Electronic Supplementary Information

Novel 1,2,3-triazole derivatives as mimics of steroidal system – synthesis, crystal structures determination, Hirshfeld surfaces analysis and molecular docking

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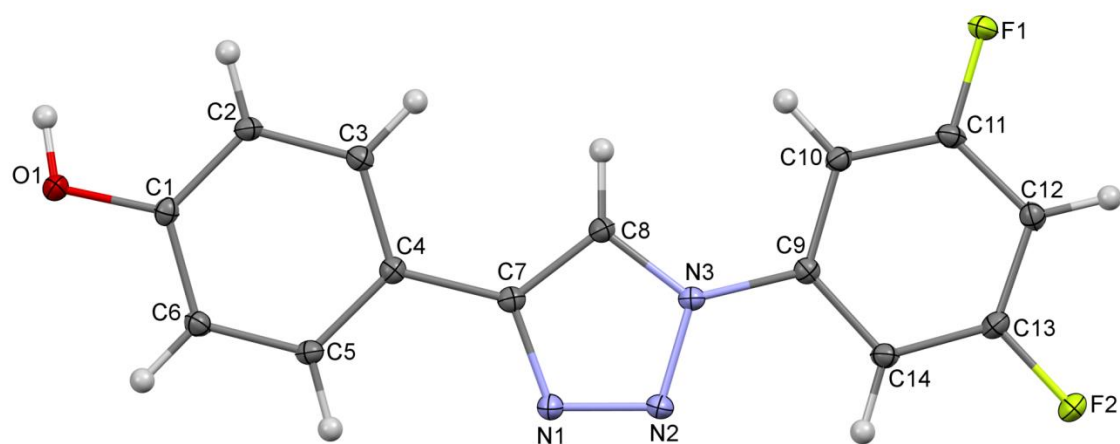
Figure S1. Molecular structure of **6b**. Thermal ellipsoids at 50%.

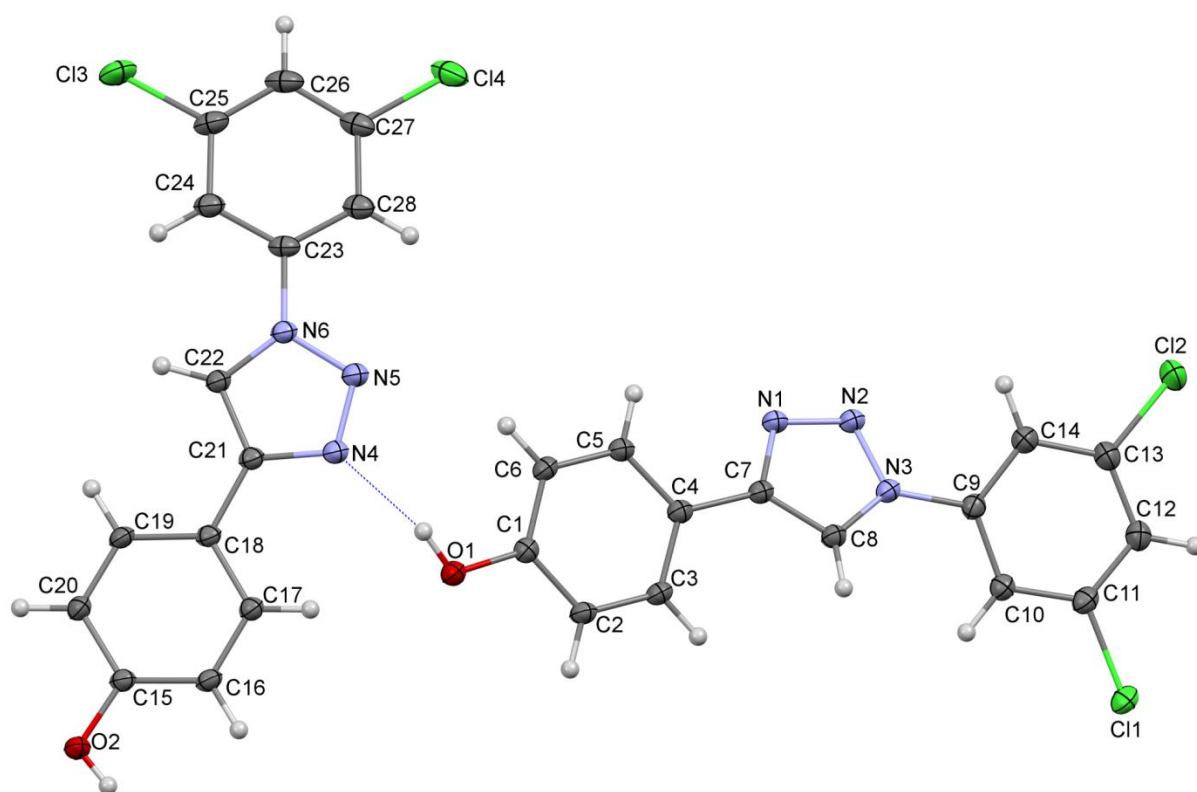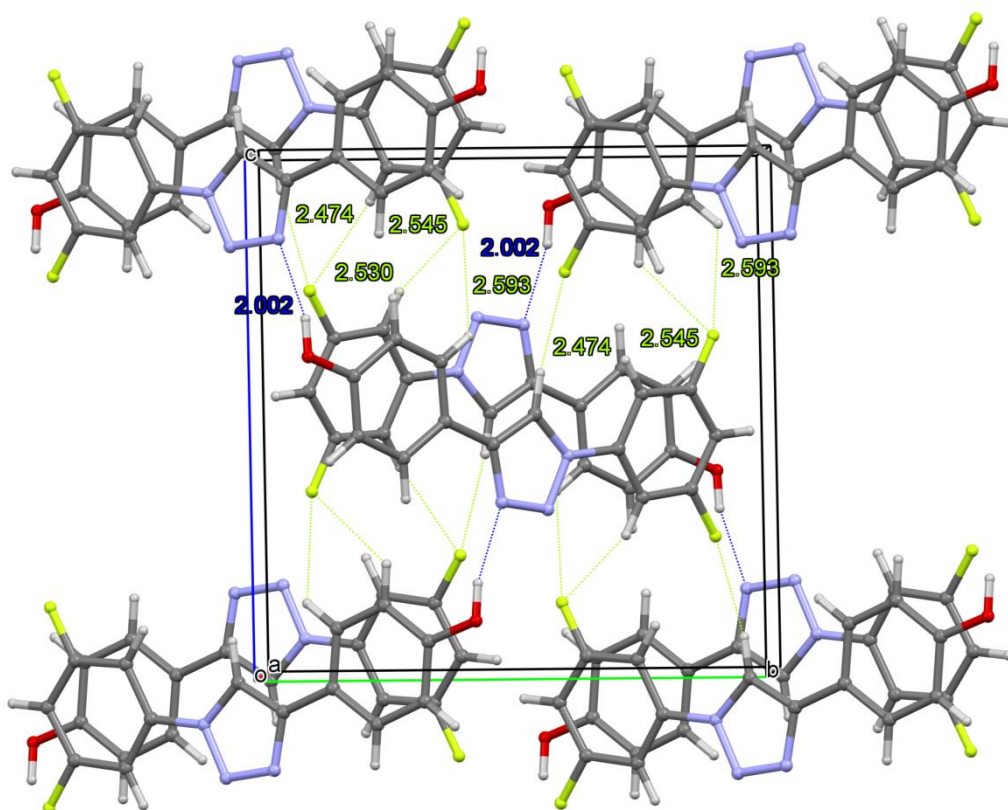**Figure S2.** Molecular structures of **6e**. Thermal ellipsoids at 50%.

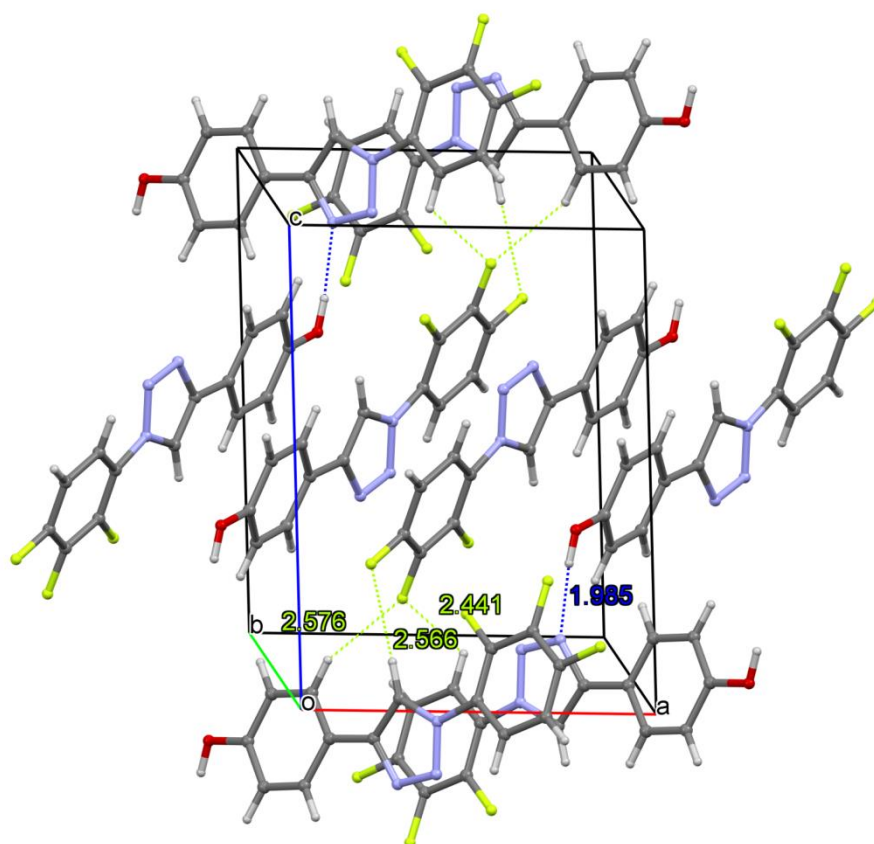**Figure S3.** Crystal packings and intermolecular interactions in **6b**.

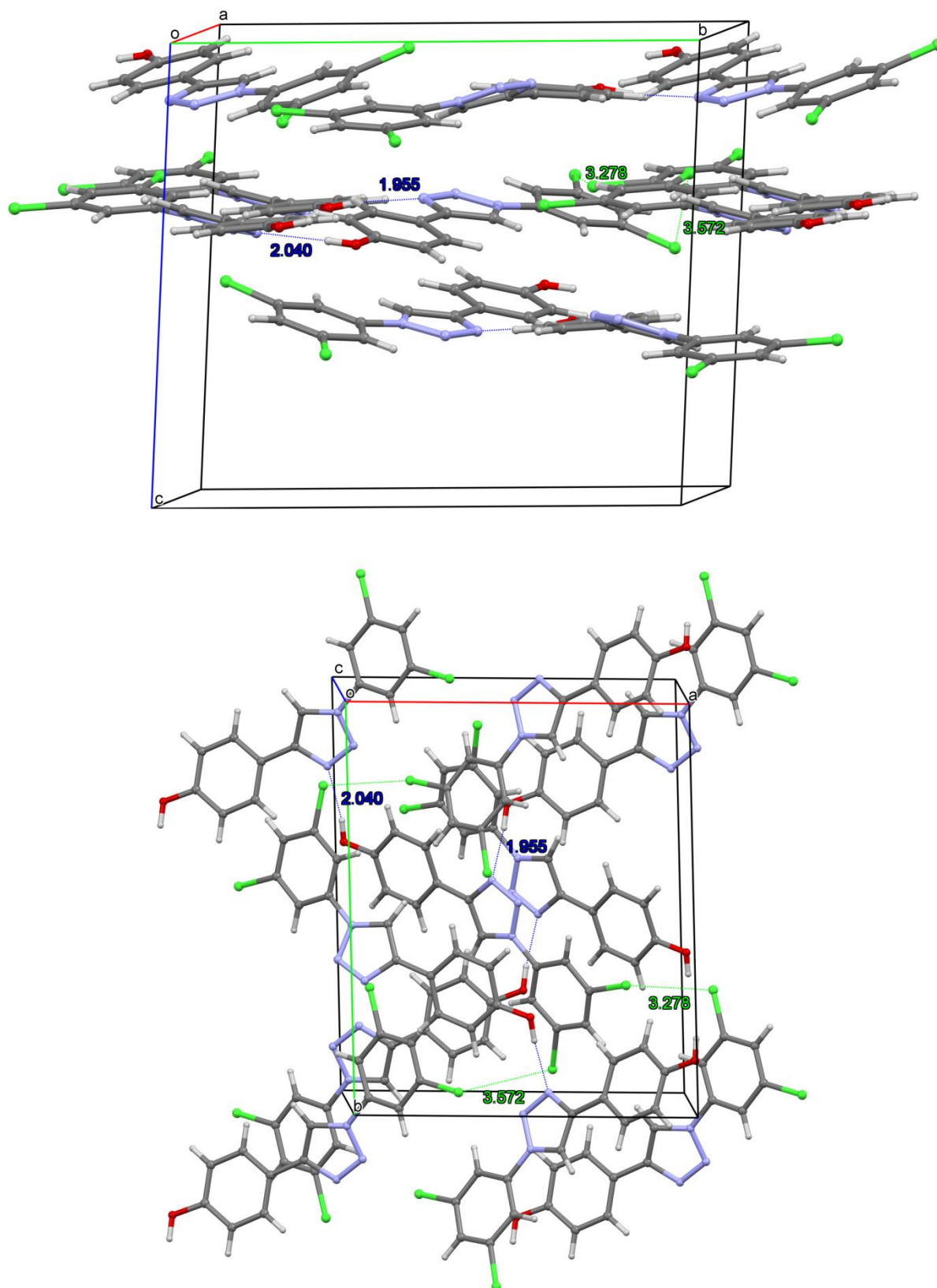**Figure S4.** Crystal packings and intermolecular interactions in **6c**.

Figure S5. Crystal packings and intermolecular interactions in **6e**.

Table S1. Bond lengths and angles for **6a-e**.

Identification code	**6a** X = F	**6b**	**6c**	**6d** X=Cl	**6e**
Bond lengths [Å]					
Mean C–C in phenol ring(s)	1.390(8)/1.393(5)	1.393(6)	1.392(6)	1.391(4)	1.390(6)/1.390(8)
Mean C–C in halogen substituted ring(s)	1.381(9)/1.384(5)	1.382(6)	1.380(7)	1.387(4)	1.382(8)/1.380(4)
C1–O1/C15–O2	1.360(4)/1.363(3)	1.360(1)	1.366(2)	1.381(2)	1.360(3)/1.359(2)
C4–C7/C18–C21	1.463(4)/1.467(4)	1.467(2)	1.467(2)	1.465(3)	1.465(3)/1.469(3)
C7–N1/C21–N4	1.374(4)/1.373(3)	1.369(1)	1.365(2)	1.374(3)	1.367(3)/1.367(3)
N1–N2/N4–N5	1.316(3)/1.307(3)	1.314(1)	1.308(2)	1.306(2)	1.312(2)/1.315(2)
N2–N3/N5–N6	1.347(3)/1.346(3)	1.351(1)	1.353(2)	1.355(2)	1.348(2)/1.342(2)
N3–C8/N6–C22	1.357(4)/1.355(3)	1.356(1)	1.355(2)	1.358(2)	1.353(3)/1.353(3)
C7–C8/C21–C22	1.356(4)/1.369(4)	1.372(2)	1.373(2)	1.372(3)	1.374(3)/1.371(3)
N3–C9/N6–C23	1.425(4)/1.422(4)	1.423(1)	1.431(2)	1.424(2)	1.432(3)/1.424(3)
C10–F1	-	-	1.345(2)	-	-
C11–X1/X2/C25–F2/Cl3	X1=F1 1.358(3)/1.361(3)	X1=F1 1.354(1)	X2=F2 1.340(2)	X1=Cl1 1.740(2)	X1=Cl1 1.726(2)/1.736(3)
C12–F3	-	-	1.347(2)	-	-
C13–X2/C27–Cl4	-	X2=F2 1.358(1)	-	-	X2=Cl2 1.725(2)/1.724(3)
The torsion angles between the planes of the six-membered rings [°]					
plane$_{C1-C6}$ and plane$_{C9-C14}$	43.28	3.54	3.66	49.35	9.79
plane$_{C15-C20}$ and plane$_{C23-C28}$	50.41	-	-	-	0.90

Table S2. Structural parameters for intramolecular interactions in **6a-e**

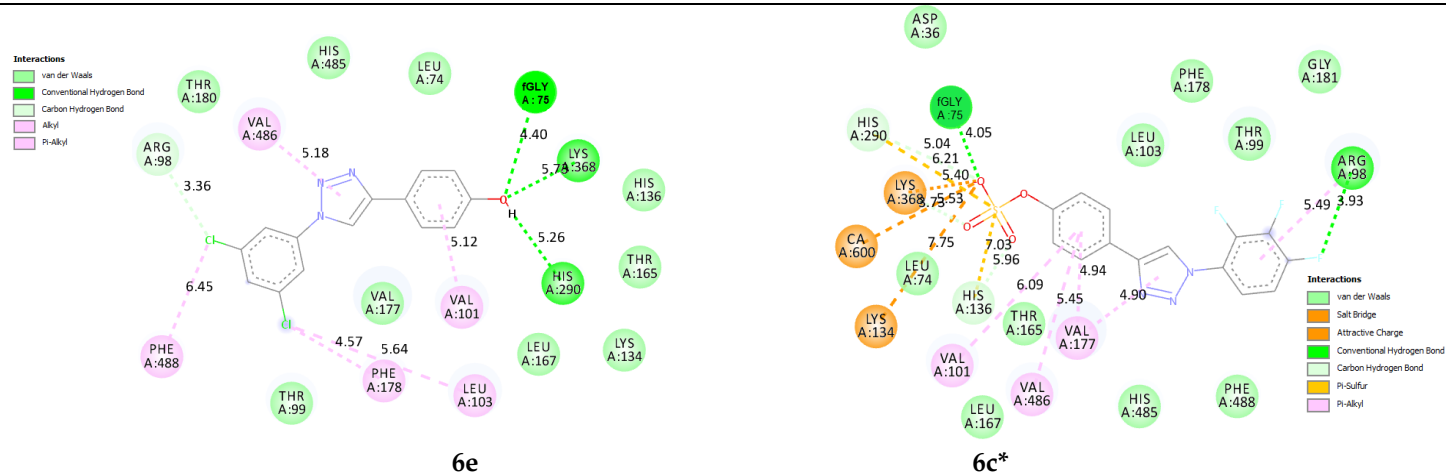| **6a**				
Hydrogen bonds				
D-H...A	d(D-H) [Å]	d(H...A) [Å]	d(D...A) [Å]	<(DHA) [°]
O2-H2...N1[i]	0.97(4)	1.85(4)	2.770(3)	157(3)
O2-H2...N2[i]	0.97(4)	2.53(4)	3.265(3)	133(3)
O1-H1...N5	1.02(4)	2.55(4)	3.200(3)	122(3)
O1-H1...N4	1.02(4)	1.82(4)	2.758(3)	151(3)
C22-H22...F1[ii]	0.95	2.34	3.288(3)	173.3
C26-H26...O2[iii]	0.95	2.57	3.291(4)	132.7
C8-H8...F2[iv]	0.95	2.52	3.349(3)	146.5
C12-H12...O1[iv]	0.95	2.45	3.192(4)	134.5
Symmetry transformations used to generate equivalent atoms: [i] x, y+1 , z; [ii] x, y+1 ,z-1; [iii] x, y, z-1; [iv] x, y, z+1				
6b				
Hydrogen bonds				
D-H...A	d(D-H) [Å]	d(H...A) [Å]	d(D...A) [Å]	<(DHA) [°]
C8-H8...F2[i]	0.95	2.47	3.4075(16)	167.2
C10-H10...F2[i]	0.95	2.53	3.4552(15)	164.5
C2-H2...F1[ii]	0.95	2.55	3.1779(14)	124.2

D-H...A	d(D-H) [Å]	d(H...A) [Å]	d(D...A) [Å]	<(DHA) [°]
C12-H12...O1[iii]	0.95	2.43	3.2566(15)	145.0
O1-H1...N1[iv]	0.867(19)	2.002(19)	2.8454(15)	164.0(16)
O1-H1...N2[iv]	0.867(19)	2.648(18)	3.3207(14)	135.3(14)

Symmetry transformations used to generate equivalent atoms: [i] x+1/2, -y+3/2, z+1/2; [ii] 2 -x+3/2, y-1/2, -z+3/2; [iii] x-1, y+1, z; [iv] x+1/2, -y+1/2, z+1/2

6c

Hydrogen bonding

D-H...A	d(D-H) [Å]	d(H...A) [Å]	d(D...A) [Å]	<(DHA) [°]
O1-H1...N1[i]	0.87(2)	1.99(2)	2.8514(18)	174.4(18)
C8-H8...F3[ii]	0.95	2.58	3.5259(19)	178.2
C6-H6...N1[i]	0.95	2.66	3.348(2)	129.9
C14-H14...F2[iii]	0.95	2.44	2.9197(19)	111.0
C13-H13...O1[iv]	0.95	2.53	3.423(2)	156.1

Symmetry transformations used to generate equivalent atoms: [i] -x+2, y+1/2, -z+3/2; [ii] -x+1, y+1/2, -z+1/2; [iii] 3 x, -y+1/2 ,z+1/2; [iv] x-1, y-1, z

6d

Hydrogen bonding

D-H...A	d(D-H) [Å]	d(H...A) [Å]	d(D...A) [Å]	<(DHA) [°]
O1-H1...O1[i]	0.78(3)	2.30(3)	3.0651(12)	165(3)
C8-H8...N2[ii]	0.95	2.68	3.606(3)	163.7
C8-H8...N1[ii]	0.95	2.63	3.566(3)	167.4

Possible halogen bonding interaction

Cl1...Cl1[iii]	3.6618(8)			

Symmetry transformations used to generate equivalent atoms: [i] -x+1, y-1/2, -z+1/2; [ii] x, y+1, z; [iii] 2-x; 1/2+y, 3/2-z

6e

Hydrogen bonding

D-H...A	d(D-H) [Å]	d(H...A) [Å]	d(D...A) [Å]	<(DHA) [°]
O2-H2A...N1[i]	0.78(3)	2.04(3)	2.813(3)	170(3)
O1-H1...N4	0.86(3)	1.96(3)	2.801(3)	167(3)
C16-H16...N2[i]	0.95	2.66	3.515(3)	150.1
C24-H24...O1[ii]	0.95	2.57	3.135(3)	118.0
C28-H28...Cl2[iii]	0.95	2.80	3.698(3)	158.7

Halogen bonding

Cl4...Cl1[iv]	3.278(2)			

Symmetry transformations used to generate equivalent atoms: [i] x+1, y, z; [ii] -x+1,-y+1,-z+1; [iii] -x, y-1/2, -z+3/2; [iv] x, -1+y, z

Table S3. The ligand-protein (AROM) interactions (and distances [Å]) identified using BIOVIA, Dassault Systémes, Discovery Studio Visualiser.

6a

6b

No.	Type of interaction							
	van der Waals	Conventional HB	Alkyl	π-π-T-shape	π-alkyl	Carbon HB	Sulfur-X	Halogen
6a	ARG115, PHE134, TRP224, ILE305, ASP309, THR310, LEU372, VAL373	MET374 (3.45)	-	-	ILE133 (5.05), ALA306 (5.35), VAL370 (5.37, 5.46), LEU477 (6.06)	-	-	-
6b	ARG115, PHE134, TRP224, ILE305, THR310, VAL373, MET374, ILE395, LEU477	LEU372 (3.48)	-	-	ILE133 (4.79), ALA306 (5.26), VAL370 (5.46, 5.50)	-	-	ASP309 (3.98)
6c	ARG115, PHE134, PHE221, GLU302, THR310, LEU372, VAL373, ILE395	-	-	TRP224 (7.18)	ILE133 (5.22), ALA306 (5.82), VAL370 (5.46), MET374 (6.28), LEU477 (5.81)	ALA306 (2.84)	MET374 (3.29)	ILE305 (3.82), ASP309 (4.12)
6d	ARG115, PHE134, ASP309, THR310, VAL370, LEU372, VAL373, ILE395	-	ILE133 (5.50), TRP224 (4.32), ILE305 (7.01), ALA306 (3.46)	-	ILE133 (5.13), ALA306 (5.87), MET374 (6.05), LEU477 (6.10)	-	MET374 (3.44)	-

Compound							
6e	PHE221, MET303, ILE305, ASP309, THR310, VAL369, ASP371, VAL373, SER478	GLU302 (4.91)	PHE134 (6.28), VAL370 (5.37), LEU477 (5.01)	TRP224 (6.90)	ILE133 (5.03), ALA306 (5.13), VAL370 (5.01), LEU477 (4.93)	-	-	MET374 (3.74)
Androstenedione	ILE133, PHE134, PHE221, ILE305, ASP309, THR310, LEU372, VAL373, LEU477, SER478	ARG115 (4.05), MET374 (4.03)	TRP224 (7.49), VAL370 (6.51)	-	-	ALA306 (3.36)	-	-

Table S4. The ligand-protein (STS) interactions (and distances [Å]) identified using BIOVIA, Dassault Systémes, Discovery Studio Visualiser.

6e

6c*

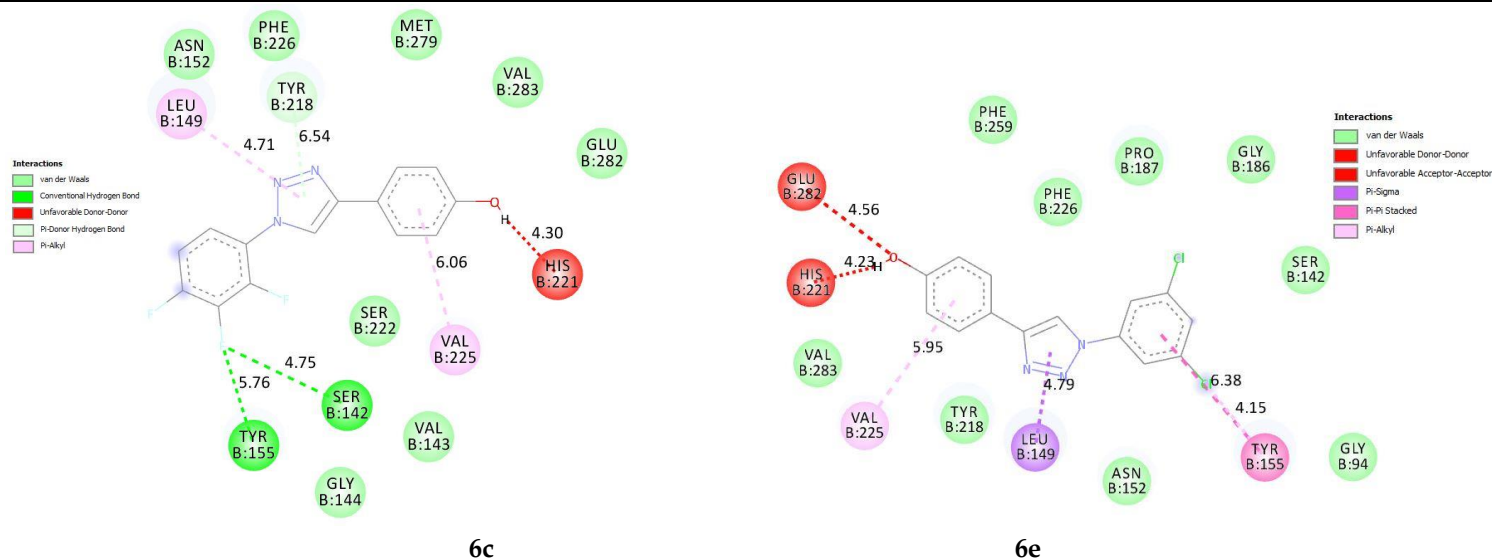| No. | Type of interaction | | | | | | | | | | | |
	van der Waals	Conventional HB	π-cation	Alkyl	π-π-T-shape	π-alkyl	Carbon HB	π-sulfur	Salt bridge	Attractive charge	Halogen	Unfavorable donor-donor
6a	LEU74, THR99, LEU103, LYS134, HIS136, THR165, LEU167, THR180, HIS290, THR484, VAL486	-	LYS368 (6.86)	-	PHE488 (7.37)	VAL101 (5.39), VAL177 (4.87)	HIS485 (5.13)	-	-	-	ARG98 (3.77)	-
6a*	LEU74, THR99, VAL101, LEU103, THR165, LEU167, THR180, THR484, PHE488	fGLY75 (4.21)	-	-	HIS485 (5.02)	ARG98 (5.39), VAL177 (4.76), VAL486 (5.02, 5.20)	HIS136 (6.24), HIS485 (4.47)	HIS290 (6.07), HIS136 (7.23)	-	LYS368 (5.83)	-	-

6b	LEU74, fGLY75, THR99, LEU103, HIS136, LEU167, VAL177, PHE178, THR180, HIS290, PHE488	-	-	-	-	ARG98 (6.05), VAL101 (5.02), VAL486 (5.02)	ARG98 (6.05)	-	-	-	ARG98 (2.96)	LYS368 (4.76)
6b*	LEU74, THR99, LEU103, THR165, LEU167, PHE178, THR180, GLY181, PHE488	fGLY75 (4.07), LYS368 (5.20)	-	-	-	VAL101 (6.15), VAL177 (4.63, 4.66), VAL486 (5.44)	HIS136 (5.66), HIS290 (5.17)	HIS136 (7.10), HIS290 (6.10)	-	LYS134 (7.38), LYS368 (7.45)	ARG98 (3.08)	-
6c	LEU74, LEU103, HIS136, THR165, LEU167, THR180, LYS368, THR484, HIS485, VAL486	fGLY75 (4.37), HIS290 (4.91)	-	-	PHE488 (7.31)	ARG98 (6.36), VAL101 (5.34), VAL177 (4.90)	ARG98 (3.24), THR99 (3.91)	-	-	-	ARG98 (3.55, 5.93)	-
6c*	ASP36, LEU74, THR99, LEU103, THR165, LEU167, PHE178, GLY181, HIS485, PHE488	fGLY75 (4.05)	-	-	-	ARG98 (5.49), VAL101 (6.09), VAL177 (4.90, 4.94), VAL486 (5.45)	HIS136 (5.96), HIS290 (5.04), LYS368 (3.73)	HIS136 (7.03), HIS290 (6.21)	LYS134 (7.75), LYS368 (5.40), Ca^{2+} (5.53)	LYS134 (7.75), LYS368 (5.40), Ca^{2+} (5.53)	-	-
6d	LEU74, THR99, LYS134, HIS136, THR165, LEU167, VAL177, PHE488	fGLY75 (4.31), HIS290 (5.65), LYS368 (5.66)	-	LEU103 (5.89), PHE178 (5.09)	-	ARG98 (6.12), VAL101 (4.97), VAL486 (5.05),	-	-	-	-	-	-

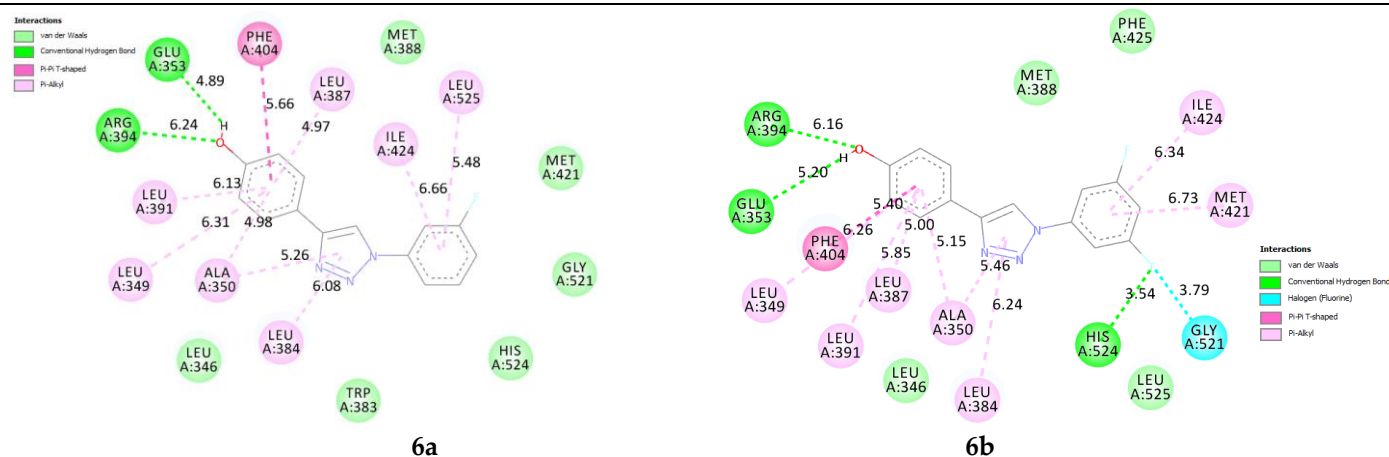|											
6d*	LEU74, THR99, LEU103, THR165, LEU167, THR180, THR484, HIS485, PHE488	fGLY75 (4.18), LYS368 (5.37)	-	-	-	ARG98 (5.34), VAL101 (6.26), VAL177 (4.84), VAL486 (5.25, 5.41)	HIS136 (6.04)	HIS136 (7.26), HIS290 (6.20)	-	LYS134 (7.93), LYS368 (7.26)	-	-
6e	LEU74, THR99, LYS134, HIS136, THR165, LEU167, VAL177, THR180, HIS485	fGLY75 (4.40), HIS290 (5.26), LYS368 (5.73)	-	LEU103 (5.64), PHE178 (4.57), PHE488 (6.45)	-	VAL101 (5.12), VAL486 (5.18)	ARG98 (3.36)	-	-	-	-	-
6e*	LEU74, THR99, THR165, LEU167, HIS485	fGLY (4.12)	-	ARG98 (3.17), PHE178 (4.47)	-	VAL101 (5.86), LEU103, (6.02) VAL177 (4.86, 4.90), VAL486 (5.84)	ARG98 (3.94), HIS136 (6.08), LYS368 (5.69)	HIS136 (7.03), HIS290 (6.28)	LYS134 (7.88), LYS368 (5.33), Ca²⁺ (3.84)	LYS134 (7.88), LYS368 (5.33), Ca²⁺ (3.84)	-	-
E1	LEU74, ARG98, THR99, GLY100, LYS134, HIS136, THR165, LEU167, VAL486, PHE488	fGLY75 (4.07), HIS290 (5.27)	LYS368 (5.08)	LEU103 (6.83), VAL177 (6.11)	-	VAl101 (4.37)	-	-	-	-	-	-
E1S	ASP36, LEU74, ARG98, THR99, GLY100, LEU103, THR165, THR180, THR484, PHE488	fGLY75 (3.47)	-	HIS485 (7.00), VAL486 (4.89)	-	VAL101 (3.80), VAL486 (6.35)	HIS136 (6.18), HIS290 (5.08)	HIS136 (7.18), HIS290 (5.08)	LYS134 (5.16), LYS368 (5.07), Ca²⁺ (3.47)	LYS134 (5.16), LYS368 (5.07), Ca²⁺ (3.47)	-	-

* in sulfated form

Table S5. The ligand-protein (17β-HSD1) interactions (and distances [Å]) identified using BIOVIA, Dassault Systémes, Discovery Studio Visualiser.

6c

6e

No.	Type of interaction											
	van der Waals	*Conventional HB*	*Alkyl*	*π-alkyl*	*Carbon HB*	*Halogen*	*Unfavorable donor-donor*	*π-donor HB*	*π-σ*	*π-π stacked*	*Unfavorable acceptor-acceptor*
6a	PRO187, TYR218, HIS221, PHE226, PHE259, GLU282, VAL283	-	-	VAL225 (5.79)	-	ASN152 (5.73)	-	-	LEU149 (5.01)	TYR155 (6.65)	
6b	ASN152, HIS221, TYR218, PHE226, PHE259, GLU282, VAL283	-	-	VAL225 (5.82)	PRO187 (4.11)	GLY186 (4.58)	-	-	LEU149 (4.91)	TYR155 (6.55)	-

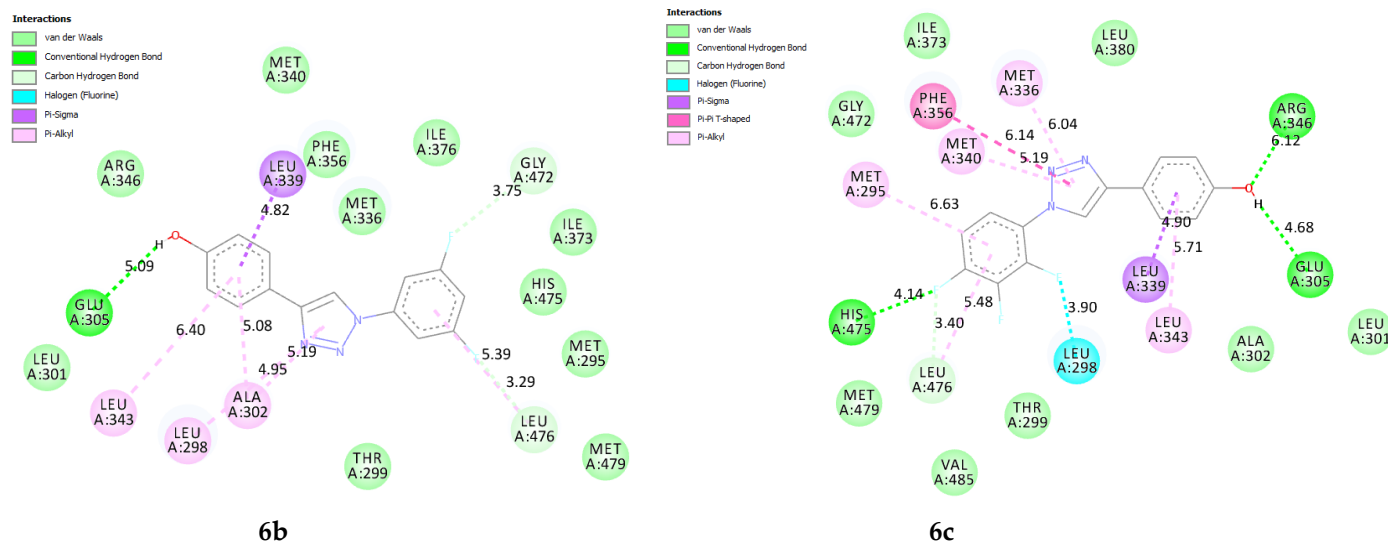|											
6c	VAL143, GLY144, ASN152, SER222, PHE226, MET279, GLU282, VAL283	SER142 (4.75), TYR155 (5.76)	-	LEU149 (4.71), VAL225 (6.06)	-	-	HIS221 (4.30)	TYR218 (6.54)	-	-	-
6d	GLY94, ASN152, PRO187, TYR218, HIS221, PHE226, PHE259, GLU282, VAL283	-	-	VAL225 (5.86)	-	TYR155 (4.10)	-	-	LEU149 (4.91)	TYR155 (6.56)	-
6e	GLY94, SER142, ASN152, GLY186, PRO187, TYR218, PHE226, PHE259, VAL283	-	-	TYR155 (6.38), VAL225 (5.95)	-	-	HIS221 (4.23)	-	Leu149 (4.79)	TYR155 (6.38)	GLU282 (4.56)
E1	SER142, VAL143, ASN152, TYR155, TYR218, PHE226, ARG258, VAL283	HIS221 (5.20), GLU282 (4.90)	LEU149 (4.60), PRO187 (6.42), PHE259 (7.76)	VAL225 (5.69)	-	-	-	-	-	-	-

Table S6. The ligand-protein (ERα) interactions (and distances [Å]) identified using BIOVIA, Dassault Systémes, Discovery Studio Visualiser.

6a

6b

No.	Type of interaction								
	van der Waals	Conventional HB	Alkyl	π-π-T-shape	π-alkyl	Carbon HB	π-sulfur	Halogen	π-anion
6a	LEU346, TRP383, MET388, MET421, GLY521, HIS524	GLU353 (4.89), ARG394 (6.24)	-	PHE404 (5.66)	LEU349 (6.31), ALA350 (4.98, 5.26), LEU384 (6.08), LEU391 (6.13), ILE424 (6.66), LEU525 (5.48)	-	-	-	-
6b	LEU346, MET388, PHE425, LEU525	ARG394 (6.16), GLU353 (5.20), HIS524 (3.54)	-	PHE404 (5.40)	LEU349 (6.26), LEU391 (5.85), LEU387 (5.00), ALA350 (5.15, 5.46), LEU384 (6.24), MET421 (6.73), ILE424 (6.34)	-	-	GLY521 (3.79)	-

6c	GLU353, ALA405, MET421, ILE424, LEU428	ARG394 (6.27), PHE404 (4.44), HIS524 (3.19)	-	PHE404 (5.09)	LEU349 (6.58), ALA350 (5.75), LEU384 (5.68, 6.21), LEU387 (4.85), LEU391 (5.10), LEU525 (6.25)	-	MET388 (5.00)	GLY521 (3.82)	-
6d	LEU428, GLY521	GLU353 (4.54), ARG394 (6.31)	MET421 (4.00), ILE424 (4.16), HIS524 (3.90)	PHE404 (6.12)	LEU349 (6.61), ALA350 (5.70), LEU384 (5.01, 5.18), LEU387 (4.84), LEU391 (5.20), LEU525 (5.99)	-	MET388 (5.53)	-	-
6e	MET343, LEU346, TRP384, ILE424, LEU428	THR347 (3.64), ASP351 (4.54), LYS529 (6.24)	LEU387 (4.28), MET388 (3.53), LEU391 (4.69), PHE404 (6.53), MET421 (5.46), PHE425 (5.78)	PHE404 (3.84)	ALA350 (4.62, 4.62), LEU525 (5.02, 5.21)	LEU384 (4.28)	-	-	ASP351 (6.20)
E2	MET343, LEU346, LEU349, LEU384, MET421, LEU428, GLY521, HIS524, LEU525	GLU353 (4.67), ARG394 (6.52)	MET388 (6.25), PHE404 (6.20), ILE424 (6.92)	PHE404 (5.20)	ALA350 (5.70), LEU387 (5.20), LEU391 (4.64)	-	-	-	-

Table S7. The ligand-protein (ERβ) interactions (and distances [Å]) identified using BIOVIA, Dassault Systémes, Discovery Studio Visualiser.

6b

6c

No.	Type of interaction								
	van der Waals	*Conventional HB*	*Alkyl*	*π-π-T-shape*	*π-alkyl*	*Carbon HB*	*π-sulfur*	*Halogen*	*π-Sigma*
6a	LEU301, GLU305, ARG346, PHE356, MET340, LEU298, ILE376, ILE373, HIS475, MET295, LEU490	-	-	-	LEU343 (6.50), ALA302 (5.05, 5.16), LEU476 (5.14)	-	MET336 (5.90)	GLY472 (3.89)	LEU339 (4.63)
6b	LEU301, ARG346, MET340, PHE356, MET336, ILE376, ILE373, HIS475, MET295, MET479, THR299	GLU305 (5.09)	-	-	LEU343 (6.40), ALA302 (4.95, 5.08), LEU298 (5.19), LEU476 (5.39)	LEU476 (3.29), GLY472 (3.75)	-	LEU476 (3.29), GLY472 (3.75)	LEU339 (4.82)

6c	GLY472, ILE373, LEU380, LEU301, ALA302, THR299, VAL485, MET479	ARG346 (6.12), GLU305 (4.68), HIS475 (4.14)	-	PHE356 (6.14)	MET295 (6.63), MET340 (5.19), MET336 (6.04), LEU343 (5.71)	LEU476 (3.40)	-	LEU298 (3.90)	LEU339 (4.90)
6d	LEU301, ARG346, PHE356, MET340, LEU298, GLY472, THR299, LEU490	GLU305 (4.88)	ILE373 (5.09), HIS475 (6.60), ILE376 (4.13)	-	LEU476 (5.05), MET295 (6.60), LEU343 (6.57), ALA302 (4.49, 5.01)	-	MET336 (5.90)	-	MET336 (5.90), LEU339 (4.57)
6e	LEU301, PHE356, MET340, LEU298, GLY472, VAL486, THR299, LEU490	ARG346 (6.02), GLU305 (5.28), LEU339 (3.69)	ILE373 (5.10), ILE376 (3.98), HIS475 (4.14, 5.14), MET479 (4.99), MET295 (4.55), LEU476 (3.36)	-	LEU343 (6.54), ALA302 (4.99, 5.06), LEU476 (5.10)	-	MET336 (5.95)	-	LEU339 (4.62), MET336 (5.95)
E2	GLY472, MET479, LEU476, MET295, LEU298, LEU301, ARG346, MET336, LEU380, ILE373	HIS475 (4.21), GLU305 (4.69)	ILE376 (7.09), MET340 (6.43), PHE356 (4.53)	PHE356 (5.40)	LEU339 (6.07), ALA302 (4.48), LEU343 (6.22)	-	-	-	-