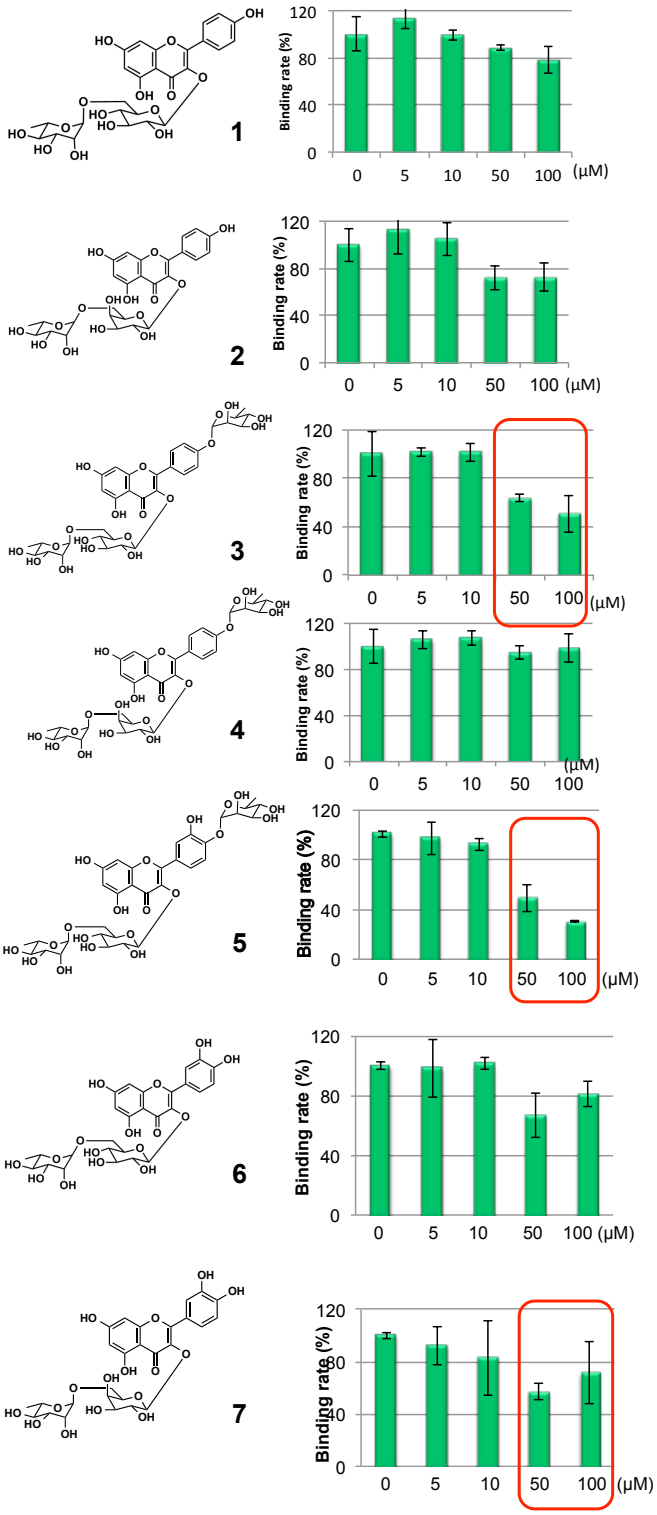

Figure S1 Screening results of compounds **1**-**7**. rHes1-hFANCF interaction inhibition.

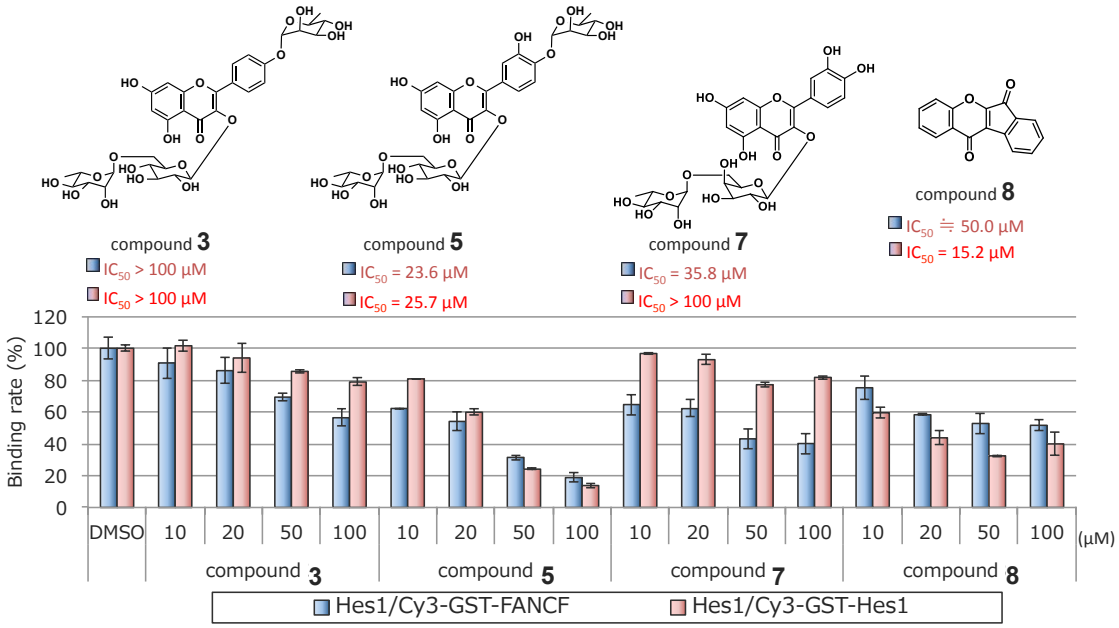

Figure S2 Protein interaction inhibition activities of compounds **3**, **5**, **7** and **8**.

(The data of **3**, **5**, **7** were same in the manuscript, Figure 6.) hFANCF-hHES1 and hHES1 dimer assay were performed on hHES1 immobilized microplates. Cy3-GST-FANCF or Cy3-GST-HES1 was added to initiate complex formation. Complex formation was monitored by determining fluorescence (Ex 544/Em 590). Immobilization; hHES1 (5 μg/ml), Cy3-proteins; Cy3-GST-hFANCF (20 μg/ml, 0.3 μM), Cy3-GST-hHES1 (7.4 μg/ml, 0.3 mM).

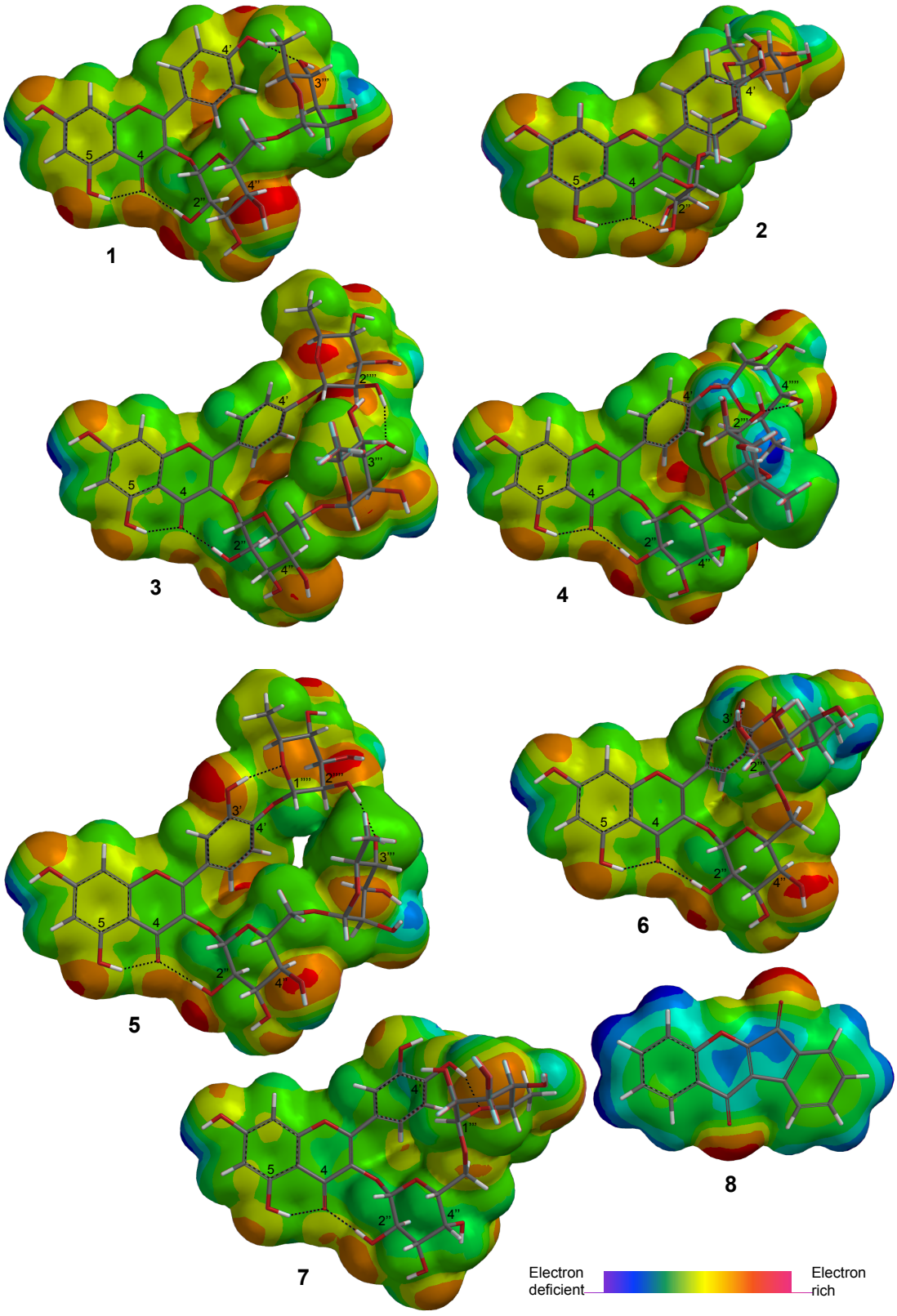

Figure S3 The stable structures and electrostatic potential energy surfaces of isolated compounds. Calculations were performed by Spartan 10 software (B3LYP/6-31G*).

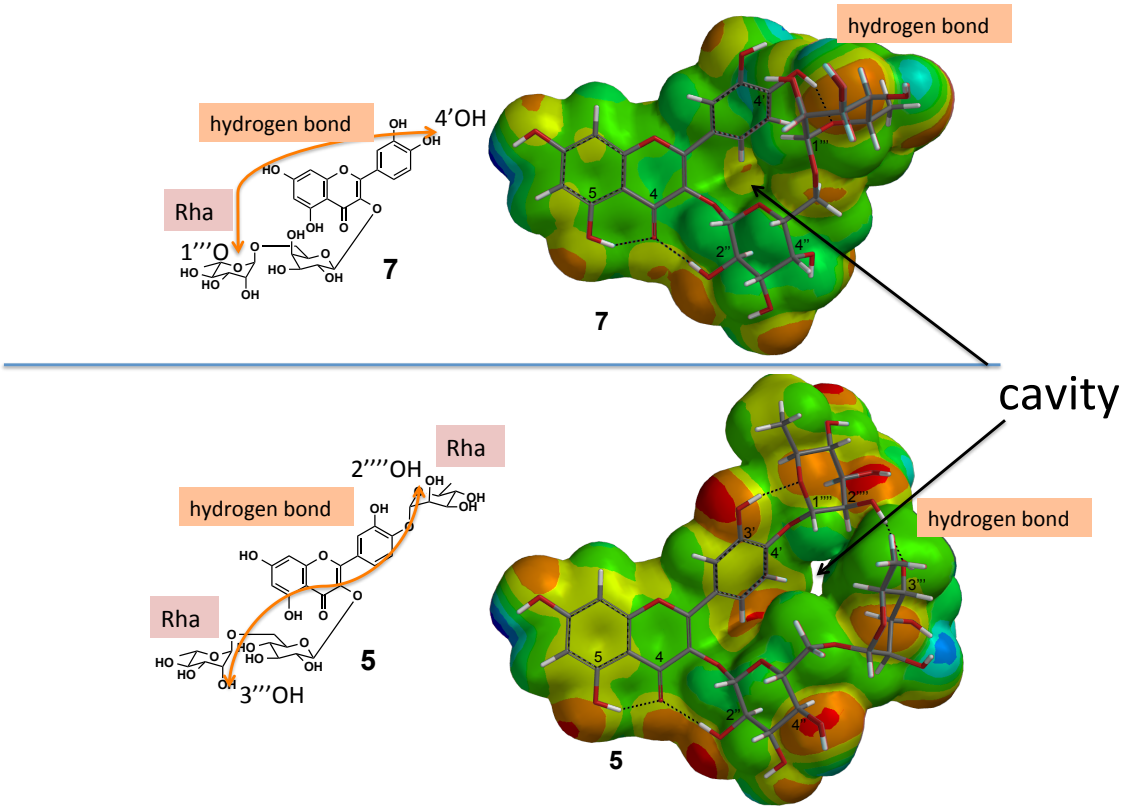

Figure S4 The comparison of structures of **7** and **5**. The internal hydrogen bonds between O at the 1''' position of rhamnose and OH at the 4' position (compound **7**) and between OH at the 3''' position of rhamnose and OH at the 2'''' position of rhamnose (compound **5**) were observed to make the folding structures. There is difference in size of cavities which were made by hydrogen bonds.

Molecular modeling calculations

All molecular modeling calculations were conducted by Spartan 10 software (Wavefunction). The stable conformers of compound **1-8** were obtained using molecular mechanism calculation to afford 4, 11, 7, 12, 9, 9, 10 and 1 stable conformers,

respectively. The conformers with a relative energy of 0-5 kJ mol^{-1}, 3, 3, 1, 4, 4, 4, 2 and 1 conformers for compound **1**-**8**, respectively, were optimized using Hartree-Fock/3-21G calculation followed by DFT methods supporting no solvent (vacuum conditions, B3LYP/6-31G*). Lowest energy (global minimum) structures were presented in **Figure S3**. Relative energy for local minimum conformers were 0, 0.01 and 1.98 kJ mol^{-1} for compound **1**, 0, 3.90 and 3.94 kJ mol^{-1} for compound **2**, 0, 2.30, 3.07 and 4.40 kJ mol^{-1} for compound **4**, 0, 0.12, 1.31 and 2.04 kJ mol^{-1} for compound **4**, 0, 0.09, 1.48 and 1.63 kJ mol^{-1} for compound **6**, 0 and 1.77 kJ mol^{-1} for compound **7**, respectively.

Atomic coordinates for compound **1**

Atom	X	Y	Z
C	4.68376	-1.338838	0.155487
C	7.246589	-0.292672	0.426456
C	5.702253	-2.187022	0.565891
C	4.893684	0.023087	-0.12348
C	6.21238	0.544789	0.01578
C	6.984517	-1.643522	0.696528
O	3.441556	-1.887376	0.014257
C	2.350553	-1.154608	-0.359915
C	2.491153	0.192117	-0.602932
C	3.782737	0.847307	-0.53635
O	3.924008	2.07253	-0.806254

C	1.14639	-1.98179	-0.445523
C	-1.155362	-3.612989	-0.538288
C	0.002978	-1.576789	-1.161498
C	1.117521	-3.241992	0.191621
C	-0.011086	-4.043813	0.151254
C	-1.124789	-2.382375	-1.214505
H	5.517579	-3.233884	0.771003
H	8.245955	0.120049	0.530954
H	1.990168	-3.583574	0.735909
H	-0.036588	-5.000947	0.66193
H	-0.002521	-0.625694	-1.673823
H	-1.994859	-2.062569	-1.778896
O	7.965733	-2.493409	1.098362
O	6.4698	1.834429	-0.238718
O	1.432132	0.96135	-1.028448
H	5.607029	2.24895	-0.513342
H	8.80658	-2.011751	1.146313
O	-2.246566	-4.410251	-0.519142
H	-3.025914	-3.91925	-0.86408
C	0.862945	1.869355	-0.098431
C	-0.212652	4.111446	0.067141
C	-1.109396	2.111968	1.229789
C	-1.488251	3.423215	0.528836
C	0.61647	3.193665	-0.826828
O	-0.350262	1.286176	0.34208
O	1.80952	3.88167	-1.136134
O	-0.584872	5.308567	-0.603466
O	-2.204857	4.232472	1.450594
C	-2.310626	1.314677	1.709445
O	-3.189062	1.058859	0.610413
C	-4.505937	0.769404	0.972157
C	-4.137634	-1.617626	0.97175

C	-4.936425	-0.493768	-1.151398
C	-4.966851	-1.773228	-0.306226
C	-5.347817	0.718013	-0.309698
O	-6.737502	0.628094	0.016321
O	-5.779169	-0.661543	-2.287154
O	-4.495361	-2.869301	-1.099547
C	-4.239364	-2.798184	1.924388
O	-4.643704	-0.459553	1.680287
H	1.548107	2.016924	0.75125
H	2.535564	3.22993	-1.249467
H	0.040492	2.958481	-1.737144
H	0.237664	5.687211	-0.956855
H	0.391857	4.354258	0.957867
H	-2.108269	3.183075	-0.345992
H	-2.223309	5.122161	1.059401
H	-0.507953	2.355535	2.122717
H	-1.971576	0.369386	2.14943
H	-2.831371	1.898927	2.478773
H	-4.904416	1.524768	1.663156
H	-5.222637	1.639127	-0.884874
H	-6.801197	0.057054	0.802047
H	-6.679289	-0.462693	-1.968321
H	-3.921092	-0.343168	-1.53204
H	-6.008645	-1.978594	-0.012312
H	-4.912	-2.750659	-1.972739
H	-3.090919	-1.438594	0.698669
H	-5.284996	-3.001373	2.182044
H	-3.804572	-3.692497	1.470179
H	-3.694642	-2.577962	2.847672

Atomic coordinates for compound **2**

Atom	X	Y	Z
C	3.929254	-1.866517	-0.350891
C	6.527173	-1.426211	-1.229102
C	4.517254	-2.818282	-1.171162
C	4.585099	-0.688732	0.049987
C	5.920207	-0.479923	-0.407193
C	5.825475	-2.580181	-1.604153
O	2.663642	-2.129128	0.090359
C	1.977211	-1.249734	0.873453
C	2.518715	-0.032179	1.208416
C	3.895668	0.284381	0.868623
O	4.467744	1.345461	1.245721
C	0.671895	-1.783141	1.27446
C	-1.855503	-2.781464	1.992787
C	0.116945	-1.496509	2.535591
C	-0.035937	-2.629718	0.404532
C	-1.289991	-3.117642	0.753212
C	-1.123073	-2.000858	2.897521
H	3.989393	-3.718843	-1.457853
H	7.542882	-1.247167	-1.569998
H	0.39202	-2.888658	-0.558259
H	-1.842415	-3.753846	0.066798
H	0.65867	-0.860834	3.224895
H	-1.560835	-1.769533	3.863286
O	6.383466	-3.525624	-2.404212
O	6.601053	0.620882	-0.064259
O	1.812237	0.843376	2.008196
H	5.994821	1.159817	0.513532
H	7.288621	-3.259755	-2.630525
O	-3.10489	-3.178101	2.350622
H	-3.655206	-3.230293	1.541562
C	1.05789	1.888801	1.403024

C	1.022152	3.982777	0.044743
C	-0.800656	2.268307	-0.050984
C	-0.064161	3.362556	-0.833491
C	1.916782	2.895779	0.632509
O	0.094206	1.317474	0.540174
O	2.870343	3.544208	1.445681
O	1.792733	4.862004	-0.764501
C	-1.758844	1.498425	-0.950771
O	-2.813632	0.938637	-0.158516
C	-3.244203	-0.325553	-0.562145
C	-4.955048	0.512447	-2.048255
C	-5.572561	0.00461	0.345151
C	-6.07192	0.055445	-1.10388
C	-4.283984	-0.81446	0.455024
O	-4.571747	-2.208824	0.200515
O	-6.596149	-0.50002	1.197163
O	-7.171491	0.940268	-1.220217
C	-5.342897	0.44747	-3.515333
O	-3.812394	-0.358118	-1.868132
H	0.57915	2.380756	2.262214
H	3.560665	2.86707	1.61953
H	2.391847	2.363212	-0.203421
H	2.626356	4.986294	-0.275786
H	0.552589	4.537535	0.874023
H	-1.385509	2.759359	0.744334
H	-2.188045	2.171972	-1.701224
H	-1.20488	0.715711	-1.4786
H	-2.402922	-1.026051	-0.617488
H	-3.886675	-0.770637	1.470019
H	-4.560177	-2.320336	-0.767061
H	-6.582584	-1.466936	1.084009
H	-5.372001	1.028053	0.678769

H	-6.371023	-0.966261	-1.403372
H	-7.745572	0.744296	-0.459399
H	-4.672399	1.537647	-1.777866
H	-4.514658	0.785884	-4.145469
H	-6.213574	1.083791	-3.696854
H	-5.595943	-0.580181	-3.800224
O	0.507857	2.800846	-2.00361
H	1.185411	3.44219	-2.283909
H	-0.799217	4.140847	-1.100672

Atomic coordinates for compound **3**

Atom	**X**	**Y**	**Z**
C	4.474219	-2.952705	-0.36356
C	7.2137	-3.386255	-0.136314
C	4.910522	-4.16378	0.153959
C	5.360186	-1.937437	-0.774801
C	6.759842	-2.177197	-0.655872
C	6.290979	-4.364245	0.26233
O	3.122072	-2.783138	-0.483471
C	2.585708	-1.617404	-0.947426
C	3.39815	-0.569614	-1.289308
C	4.843248	-0.689605	-1.284041
O	5.587541	0.248849	-1.680271
C	1.123152	-1.661198	-1.042946
C	-1.671811	-1.75702	-1.229197
C	0.45132	-0.990727	-2.082454
C	0.368468	-2.406561	-0.120991
C	-1.020004	-2.451053	-0.20093
C	-0.930276	-1.046263	-2.179748
H	4.209956	-4.932327	0.455682

H	8.283944	-3.55041	-0.047876
H	0.87333	-2.948535	0.672161
H	-1.602301	-3.01891	0.515721
H	1.015481	-0.420326	-2.80902
H	-1.457767	-0.528648	-2.974514
O	6.693256	-5.557755	0.770958
O	7.647734	-1.246981	-1.031374
O	2.866745	0.610418	-1.749858
H	7.126194	-0.470308	-1.370912
H	7.662807	-5.586665	0.794161
O	-3.033467	-1.729688	-1.372348
C	3.043224	1.741675	-0.915062
C	3.19133	4.235139	-1.030109
C	1.952163	3.025328	0.732965
C	1.949323	4.281775	-0.147323
C	3.251783	2.94096	-1.839799
O	1.88676	1.872217	-0.112987
O	4.507244	2.889693	-2.494453
O	3.17627	5.386285	-1.866962
O	1.961637	5.431241	0.688008
C	0.841362	2.972048	1.76348
O	-0.443538	3.024442	1.143099
C	-1.424547	3.657233	1.932917
C	-1.963234	1.725687	3.248109
C	-3.305751	2.155039	1.155789
C	-3.336014	1.569624	2.576771
C	-2.734352	3.575628	1.133051
O	-3.750986	4.399558	1.713386
O	-4.618739	2.181653	0.567484
O	-3.615222	0.177598	2.575449
C	-1.967392	1.296718	4.706393
O	-1.550292	3.103587	3.217485

H	3.926815	1.604191	-0.273545
H	4.843774	1.97102	-2.455224
H	2.428105	2.940267	-2.571501
H	3.96918	5.328413	-2.425629
H	4.076702	4.265688	-0.373152
H	1.046626	4.263349	-0.774888
H	2.232983	6.169244	0.116113
H	2.896176	3.009758	1.306677
H	0.93592	2.047362	2.346125
H	0.97336	3.823837	2.439961
H	-1.147731	4.706641	2.11457
H	-2.539689	3.875038	0.095055
H	-3.549028	5.328057	1.524367
H	-5.025722	3.0051	0.897343
H	-2.688215	1.513333	0.521145
H	-4.080964	2.124342	3.168821
H	-4.471483	-0.000202	2.14116
H	-1.245445	1.115972	2.682113
H	-2.298581	0.258344	4.786299
H	-2.646165	1.931608	5.286568
H	-0.962922	1.387342	5.13188
C	-3.824715	-1.647803	-0.17446
C	-4.95272	-3.770277	-0.386314
C	-6.091625	-1.741795	-1.309676
C	-6.299546	-3.066337	-0.57303
C	-5.082647	-0.851243	-0.578917
O	-4.092712	-2.900939	0.383154
O	-5.731308	-0.299953	0.579379
O	-7.334497	-1.070624	-1.486414
O	-7.16751	-3.904729	-1.317998
C	-5.056361	-5.080335	0.374124
H	-3.265477	-1.109611	0.594389

H	-4.768091	-0.033895	-1.235405
H	-5.539106	0.665638	0.559078
H	-5.714888	-1.965998	-2.314126
H	-7.496391	-0.630316	-0.631254
H	-7.884278	-3.321081	-1.62227
H	-6.716342	-2.856533	0.426709
H	-4.502243	-3.942253	-1.373896
H	-5.461705	-4.906546	1.376997
H	-4.070387	-5.545144	0.474119
H	-5.721957	-5.764069	-0.15951

Atomic coordinates for compound **4**

Atom	**X**	**Y**	**Z**
C	4.818149	-2.09484	1.039506
C	7.506848	-1.847995	1.700687
C	5.363992	-3.007111	1.930992
C	5.564571	-1.053088	0.460292
C	6.942294	-0.940178	0.808216
C	6.718579	-2.868174	2.251691
O	3.499365	-2.256258	0.72088
C	2.848163	-1.413575	-0.133807
C	3.512198	-0.350295	-0.69148
C	4.927424	-0.132764	-0.451489
O	5.559755	0.813394	-0.994891
C	1.451161	-1.813292	-0.328256
C	-1.216856	-2.631189	-0.649213
C	0.759945	-1.562108	-1.52557
C	0.781085	-2.500162	0.703458
C	-0.537626	-2.89347	0.551026
C	-0.558041	-1.974596	-1.697068

H	4.768413	-3.805078	2.356129
H	8.558063	-1.746809	1.955589
H	1.29932	-2.715379	1.631395
H	-1.065717	-3.409358	1.346629
H	1.253582	-1.031515	-2.329371
H	-1.080613	-1.758813	-2.619808
O	7.232717	-3.773687	3.123998
O	7.704258	0.032673	0.292068
O	2.890353	0.501725	-1.572146
H	7.119968	0.565667	-0.312077
H	8.173822	-3.584323	3.264523
O	-2.523004	-3.026456	-0.667601
C	2.473152	1.768796	-1.076598
C	2.335261	4.189578	-1.665541
C	0.466273	2.946996	-0.554071
C	0.82034	4.121834	-1.479797
C	2.910065	2.835713	-2.080108
O	1.066666	1.721506	-0.981901
O	4.309229	3.007001	-2.158129
O	2.599806	5.169804	-2.66368
C	-1.03639	2.733518	-0.50127
O	-1.358246	1.848869	0.573856
C	-2.742245	1.694321	0.761813
C	-2.928847	3.187492	2.638444
C	-2.567894	0.745244	3.09164
C	-3.271077	2.012899	3.567455
C	-2.928089	0.446841	1.63668
O	-4.301506	0.046244	1.569373
O	-2.986404	-0.383491	3.858027
O	-2.839292	2.211885	4.917086
C	-3.643077	4.478366	3.008448
O	-3.352044	2.847589	1.30812

H	2.926761	1.948769	-0.088077
H	4.753757	2.150124	-1.975466
H	2.481144	2.545267	-3.051321
H	3.521915	5.025219	-2.938526
H	2.806189	4.479306	-0.711943
H	0.826158	3.194928	0.459423
H	-1.53355	3.699917	-0.353581
H	-1.373726	2.310213	-1.455197
H	-3.254336	1.555052	-0.197928
H	-2.281881	-0.349743	1.248419
H	-4.434212	-0.516261	2.355137
H	-2.97846	-0.088853	4.784698
H	-1.481429	0.889009	3.174691
H	-4.356681	1.844558	3.526985
H	-3.456036	2.822152	5.348119
H	-1.841001	3.342849	2.654156
H	-4.729466	4.332803	3.005278
H	-3.328985	4.82501	3.999362
H	-3.403695	5.263146	2.284777
C	-3.260697	-3.161006	-1.891778
C	-4.098565	-0.903233	-1.90502
C	-5.371716	-2.700244	-0.644923
C	-5.475246	-1.387192	-1.426003
C	-4.601818	-3.757378	-1.441526
O	-3.406901	-1.963828	-2.596145
O	-5.323534	-4.138244	-2.597194
O	-6.67461	-3.221725	-0.391873
O	-6.155269	-0.409339	-0.645906
C	-4.189708	0.262452	-2.876634
H	-2.731117	-3.835539	-2.572247
H	-4.395769	-4.627276	-0.799707
H	-6.247154	-4.214671	-2.29851

H	-4.842164	-2.509814	0.30025
H	-7.223724	-2.446191	-0.179726
H	-5.577196	-0.18341	0.113145
H	-6.105665	-1.565384	-2.304226
H	-3.503258	-0.618344	-1.027079
H	-3.19221	0.626303	-3.142677
H	-4.761354	1.079568	-2.427156
H	-4.697396	-0.05357	-3.793867
O	0.17342	3.951308	-2.729298
H	0.670519	4.514122	-3.349654
H	0.47916	5.052488	-0.994731

Atomic coordinates for compound **5**

Atom	**X**	**Y**	**Z**
C	5.21156	-2.259126	0.169318
C	7.97345	-2.238067	0.497851
C	5.825664	-3.401772	0.660399
C	5.926347	-1.093945	-0.167265
C	7.340871	-1.09902	0.007271
C	7.215532	-3.373421	0.819125
O	3.854208	-2.307698	0.00948
C	3.141158	-1.237342	-0.443834
C	3.778326	-0.063327	-0.747512
C	5.221465	0.067975	-0.652948
O	5.811194	1.139594	-0.956849
C	1.704071	-1.531378	-0.545326
C	-1.011466	-2.187724	-0.731393
C	0.904608	-0.934512	-1.535006
C	1.131428	-2.452147	0.343566
C	-0.224837	-2.781839	0.279592

C	-0.43845	-1.276308	-1.619022
H	5.253305	-4.286473	0.909723
H	9.052012	-2.223945	0.626334
H	1.728694	-2.930637	1.11102
H	1.329322	-0.216105	-2.222207
H	-1.073415	-0.851233	-2.390022
O	7.793588	-4.503327	1.301579
O	8.072009	-0.016789	-0.289299
O	3.0902	1.035038	-1.207343
H	7.439521	0.678819	-0.615066
H	8.752682	-4.371965	1.36605
O	-2.336767	-2.531801	-0.950255
C	2.817629	2.045767	-0.25173
C	2.588086	4.509095	0.029909
C	1.030917	2.880619	1.070338
C	1.140153	4.27217	0.436539
C	3.081753	3.404615	-0.903639
O	1.461868	1.90076	0.1229
O	4.455346	3.637843	-1.134424
O	2.661072	5.792548	-0.576904
O	0.699321	5.240153	1.380667
C	-0.377575	2.518062	1.52219
O	-1.348786	2.803937	0.507664
C	-2.335685	3.719742	0.888501
C	-3.922259	1.979353	1.402129
C	-3.927199	2.979333	-0.915218
C	-4.782799	2.364184	0.195924
C	-3.099842	4.148844	-0.369563
O	-3.968515	5.246039	-0.070668
O	-4.769305	3.387947	-1.988161
O	-5.482105	1.230876	-0.324382
C	-4.70738	1.43137	2.582113

O	-3.248555	3.179884	1.844566
H	3.469564	1.915382	0.627419
H	4.898696	2.781648	-1.317378
H	2.502711	3.437049	-1.841
H	3.57816	5.898946	-0.880583
H	3.212067	4.487158	0.93897
H	0.508949	4.287268	-0.462231
H	0.992773	6.100271	1.034569
H	1.678988	2.844742	1.963252
H	-0.410612	1.44474	1.738865
H	-0.61424	3.068259	2.437509
H	-1.896835	4.592209	1.385378
H	-2.403233	4.507017	-1.132206
H	-4.308825	5.097903	0.828665
H	-5.098504	4.269376	-1.729936
H	-3.259534	2.208386	-1.314961
H	-5.519622	3.111717	0.531429
H	-5.803329	1.506304	-1.20228
H	-3.168133	1.247458	1.082819
H	-5.152374	0.465509	2.325544
H	-4.039045	1.288882	3.436715
H	-5.504956	2.12181	2.878037
C	-3.292966	-2.322805	0.084494
C	-3.928161	-4.664179	0.287727
C	-5.254612	-3.190953	-1.25246
C	-5.323778	-4.346824	-0.248897
C	-4.619591	-1.955999	-0.604505
O	-3.398199	-3.462104	0.919714
O	-5.55431	-1.444814	0.339381
O	-6.557117	-2.888005	-1.737104
O	-5.845727	-5.507866	-0.87291
C	-3.913322	-5.75914	1.339422

H	-2.969734	-1.514025	0.748194
H	-4.399403	-1.202974	-1.369642
H	-5.599644	-0.475358	0.204989
H	-4.661349	-3.509544	-2.115646
H	-6.952386	-2.348846	-1.025722
H	-6.606949	-5.196204	-1.392992
H	-5.955679	-4.03578	0.599169
H	-3.27505	-4.934376	-0.551542
H	-4.507488	-5.461132	2.209641
H	-4.341494	-6.6718	0.916817
H	-2.89044	-5.968725	1.669311
O	-0.693305	-3.670414	1.188282
H	-1.676571	-3.711917	1.161227

Atomic coordinates for compound **6**

Atom	**X**	**Y**	**Z**
C	3.713496	-1.979896	0.125423
C	6.153638	-1.895284	1.457815
C	4.254177	-3.170701	0.58896
C	4.347003	-0.734716	0.303992
C	5.597429	-0.708912	0.987077
C	5.481243	-3.10937	1.257131
O	2.522176	-2.062971	-0.54151
C	1.892365	-0.950608	-1.018197
C	2.429054	0.292283	-0.816239
C	3.718089	0.472526	-0.179388
O	4.239026	1.612762	-0.036071
C	0.639477	-1.256484	-1.711835
C	-1.79178	-1.828479	-2.977728
C	0.288153	-0.609096	-2.90718

C	-0.235564	-2.211401	-1.159721
C	-1.45519	-2.462962	-1.766115
C	-0.908982	-0.912427	-3.549841
H	3.749167	-4.115773	0.433764
H	7.106517	-1.857174	1.977986
H	0.008661	-2.712288	-0.229243
H	0.956301	0.12869	-3.334977
H	-1.18687	-0.422417	-4.47734
O	5.990783	-4.287914	1.701765
O	6.2452	0.446415	1.188571
O	1.784831	1.417258	-1.274389
H	5.685439	1.164468	0.786168
H	6.840441	-4.124109	2.140517
O	-2.985087	-2.102431	-3.557341
H	-3.43636	-2.71959	-2.949818
C	1.175863	2.238485	-0.292983
C	0.617691	4.619522	0.180176
C	-0.996015	2.773962	0.568994
C	-0.85623	4.240687	0.130688
C	1.453663	3.689133	-0.690299
O	-0.211487	1.942989	-0.300877
O	2.809554	4.047293	-0.514972
O	0.728708	5.976485	-0.230173
O	-1.618682	5.056897	1.006435
C	-2.442533	2.298239	0.514514
O	-2.692447	1.1567	1.343625
C	-2.531987	-0.102665	0.727974
C	-4.847856	-0.293128	0.062575
C	-4.147706	-1.173068	2.328855
C	-5.09324	-1.360267	1.140584
C	-2.692308	-1.124096	1.863828
O	-2.307766	-2.427701	1.404336

O	-4.261768	-2.271051	3.232756
O	-6.446234	-1.407887	1.601981
C	-5.653194	-0.527775	-1.205336
O	-3.461391	-0.31891	-0.31586
H	1.601432	2.02532	0.699456
H	3.363681	3.239674	-0.573236
H	1.143609	3.800287	-1.74172
H	1.679206	6.178703	-0.246322
H	0.962155	4.512938	1.222616
H	-1.215336	4.337683	-0.906973
H	-1.305019	5.965161	0.856673
H	-0.638281	2.683475	1.607098
H	-3.07775	3.095376	0.907605
H	-2.727631	2.088958	-0.522582
H	-1.554813	-0.19521	0.24752
H	-2.040084	-0.829328	2.694928
H	-2.706238	-3.03737	2.054943
H	-5.208165	-2.497082	3.259652
H	-4.385876	-0.226199	2.837506
H	-4.912221	-2.346139	0.700429
H	-6.672026	-0.527126	1.947427
H	-5.08896	0.69484	0.486604
H	-6.717865	-0.611243	-0.969223
H	-5.502963	0.293677	-1.911666
H	-5.323278	-1.453238	-1.687828
O	-2.409432	-3.299159	-1.238296
H	-2.474556	-3.086828	-0.278006

Atomic coordinates for compound **7**

Atom	**X**	**Y**	**Z**

C	4.325338	-1.809246	-0.012731
C	6.93328	-1.477628	0.889404
C	5.059198	-2.940865	0.309238
C	4.841223	-0.504694	0.10014
C	6.181592	-0.352054	0.562455
C	6.370659	-2.75537	0.760437
O	3.05259	-2.00867	-0.472817
C	2.236132	-0.968597	-0.800701
C	2.658097	0.32749	-0.656549
C	4.016429	0.631567	-0.236956
O	4.444916	1.813864	-0.160052
C	0.914099	-1.419887	-1.253273
C	-1.683196	-2.197509	-1.920352
C	0.185232	-0.702356	-2.216173
C	0.359281	-2.574403	-0.67062
C	-0.936316	-2.948916	-0.996403
C	-1.10396	-1.102998	-2.555989
H	4.638561	-3.933241	0.206471
H	7.952486	-1.342526	1.240407
H	0.907277	-3.145738	0.070198
H	0.611475	0.179814	-2.673816
H	-1.686474	-0.544791	-3.282145
O	7.072329	-3.877289	1.063556
O	6.72911	0.862728	0.692038
O	1.852591	1.382156	-1.008911
H	6.037746	1.521012	0.411283
H	7.964871	-3.629859	1.3523
O	-2.992043	-2.582248	-2.105195
H	-3.550267	-1.867019	-1.718778
C	1.143908	2.083041	0.011094
C	0.494573	4.41618	0.675076
C	-1.149606	2.529292	0.623575

C	-0.965959	4.043152	0.452664
C	1.408081	3.574006	-0.207713
O	-0.223311	1.767018	-0.168778
O	2.725841	3.959529	0.117336
O	0.641595	5.796855	0.361201
C	-2.565807	2.099084	0.228779
O	-3.063481	1.030518	1.046898
C	-3.076513	-0.252491	0.483814
C	-5.343364	-0.042398	-0.361231
C	-4.979071	-0.950947	1.965553
C	-5.857466	-1.010504	0.707979
C	-3.513393	-1.208109	1.610778
O	-3.462325	-2.574341	1.205315
O	-5.454346	-1.879399	2.934293
O	-7.193454	-0.658903	1.029495
C	-6.103219	-0.128248	-1.673395
O	-3.952017	-0.346534	-0.644144
H	1.498133	1.757473	1.002852
H	3.356326	3.28425	-0.217065
H	1.166421	3.778358	-1.261741
H	1.597602	5.938501	0.246693
H	0.765309	4.232491	1.727638
H	-1.002973	2.292823	1.690364
H	-3.2533	2.93584	0.37979
H	-2.587239	1.830627	-0.830236
H	-2.094419	-0.522143	0.083653
H	-2.877664	-1.032304	2.488602
H	-2.545013	-2.888348	1.129197
H	-5.100076	-2.743041	2.655039
H	-5.075785	0.043046	2.411927
H	-5.810672	-2.033507	0.299242
H	-7.394912	-1.143925	1.848573

H	-5.401276	0.978313	0.035216
H	-5.6942	0.577982	-2.402722
H	-7.155932	0.109673	-1.499752
H	-6.045842	-1.138838	-2.095016
O	-1.386036	4.425685	-0.847129
H	-0.988822	5.302894	-0.992292
H	-1.583584	4.541477	1.219315
O	-1.539961	-3.994694	-0.351045
H	-2.43348	-4.056472	-0.747884

Atomic coordinates for compound **8**

Atom	**X**	**Y**	**Z**
C	3.443972	-1.352535	-0.000078
C	3.248653	1.445348	0.000782
C	2.196108	-0.724835	0.001046
C	4.588411	-0.566853	-0.001321
C	4.493465	0.835027	-0.001034
C	2.071341	0.677296	0.00173
O	1.096267	-1.558808	0.001002
C	-0.10192	-0.967193	0.001413
C	-0.350477	0.369913	0.002066
C	0.738909	1.336808	0.002299
C	-1.398348	-1.754082	0.000759
C	-2.449014	-0.692188	0.001557
C	-1.81883	0.571172	0.001665
C	-3.828465	-0.815126	0.000552
C	-4.597725	0.360111	-0.000724
C	-3.975248	1.608651	-0.001637
C	-2.572938	1.733376	-0.000176
O	-1.516626	-2.961602	-0.001217

O	0.586565	2.558181	0.002634
H	3.489146	-2.436477	-0.00064
H	5.563698	-1.044873	-0.002455
H	5.396437	1.4383	-0.002707
H	3.141114	2.525517	0.000848
H	-2.089553	2.703945	-0.000976
H	-4.584763	2.508334	-0.003944
H	-5.681924	0.297046	-0.001562
H	-4.292789	-1.797288	0.0004