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Supplementary Materials

Halogen-Based 17β-HSD1 Inhibitors: Insights from DFT, Docking, and Molecular Dynamics Simulation Studies

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Table S1. Quantum chemical descriptors (in eV) of newly designed inhibitors.

Molecules	S	η	μ	ω	E_g
Ref	**-0.24**	**2.12**	**-3.39**	**2.72**	4.24
$_{F}R_1$	-0.24	2.12	-3.49	2.88	4.24
$_{F}R_2$	-0.23	2.17	-3.62	3.03	4.33
$_{F}R_3$	-0.24	2.12	-3.52	2.92	4.24
$_{F}R_4$	-0.23	2.18	-3.85	3.41	4.35
$_{Cl}R_1$	-0.25	1.99	-3.63	3.31	3.98
$_{Cl}R_2$	-0.23	2.20	-3.71	3.14	4.39
$_{Cl}R_3$	-0.24	2.12	-3.57	3.00	4.24
$_{Cl}R_4$	-0.23	2.20	-3.99	3.62	4.40
$_{Br}R_1$	-0.29	1.74	-3.87	4.30	3.47
$_{Br}R_2$	-0.23	2.17	-3.75	3.24	4.33
$_{Br}R_3$	-0.24	2.12	-3.56	3.00	4.24
$_{Br}R_4$	-0.26	1.95	-4.22	4.57	3.91
$_{I}R_1$	-0.32	1.54	-4.06	5.36	3.08
$_{I}R_2$	-0.23	2.17	-3.76	3.26	4.34
$_{I}R_3$	-0.24	2.11	-3.59	3.05	4.23
$_{I}R_4$	-0.29	1.73	-4.49	5.83	3.46

Table S2. The binding energy/docking score of newly designed halogen-based inhibitors against with 17β-HSD1 receptor.

Molecules	Binding free energy (Kcal/mol)	Binding affinity (Ki)
Reference (R)	-10.21	32.98 nM
$_{F}R_1$	-10.5	20.16 nM
$_{F}R_2$	-10.29	28.43 nM
$_{F}R_3$	-10.26	32.71 nM
$_{F}R_4$	-10.53	19.05 nM
$_{Cl}R_1$	-10.86	10.91 nM
$_{Cl}R_2$	-10.82	11.73 nM
$_{Cl}R_3$	-10.72	13.85 nM
$_{Cl}R_4$	-11.58	3.27 nM
$_{Br}R_1$	-11.46	3.99 nM
$_{Br}R_2$	-11.23	5.89 nM
$_{Br}R_3$	-11.01	8.46 nM
$_{Br}R_4$	-11.71	2.59 nM
$_{I}R_1$	-11.69	2.68 nM
$_{I}R_2$	-11.4	4.40 nM
$_{I}R_3$	-11.29	5.27 nM
$_{I}R_4$	-11.94	1.78 nM

Table S3. The detailed information on hydrogen bond and π-bond interactions between 17β-HSD1 receptor and halogen-based inhibitors.

Molecules	H-bond Interacting Residues	No of Interactions	π -bond Interacting Residues	No of Interactions
$_{F}R_{1}$	Gly 141, Lys159, His221	3	Val143, Leu149, Cys185, Pro187, His221, Phe226	6
$_{F}R_{2}$	Ser142, Cys185, His221, Glu282	4	Val143, Met147, Leu149, Pro187, Val225, Phe259	9
$_{F}R_{3}$	Ile14, Gly15, Thr140, Gly144	5	Val143, Cys185, Pro187, Val188	6
$_{F}R_{4}$	Gly186, Val188, His221	3	Val143, Met147, Leu149, Tyr155, Cys185, Pro187, Val225, Phe226	11
$_{Cl}R_{1}$	Gly141, Lys159, His221	3	Val143, Leu149, Cys185, Pro187, Phe226, Phe259	6
$_{Cl}R_{2}$	Val188, His221	2	Val143, Leu149, Cys185, Gly186, Pro187, Ala191, Lys195, Val225, Phe226	11
$_{Cl}R_{3}$	Gly186, Val188	2	Val143, Leu149, Pro187, Ala191, Lys195, Val225, Phe226, Phe259, Met279	10
$_{Cl}R_{4}$	Gly186, Pro187, Val188	3	Val143, Leu149, Cys185, Pro187, Lys195, His221, Val225, Phe226, Phe259	15
$_{Br}R_{1}$	Gly141, Asn152, Lys159, His221	4	Val143, Leu149, Tyr155, Cys185, Lys195, His221, Phe259	7
$_{Br}R_{2}$	Glu194, Tyr218, His221, Ser222	4	Val143, Gly186, Pro187, Glu194, Lys195, His221, Val225, Phe259	12
$_{Br}R_{3}$	Gly186, Val188	2	Val143, Leu149, Pro187, Ala191, Lys195, His221, Val225, Phe226, Phe259, Met279	11
$_{Br}R_{4}$	His221	1	Val143, Tyr155, Gly186, Pro187, Lys195, His221, Val225, Phe259	13
$_{I}R_{1}$	Gly141, Asn152, Tyr218, His221	4	Val143, Leu149, Tyr155, Cys185, Pro187, Val188, His221, Phe259	10
$_{I}R_{2}$	Val188, His221, Ser222	3	Val143, Leu149, Cys185, Pro187, Ala191, Lys195, Val225, Phe226	9
$_{I}R_{3}$	Gly186, Val188	2	Val143, Leu149, Pro187, Ala191, Lys195, His221, Val225, Phe226, Phe259, Met279	12
$_{I}R_{4}$	Val188	1	Leu149, Cys185, Pro187, Lys195, Val225, Phe226, Phe259	8

Table S4. The 17β-HSD1 receptor residues are involved in the halogen bond interactions with halogen-based inhibitors.

Molecules	Halogen Bond Interacting Residues	No of Interactions
$_{F}R_{1}$	Leu149, Met279, Leu262, Val143	7
$_{F}R_{2}$	His221, Ser222, Val225, Met279, Tyr218, Val283	9
$_{F}R_{3}$	Val143, Leu149, Gly144	9
$_{F}R_{4}$	Val225, Val188, Ile14, Lys195, His221, Met279, Phe259, Glu194, Phe226, Tyr155	22
$_{Cl}R_{1}$	Leu149, Leu262, Met279, Phe259	8
$_{Cl}R_{2}$	Ser142, Cys185, Tyr155	4
$_{Cl}R_{3}$	Met279, Phe259, His221, Leu149, Leu262, Val225	8
$_{Cl}R_{4}$	Val225, Ile14, Val188, Lys195, His221, Phe259, Glu194, Phe226, Tyr155	18
$_{Br}R_{1}$	Leu149, Met279, His221, Ser222, Tyr218, Val283	11
$_{Br}R_{2}$	Val143, Gly186, Pro187	6
$_{Br}R_{3}$	Met279, Phe259, Glu282, His221, Leu262, Val225	8
$_{Br}R_{4}$	Leu149, Val143, Met279, Tyr155, Lys159, Pro150, Tyr218, Gly186, Phe259, Pro187	19
$_{I}R_{1}$	His221, Met279, Ser222, Leu149, Tyr218, Val225, Val283	10
$_{I}R_{2}$	Cys185, Ser142, Tyr155	5
$_{I}R_{3}$	Glu282, Met279, Phe259, Val225, His221	9
$_{I}R_{4}$	Ala191, Leu149, Met279, Phe259, Val225, Cys185, Ser142, Tyr155	13