SUPPORTING INFORMATION

Synthesis and Biological Evaluation of a New Series of 1,2,4-triazolo[1,5-*a*]-1,3,5-triazine as Human A_{2A} Adenosine Receptor Antagonists with Improved Water Solubility

Stephanie Federico,[#] Silvia Paoletta,[■] Siew Lee Cheong,[§] Giorgia Pastorin,[§] Barbara Cacciari,[≠] Stefano Stragliotto,[■] Karl Norbert Klotz,[▼] Jeffrey Siegel,[◆] Zhan-Guo Gao,[◆] Kenneth A. Jacobson,[◆] Stefano Moro*[■] and Giampiero Spalluto*[#]

[#]*Dipartimento di Scienze Farmaceutiche, Università di Trieste, Piazzale Europa 1, I-34127 Trieste, Italy*

[■]*Molecular Modeling Section (MMS), Dipartimento di Scienze Farmaceutiche, Università di Padova, via Marzolo 5, I-35131 Padova, Italy*

[§]*Department of Pharmacy, National University of Singapore, 3 Science Drive 2, Singapore 117543*

[≠]*Dipartimento di Scienze Farmaceutiche, Università degli Studi di Ferrara, via Fossato di Mortara 17-19, I-44100 Ferrara, Italy*

[▼]*Institut für Pharmakologie, Universität of Würzburg, D-97078 Würzburg, Germany*

[◆]*Molecular Recognition Section (MRS), Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA*

Contents of Supporting Information:

- **Table 1:** Elemental analyses of all newly synthetized adenosine antagonists.
- **Figures 1-3**

Table 1. Elemental analyses of all synthesized compounds.

compd	formula	MW	Calcd			Found		
			% C	%H	%N	%C	%H	%N
8	$C_{12}H_{13}N_7O$	271.28	53.13	4.83	36.14	52.78	4.77	35.99
7	$C_{17}H_{22}N_8O_3$	386.41	52.84	5.74	29.00	52.91	5.72	29.04
11	$C_{21}H_{28}N_8O_3$	440.50	57.26	6.41	25.44	57.45	6.46	25.71
10	$C_{15}H_{20}N_8O_3$	360.37	49.99	5.59	31.09	50.09	5.66	30.89
12	$C_{16}H_{22}N_8O_3$	374.40	51.33	5.92	29.93	51.15	5.78	29.78
13	$C_{18}H_{26}N_8O_3$	402.45	52.72	6.51	27.84	52.88	6.53	28.00
14	$C_{19}H_{28}N_8O_5$	448.48	50.88	6.29	24.99	50.66	6.09	24.76
37	$C_{22}H_{33}N_9O_5$	503.55	52.47	6.61	25.03	52.65	6.65	25.13
38	$C_{16}H_{19}N_9O_5F_6$	531.31	36.17	3.60	23.72	36.25	3.54	23.81
9	$C_{14}H_{15}N_8O_3F_3$	432.31	38.90	3.50	25.92	39.02	3.53	25.90
31	$C_{18}H_{23}N_8O_3F_3$	456.42	47.37	5.08	24.55	47.51	5.12	24.62
30	$C_{12}H_{13}N_8O_3F_3$	374.28	38.51	3.50	29.94	38.38	3.44	29.89
32	$C_{13}H_{15}N_8O_3F_3$	388.31	40.21	3.89	28.86	40.09	3.70	28.73
33	$C_{15}H_{19}N_8O_3F_3$	416.36	43.27	4.60	26.91	43.11	4.63	26.87
20	$C_{15}H_{22}N_8O_5F_3$	450.37	40.00	4.70	24.88	39.78	4.55	24.57
15	$C_{19}H_{20}N_8O$	376.42	60.63	5.36	29.77	60.74	5.37	29.83
16	$C_{19}H_{19}N_8OCl$	410.86	55.54	4.66	27.27	55.31	4.72	27.40
17	$C_{19}H_{19}N_8OF$	394.41	57.86	4.86	28.41	57.55	4.83	28.65
18	$C_{19}H_{19}N_8OCl$	410.86	55.54	4.66	27.27	55.28	4.66	27.18
19	$C_{19}H_{19}N_8OBr$	455.31	50.12	4.21	24.61	49.97	4.14	24.48
20	$C_{17}H_{22}N_8O_2$	370.41	55.12	5.99	30.25	55.20	6.03	30.31

Figure 1: Hypothetical binding mode of compound **28** obtained after docking simulations inside the hA_{2A} AR binding site. The pose is viewed from the membrane side facing TM6, TM7 and TM1. The view of TM7 is partially omitted. Side chains of some amino acids important for ligand recognition and H-bonding interactions are highlighted. Hydrogen atoms are not displayed.

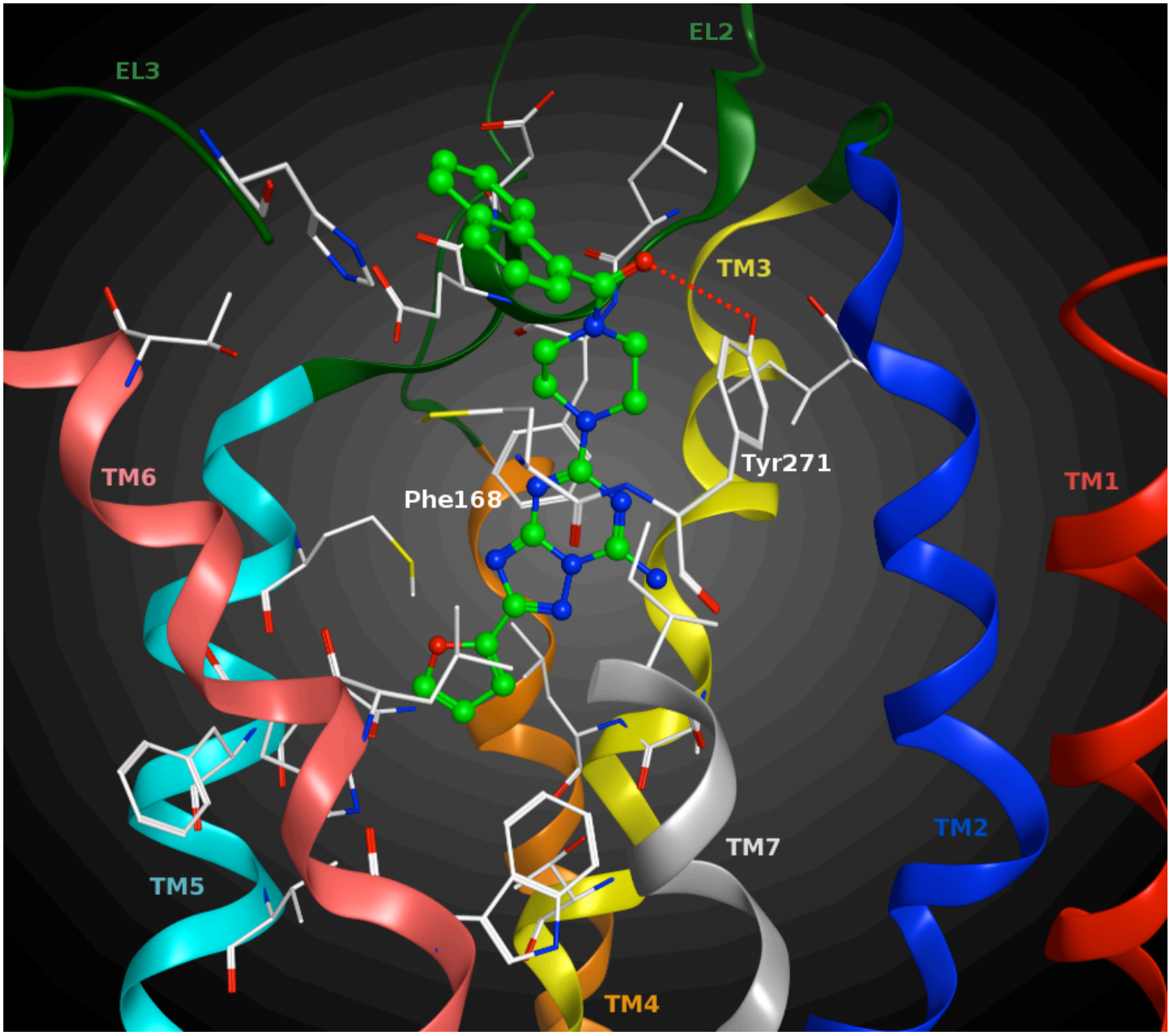

Figure 2: Hypothetical binding mode of compound **37** obtained after docking simulations inside the hA_{2A} AR binding site. The pose is viewed from the membrane side facing TM6, TM7 and TM1. The view of TM7 is partially omitted. Side chains of some amino acids important for ligand recognition and H-bonding interactions are highlighted. Hydrogen atoms are not displayed.

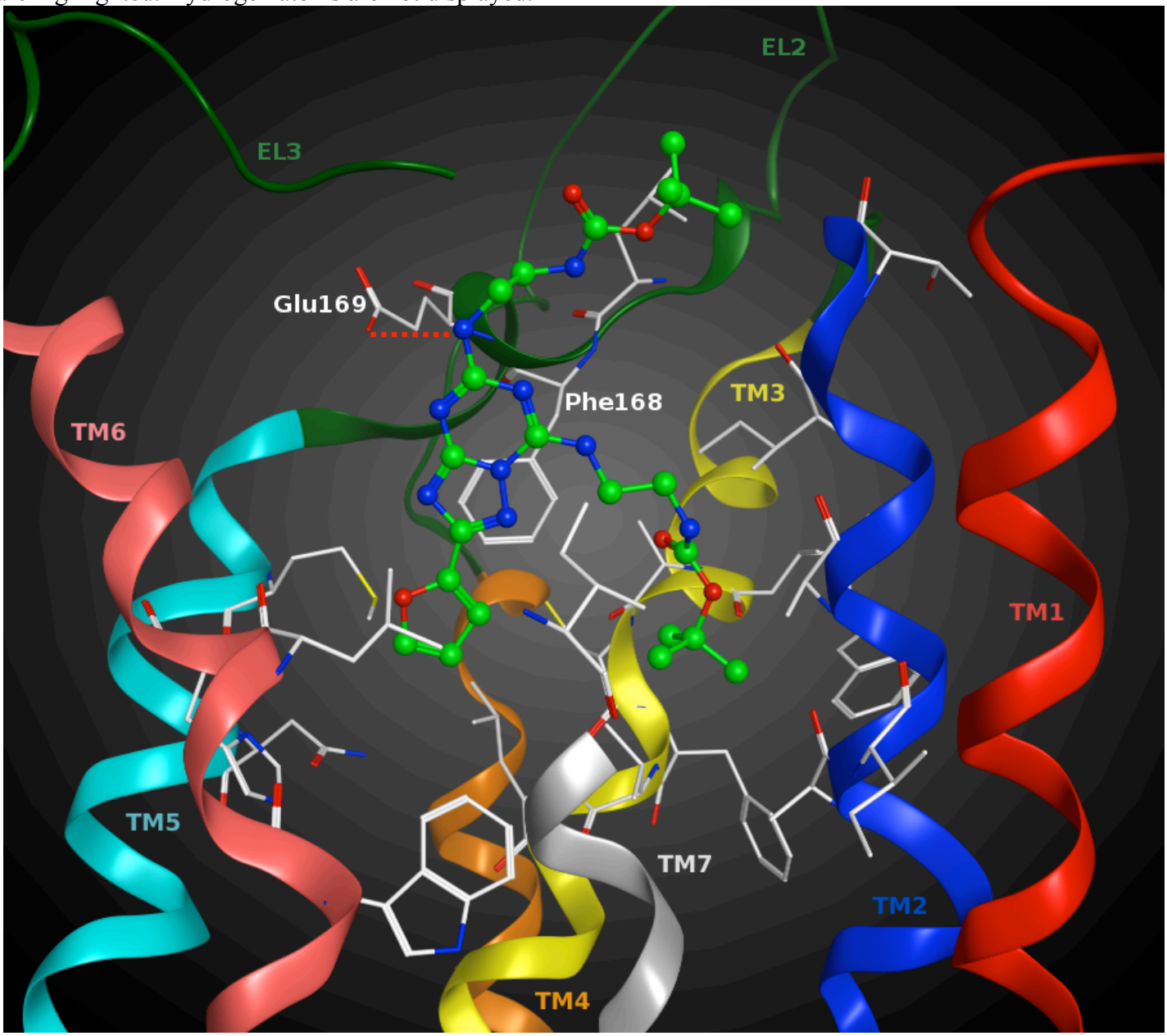

Figure 3: Hypothetical binding mode of compound **43** obtained after docking simulations inside the hA_{2A} AR binding site. The pose is viewed from the membrane side facing TM6, TM7 and TM1. The view of TM7 is partially omitted. Side chains of some amino acids important for ligand recognition and H-bonding interactions are highlighted. Hydrogen atoms are not displayed.