Supporting Information

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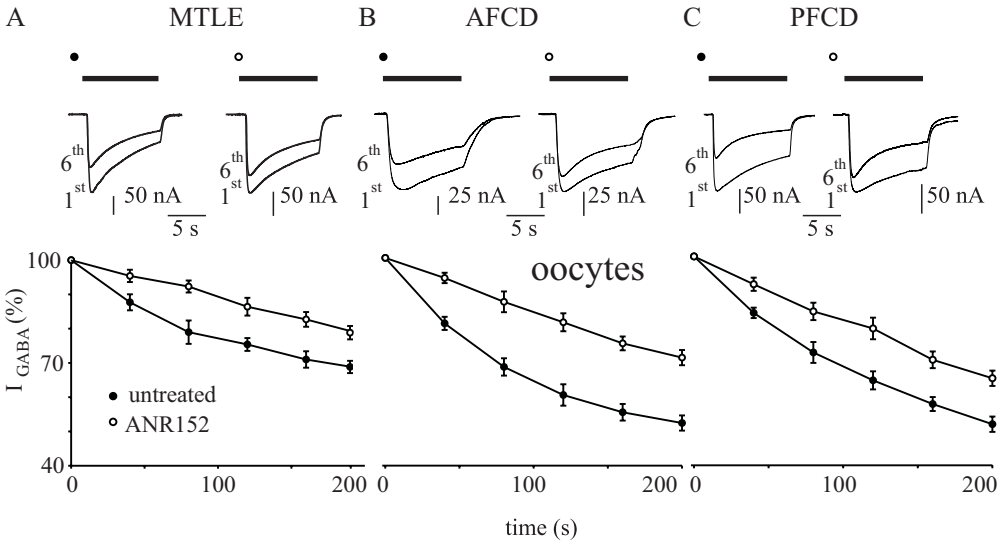

Fig. S1. The A_{2A} antagonist ANR152 (100 nM) decreases I_{GABA} desensitization in oocytes injected with human epileptic cortex membranes as indicated. (*A*) (*Top*) Current traces elicited by the first and sixth GABA applications to single oocytes, representative of 11 microinjected with MTLE membranes (4 frogs; patients 2 and 3). Holding potential, −60 mV. (*A*) (*Bottom*) Time courses averaged from 11 oocytes before (filled circles) and after a 1-h treatment with ANR152 (open circles). I_{GABA} values were normalized to the first I_{GABA} peak current, with I_{GABA} amplitudes ranging from −175 ± 11 nA in untreated oocytes to −162 ± 9 nA after ANR152 treatment ($P > .05$); 500 μM GABA, 10 s duration, 40 s interval. (*B*) (*Top*) Representative currents as in (*A*) in oocytes injected with AFCD membranes representative of 9 experiments (2 frogs, patients 10 and 12). (*Bottom*) Time courses averaged from 9 oocytes treated as indicated. I_{GABA} was normalized to −81.3 ± 4 nA (filled circles) and −90.5 ± 2 nA (open circles) ($P > .05$). (*C*) (*Top*) Representative currents as n (*A*) in oocytes injected with PFCD membranes representative of 8 experiments (2 frogs, patient 6). (*Bottom*) Time courses averaged from 8 oocytes treated as indicated. I_{GABA} was normalized as in (*A*) to −169 ±10 nA (filled circles) and −140 ± 9 nA (open circles) ($P > .02$). Note that at a concentration of 100 nM, ANR152 interferes with A_1 activity (see Table 2).

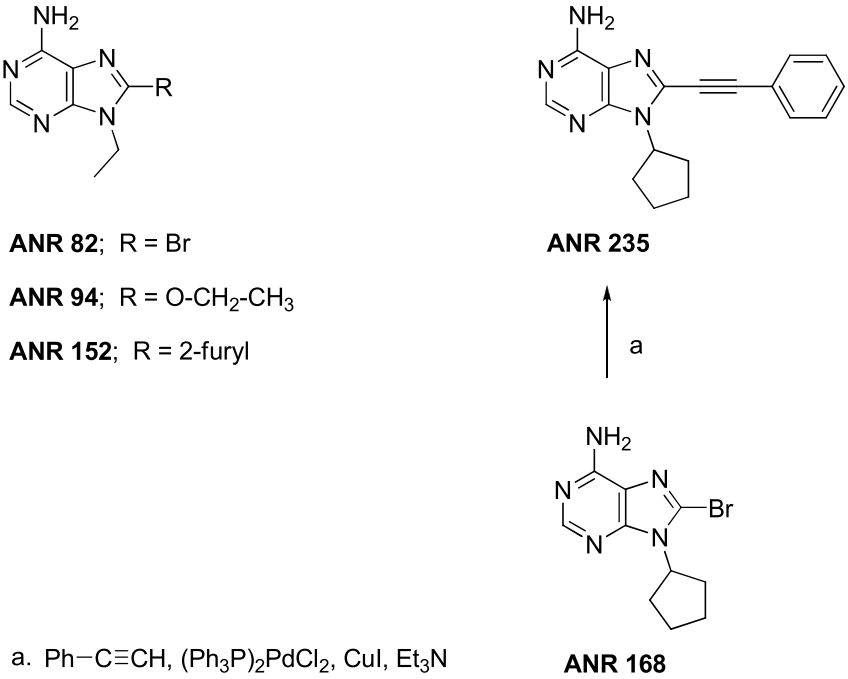

Fig. S2. Adenine derivative structures and ANR 235 synthetic scheme.

Table S1. Clinical and neurophysiological characteristics of epileptic patients

Patient	Sex	Age	Age at onset of epilepsy	MRI findings	Epileptogenic zone	Surgery	Histopathology
1	F	37 years	12 years	R-T-Mes	R-T-Mes-Lat	ETL	MES
2	M	42 years	15 years	R-T-Mes	R-T-Mes-Lat	ETL	MES
3	M	40 years	1 year	L-T-Mes	L-T-Mes-Lat	ETL	MES
4	F	38 years	19 years	R-T-Mes	R-T-Mes-Lat	ETL	MES
5	M	18 years	11 years	R-T-Mes	R-T-Mes-Lat	ETL	MES
6	F	3 months	1 month	R-T-FCD R-T-Mes-Lat	LES	FCD IIA	
7	M	2 years	0.5 month	R-T-FCD	R-T-Mes-Lat	LES	FCD IIB
8	M	5 years	4 years	R-F-FCD	R-F	LES	FCD IIA
9	F	12 years	3 years	R-T-FCD	R-T-Mes-Lat	LES	FCD IIA
10	M	48 years	6 years	L-T-FCD	L-T-Mes-Lat	LES	FCD IIA
11	F	38 years	19 years	R-T-FCD	R-T-Mes-Lat	ETL	FCD IA
12	F	19 years	11 years	R-T-FCD	R-T-Mes-Lat	ATL	FCD IIA
13	M	61 years	16 years	R-T-Ant	R-T-Mes-Ant	ATL	MES
14	F	57 years	9 years	L-T-Ant	L-T-Mes-Ant	ATL	MES
15	M	33 years	5 years	L-T-Mes	L-T-Mes-Lat	ETL	MES
16	F	32 years	12 years	R-T-Mes	R-T-Mes-Lat	ETL	MES
17	M	20 years	8 years	L-T-Mes	L-T-Mes-Lat	ETL	MES
18	F	50 years	12 years	L-T-Ant	L-T-Mes-Ant	ATL	MES
19	F	44 years	17 years	L-T-Ant	L-T-Mes-Ant	ATL	MES
20	F	25 years	11 years	R-F-FCD	R-F	LES	FCD IIB
21	F	21 years	24 years	L-T-FCD	L-T-Mes-Lat	LES	FCD IIB
22	M	22 years	5 months	L-T-Mes	L-T-Mes-Lat	LES + ETL	G
23	M	13 years	2 months	L-T-Ant	R-T-Mes-Ant	ATL	G

T, temporal; F, frontal; L, left; R, right; Lat, lateral; Mes, mesial; Ant, anterior; ETL, extensive temporal lobectomy; LES, lesionectomy; ATL anterior-temporal lobectomy; MES, hippocampal mesial sclerosis; G, ganglioglioma (grade I).

Table S2. Affinities of 8-substituted-9-ethyladenines in radioligand binding assays to human adenosine A_1, A_{2A}, and A_3 receptors

	K_i, nM (95% CI)			Selectivity	
Compound	K_i A_1	K_i A_{2A}	K_i A_3	A_1/A_{2A}	A_3/A_{2A}
ANR82	280 (250–320)	52 (24–110)	27,800 (22,300–34,700)	5	535
ANR94	2,400 (2,100–2,600)	46 (24–91)	21,000 (11,000–41,000)	52	457
ANR152	24 (16–34)	3.7 (3.0–4.6)	4,700 (2,900–7,600)	6	1,270
				A_1/A_3	A_{2A}/A_3
ANR235	3,320 (3,082–3,580)	1,320 (871–1,990)	30 (18–50)	111	44

Table S3. The A_{2A} antagonist ANR94 specifically modulates $GABA_A$ receptors in human patch-clamped pyramidal neurons in temporal slices obtained from patients with epileptic low-grade glioma

Drug treatment (dose)	Tested neurons [patients]	I_{GABA}, %, before treatment (*n*)	I_{GABA}, %, after treatment	*P*
MTLE				
ANR94 (100 nM)	10 [13–15]	72 ± 4*	69 ± 4*	>0.5
Epileptic periglioma tissue				
ANR94 (100 nM)	3 [22]	46 ± 4 (**3**)	59 ± 6	<0.05
ANR94 (100 nM)	5 [23]	85 ± 4 (**5**)	**65 ± 3**	<0.05

I_{GABA} (%) values represent the tenth I_{GABA} amplitude normalized to the first of the rundown protocol. *n*, number of oocytes responsive to AR antagonists. Set of cells in which rundown increases and *n* are in bold. *, Not significantly different.