SUPPLEMENTARY INFORMATION

Comparative study of carborane- and phenyl-modified adenosine derivatives as ligands for the A2A and A3 adenosine receptors based on a rigid *in silico* docking and radioligand replacement assay

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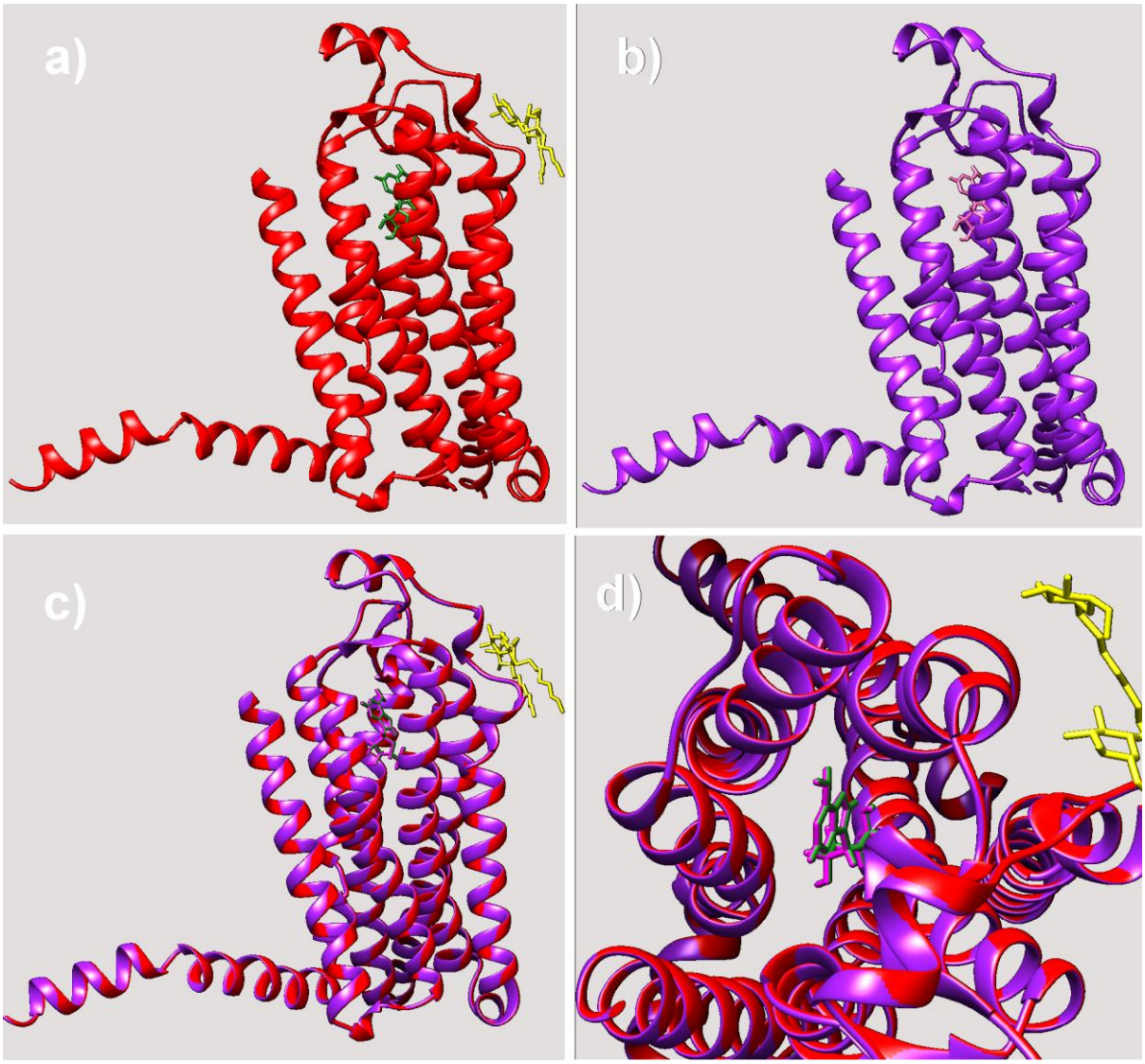

Figure S1. a) Best docking pose of adenosine obtained with SwissDock web server and considering human A2A receptor (PDB code: 2YDO), as protein input, with thioglucoside, crystallization helper molecules; b) SwissDock best-docked pose of adenosine considering human A2A receptor (PDB code: 2YDO), as protein input, without the crystallization helper molecules; c) superimposition of SwissDock best-docked poses obtained with and without the crystallization helper molecules. d) Enlargement of the superimposition viewed from the extracellular region, green for adenosine in the best-docked pose with thioglucoside, red for the protein in the best-docked structure with crystallization helper molecules, pink for adenosine in the best-docked pose without crystallization helper molecules, purple best-docked structure without crystallization helper molecules; yellow for crystallization helper molecules.

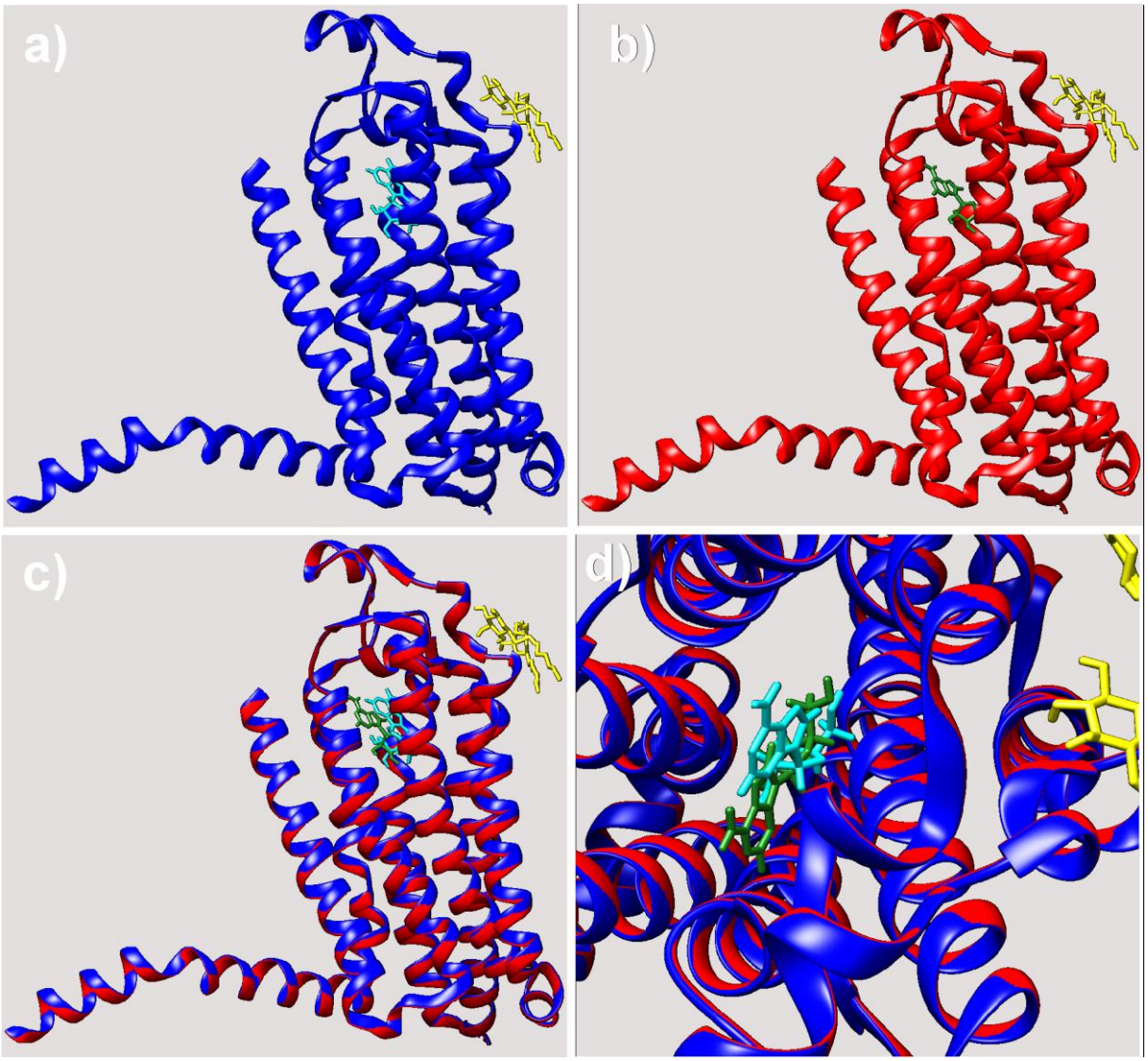

Figure S2. a) X-ray structure thermostabilized human A2A receptor with adenosine bound (PDB code: 2YDO),[28] b) PatchDock best-docked pose obtained with adenosine as a ligand and considering human A2A receptor (PDB code: 2YDO), as protein input, with the crystallization helper molecules. c) Superimposition of the reference complex (PDB code: 2YDO) and best docking pose of adenosine. d) Enlargement of the binding pockets viewed from the extracellular region; blue for receptor in the X-ray reference structure (PDB: 2YDO); cyan for adenosine in A2A receptor reference structure (PDB: 2YDO); red for the protein in the best-docked structure; green for adenosine in the best-docked pose; yellow for crystallization helper molecules.

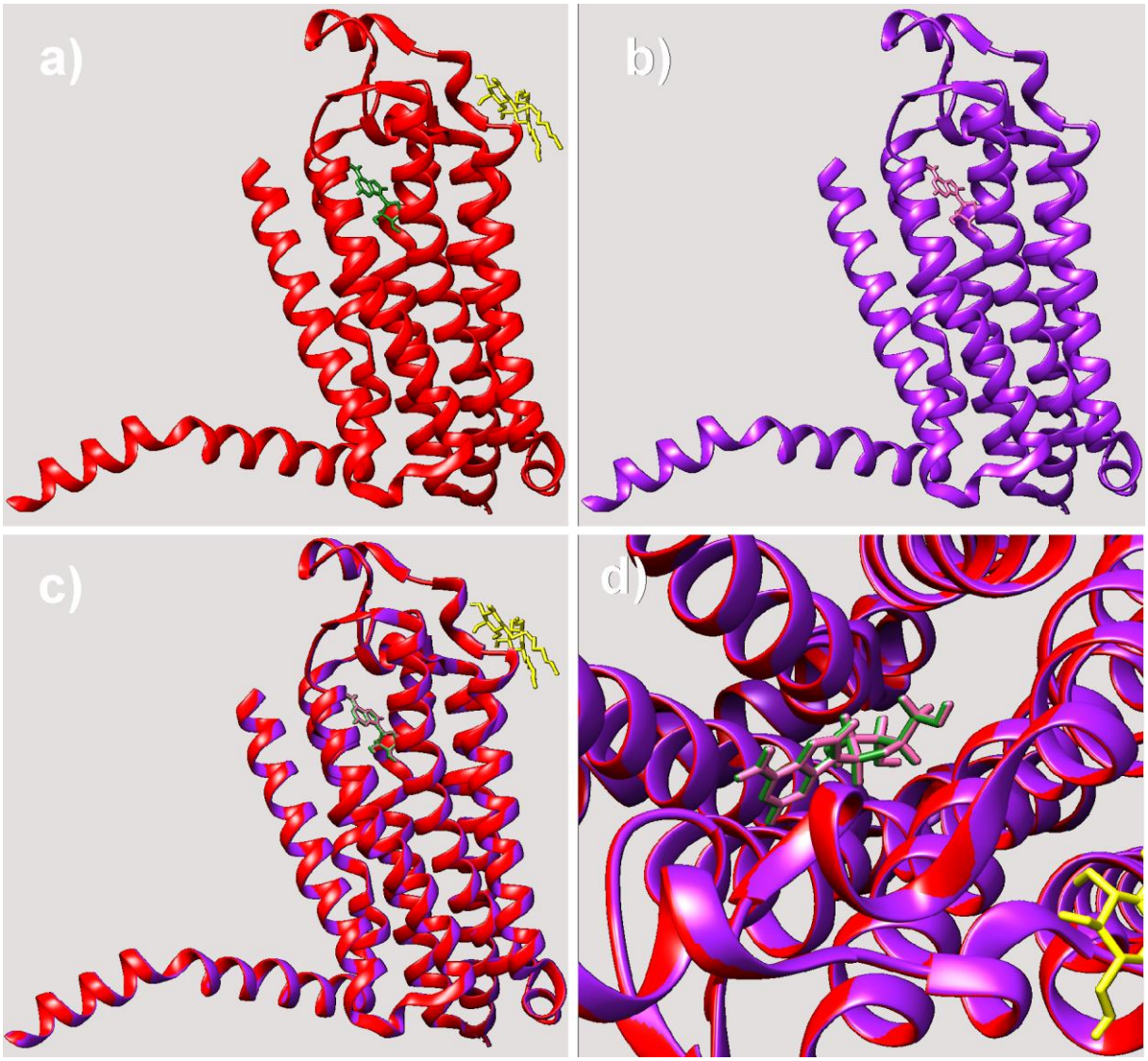

Figure S3. a) Best docking pose of adenosine obtained with PatchDock web server and considering human A2A receptor (PDB code: 2YDO), as protein input, with crystallization helper molecules, b) PatchDock best-docked pose of adenosine considering human A2A receptor (PDB code: 2YDO), as protein input, without the crystallization helper molecules, c) superimposition of PatchDock best-docked poses obtained with and without the crystallization helper molecules. d) Enlargement of the superimposition viewed from the extracellular region. Green for adenosine in the best-docked pose with thioglucoside; red for the protein in the best-docked structure with crystallization helper molecules; pink for adenosine in the best-docked pose without crystallization helper molecules; purple best-docked structure without crystallization helper molecules; yellow for crystallization helper molecules.

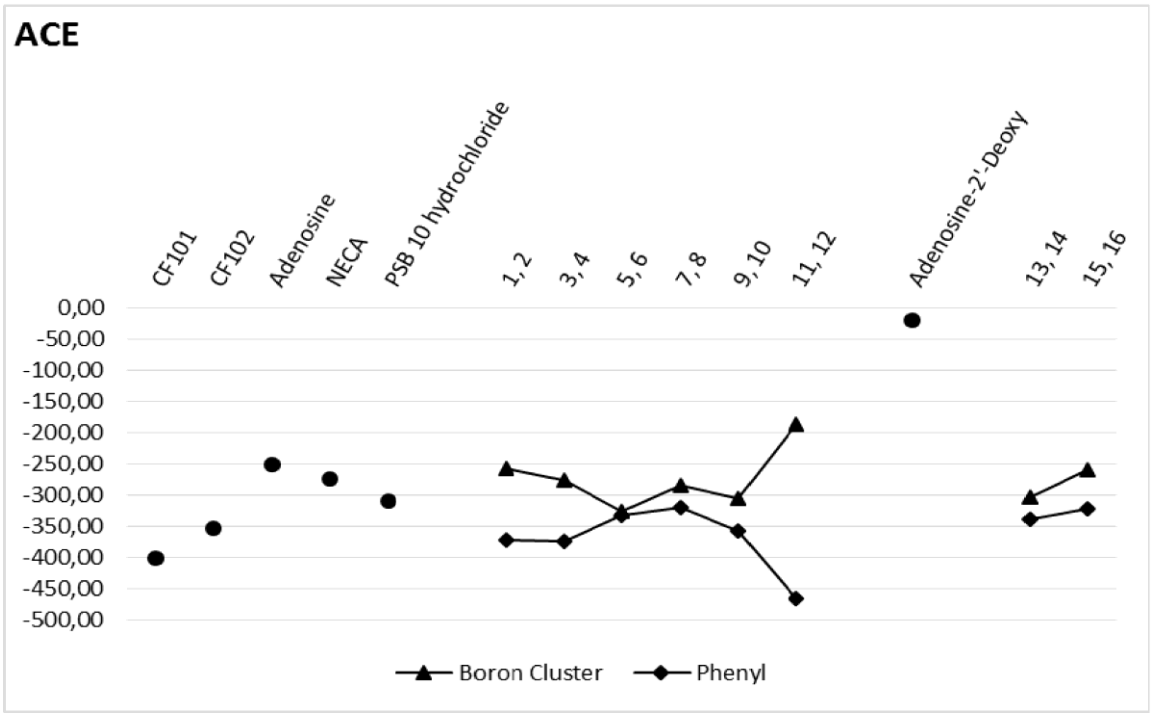

Figure S4. Desolvation energy (ACE) for the A3 protein-ligand interaction ● for reference molecules (CF101, CF102, adenosine, 2′-deoxyadenosine, NECA and PSB 10 hydrochloride); ▲ for molecules bearing boron clusters (**1**, **3**, **5**, **7**, **9**, **11**, **13**, **15**); ◆ for ligands with phenyl ring (**2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**).

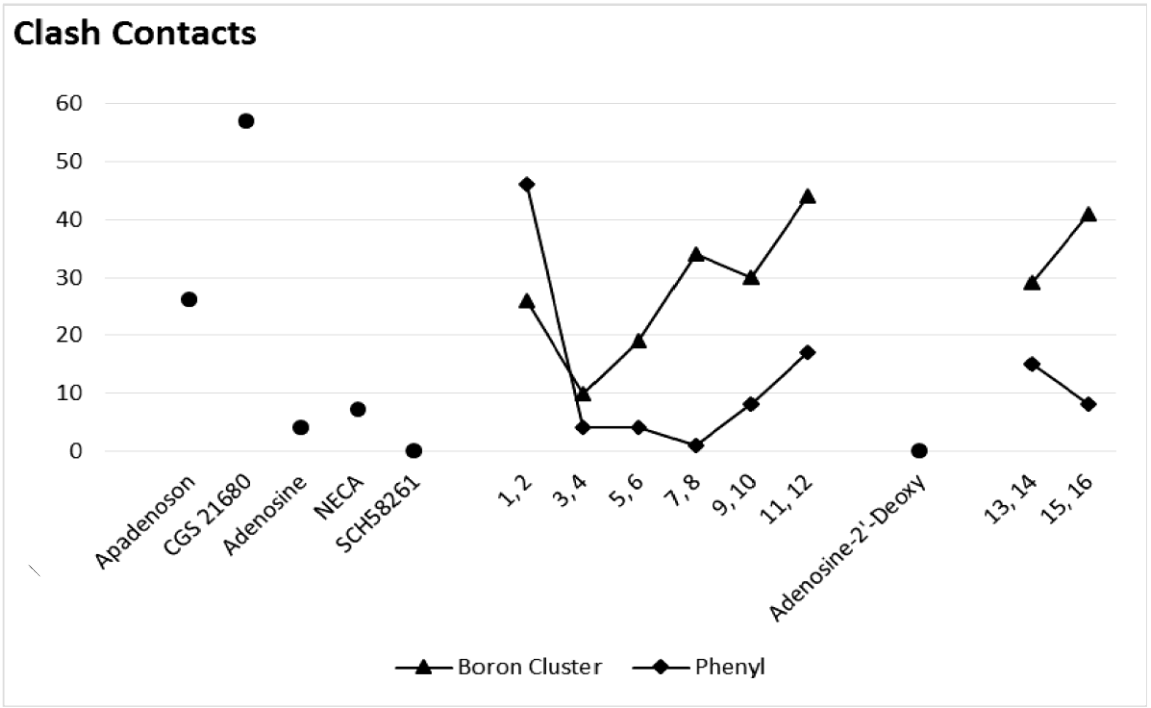

Figure S5. Clash contact involved in the A2A protein-ligand interaction ● for reference molecules (apadenoson, CGS 21680, adenosine, SCH58261, 2′-deoxyadenosine and NECA); ▲ for molecules bearing boron clusters (**1**, **3**, **5**, **7**, **9**, **11**, **13**, **15**); ◆ for ligands with phenyl ring (**2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**).

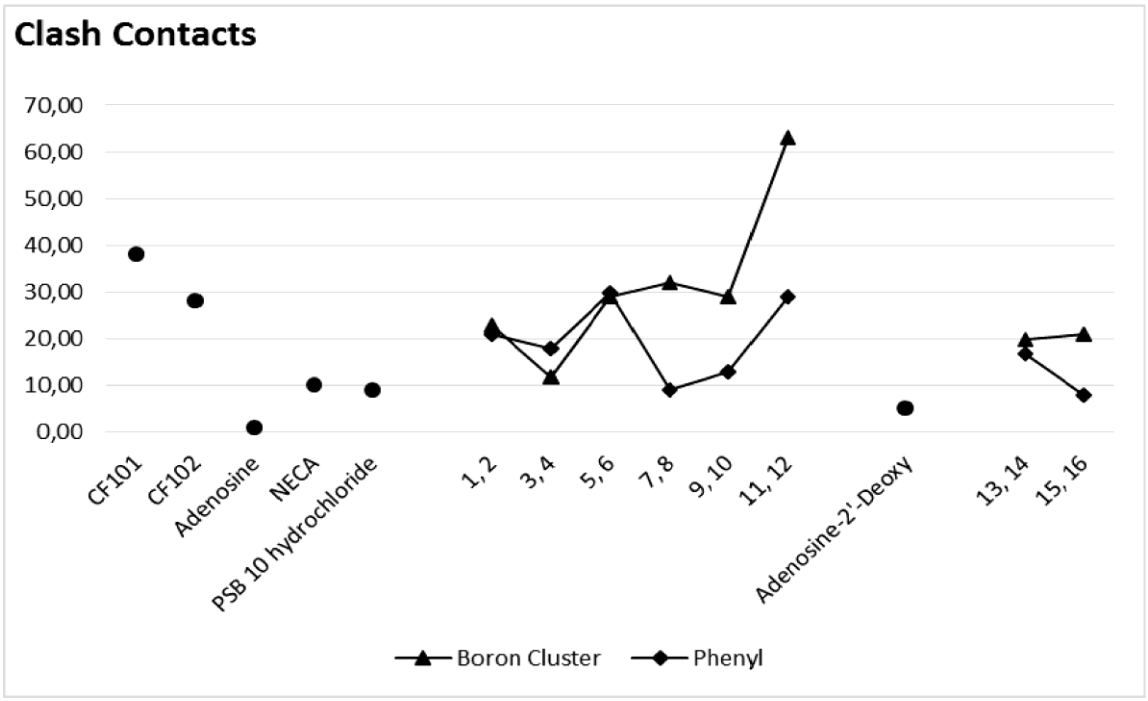

Figure S6. Clash contact involved in the A3 protein-ligand interaction ● for reference molecules (CF101, CF102, Adenosine, 2′-deoxyadenosine, NECA and PSB 10 hydrochloride); ▲ for molecules bearing boron clusters (**1**, **3**, **5**, **7**, **9**, **11**, **13**, **15**); ◆ for ligands with phenyl ring (**2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**).

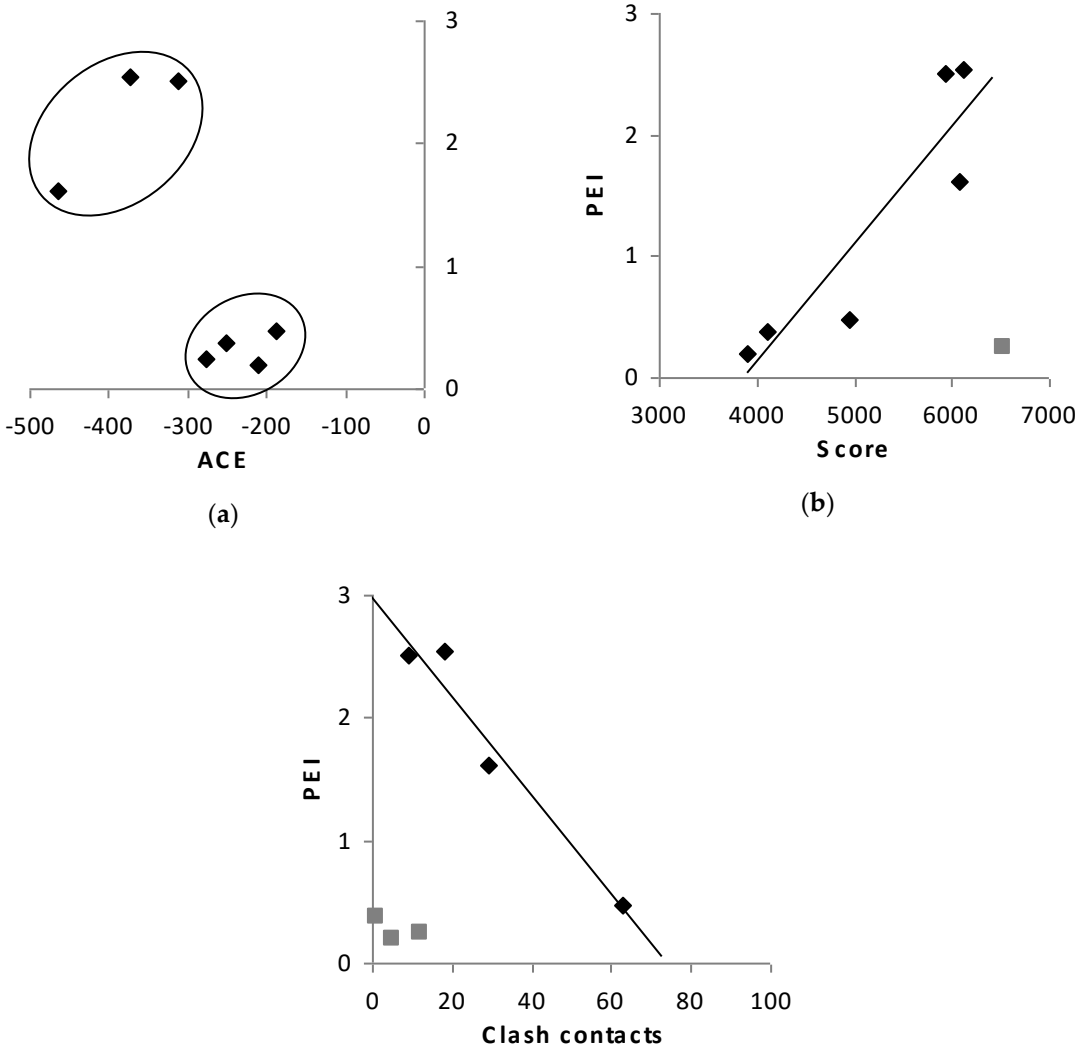

Figure 7S. Relationships of desolvation energy, ACE (a), geometric scores (b) and clash contacts (c) *versus* ligand efficiency for A3 receptor and for the compounds **3**, **4**, **11**, **12**, PSB 10, adenosine and 2'-deoxyadenosine as ligands. Ligand efficiency was expressed as PEI (potency efficiency index) calculated according to the equation PEI = (inhibition at 10 μM, ratio) / (MW, kD). PEI values of the compounds are 0.24, 2.54, 0.48, 1.61, 2.51, 0.37, 0.20, respectively.

Table S1. Docking results of molecule **1**-**16** towards adenosine receptor A2A.

Molecule	Score[1]	ACE[2]	Clash Contacts
Apadenoson	6606	-363.31	26
CGS 21680	6470	-334.18	3
Adenosine	4218	-207.74	4
NECA	4446	-216.00	7
SCH58261	5918	-284.37	0
1	5300	-263.44	26
2	4538	-44.88	46
3	6032	-272.99	10
4	6286	-281.97	4
5	5336	-273.61	19
6	5568	-299.64	4
7	5202	-277.51	34
8	6104	-297.73	1
9	5198	-245.86	30
10	6178	-297.22	8
11	4618	-220.47	44
12	5618	-224.77	17
2′-Deoxyadenosine	4266	-198.57	0
13	5000	-244.14	41
14	5216	-311.93	8
15	5108	-255.24	29
16	5106	-263.44	15

Score[1] - geometric shape complementarity score; ACE[2] (atomic contact energies) - desolvation free energies required to transfer atoms from water to a protein's interior.

Table S2. Docking results of molecule 1-16 towards adenosine receptor A3.

Molecule	Score[1]	ACE[2]	Clash Contacts
CF101	5922	-401.50	38
CF102	6344	-353.51	28
Adenosine	4110	-252.09	1
NECA	4686	-274.80	10
PSB 10 hydrochloride	5926	-310.94	9
1	5492	-256.90	23
2	5868	-372.38	21
3	6530	-276.46	12
4	6120	-373.31	18
5	5552	-326.72	29
6	6188	-331.94	10
7	5866	-283.52	32
8	6044	-320.62	9
9	5688	-305.78	29
10	6062	-356.64	13
11	4942	-186.65	63
12	6086	-465.12	29
2′-Deoxyadenosine	3898	-21.73	5
13	5314	-260.20	21
14	5452	-322.73	8
15	5518	-304.00	20
16	5580	-337.54	17

Score[1] - geometric shape complementarity score; ACE[2] (atomic contact energies) - desolvation free energies required to transfer atoms from water to a protein's interior.

Table S3. Binding pockets of molecules **1**-**16** for adenosine receptor A2.

Molecule	Binding Pocket[1]		
	E[2]	T[3]	C[4]
Apadenoson	S2.65, T2.66, L45.51, F45.52, E169	L3.33, L7.32, I7.39, H7.43	
CGS 21680	S2.65, F45.52, E169, His264		
Adenosine		A2.61	
NECA	F45.52, E169	L7.32	
SCH58261		W6.48	
1	Ser77, F45.52, E169,	I2.64, V3.32, T3.36, W6.48, L6.51, H7.43	
2			K6.29, I8.47
3	L45.51, F45.52,	M5.38, H6.52, L7.32	
4		T3.36, I7.39	
5	F45.52, E169		
6	S2.65, F45.52, E169	A2.61, I2.64, M7.35, I7.39	
7	F45.52, E169	A2.61, W6.48, L6.51,	
8	S2.65	A2.61, M7.35, I7.39	
9	F45.52	A2.61, V3.32, T3.36, N5.42, C5.46, W6.48, L6.51, H6.52	
10	F45.52, E169	A2.61	
11	L45.51, F45.52	L7.32, Y7.36	
12	L45.51, F45.52, E169	I7.39	
Adenosine-2′-Deoxy	F45.52	A2.61, I7.39	
13		A2.61, V3.32, L3.33, T3.36, N5.42, W6.48, L6.51, H7.43	
14	F45.52	A2.61, I2.64, I7.39	
15	S2.65, F45.52, E169	A2.61, L3.33, T3.36, W6.48, L6.51	
16	F45.52	A2.61, V3.32, T3.36, L6.51, H6.52, M7.35	

Binding Pocket[1] - residues with more than 10 contacts; E[2] - extracellular region; T[3] - transmembrane region; C[4] - cytoplasmic region.

Table S4. Binding pockets of molecules **1-16** for adenosine receptor A3.

Molecule	Binding Pocket[1]		
	E[2]	T[3]	C[4]
CF101	M5.38	A2.61, V2.64, L3.32, L3.33, S5.42, F5.43, I5.47, L6.51	
CF102	F45.52	L3.32, W6.48, L7.35, I7.39	
Adenosine	F45.52	L3.32, L7.36, I7.39	
NECA	F45.52	L3.32, I7.39	
PSB 10 hydrochloride	F45.52	L3.32, L7.35, L7.36	
1		L6.51, N6.55, L7.35, L7.36, I7.39	
2	M5.38	L3.32, W6.48, L7.35, I7.39	
3	M5.38	L3.33, S5.42, I5.47, W6.48, L7.35, I7.39	
4	F45.52	V2.64, L3.33, L7.36, I7.39	
5	F45.52	A2.61, L3.32, L3.33, T3.36, S5.42, W6.48, L6.51	
6	F45.52	L6.51, L7.35, I7.39	
7	F45.52, M5.38	A2.61, L3.32, S5.42, I5.47, W6.48, L6.51, N6.55, I7.39	
8		W6.48, L6.51, L7.35, I7.39	
9	M5.38	A2.61, L3.32, L3.33, S5.42, W6.48, L6.51, I7.39	
10	F45.52,	L3.32, L7.35, I7.39	
11	L8, S2.65, Q45.51, F45.52, Q7.32	L7.36	
12		L3.33, S5.42, F5.43, I5.47, W6.48, S6.52	
Adenosine-2′-Deoxy			K6.32, K8.49
13	F45.52, M5.38	V2.64, L3.32, L6.51, N6.55, L7.36	
14	F45.52	L7.35, L7.36, I7.39	
15	F45.52	A2.61, L7.35, L7.36, I7.39	
16	F45.52	A2.61, V2.64, L6.51, L7.35, I7.39	

Binding Pocket[1] - residues with more than 10 contacts; E[2] - extracellular region; T[3] - transmembrane region; C[4] - cytoplasmic region.