

RSC Advances

Supplementary Information

Isostructurality and Energetics of Competitive C–H··· π Interactions in Adamantane-Benzoate Hybrids: A Computational ADME Study†

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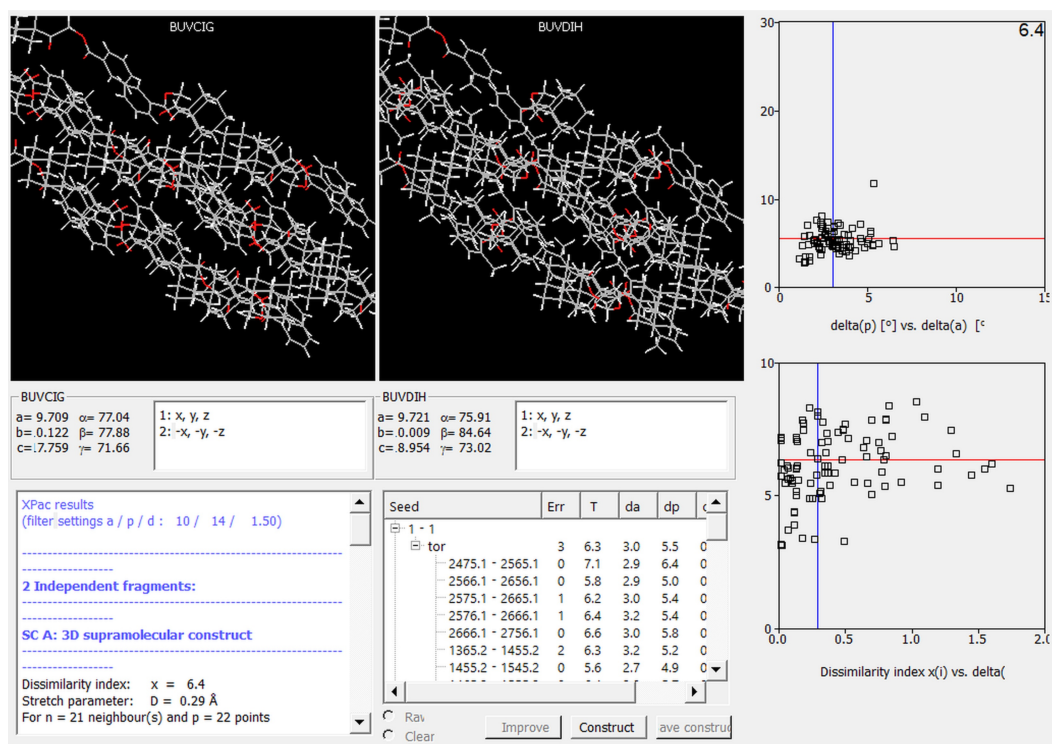


Figure S1. XPac results for BUVCI G-BUVDIH pair.

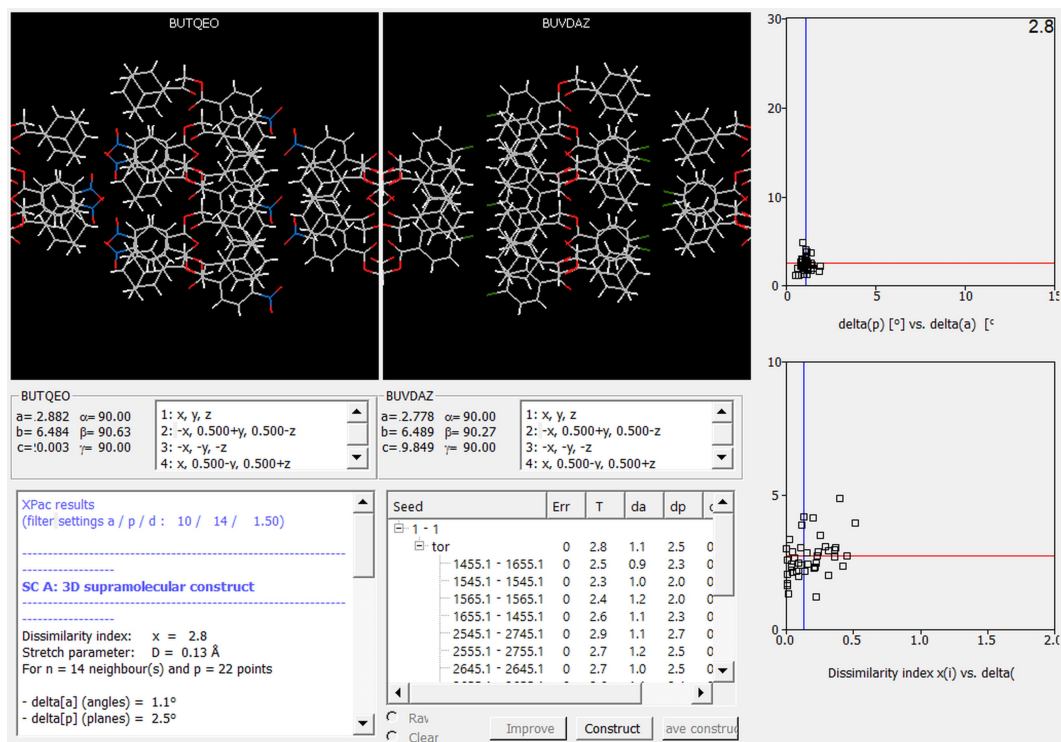


Figure S2. XPac results for BUVD AZ-BUTQEO pair.

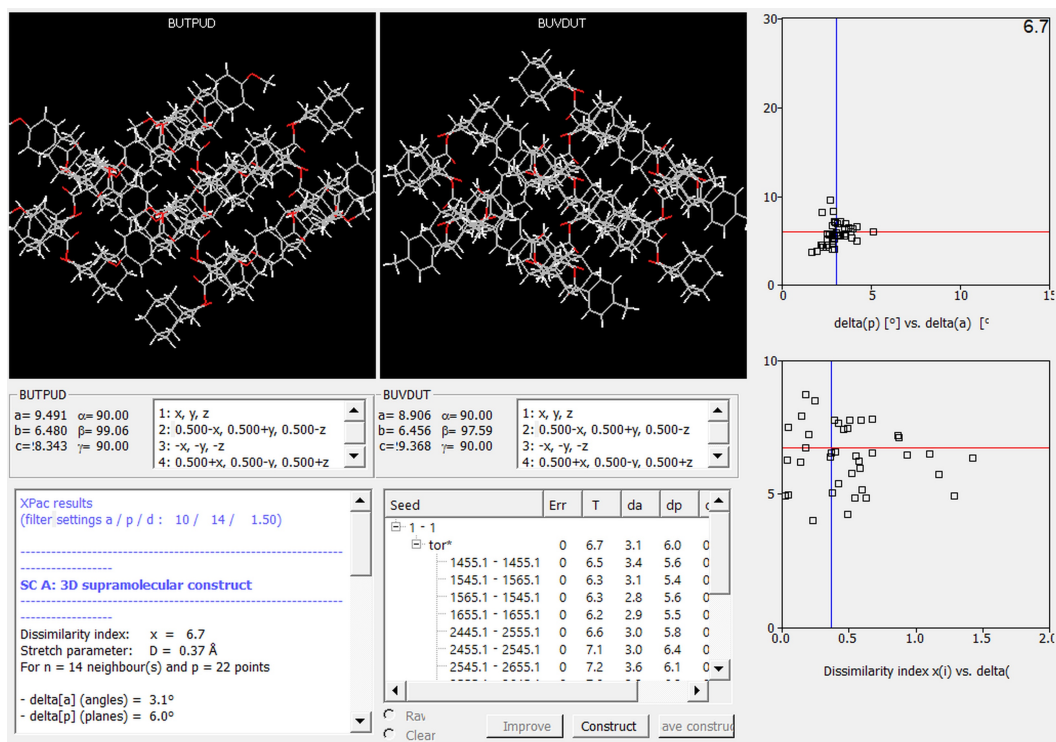


Figure S3. XPac results for BUVDUT–BUTPUD pair.

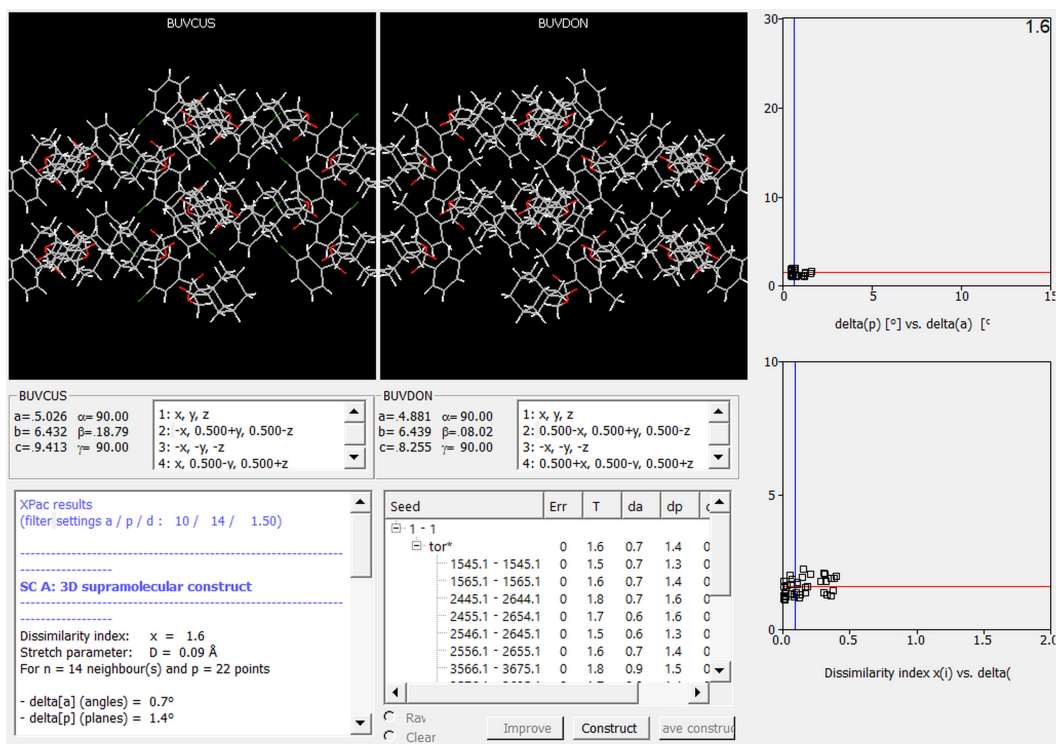


Figure S4. XPac results for BUVCUS–BUVDON pair.

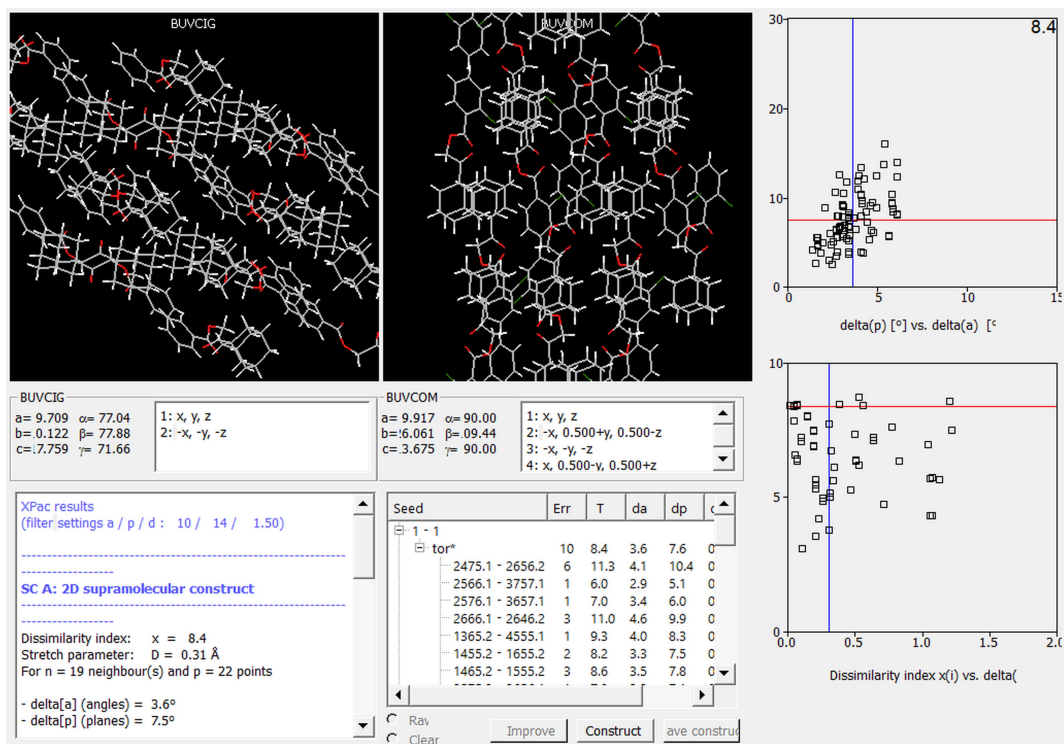


Figure S5. XPac results for BUVCIQ-BUVCOM pair.

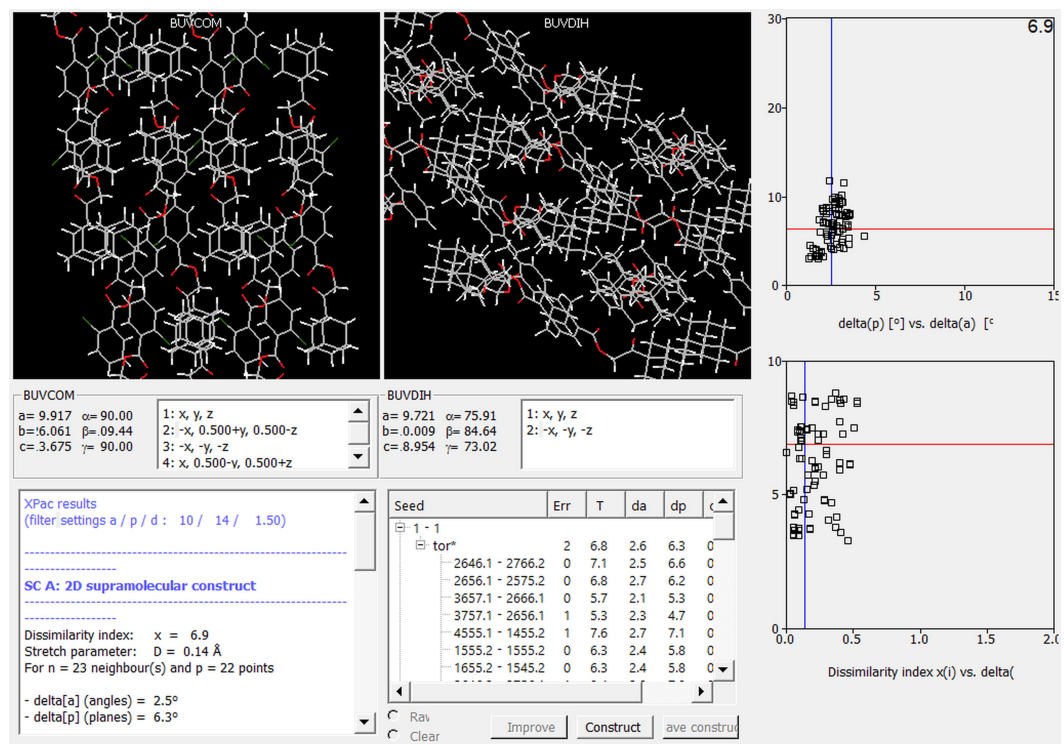


Figure S6. XPac results for BUVCOM-BUVDIH pair.

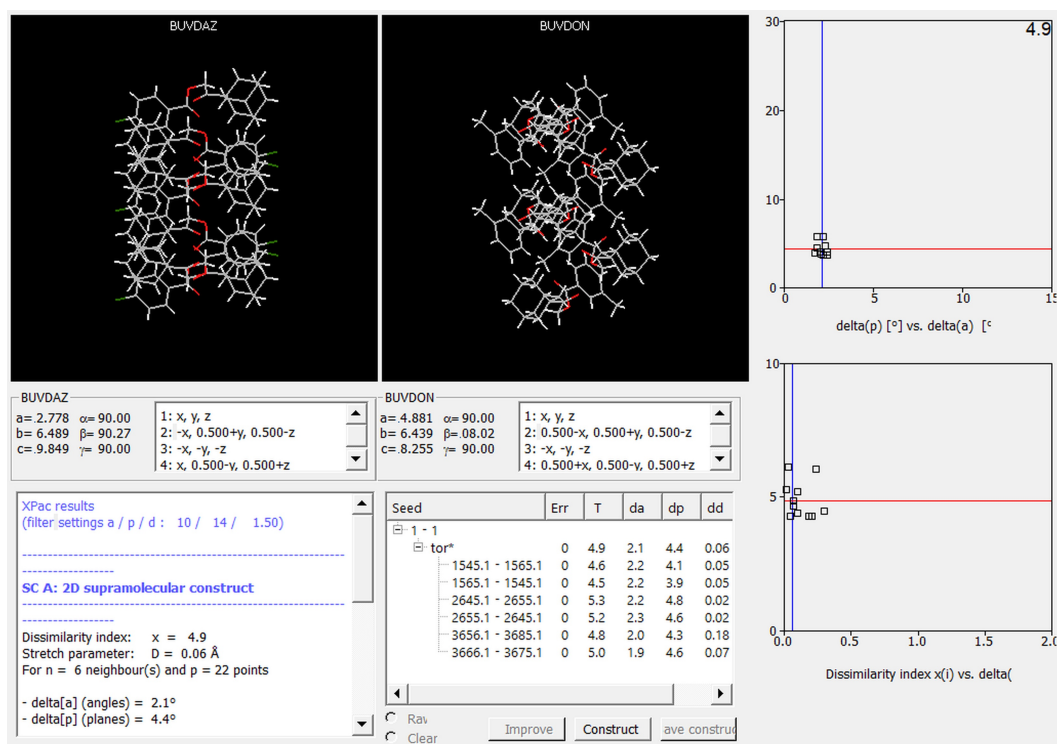


Figure S7. XPac results for BUVDAZ-BUVDON pair.

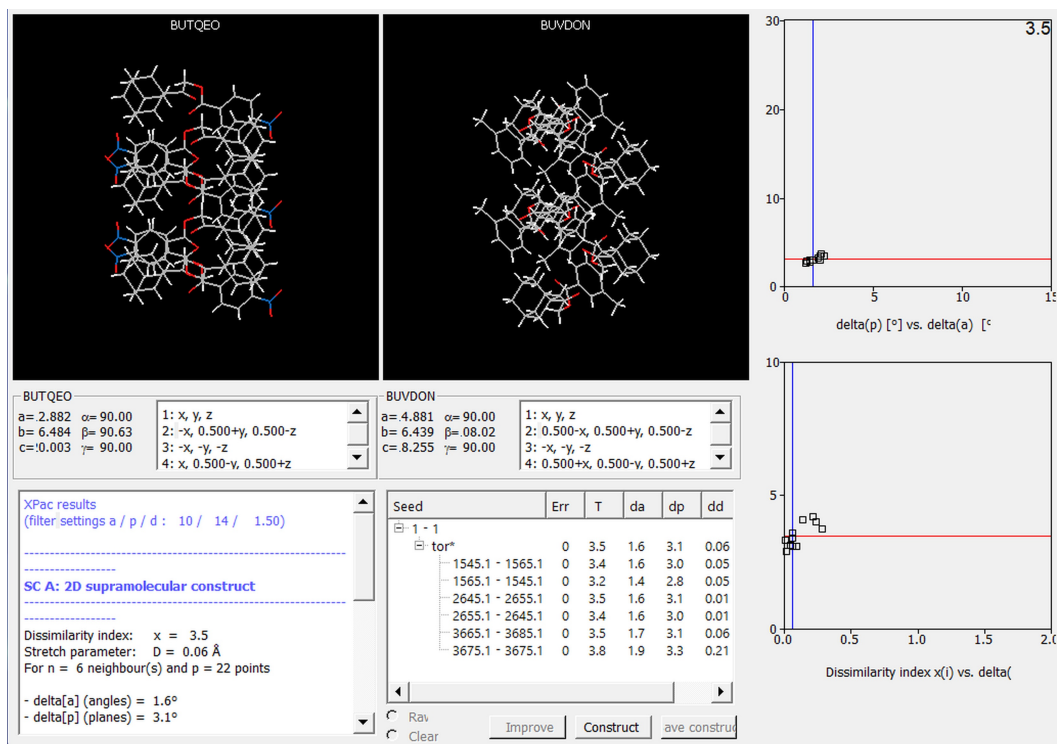


Figure S8. XPac results for BUVDON-BUTQEO pair.

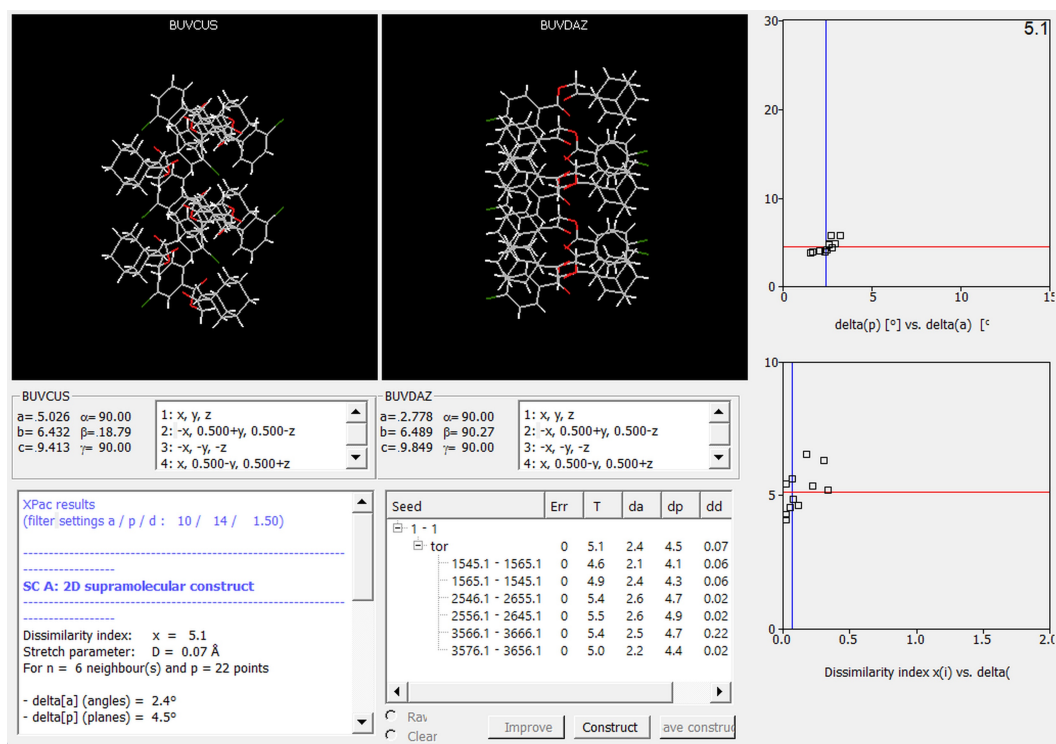


Figure S9. XPac results for BUVCUS-BUVDZ pair.

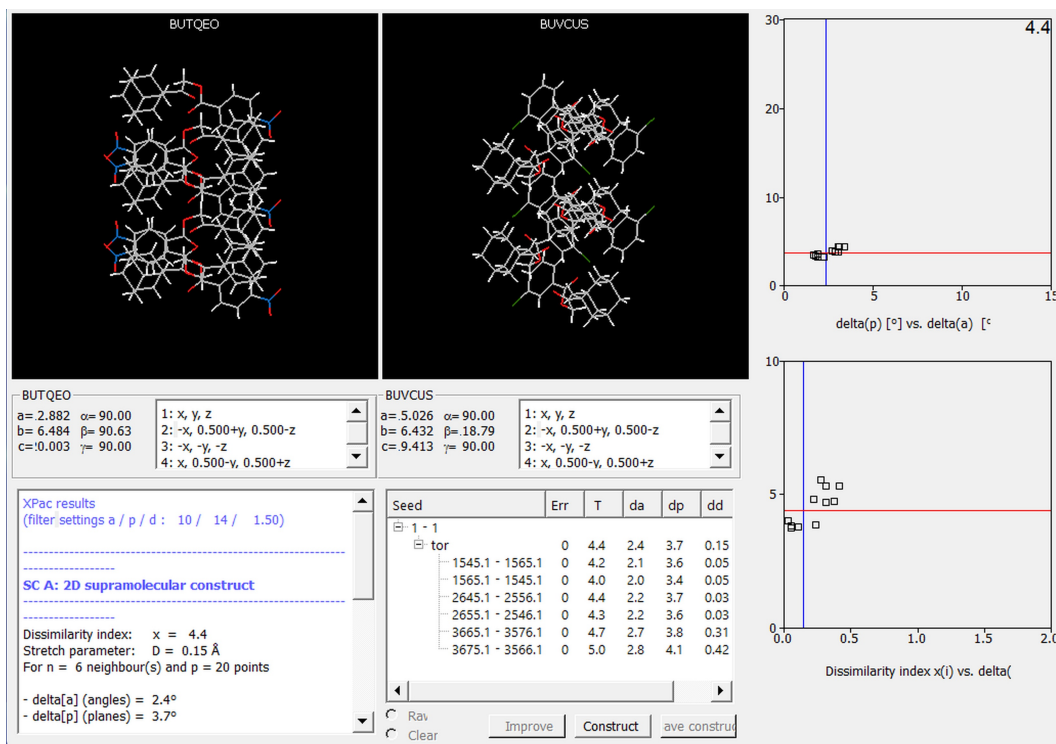


Figure S10. XPac results for BUVCUS-BUTQEO pair.

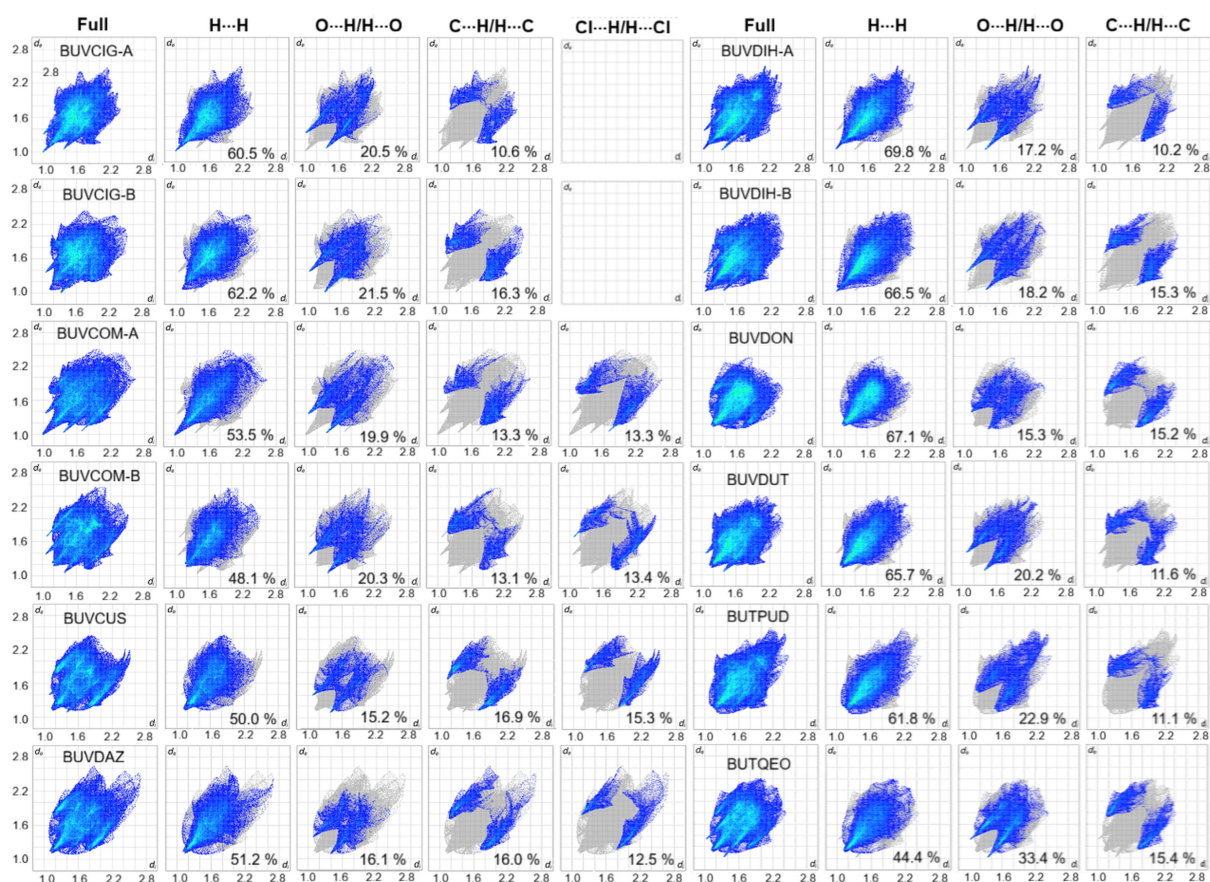


Figure S11. Fingerprint plots showing the percentage contributions for individual atom–atom contacts.

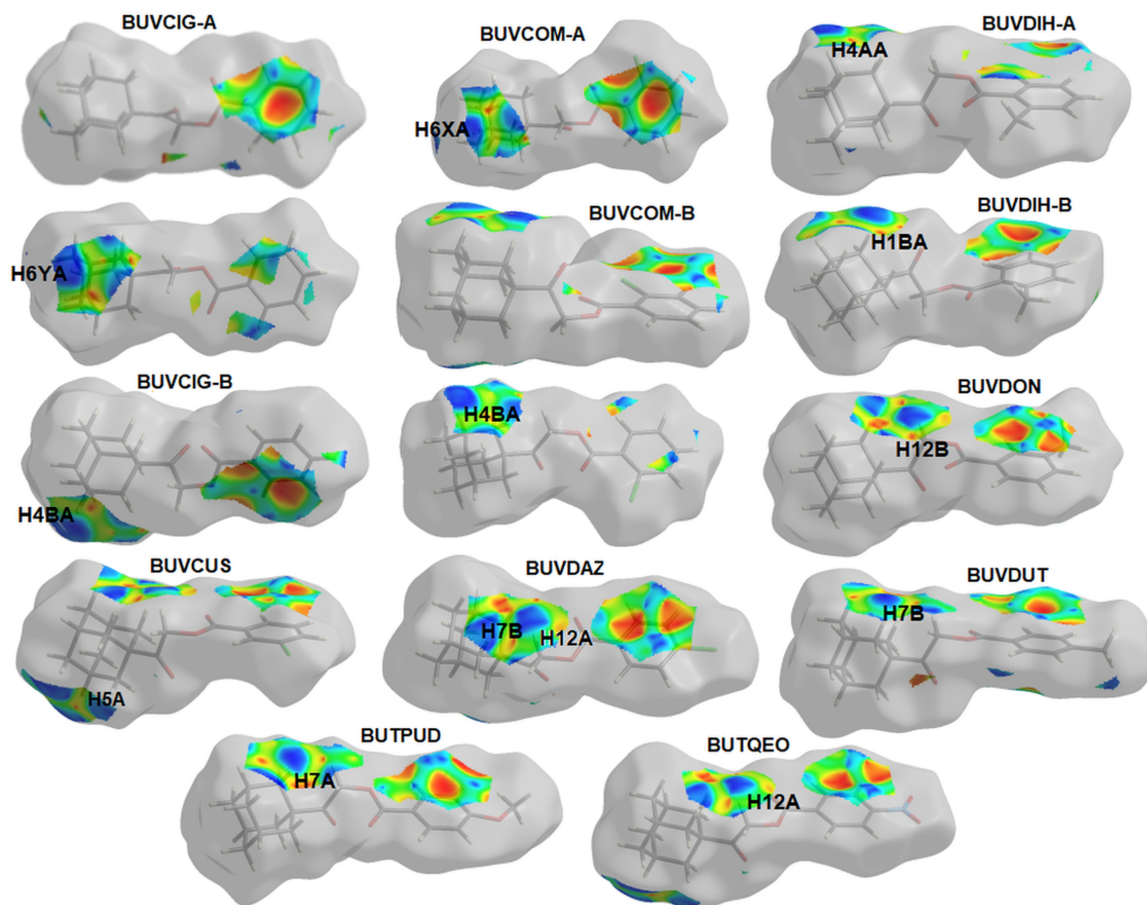


Figure S12. View of the three-dimensional Hirshfeld surfaces mapped over shape-index for visualizing intermolecular C-H \cdots π interactions.

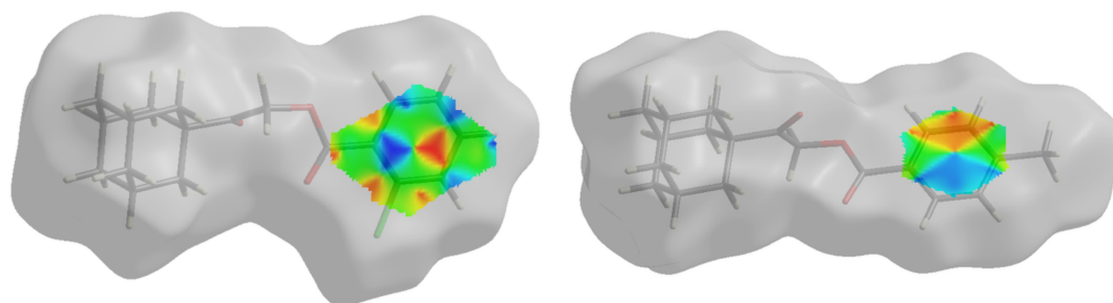


Figure S13. Hirshfeld surfaces of BUVCOM (left) and BUVDUT (right) mapped over shape-index showing the 'bow-tie' patterns of touching red and blue triangles depicting $\pi\cdots\pi$ interaction.

Tables

Table S1. Total electrostatic energies $E_{\text{tot}}^{\text{elec}}$ (kJ/mol)^a for dimers involving different types of contacts.

Compound	Dimer	Interactions	E_{tot}	% ^b
BUVCIG	1	—	37.25	—
		H12D···O2A	3.70	9.93
		H4BA···Cg5	8.22	22.07
	2	—	31.07	—
		H6YA···Cg13	4.74	15.25
		H12B···O2B	6.29	20.24
BUVCOM	1	—	34.35	—
		H12C···O2A	4.67	13.60
		H4BA···Cg5	4.39	12.78
	2	—	26.17	—
		H18B···O3A	2.63	10.05
		H17B···Cl1A	5.16	19.72
H9XA···Cl1B	3.93	15.02		
BUVDUT	1	—	24.46	—
		H20C···O2	4.29	17.54
		Cg5···Cg5	5.45	22.28

^a Calculated by Charger tool of MoProViewer.

^b Percentage of the total electrostatic energy of the dimer.

Table S2. Enrichment ratios E_{XY} (reciprocal contacts merged) of intermolecular interactions.^[a]

BUVCIG–Mol A						BUVCIG–Mol B				
	H	C	O ^a	O ^b	O ^c	H	C	O ^a	O ^b	O ^c
H	1.01	—	—	—	—	0.89	—	—	—	—
C	0.91	1.49	—	—	—	1.24	0.52	—	—	—
O ^a	1.06	0.85	0.00	—	—	1.34	0.29	0.00	—	—
O ^b	1.32	0.33	0.00	0.00	—	1.37	0.15	0.00	0.00	—
O ^c	1.13	0.90	0.00	0.00	0.00	1.32	0.36	0.00	0.00	0.00

BUVCOM–Mol A					BUVCOM–Mol B					
	H	C	Cl	O ^a	O ^b	H	C	Cl	O ^a	O ^b
H	0.87	—	—	—	—	0.90	—	—	—	—
C	1.18	0.81	—	—	—	0.92	1.73	—	—	—
Cl	1.31	0.60	0.00	—	—	1.35	0.48	0.78	—	—
O ^a	1.33	0.58	0.00	0.00	—	1.41	0.68	0.00	0.00	—
O ^b	1.42	0.25	0.14	0.00	0.00	1.60	0.18	0.00	0.00	0.00

BUVCUS					BUVDAZ					
	H	C	Cl	O ^a	O ^b	H	C	Cl	O ^a	O ^b
H	0.85	—	—	—	—	0.89	—	—	—	—
C	1.24	0.60	—	—	—	1.18	0.73	—	—	—
Cl	1.45	0.43	0.00	—	—	1.11	0.49	/	—	—
O ^a	1.22	0.78	0.00	0.00	—	1.33	0.64	0.00	0.00	—
O ^b	1.22	0.87	0.00	0.00	/	1.29	0.74	0.00	0.00	/

BUVDIH–Mol A					BUVDIH–Mol B					
	H	C	O ^a	O ^b	O ^c	H	C	O ^a	O ^b	O ^c
H	1.00	—	—	—	—	0.92	—	—	—	—
C	0.88	1.71	—	—	—	1.18	0.59	—	—	—
O ^a	1.18	0.75	0.00	—	—	1.20	1.20	1.20	1.20	1.20
O ^b	1.33	0.14	0.00	0.00	—	1.28	0.36	0.00	0.00	—
O ^c	1.11	1.03	0.00	0.00	0.00	1.37	0.00	0.00	0.00	0.00

BUVDON					BUVDUT					
	H	C	O ^a	O ^b	O ^c	H	C	O ^a	O ^b	O ^c
H	0.98	—	—	—	—	0.99	—	—	—	—
C	1.09	0.66	—	—	—	0.91	1.61	—	—	—
O ^a	1.10	0.75	0.00	—	—	1.10	0.93	/	—	—
O ^b	1.15	0.72	0.00	/	—	1.38	0.03	0.00	0.00	—
O ^c	0.94	0.54	/	0.00	0.00	1.19	0.80	0.00	0.00	0.00

BUTPUD					BUTQEO					
	H	C	O ^a	O ^b	O ^c	H	C	N	O ^a	O ^b
H	0.99	—	—	—	—	0.87	—	—	—	—
C	0.90	1.63	—	—	—	1.17	0.87	—	—	—
O ^a	1.27	0.62	0.00	—	—	0.82	0.10	/	—	—
O ^b	1.20	0.56	0.00	/	—	1.31	0.86	0.00	0.00	—
O ^c	1.35	0.31	/	0.00	0.00	1.30	0.88	0.00	0.00	/

^[a] E_{XY} values lower than 1.0% were not reported (/), as they are not meaningful. O^a, O^b, O^c, O^d, and O^e are oxygen ester O=C, oxygen ketone O=C, oxygen ester O–C, oxygen ether O–C, and oxygen O=N, respectively.

Table S3. Calculated electrostatic potential (V_s) (in kJ/mol) at the surface (isosurface 0.001 a.u.) of *para*-substituted AOEB derivatives.

Compound	R	V^a	V^b	V^c	V^d	V^e	V_R^f
BUVCIG	H	-149.8	-159.0	-129.0	+90.5	-61.5	—
BUTQEO	NO ₂	-107.4	-133.0	-104.7	+106.3	-5.9	-132.1
	—	—	—	—	—	—	-132.9
BUTPUD	OCH ₃	-152.9	-163.6	-140.2	+84.5	-89.1	-105.4
BUVDUT	CH ₃	-149.5	-160.9	-139.8	+87.9	-67.6	-90.3
BUVDAZ	Cl	-148.5	-129.5	-49.6	+101.5	-35.8	-71.8

^abenzoate carbonyl oxygen; ^bcarbonyl oxygen adjacent to adamantane; ^cester ether oxygen; ^dmethylene bridge; ^ephenyl ring face; ^fsubstituent group R .

Table S4. Topological properties (in a.u.) at the Bond Critical Point CP (3,−1) of selected intermolecular H···C interactions^a

#CP	Interaction	$\rho \times 10^3$	$\nabla^2\rho \times 10^3$	$G(r) \times 10^3$	$V(r) \times 10^3$	$G(r)/ V(r) $
BUVCIG						
58	H7YA···C19B	5.08	13.74	2.89	-2.35	1.23
82	H6YA···C16B	4.47	12.05	2.61	-2.20	1.18
66	H9BB···C19A	6.37	17.95	3.77	-3.06	1.23
85	H4BA···C16A	5.22	14.79	3.21	-2.72	1.18
BUVCOM						
60	H7B···C14	6.01	17.72	3.80	-3.17	1.20
BUVCUS						
67	H7YA···C19B	5.90	15.61	3.36	-2.81	1.20
52	H6YA···C16B	4.90	12.60	2.69	-2.22	1.21
BUVDAZ						
79	H7B···C17	4.98	13.37	2.88	-2.41	1.19
BUVDIH						
70	H7B···C14	5.53	15.02	3.22	-2.68	1.20
BUVDON						
76	H7YA···C19B	6.02	15.59	3.37	-2.83	1.19
65	H6YA···C16B	4.72	12.09	2.59	-2.15	1.20
BUVDUT						
83	H7B···C14	5.34	14.12	3.01	-2.49	1.21
BUTPUD						
87	H5A···C18	5.51	13.67	2.96	-2.50	1.18
79	H7A···C15	5.36	14.78	3.16	-2.63	1.20
BUTQEO						
78	H5A···C18	5.46	14.12	3.00	-2.46	1.22
77	H7A···C15	4.28	11.26	2.39	-1.97	1.22

^a All values are in atomic units (a.u.). Factors of 10^3 are applied to the raw data for clarity. $G(r)$ is the kinetic energy density and $V(r)$ is the potential energy density.

Table S5. QTAIM dimerization energies (ΔE), H \cdots C distances, and H-bond binding energy (BE) involving methylene and methine H-atoms for AOEB with C–H \cdots π interactions (kJ/mol, Å).

Compound	Symmetry	Interactions	ΔE	H \cdots C ^[a]	BE ^[b]	H \cdots C ^[c]	BE ^[d]
BUVCIG	$-1 + x, 1 + y, z$	H7YA \cdots C19B	-15.56	2.953	-1.40	—	—
		H6YA \cdots C17B	—	—	—	3.063	-1.03
	$1 + x, y, z$	H9BB \cdots C19A	-17.03	2.850	-2.46	—	—
		H4BA \cdots C16A	—	—	—	2.973	-1.68
		H3BB \cdots C18A	—	3.073	-0.68	—	—
BUVCOM	x, y, z	H4BA \cdots C19B	-20.00	2.954	-1.67	—	—
		H5BB \cdots C18A	—	3.082	-0.51	—	—
		H4BA \cdots C19B	—	—	—	3.103	-0.78
BUVDIH	x, y, z	H9AA \cdots C14B	-18.79	2.996	-1.60	—	—
		H4AA \cdots C16B	—	—	—	3.102	-0.82
BUVDUT	$1-x, 1-y, -z$	H5B \cdots C18	-17.78	2.897	-1.75	—	—
		H7B \cdots C19	—	3.017	-1.05	—	—
BUTPUD	$-x, 2-y, -z$	H5A \cdots C18	-18.49	2.905	-2.03	—	—
		H7B \cdots C19	—	2.965	-1.90	—	—
Model-methylene	Vacuum	—	-12.1	—	—	—	—
Model-methine	Vacuum	—	-10.8	—	—	—	—

^[a] Methylene H-atom. ^[b] H-bond binding energy for methylene H-atom. ^[c] Methine H-atom. ^[d] H-bond binding energy for methine H-atom.

Table S6. R factors and GoF values for five AOEB crystal structures

Compound	$R_{all}^{[a]}$	$R_{gt}^{[b]}$	$wR_{ref}^{[c]}$	$wR_{gt}^{[d]}$	GoF ^[e]
BUVCIG	0.0845	0.0650	0.2415	0.2159	1.031
BUVCOM	0.1599	0.0633	0.2155	0.1645	1.010
BUVDIH	0.0839	0.0652	0.2181	0.1943	1.027
BUVDUT	0.0639	0.0439	0.1311	0.1165	1.073
BUTPUD	0.0698	0.0538	0.1772	0.1576	1.041

^[a] R_{all} : R-factor based on all reflections; ^[b] R_{gt} : R-factor for reflections with $I > 2\sigma(I)$; ^[c] wR_{ref} : weighted R-factor based on all reflections used in refinement; ^[d] wR_{gt} : weighted R-factor for reflections with $I > 2\sigma(I)$; ^[e]GoF: Goodness-of-Fit on F^2 .

Table S7. Calculated energies and BSSE correction for five AOEB crystal structures

Compound	$E_{RB3LYP}^{[a]}$	$E_{CP}^{[b]}$	$E_{BSSE}^{[c]}$	$\sum E_{frag}^{[d]}$	$\Delta E_{raw}^{[e]}$	$\Delta E_{corr}^{[f]}$
BUVCIG	-264,091.95	-509,321.32	1.64	-509,317.25	-5.70	-4.07
BUVCOM	-552,488.08	-797,718.28	1.42	-797,713.51	-6.19	-4.78
BUVDIH	-288,762.99	-533,992.88	1.37	-533,988.40	-5.86	-4.49
BUVDUT	-288,769.49	-534,000.77	1.24	-533,996.52	-5.49	-4.25
BUTPUD	-335,953.60	-581,185.00	1.50	-581,180.57	-5.93	-4.42
Model-methylene	-264,094.37	-509,327.46	0.82	-509,324.85	-3.43	-2.61
Model-methine	-264,094.37	-509,327.36	0.64	-509,324.77	-3.23	-2.59

All energy values are reported in kcal/mol.

^[a] E_{RB3LYP} : Total energy (RB3LYP level); ^[b] E_{CP} : Counterpoise corrected total energy; ^[c] E_{BSSE} : Basis Set Superposition Error energy; ^[d] $\sum E_{frag}$: Sum of individual fragment energies; ^[e] ΔE_{raw} : Complexation energy (raw); ^[f] ΔE_{corr} : Complexation energy (BSSE corrected).

Table S8. UFF optimized cartesian coordinates (Å) for Adamantane and Benzoic acid fragments

Adamantane Fragment				Benzoic acid Fragment			
Atom	X	Y	Z	Atom	X	Y	Z
C	-0.25501	-0.02097	1.04239	C	3.21010	0.54939	-0.03397
C	0.08724	-1.22430	0.14632	C	2.33534	-0.53244	0.06998
C	-1.02470	-1.44080	-0.89521	C	0.95573	-0.31713	0.08846
C	-2.35526	-1.70051	-0.16703	C	0.44963	0.98564	0.00262
C	-2.71143	-0.49987	0.72721	C	-1.00524	1.26536	0.01819
C	-2.83778	0.76071	-0.14633	C	1.33225	2.06835	-0.10173
C	-1.50995	1.03443	-0.87436	C	2.71063	1.84895	-0.11984
C	-0.39527	1.23689	0.16708	O	-1.52153	2.36545	-0.05234
C	-1.16062	-0.17490	-1.75956	O	-1.75192	0.15165	0.12171
C	-1.58995	-0.28871	1.75957	H	4.28389	0.37889	-0.04807
H	0.53958	0.12858	1.78175	H	2.72679	-1.54445	0.13681
H	1.04572	-1.05398	-0.35924	H	0.28517	-1.16896	0.16990
H	0.20640	-2.12590	0.75966	H	-2.67270	0.48770	0.11950
H	-0.77604	-2.29833	-1.53020	H	0.94836	3.08429	-0.16905
H	-3.15467	-1.87299	-0.89810	H	3.39343	2.69124	-0.20081
H	-2.27791	-2.61024	0.44099				
H	-3.65917	-0.69000	1.24301				
H	-3.64543	0.63039	-0.87707				
H	-3.10773	1.62233	0.47657				
H	-1.60546	1.93257	-1.49454				
H	-0.62342	2.10665	0.79537				
H	0.55496	1.44931	-0.33810				
H	-0.22350	0.01336	-2.29774				
H	-1.93960	-0.32122	-2.51787				
H	-1.49955	-1.17430	2.40053				
H	-1.83854	0.55495	2.41509				

Table S9. Selected NBO parameters for the C–H··· π interactions in the experimental (BUVCIG) and idealized (Methylenic and Methinic) models.

Model	Donor	Acceptor	Occup.^a	$E^{(2)}$ ^b
BUVCIG	$\pi(\text{C}=\text{C})_{\text{ring}}$	$\sigma^*(\text{C}-\text{H})_{\text{methy}}$	0.017	7.70
	$\pi(\text{C}=\text{C})_{\text{ring}}$	$\sigma^*(\text{C}-\text{H})_{\text{methi}}$	0.014	5.06
Methylenic	$\pi(\text{C}=\text{C})_{\text{ring}}$	$\sigma^*(\text{C}-\text{H})_{\text{methy}}$	0.015	6.53
Methinic	$\pi(\text{C}=\text{C})_{\text{ring}}$	$\sigma^*(\text{C}-\text{H})_{\text{methi}}$	0.012	4.10

^a Occupancy of the antibonding orbital σ^* (units in e^-).

^b Second-order perturbation stabilization energy in kJ/mol (1 kcal/mol = 4.184 kJ/mol).

Table S10. BOILED-Egg plot and SwissADME properties for BUVCIG

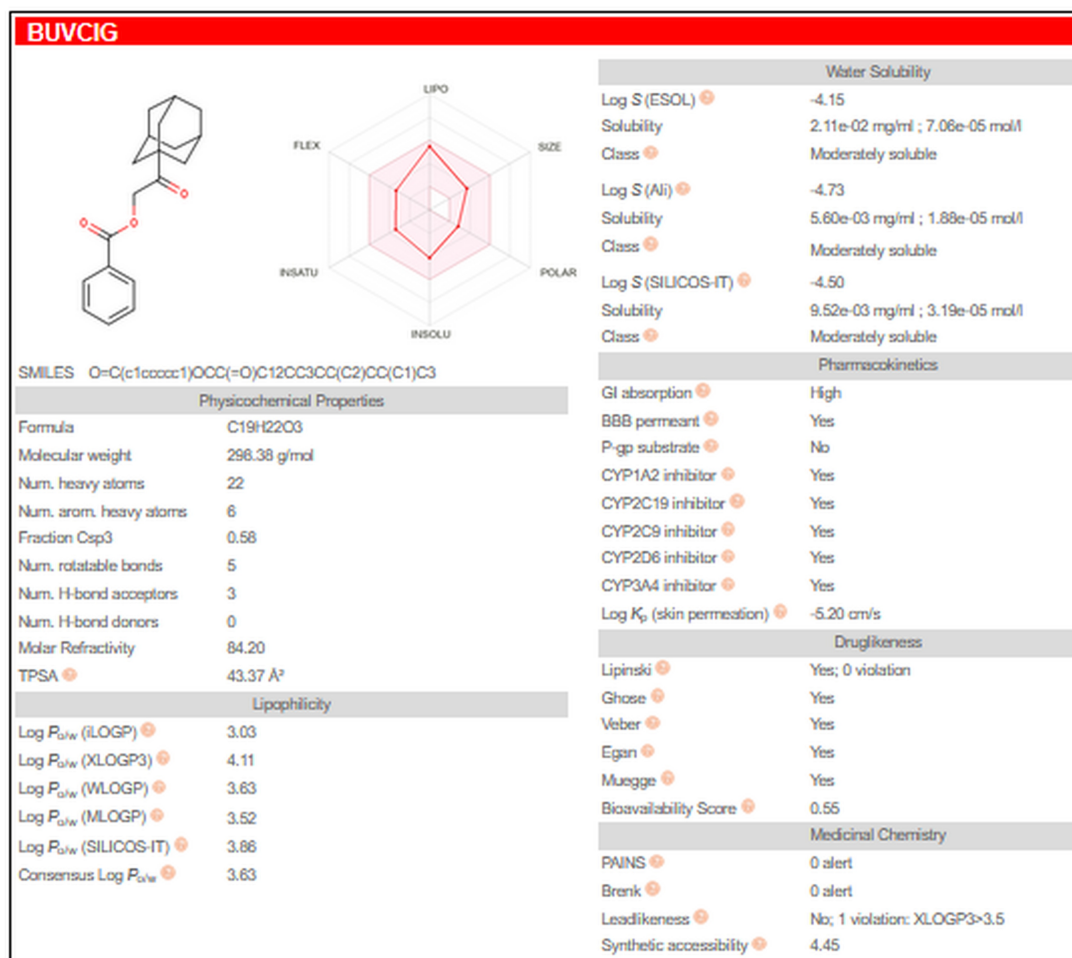
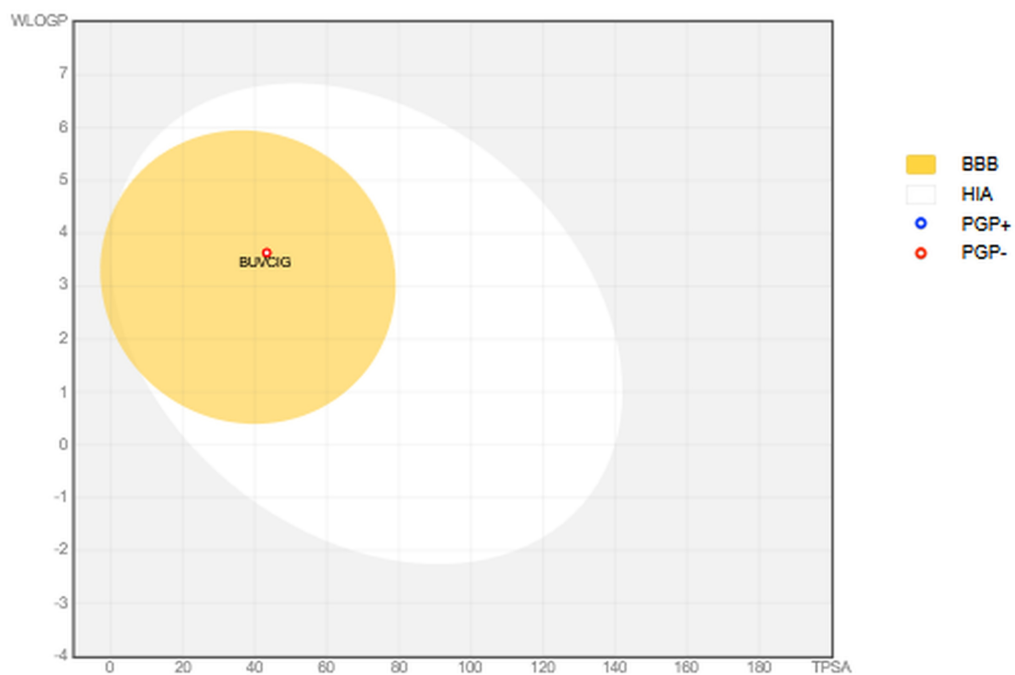


Table S11. BOILED-Egg plot and SwissADME properties for BUVCOM

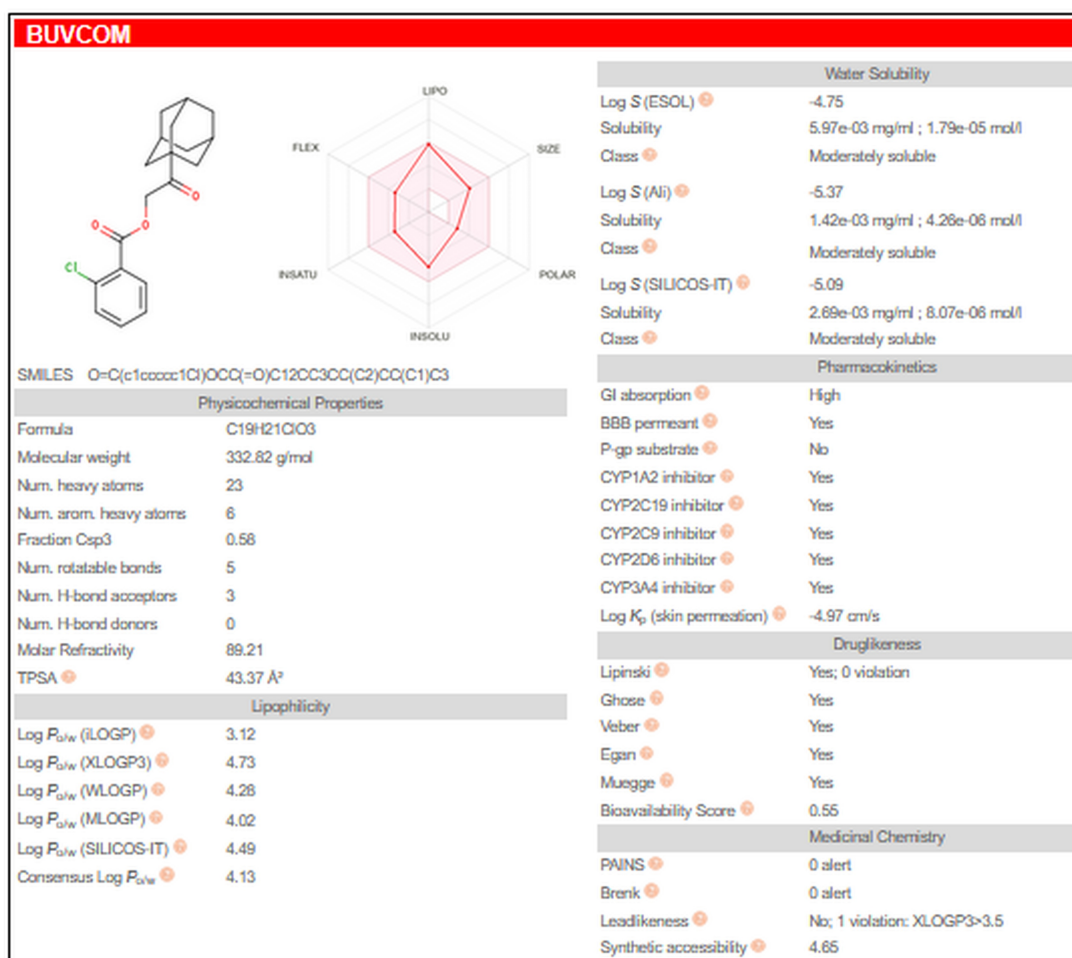
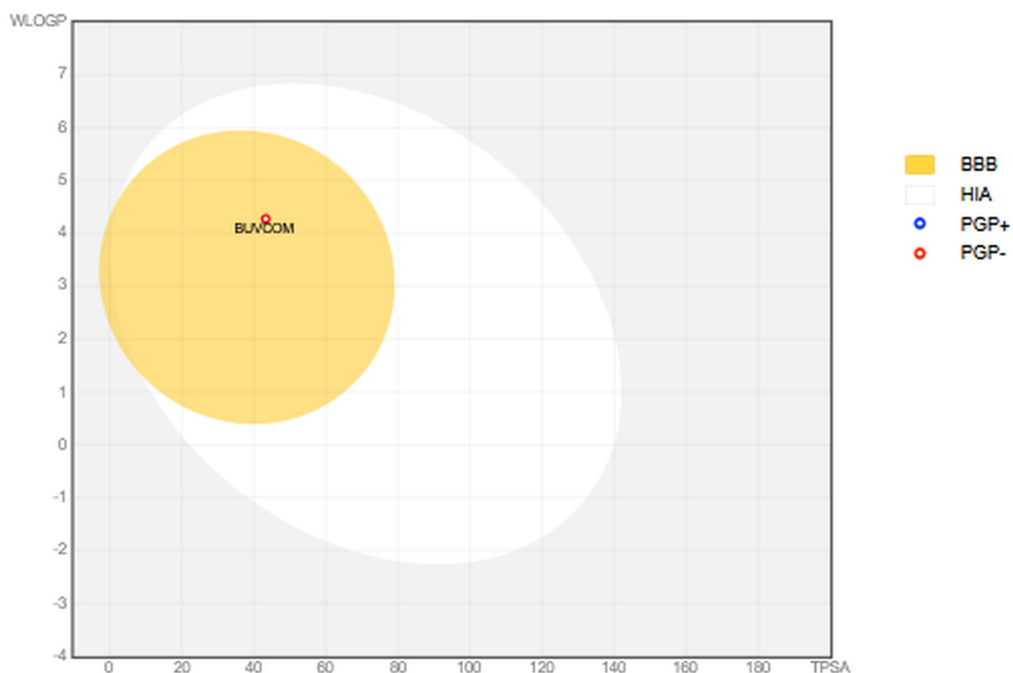
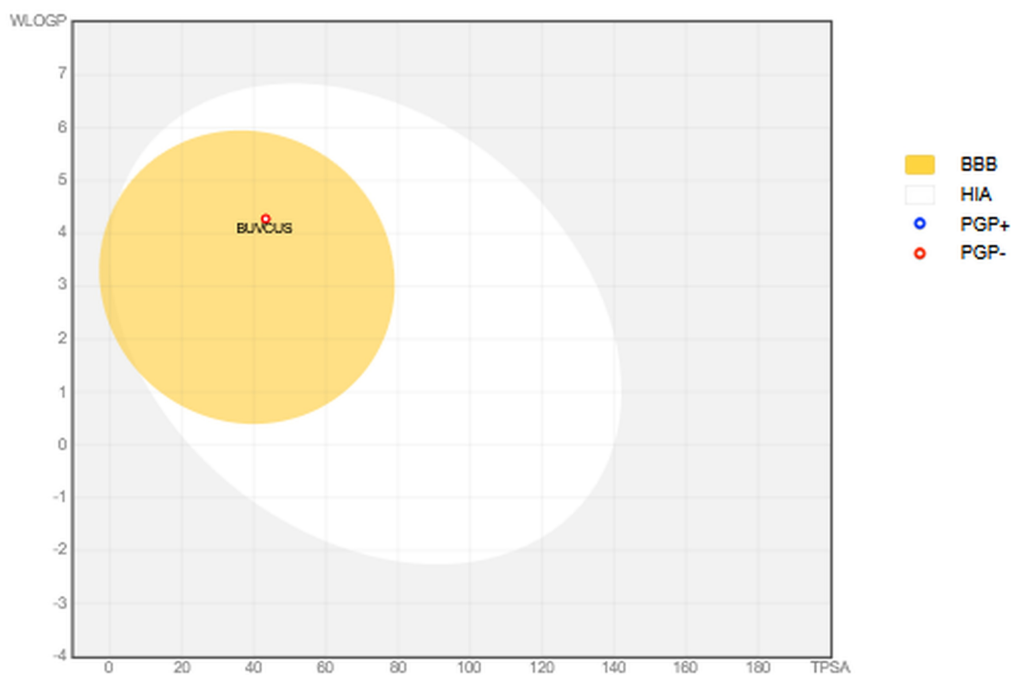


Table S12. BOILED-Egg plot and SwissADME properties for BUVCUS



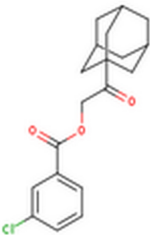

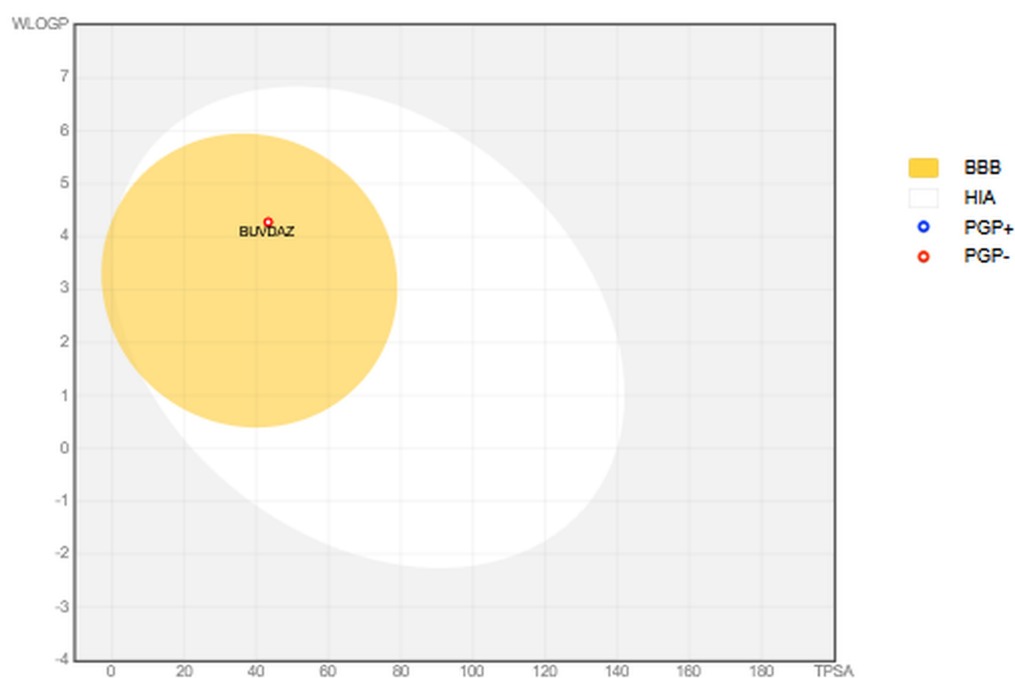
BUVCUS	
	
	
SMILES <chem>Clc1ccccc1C(=O)OCC(=O)C12CC3CC(C2)CC(C1)C3</chem>	
Physicochemical Properties	
Formula	C ₁₉ H ₂₁ ClO ₃
Molecular weight	332.82 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	6
Fraction Csp ³	0.58
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	0
Molar Refractivity	89.21
TPSA	43.37 Å ²
Lipophilicity	
Log P _{ow} (ILOGP)	3.34
Log P _{ow} (XLOGP3)	4.73
Log P _{ow} (WLOGP)	4.28
Log P _{ow} (MLOGP)	4.02
Log P _{ow} (SILICOS-IT)	4.49
Consensus Log P _{ow}	4.17
Water Solubility	
Log S (ESOL)	-4.75
Solubility	5.97e-03 mg/ml ; 1.79e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-5.37
Solubility	1.42e-03 mg/ml ; 4.26e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-5.09
Solubility	2.69e-03 mg/ml ; 8.07e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K _p (skin permeation)	-4.97 cm ² /s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	4.65

Table S13. BOILED-Egg plot and SwissADME properties for BUVDAZ



BUVDAZ	
SMILES	<chem>O=C(c1ccc(cc1)Cl)OCC(=O)C12CC3CC(C2)CC(C1)C3</chem>
Physicochemical Properties	
Formula	C ₁₉ H ₂₁ ClO ₃
Molecular weight	332.82 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	6
Fraction Csp ³	0.58
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	0
Molar Refractivity	89.21
TPSA	43.37 Å ²
Lipophilicity	
Log P _{o/w} (iLOGP)	3.38
Log P _{o/w} (XLOGP3)	4.73
Log P _{o/w} (WLOGP)	4.28
Log P _{o/w} (MLOGP)	4.02
Log P _{o/w} (SILICOS-IT)	4.49
Consensus Log P _{o/w}	4.18
Water Solubility	
Log S (ESOL)	-4.75
Solubility	5.97e-03 mg/ml ; 1.79e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-5.37
Solubility	1.42e-03 mg/ml ; 4.26e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-5.09
Solubility	2.69e-03 mg/ml ; 8.07e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K _p (skin permeation)	-4.97 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	4.54

Table S14. BOILED-Egg plot and SwissADME properties for BUVDIH

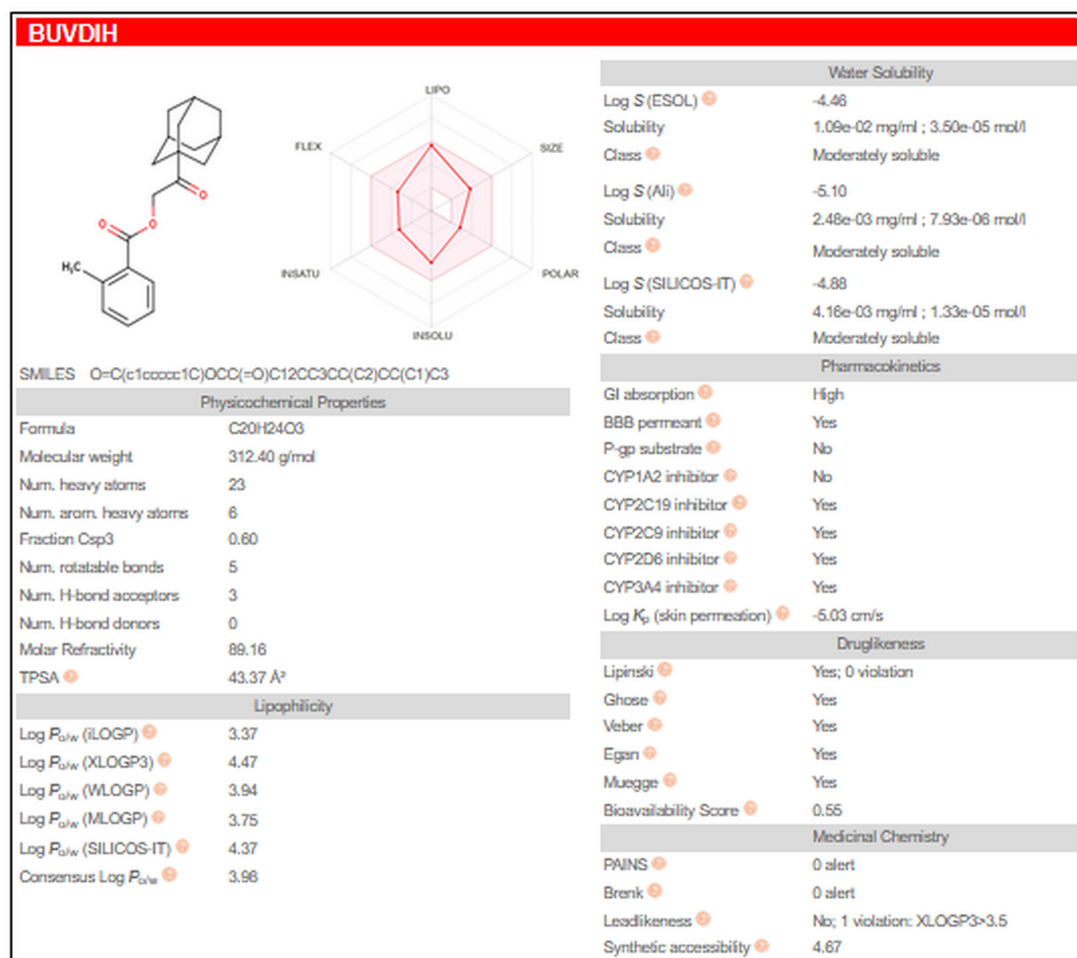
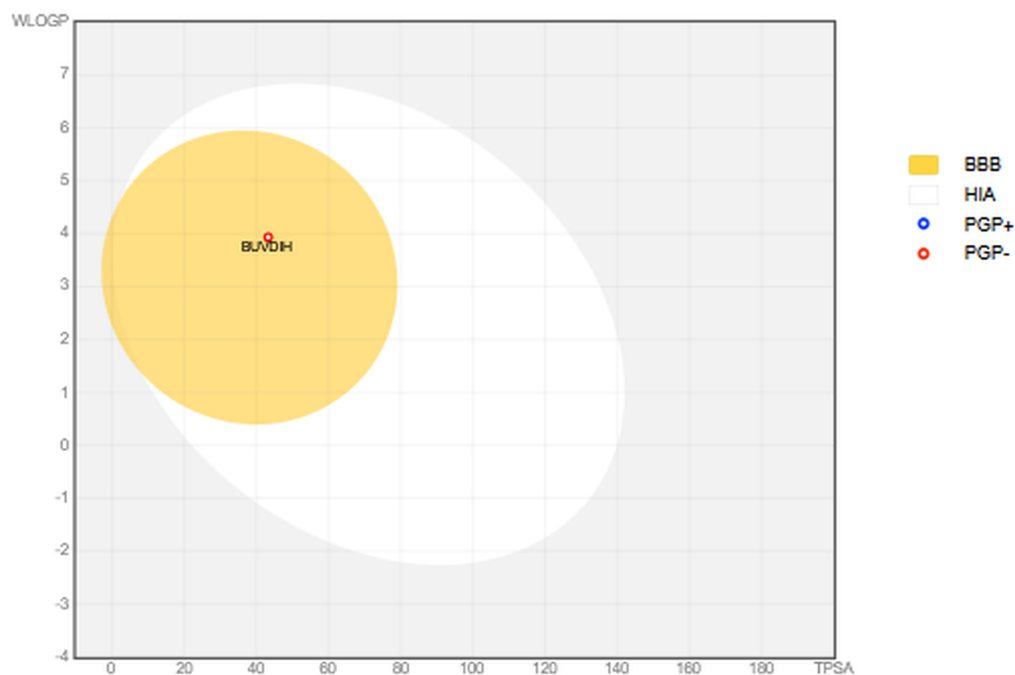
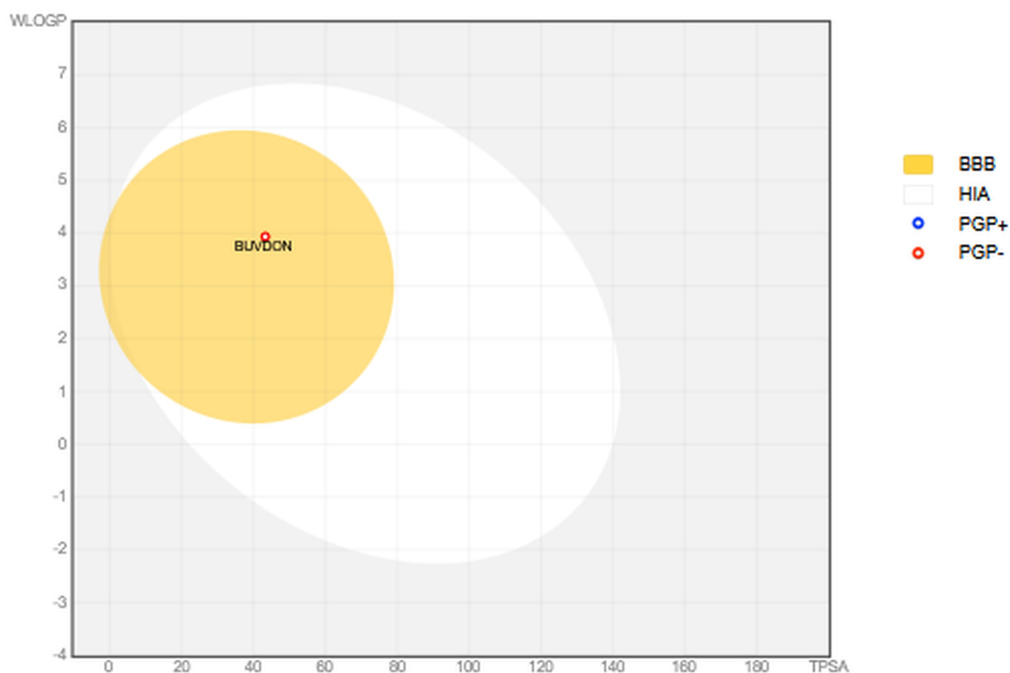


Table S15. BOILED-Egg plot and SwissADME properties for BUVDON



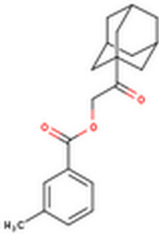

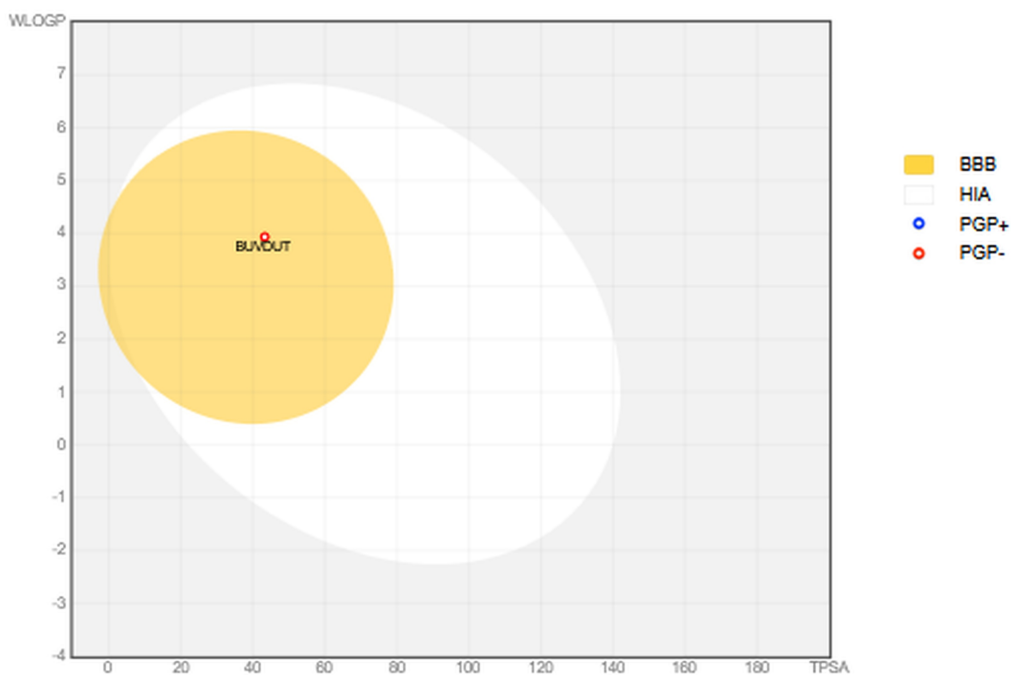
BUVDON	
	
	
SMILES <chem>Cc1cccc(c1)C(=O)OCC(=O)C12CC3CC(C2)CC(C1)C3</chem>	
Physicochemical Properties	
Formula	C20H24O3
Molecular weight	312.40 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	6
Fraction Csp3	0.60
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	0
Molar Refractivity	89.16
TPSA	43.37 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.19
Log $P_{o/w}$ (XLOGP3)	4.47
Log $P_{o/w}$ (WLOGP)	3.94
Log $P_{o/w}$ (MLOGP)	3.75
Log $P_{o/w}$ (SILICOS-IT)	4.37
Consensus Log $P_{o/w}$	3.94
Water Solubility	
Log S (ESOL)	-4.46
Solubility	1.09e-02 mg/ml ; 3.50e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-5.10
Solubility	2.48e-03 mg/ml ; 7.93e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-4.88
Solubility	4.16e-03 mg/ml ; 1.33e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.03 cm²/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	4.70

Table S16. BOILED-Egg plot and SwissADME properties for BUVDUT



BUVDUT	
SMILES <chem>O=C(c1ccc(cc1)C)OCC(=O)C12CC3CC(C2)CC(C1)C3</chem>	
Physicochemical Properties	
Formula	C20H24O3
Molecular weight	312.40 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	6
Fraction Csp3	0.60
Num. rotatable bonds	5
Num. H-bond acceptors	3
Num. H-bond donors	0
Molar Refractivity	89.16
TPSA	43.37 Å²
Lipophilicity	
Log P _{ow} (iLOGP)	3.30
Log P _{ow} (XLOGP3)	4.47
Log P _{ow} (WLOGP)	3.94
Log P _{ow} (MLOGP)	3.75
Log P _{ow} (SILICOS-IT)	4.37
Consensus Log P _{ow}	3.97
Water Solubility	
Log S (ESOL)	-4.46
Solubility	1.09e-02 mg/ml ; 3.50e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-5.10
Solubility	2.48e-03 mg/ml ; 7.93e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-4.88
Solubility	4.16e-03 mg/ml ; 1.33e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K _p (skin permeation)	-5.03 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	4.62

Table S17. BOILED-Egg plot and SwissADME properties for BUTPUD

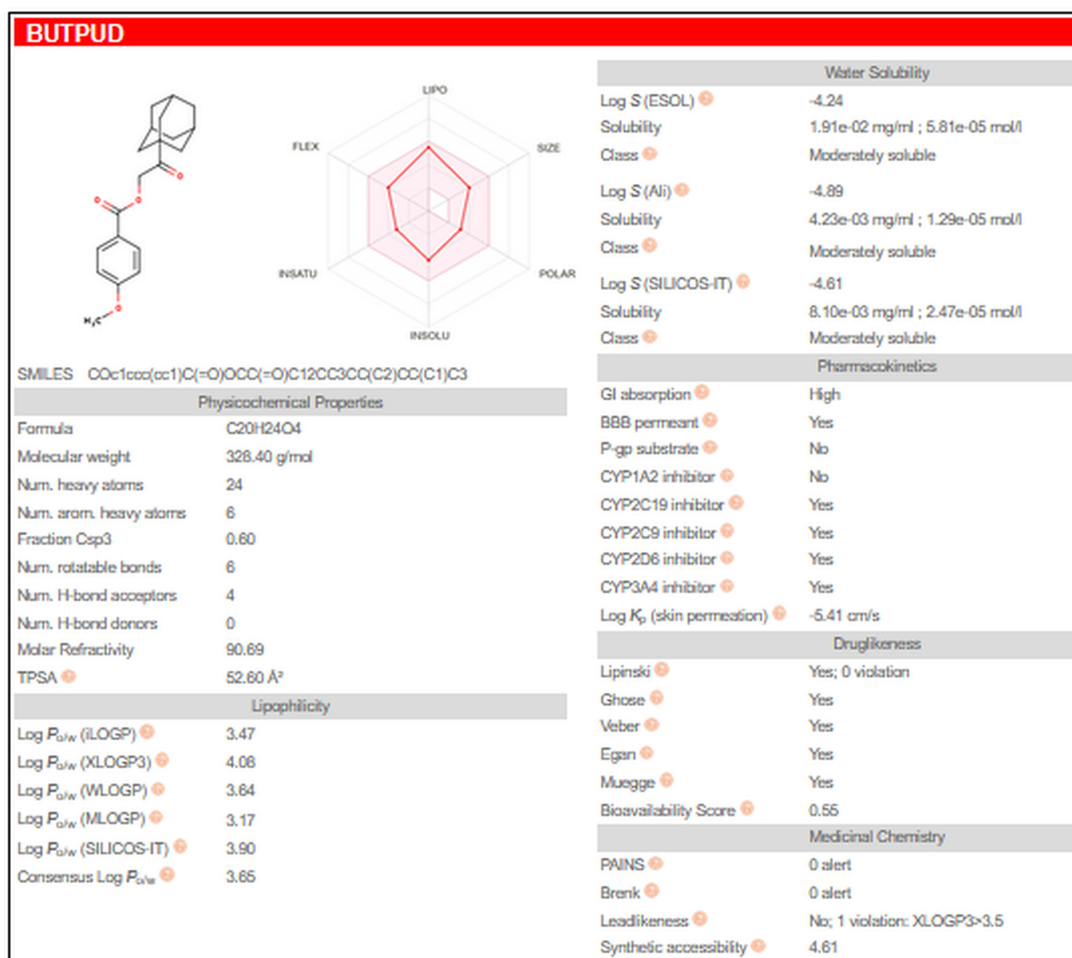
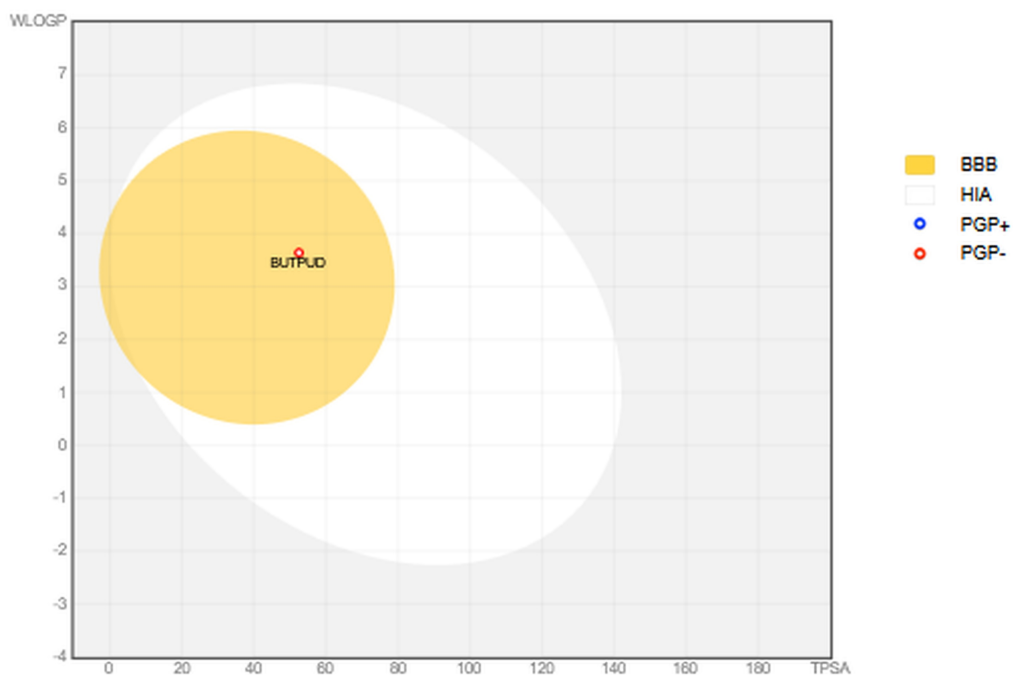
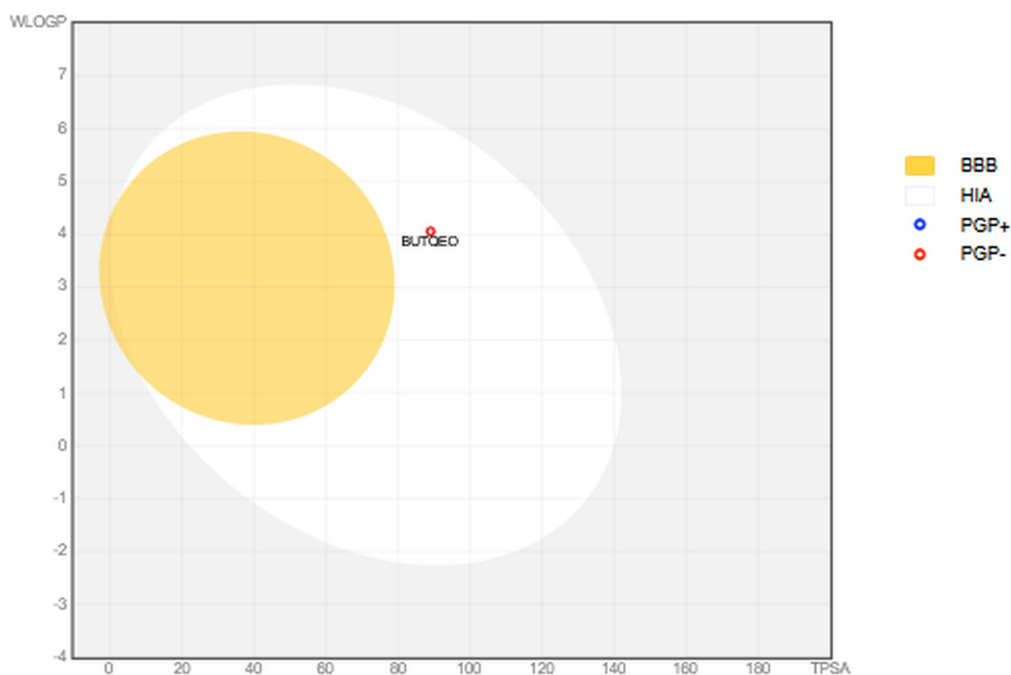
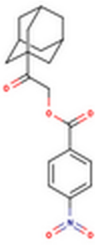
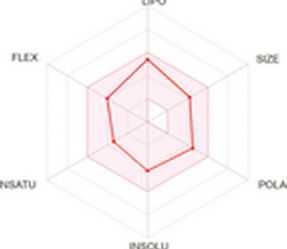


Table S18. BOILED-Egg plot and SwissADME properties for BUTQEO



BUTQEO	
	
SMILES <chem>O=C(c1ccc(cc1)N(=O)=O)OCC(=O)C12CC3CC(C2)CC(C1)C3</chem>	
Physicochemical Properties	
Formula	C ₁₉ H ₂₁ NO ₅
Molecular weight	343.37 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	6
Fraction Csp ³	0.58
Num. rotatable bonds	6
Num. H-bond acceptors	5
Num. H-bond donors	0
Molar Refractivity	93.02
TPSA	89.19 Å ²
Lipophilicity	
Log P _{ow} (iLOGP)	2.24
Log P _{ow} (XLOGP3)	3.94
Log P _{ow} (WLOGP)	4.06
Log P _{ow} (MLOGP)	2.42
Log P _{ow} (SILICOS-IT)	2.08
Consensus Log P _{ow}	2.95
Water Solubility	
Log S (ESOL)	-4.23
Solubility	2.01e-02 mg/ml ; 5.85e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-5.51
Solubility	1.05e-03 mg/ml ; 3.07e-06 mol/l
Class	Moderately soluble
Log S (SILICOS-IT)	-4.33
Solubility	1.61e-02 mg/ml ; 4.68e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K _p (skin permeation)	-5.60 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: nitro_group
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	4.64