

Supporting Information

Structure based prediction of subtype-selectivity for Adenosine receptor antagonists.

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Supporting Information includes:

- Figure SM1: full-length alignment for AR subfamily
- Figure SM2: set of 88 subtype specific AR antagonists used in the study
- A zip file with 88 ligand complexes with corresponding AR subtype models (PDB format).

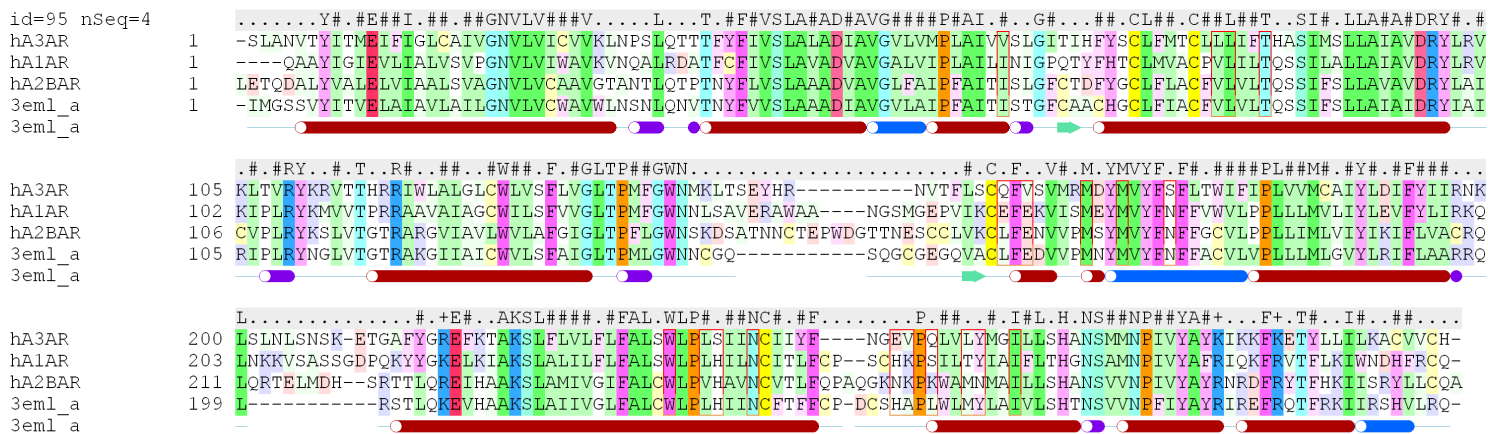
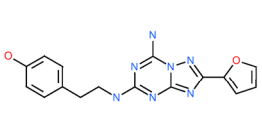
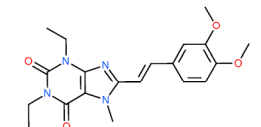
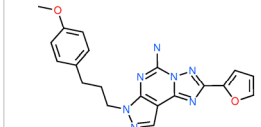
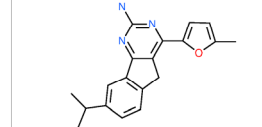
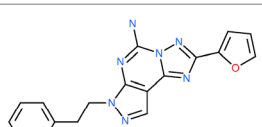
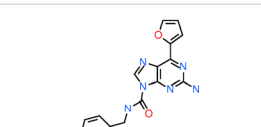
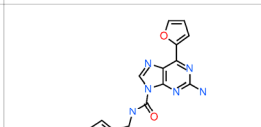
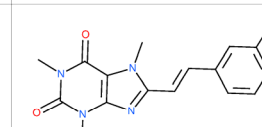
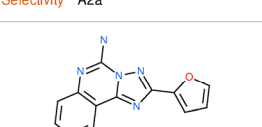
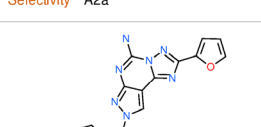
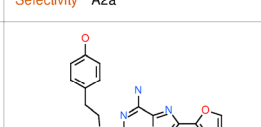
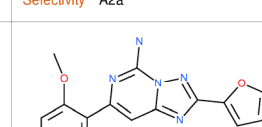
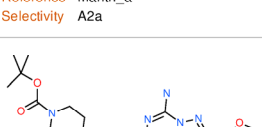
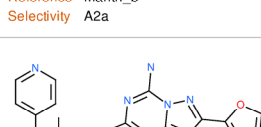
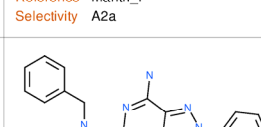
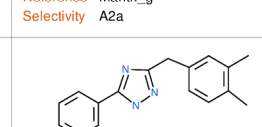
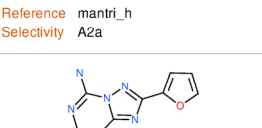
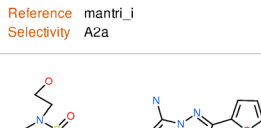
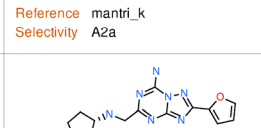
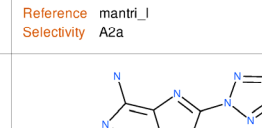
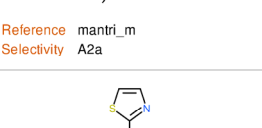
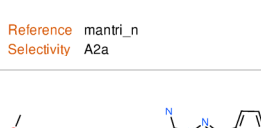
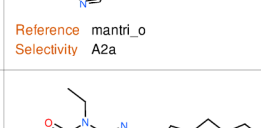

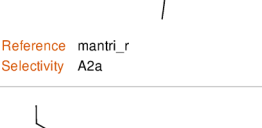



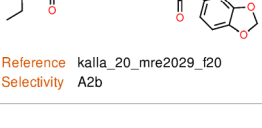
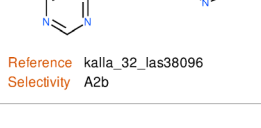
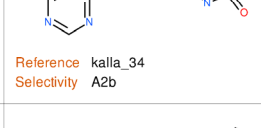

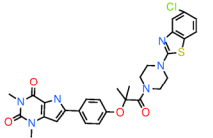
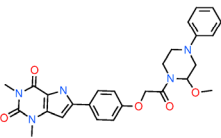
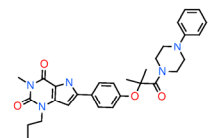
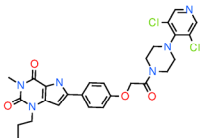
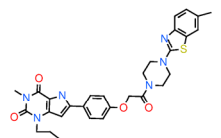
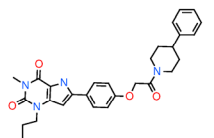
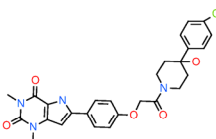
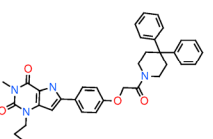
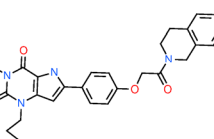
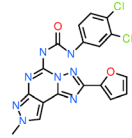
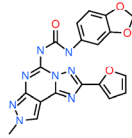
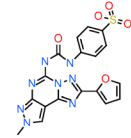
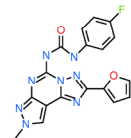
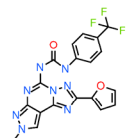
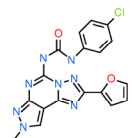
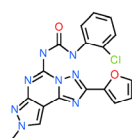
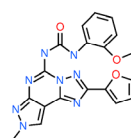
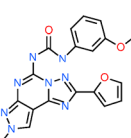
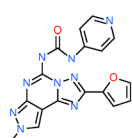
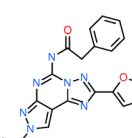
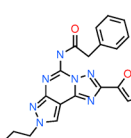
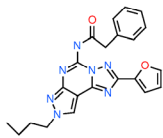
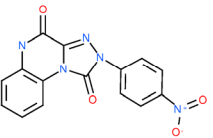
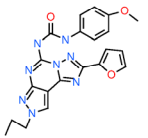
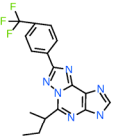


Figure SM1. Protein sequence alignment of all four human adenosine receptors, used to generate homology models. Red boxes highlight residues of the binding pocket within 6Å distance from ZM241385 compound in A2AR crystal structure (PDB code 3eml).

 <p>Reference jac0_zm241385 Selectivity A2a</p>	 <p>Reference jac0_kw6002 Selectivity A2a</p>	 <p>Reference jac0_sch442416 Selectivity A2a</p>	 <p>Reference jac0_mantri_e Selectivity A2a</p>
 <p>Reference jac0_sch58261 Selectivity A2a</p>	 <p>Reference jac0_ver6947 Selectivity A2a</p>	 <p>Reference jac0_ver7835 Selectivity A2a</p>	 <p>Reference jac0_csc Selectivity A2a</p>
 <p>Reference mantri_a Selectivity A2a</p>	 <p>Reference mantri_b Selectivity A2a</p>	 <p>Reference mantri_f Selectivity A2a</p>	 <p>Reference mantri_g Selectivity A2a</p>
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 <p>Reference mantri_r Selectivity A2a</p>	 <p>Reference mantri_s Selectivity A2a</p>	 <p>Reference kalla_10_cvt6883 Selectivity A2b</p>	 <p>Reference kalla_15_cvt6694 Selectivity A2b</p>
 <p>Reference kalla_20_mre2029_f20 Selectivity A2b</p>	 <p>Reference kalla_32_las38096 Selectivity A2b</p>	 <p>Reference kalla_34 Selectivity A2b</p>	 <p>Reference kalla_38_osip339391 Selectivity A2b</p>
 <p>Reference kalla_3_mrs1754 Selectivity A2b</p>	 <p>Reference kalla_4_psb1115 Selectivity A2b</p>	 <p>Reference kalla_5_cvt5440 Selectivity A2b</p>	 <p>Reference kalla_8_cvt6975 Selectivity A2b</p>

 <p>Reference stef_11 Selectivity A2b</p>	 <p>Reference stef_23 Selectivity A2b</p>	 <p>Reference stef_29 Selectivity A2b</p>	 <p>Reference stef_52 Selectivity A2b</p>
 <p>Reference stef_53 Selectivity A2b</p>	 <p>Reference stef_54 Selectivity A2b</p>	 <p>Reference stef_56 Selectivity A2b</p>	 <p>Reference stef_67 Selectivity A2b</p>
 <p>Reference stef_68 Selectivity A2b</p>	 <p>Reference stef_69 Selectivity A2b</p>	 <p>Reference stef_75 Selectivity A2b</p>	 <p>Reference stef_84 Selectivity A2b</p>
 <p>Reference bara_4c Selectivity A3</p>	 <p>Reference bara_4d Selectivity A3</p>	 <p>Reference bara_4e Selectivity A3</p>	 <p>Reference bara_4f Selectivity A3</p>
 <p>Reference bara_4g Selectivity A3</p>	 <p>Reference bara_4h Selectivity A3</p>	 <p>Reference bara_4i Selectivity A3</p>	 <p>Reference bara_4j Selectivity A3</p>
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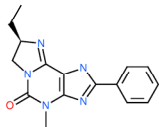
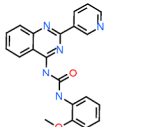
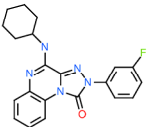
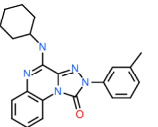
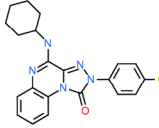
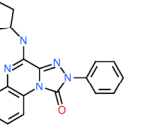
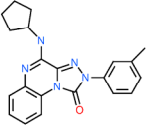
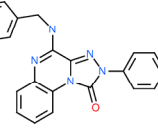
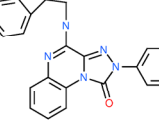
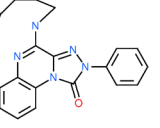
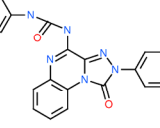
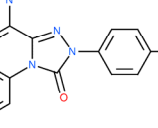
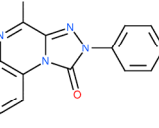
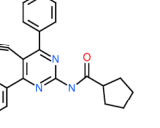
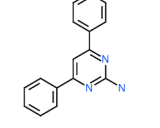
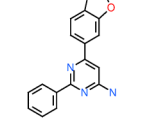
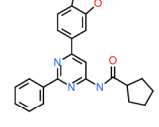
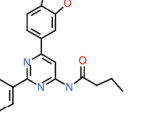
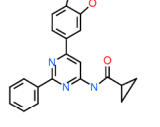
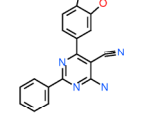
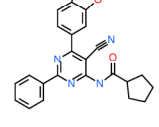
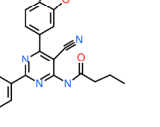
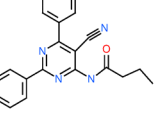
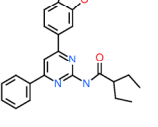
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 Reference coll_12 Selectivity A1	 Reference coll_13 Selectivity A1	 Reference coll_14 Selectivity A1	 Reference coll_16 Selectivity A1
 Reference coll_17 Selectivity A1	 Reference coll_18 Selectivity A1	 Reference coll_24 Selectivity A1	 Reference coll_5 Selectivity A1
 Reference coll_6 Selectivity A1	 Reference veld_27 Selectivity A1	 Reference veld_3 Selectivity A1	 Reference veld_43 Selectivity A1
 Reference veld_44 Selectivity A1	 Reference veld_45 Selectivity A1	 Reference veld_47 Selectivity A1	 Reference veld_52 Selectivity A1
 Reference veld_53 Selectivity A1	 Reference veld_54 Selectivity A1	 Reference veld_57 Selectivity A1	 Reference veld_7 Selectivity A1

Figure SM2. The set of 88 known subtype specific AR antagonists used in the study, comprised of 22 compounds for each AR subtype. The names of the compounds include the source reference and the compound number in the reference study, as well as the common name of the compound, if known. The reference codes are as follows: jaco¹, mantri², veld³, coll⁴, bara⁵, kalla⁶ and stef⁷.

1. Jacobson, K. A.; Gao, Z. G. Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov* **2006**, *5*, 247-264.
2. Mantri, M.; de Graaf, O.; van Veldhoven, J.; Goblyos, A.; von Frijtag Drabbe Kunzel, J. K.; Mulder-Krieger, T.; Link, R.; de Vries, H.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. 2-Amino-6-furan-2-yl-4-substituted nicotinitriles as A2A adenosine receptor antagonists. *J Med Chem* **2008**, *51*, 4449-4455.

3. van Veldhoven, J. P.; Chang, L. C.; von Frijtag Drabbe Kunzel, J. K.; Mulder-Krieger, T.; Struensee-Link, R.; Beukers, M. W.; Brussee, J.; AP, I. J. A new generation of adenosine receptor antagonists: from di- to trisubstituted aminopyrimidines. *Bioorg Med Chem* **2008**, *16*, 2741-2752.
4. Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Lucacchini, A. 1,2,4-Triazolo[4,3-a]quinoxalin-1-one: a versatile tool for the synthesis of potent and selective adenosine receptor antagonists. *J Med Chem* **2000**, *43*, 1158-1164.
5. Baraldi, P. G.; Bovero, A.; Fruttarolo, F.; Romagnoli, R.; Tabrizi, M. A.; Preti, D.; Varani, K.; Borea, P. A.; Moorman, A. R. New strategies for the synthesis of A3 adenosine receptor antagonists. *Bioorg Med Chem* **2003**, *11*, 4161-4169.
6. Kalla, R. V.; Zablocki, J. Progress in the discovery of selective, high affinity A(2B) adenosine receptor antagonists as clinical candidates. *Purinergic Signal* **2009**, *5*, 21-29.
7. Stefanachi, A.; Brea, J. M.; Cadavid, M. I.; Centeno, N. B.; Esteve, C.; Loza, M. I.; Martinez, A.; Nieto, R.; Ravina, E.; Sanz, F.; Segarra, V.; Sotelo, E.; Vidal, B.; Carotti, A. 1-, 3- and 8-substituted-9-deazaxanthines as potent and selective antagonists at the human A2B adenosine receptor. *Bioorg Med Chem* **2008**, *16*, 2852-2869.