Supporting Information

Probing Distal Regions of the A_{2B} Adenosine Receptor by Quantitative Structure - Activity Relationship Modeling of Known and Novel Agonists

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Contents:

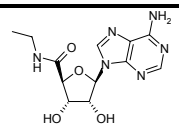
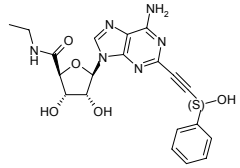
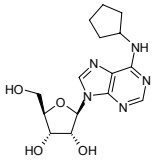
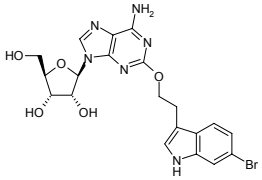
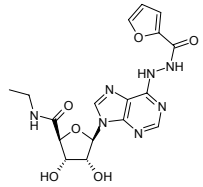
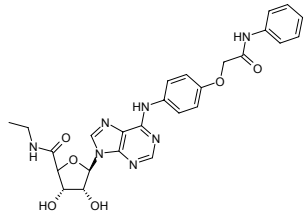
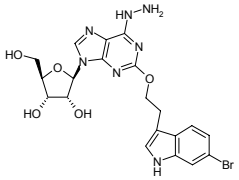
Table S1.

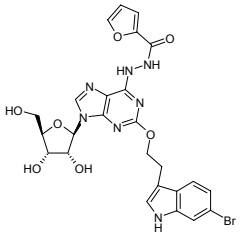
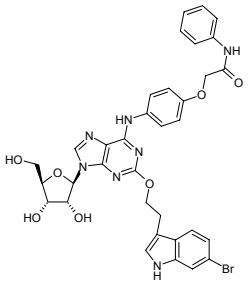
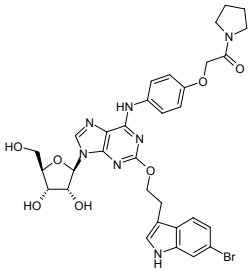
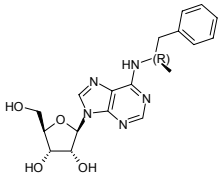
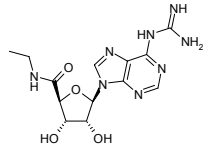
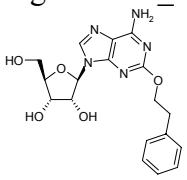
	CoMFA fields		CoMSIA fields				
	Steric	**Electrostatic**	**H-bond donor**	**H-bond acceptor**	**Steric**	**Electrostatic**	**Hydrophobic**
R^2	0.908	0.450	0.901	0.800	0.829	0.764	0.852
Q^2	0.581	0.395	0.504	0.558	0.575	0.538	0.682
SEE	0.262	0.613	0.283	0.385	0.356	0.414	0.324
C	5	1	9	5	5	4	3
F	94	43	44	38	46	40	96

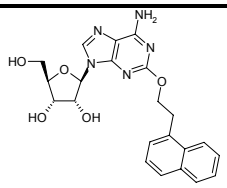
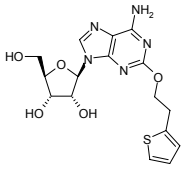
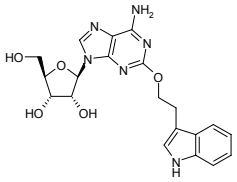
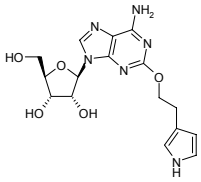
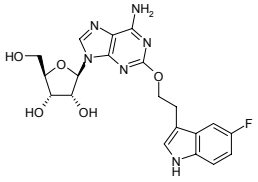
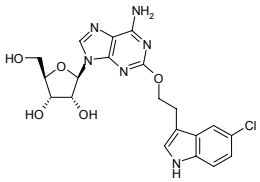
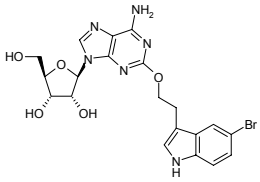
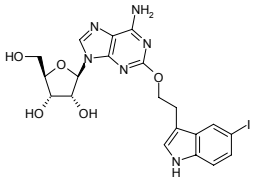
Lattice space of 1Å, attenuation factor, $\alpha = 0.5$, and MNDO atomic charges were used.

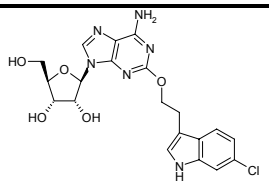
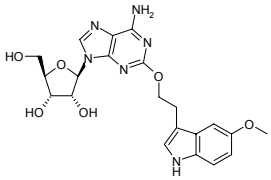
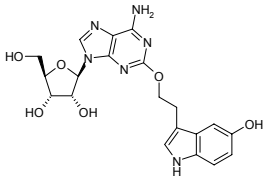
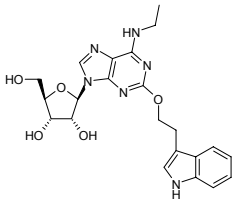
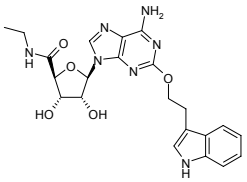
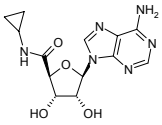
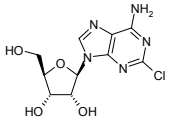
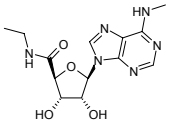
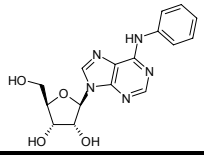
SEE – standard error of estimation. C – PLS components.

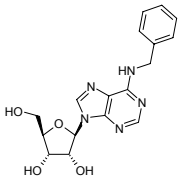
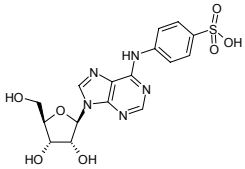
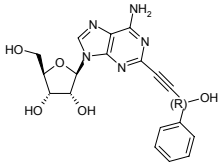
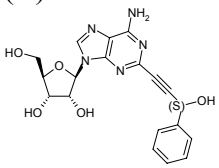
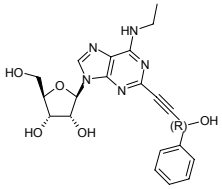
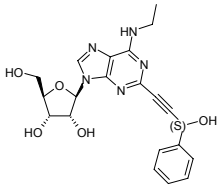
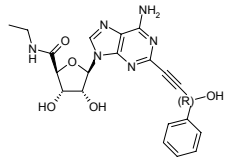
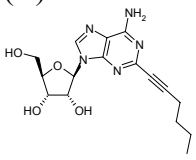
Table S2.

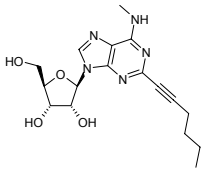
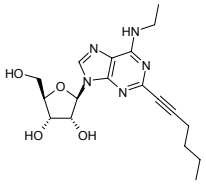
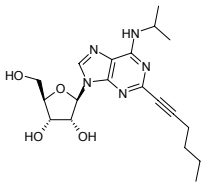
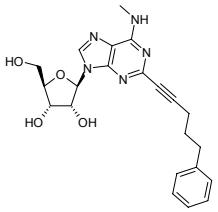
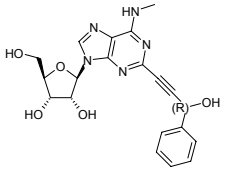
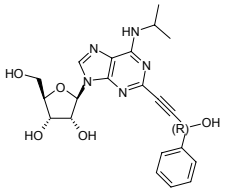
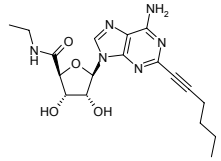
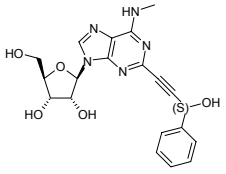
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
1	 NECA	-2.146[1] -3.491[2] -3.380[3,4] -2.204[5] -2.190[6]	0.000	0.125	-0.125
2	 (S)-PHPNECA	-2.342	1.038	0.904	0.134
3	 CPA	-4.279	-1.816	-1.704	-0.112
4	 MRS3997	-2.107	0.039	0.056	-0.017
5		-1.914	0.290	0.171	0.119
6		-0.863	1.327	1.008	0.319
7	 MRS5098	-2.241	-0.094	-0.500	0.406

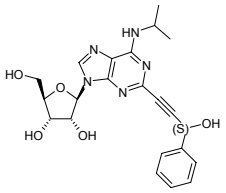
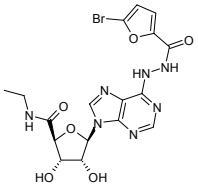
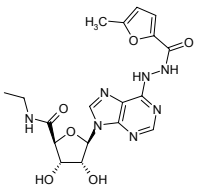
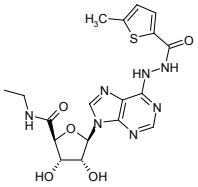
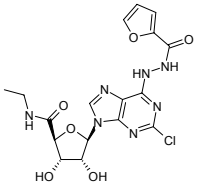
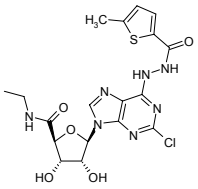
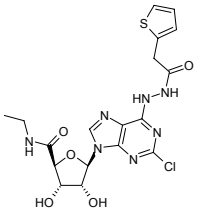
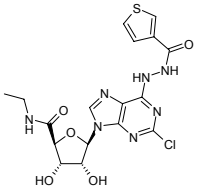
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
8	 MRS5101	-2.461	-0.315	-0.083	-1.161
9	 MRS5099	-2.155	0.009	0.802	0.793
10	 MRS5100	-2.985	-0.838	-0.422	-0.416
11*	 R-PIA	-3.225	-1.079	-0.681	-0.398
12	 6-guanidino_NECA	-1.736	0.410	0.129	0.281
13		-3.543	-1.397	-1.240	-0.157

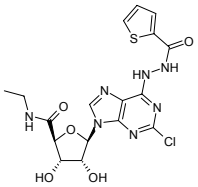
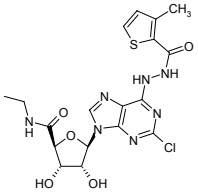
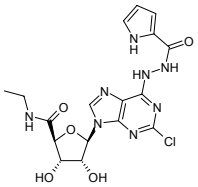
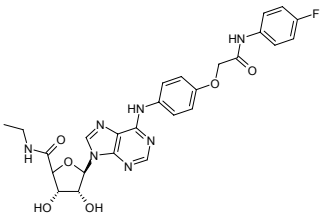
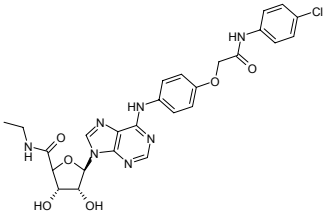
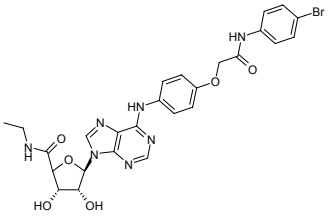
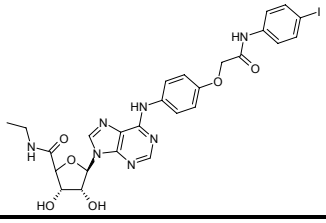
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
14*		-3.158	-1.012	-0.690	-0.322
15		-3.250	-1.104	-1.158	0.054
16		-2.476	-0.330	-0.399	0.069
17		-3.412	-1.266	-1.238	-0.028
18*		-2.885	-0.739	-0.807	0.068
19*		-3.339	-1.192	-0.868	-0.324
20		-2.562	-0.416	-0.876	0.460
21		-3.272	-1.126	-0.919	-0.207

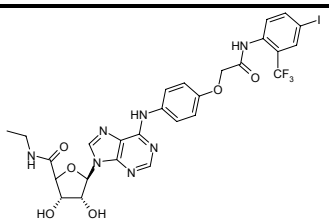
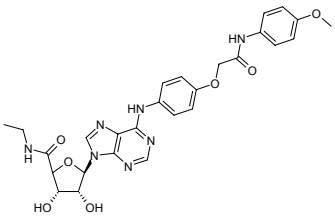
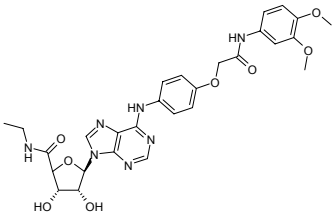
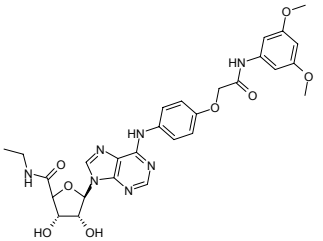
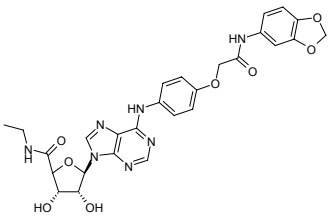
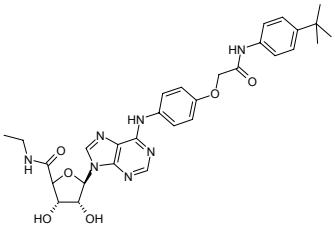
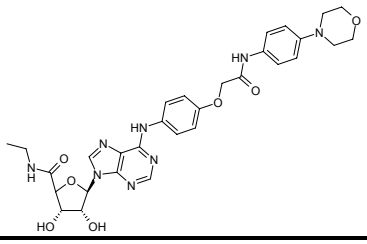
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
22		-2.335	-0.188	-0.166	-0.022
23*		-3.097	-0.951	-0.711	-0.240
24		-2.952	-0.806	-0.773	-0.033
25		-3.515	-1.368	-1.232	-0.136
26		-2.995	-0.849	-0.951	0.102
27*	 NCPCA	-3.491	-0.233	0.129	-0.362
28*	 2Cl-Ado	-3.724	-0.889	-1.016	0.127
29*		-4.380	-0.787	-0.216	-0.571
30		-5.308	-1.308	-1.298	-0.010

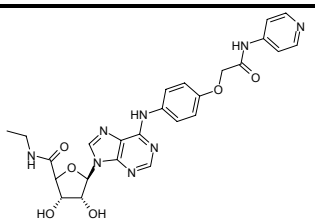
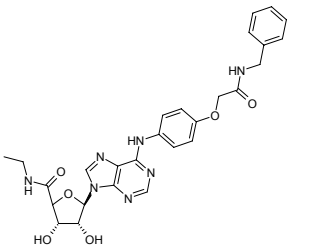
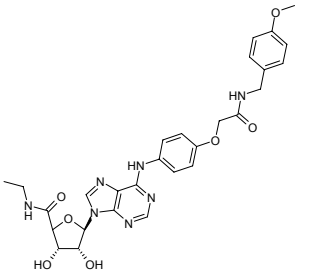
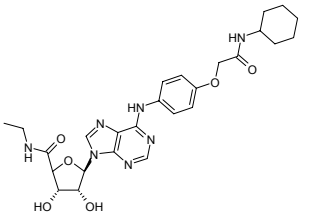
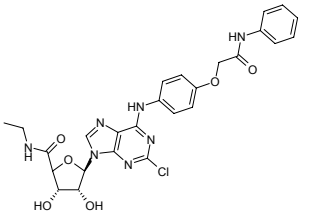
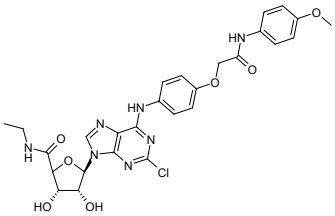
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
31		-4.799	-1.491	-1.596	0.105
32	 SPA	-4.982	-1.225	-1.285	0.060
33	 (R)-PHPAdo	-3.792	-0.412	-0.461	0.049
34	 (S)-PHPAdo	-2.964	0.416	0.507	-0.091
35		-3.959	-0.579	-0.676	0.097
36*		-2.863	0.517	0.354	0.163
37	 (R)-PHPNECA	-3.380	0.000	0.131	-0.131
38	 HEADO	-5.000	-1.620	-1.482	-0.138

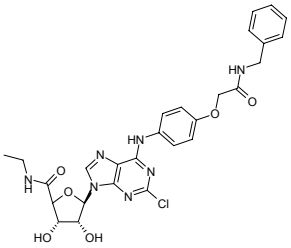
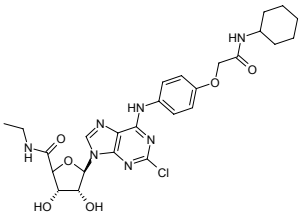
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
39*		-5.000	-1.620	-2.036	0.416
40		-5.000	-1.620	-1.846	0.226
41		-5.000	-1.620	-1.680	0.060
42		-5.000	-1.620	-1.588	-0.032
43		-5.000	-1.620	-1.078	-0.542
44		-3.949	-0.569	-0.890	0.321
45		-3.785	-0.405	-0.385	-0.020
	HENECA				
46		-3.415	-0.035	-0.031	-0.004

#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
47		-2.982	0.398	0.419	-0.021
48		-2.567	-0.363	-0.082	-0.281
49*		-2.356	-0.152	-0.033	-0.119
50		-2.436	-0.232	-0.185	-0.047
51		-2.322	-0.118	-0.120	0.002
52		-2.243	-0.039	-0.066	0.027
53*		-2.780	-0.576	-0.059	-0.517
54		-2.653	-0.449	-0.451	0.002

#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
55		-2.301	-0.097	-0.166	0.069
56		-2.532	-0.327	-0.313	-0.014
57*		-2.555	-0.351	-0.658	0.307
58		-1.182	1.009	1.085	-0.076
59*		-1.090	1.100	0.966	0.134
60		-1.021	1.169	1.245	-0.076
61		-1.480	0.710	0.756	-0.046

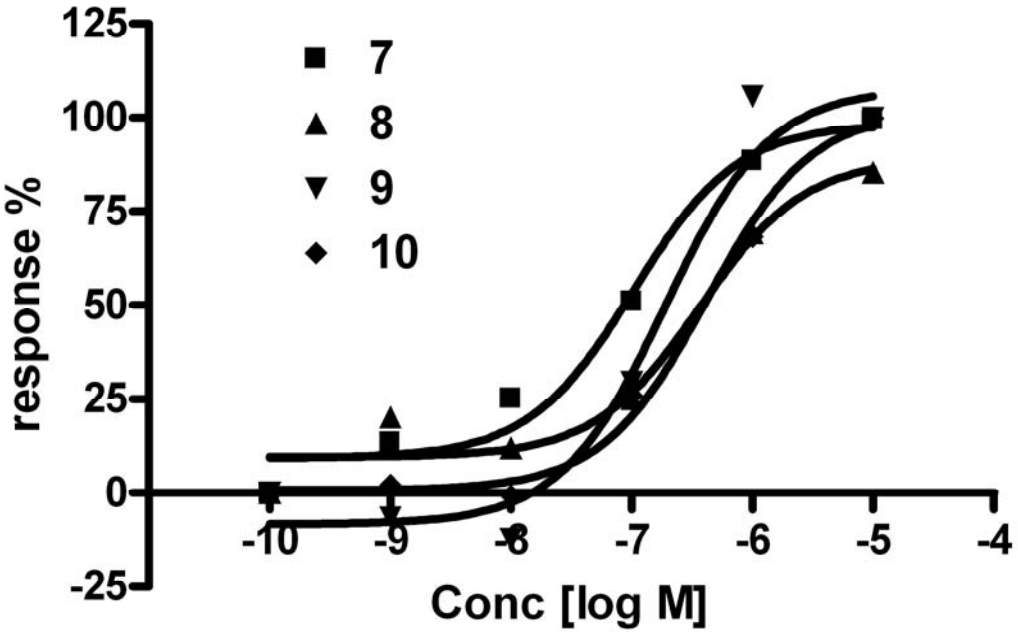
#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
62		-2.029	0.161	0.157	0.004
63*		-1.511	0.680	0.531	0.149
64		-1.657	0.533	0.373	0.160
65		-1.729	0.461	0.462	-0.001
66		-1.550	0.640	0.719	-0.079
67*		-1.215	0.976	0.246	0.730
68		-2.477	-0.287	-0.410	0.123

#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
69		-1.509	0.681	0.725	-0.044
70		-2.176	0.014	-0.020	0.034
71*		-2.380	-0.190	0.111	-0.301
72		-2.498	-0.308	-0.134	-0.174
73		-1.629	0.561	0.614	-0.053
74		-2.556	-0.366	-0.026	-0.340

#	Structure	pEC_{50}	RP, exp	RP, pred	ΔRP
75*		-2.243	-0.053	-0.387	0.334
76		-2.480	-0.290	-0.470	0.180

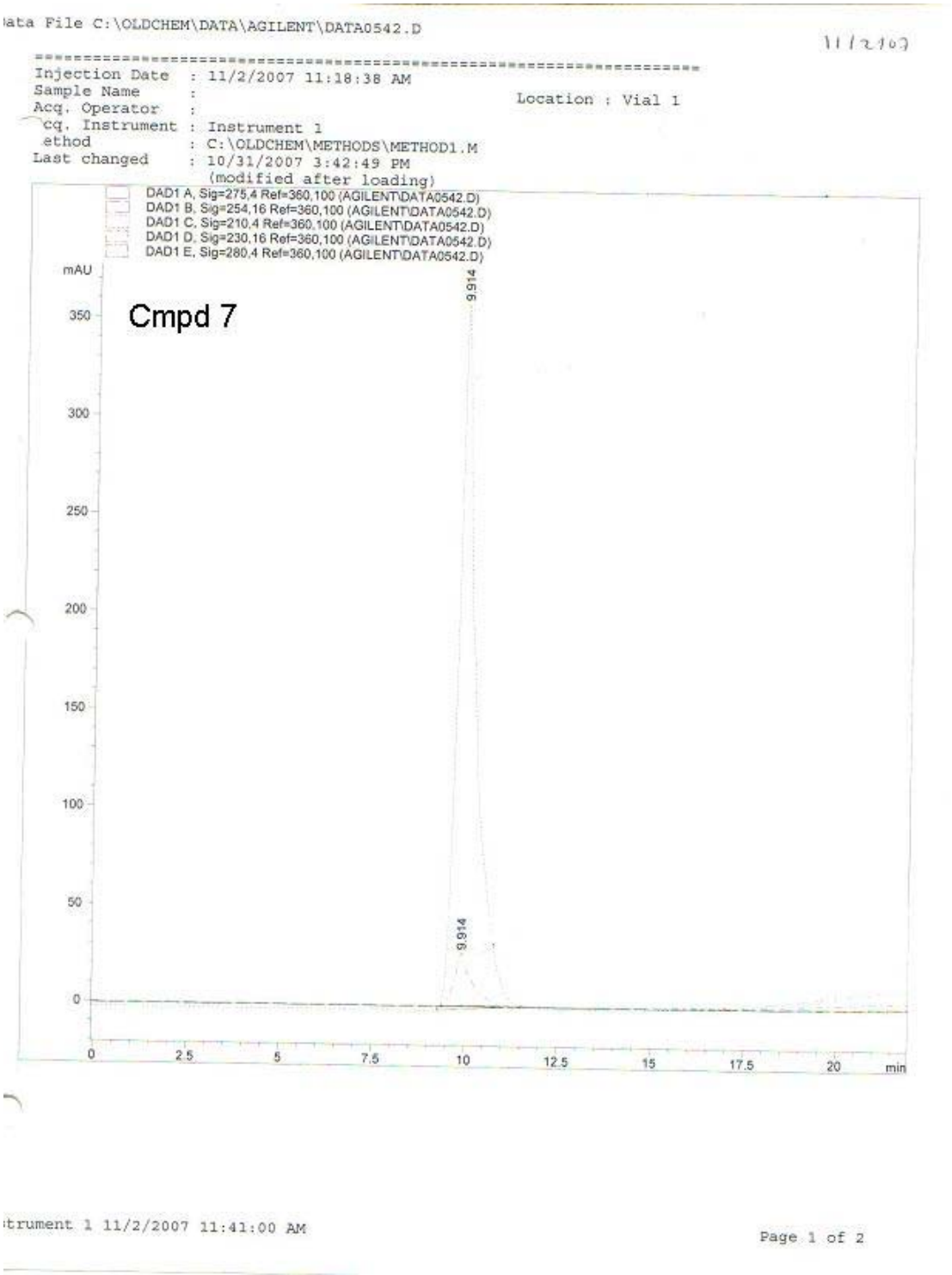
The values of pEC_{50} were calculated from experimental values of EC_{50}: compounds **4, 11 – 26** – ref. 1; **3, 27 – 32** – ref. 2; **2**, **33 – 47** – refs3 and 4; **5**, **48 – 57** – ref 5; **6**, **58 – 76** – ref 6; compounds **7 – 10** were proposed in this study. RP – NECA related potency, RP = pEC_{50} $(comp)_i$ – pEC_{50} $(NECA)_i$, where *i* represents the same reference number. The RP values were calculated with the final CoMFA/CoMSIA **Model 3**. * – compounds included to the test set, all other compounds with exception of **7 – 10** were included to the training set. ΔRP = $RP_{exp} – RP_{pred.}$

Figure S1. Pharmacological Data: cAMP Responses in A_{2B} AR-expressing CHO Cells.[a]



[a] 100% represents the maximal response to 1.

Figure S2. HPLC traces for analysis of nucleoside derivatives **7** – **10** (refer to main text for conditions)



Data File C:\OLDCHEM\DATA\AGILENT\DATA0546.D

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Acq. Instrument : Instrument 1
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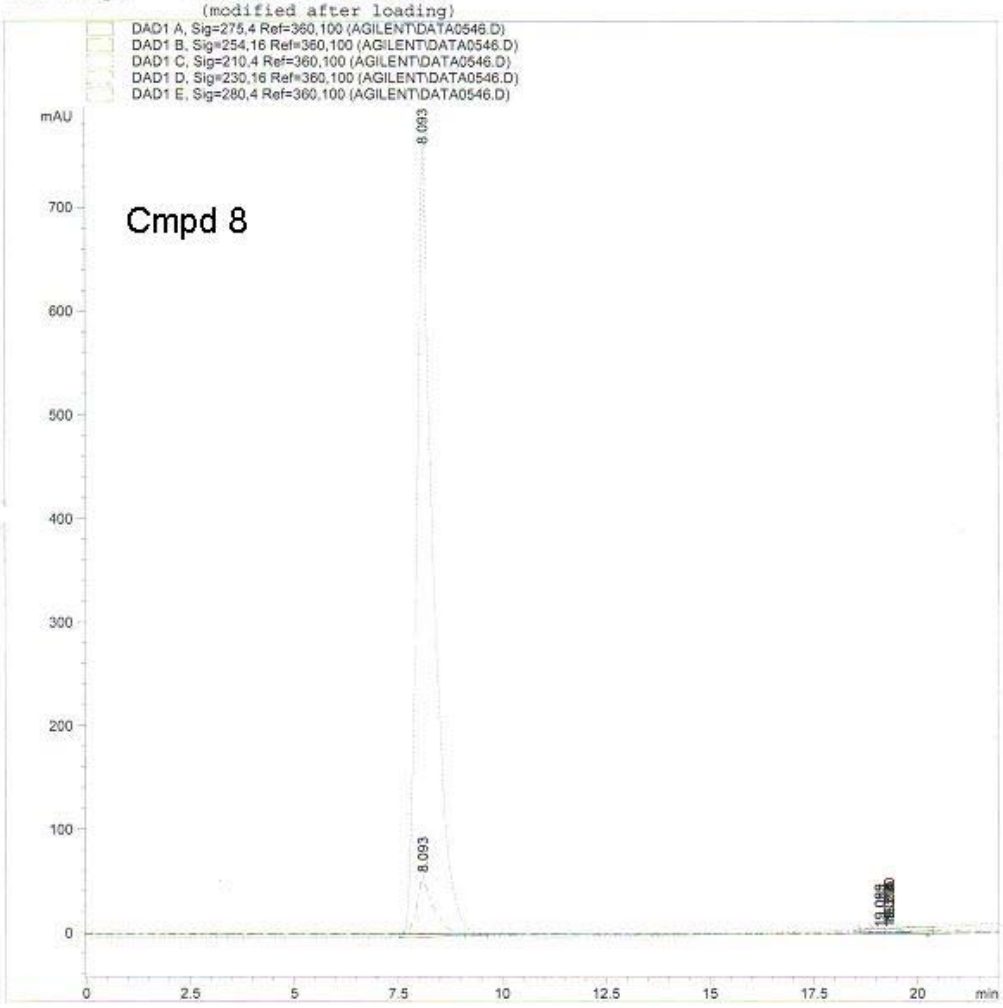

Data File C:\OLDCHEM\DATA\AGILENT\DATA0545.D

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Acq. Instrument : Instrument 1
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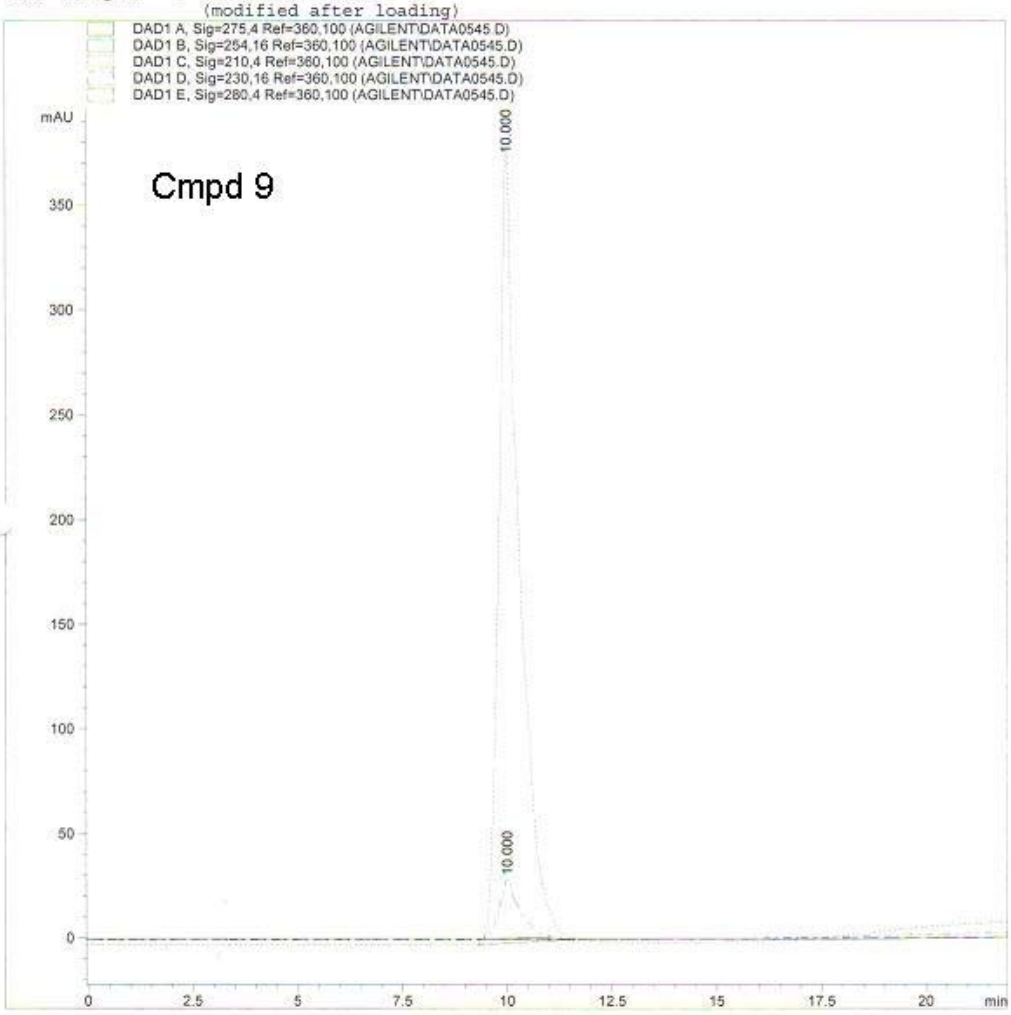

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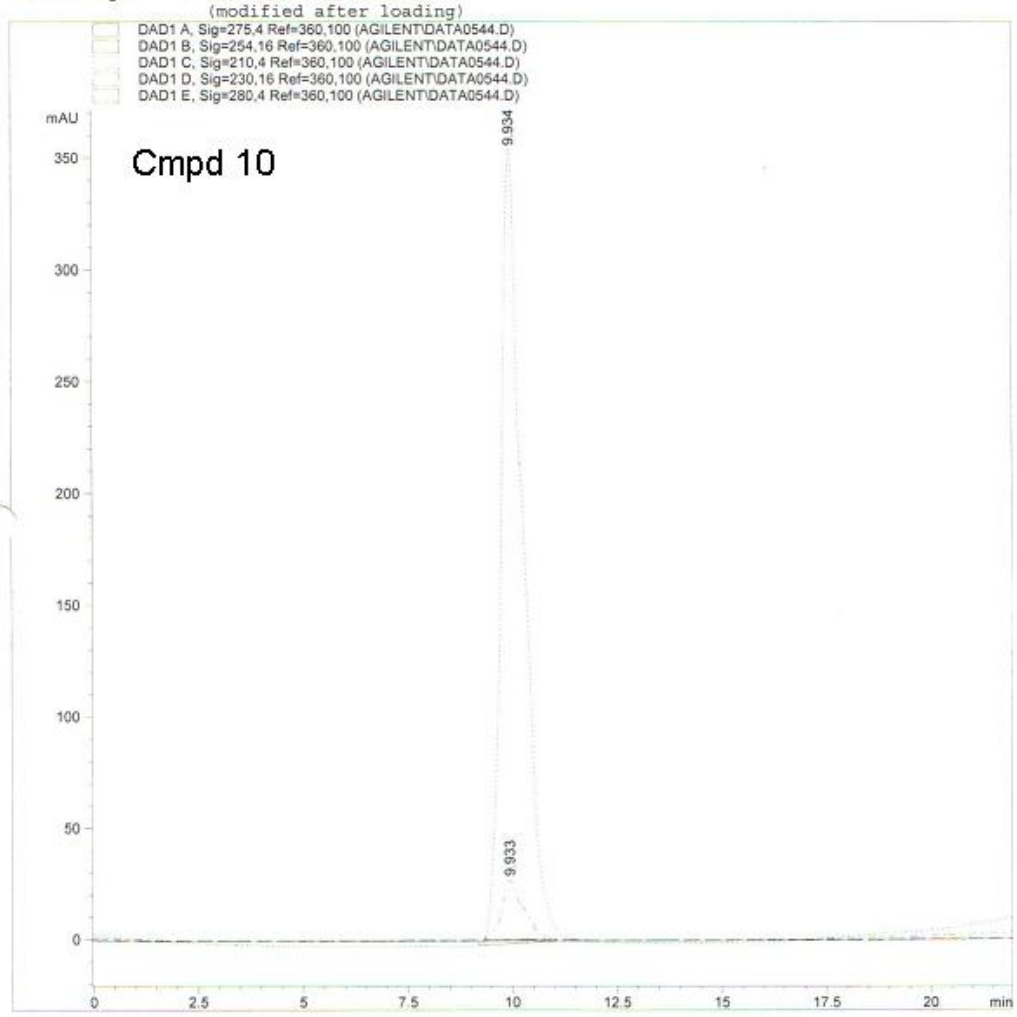

References:

1. Hayamitsu, A., et al., *J. Med. Chem.*, **2007**, *50*, 1810-1827
2. de Zwart, M., et al., *Nucl. Nucl. Nucl. Acids*, **1998**, *17*, 969-985
3. Vittori S., et al., *Nucl. Nucl. Nucl. Acids.* **2004**, *23*, 471-481
4. Volpini R., et al., *J. Med. Chem*. **2002**, *45*, 3271-3279.
5. Baraldi P.G, et al., *J. Med. Chem*. **2007**, *50*, 374-308.
6. Baraldi P.G., et al., *Bioorg. Med. Chem.*, **2007**, *15*, 2514-2527