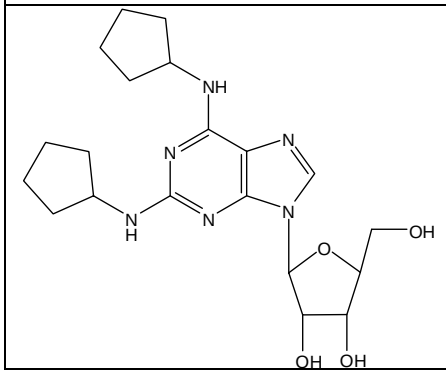
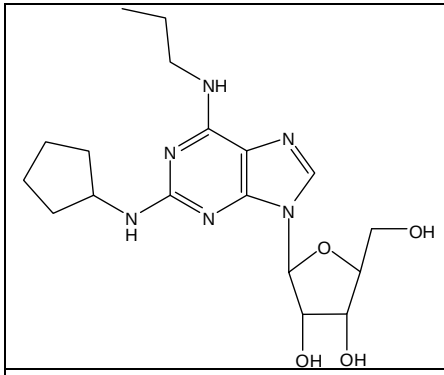
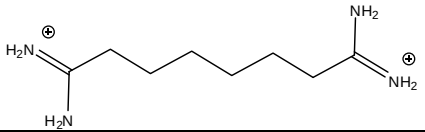
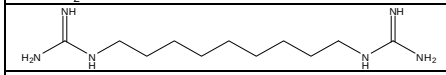
Supplementary Table 2. Listing of K_i values, Gibbs free energy ΔG^0 and energy gain/loss relative to a control compound for some of the compounds utilised in this study and listed in Supplementary Table 1. Conclusions drawn from the data with respect to substrate binding of the P2 transporter are listed in the final column.

Compound	**Ki value (μM)**	**$\Delta(G^0)$ (KJ/mol)**	**$\delta(\Delta(G^0))$ (KJ/mol)**	**Relative to**	**Conclusion**
Adenosine	0.92 ± 0.06	34.5		N/A	
Position 1					Average contribution = 7.7 kJ/mol to binding the purine ring
1-Deazaadenosine	45.4 ± 8.7	24.8	9.7	Adenosine	N1 contributesof 9.7 kJ/mol to binding of adenosine
1-Deazapurine	181 ± 33	21.4	5.7	Purine	N1 contributes of 5.7 kJ/mol to binding of adenine
Position 2					Depending on the group, substitutions on position reduce binding energy of adenosine analogs with 5 – 11 kJ/mol
2-Nitroadenosine	81 ± 22	23.4	11.1	Adenosine	
2-Hydroxy-6-aminopurine	9.7 ± 2.3	28.6	8.7	Adenine	
2,6-Diamino, 2'deoxypurine riboside	4.4 ± 1.3	30.5	7.4	2'-Deoxyadenosine	
2-Chloroadenosine	9.7 ± 3.4	28.6	5.9	Adenosine	
Position 3					N3 does not contribute to binding. Its removal re-distributes charge around the molecule, resulting in a slightly higher affinity
3-deazaadenosine	0.29 ± 0.06	37.3	-2.8	Adenosine	

Position 6					The 6-NH2 group contributes an average of 8.2 kJ/mol to binding of aminopurines
6-chloropurine riboside	15.4 ± 0.8	27.5	7.0	Adenosine	
Purine	18.1 ± 3.2	27.1	10.2	Adenine	
Purine riboside	17.1 ± 2.1	27.2	7.3	Adenosine	
Positions 6 and 1					The binding energies of positions 1 and 6 are additive, resulting in very low affinity for inosine and guanosine, and is estimated at 15.7 kJ/mol.
Guanosine	>500				
Inosine	>500				
2'-deoxyinosine	165 ± 23	21.6	16.3	2'-Deoxyadenosine	
1-deazapurine	131 ± 34	22.2	15.1	Adenine	
Positions 6 and 2					
	20 ± 9.2		7.6	Adenosine	Loss of affinity can be attributed solely to the substitution on position 2 (see above). The single substitution at the 6-amine position is therefore not (greatly) detrimental to binding, especially when the substitution is small or flexible.

	9.0 ± 1.7		5.7	Adenosine	
Position 7					
7-deazaadenosine (tubercidin)	3.8 ± 0.7	30.9	3.6	Adenosine	Small apparent contribution to binding from N7, though too small to represent a full hydrogen bond. The absence of N7, however, decreases the positive charge on N9.
Formycin A	36.5 ± 6.6	25.3	9.2	Adenosine	
Position 8					Substitutions at position 8 are detrimental to binding.
8-azidoadenosine	331 ± 142	19.9	14.6	Adenosine	
8-bromoadenosine	37.8 ± 8.2	25.2	9.2	Adenosine	
Position 9					
9-deazaadenosine	12.1 ± 3.2	28.1	6.4	Adenosine	Significant contribution of N9 to adenosine binding.
Ribose					Absence of the ribose or of just the 2'-hydroxyl group increases affinity by approximately 3 kJ/mol.
Adenine	0.30 ± 0.02	37.3	-2.8	Adenosine	
2'-deoxyadenosine	0.23 ± 0.04	37.9	-3.4	Adenosine	

Aromaticity					The aromaticity of the purines and diamidines contributes importantly to their high affinity binding of P2, as non-aromatic diamidines or diguanidines of similar length and flexibility as the aromatic diamidines display ~100-fold less affinity, corresponding to 10-11 kJ/mol in binding energy. Presumably π–π-bonds with aromatic amino acid residues are involved in substrate-transporter interactions.
	>200				
	45 ± 15	24.7	11.9	Pentamidine	
Pentamidine	0.37 ± 0.04	36.7			
Propamidine	1.9 ± 0.8	32.6			
Stilbamidine	2.4 ± 0.3	32.0			