

## Supporting Information

Discovery of

2-(2-Oxo-1-Phenyl-5-Pyridin-2-yl-1,2-Dihydropyridin-3-yl)Benzonitrile

(Perampanel): A Novel, Noncompetitive

$\alpha$ -Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropanoic Acid (AMPA)

Receptor Antagonist

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**Table s1.** HPLC Purity Data for Biologically Tested Compounds

Compound No.	Formula (M)	HRMS (Calcd) [M+H] <sup>+</sup>	HRMS (Found)	Retention time, t <sub>R</sub> (min)	% Purity (254 nm)
<b>6</b>	C <sub>23</sub> H <sub>15</sub> N <sub>3</sub> O	350.1288	350.1281	5.14	>99
<b>8a</b>	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	253.0972	253.0967	5.56	>99
<b>8b</b>	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	267.1128	267.1122	5.61	>99
<b>8c</b>	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	259.1441	259.1434	5.94	>99
<b>8d</b>	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	259.1441	259.1435	5.89	>99
<b>8e</b>	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	219.1128	219.1122	5.26	>99
<b>8f</b>	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	267.1128	267.1123	5.45	84.5
<b>9</b>	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O	251.1179	251.1175	5.36	97.6
<b>13</b>	C <sub>17</sub> H <sub>13</sub> NO	248.1070	248.1066	5.07	>99
<b>16</b>	C <sub>17</sub> H <sub>13</sub> NO	248.1070	248.1064	5.13	>99
<b>17</b>	C <sub>23</sub> H <sub>17</sub> NO	324.1383	324.1375	5.9	>99
<b>24a</b>	C <sub>22</sub> H <sub>16</sub> N <sub>2</sub> O	325.1335	325.1330	5.3	>99
<b>24b</b>	C <sub>23</sub> H <sub>15</sub> N <sub>3</sub> O	350.1288	350.1281	5.24	98.9
<b>24c</b>	C <sub>23</sub> H <sub>15</sub> N <sub>3</sub> O	350.1288	350.1284	5.26	>99
<b>24d</b>	C <sub>22</sub> H <sub>15</sub> FN <sub>2</sub> O	343.1241	343.1237	5.33	>99
<b>24e</b>	C <sub>22</sub> H <sub>15</sub> ClN <sub>2</sub> O	359.0946	359.0935	5.43	95.4
<b>24f</b>	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O	339.1492	339.1489	5.42	>99
<b>24g</b>	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	355.1441	355.1435	5.17	96.9
<b>24h</b>	C <sub>21</sub> H <sub>14</sub> FN <sub>3</sub> O	344.1194	344.1188	4.86	>99
<b>24i</b>	C <sub>21</sub> H <sub>14</sub> ClN <sub>3</sub> O	360.0898	360.0895	4.88	>99
<b>24j</b>	C <sub>22</sub> H <sub>14</sub> N <sub>4</sub> O	351.1240	351.1235	4.84	>99
<b>28a</b>	C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> O	326.1288	326.1281	4.72	>99
<b>28b</b>	C <sub>22</sub> H <sub>14</sub> N <sub>4</sub> O	351.1240	351.1239	4.59	98.5
<b>28c</b>	C <sub>19</sub> H <sub>13</sub> N <sub>3</sub> OS	332.0852	332.0851	4.66	97.0
<b>28d</b>	C <sub>21</sub> H <sub>14</sub> ClN <sub>3</sub> O	360.0898	360.0893	4.85	93.6
<b>28e</b>	C <sub>20</sub> H <sub>12</sub> N <sub>4</sub> OS	357.0805	357.0801	4.62	>99
<b>28f</b>	C <sub>22</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O	394.1162	394.1154	5.01	>99
<b>28g</b>	C <sub>20</sub> H <sub>13</sub> FN <sub>4</sub> O	345.1146	345.1143	4.27	>99
<b>33a</b>	C <sub>23</sub> H <sub>15</sub> N <sub>3</sub> O	350.1288	350.1281	4.37	98.8
<b>33b</b>	C <sub>23</sub> H <sub>15</sub> N <sub>3</sub> O	350.1288	350.1282	4.06	97.4

Compound No.	Formula (M)	HRMS (Calcd) [M+H] <sup>+</sup>	HRMS (Found)	Retention time, t <sub>R</sub> (min)	% Purity (254 nm)
<b>33c</b>	C <sub>24</sub> H <sub>16</sub> N <sub>2</sub> O	349.1335	349.1331	5.64	>99
<b>33d</b>	C <sub>24</sub> H <sub>15</sub> FN <sub>2</sub> O	367.1241	367.1237	5.66	83.8
<b>33e</b>	C <sub>22</sub> H <sub>14</sub> N <sub>2</sub> OS	355.0900	355.0892	5.54	96
<b>33f</b>	C <sub>25</sub> H <sub>15</sub> N <sub>3</sub> O	374.1288	374.1282	5.42	>99
<b>33g</b>	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	379.1441	379.1436	5.66	>99
<b>33h</b>	C <sub>22</sub> H <sub>14</sub> N <sub>2</sub> OS	355.0900	355.0893	5.54	>99
<b>38a</b>	C <sub>24</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	380.1394	380.1386	5.22	>99
<b>38b</b>	C <sub>24</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	380.1394	380.1385	5.10	>99
<b>38c</b>	C <sub>24</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	380.1394	380.1386	5.18	>99
<b>38d</b>	C <sub>22</sub> H <sub>13</sub> FN <sub>4</sub> O	369.1146	369.1143	4.89	96.7
<b>38e</b>	C <sub>24</sub> H <sub>14</sub> N <sub>4</sub> O	375.1240	375.1235	5.50	>99
<b>38f</b>	C <sub>24</sub> H <sub>14</sub> N <sub>4</sub> O	375.1240	375.1234	5.09	98.3
<b>38g</b>	C <sub>23</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	381.1346	381.134	5.00	>99

The purity of the biological tested compounds was determined by an analytical HPLC method. The parameters of the HPLC method were as follows: Accucore RP-MS column (2.1 × 50 mm, 2.6 μm); mobile phase: A = H<sub>2</sub>O with 0.1% HCO<sub>2</sub>H, B = acetonitrile with 0.1% HCO<sub>2</sub>H, 0–1 min, 0% B; 1–4 min, 0% B → 100% B; 4–8 min, 100% B; 8–11 min, 0% B; flow rate = 0.4 mL/min; detector: UV 254 nm; run time = 11 min.

**Table s2.** Inhibition of Ligand Binding to 63 Targets by Compound 6

Targets	Radioligand	Reference Compound	Ki (M) Reference Compound	% Inhibition by Compound 6 (1.25 $\mu$ M)
AMPA	[ <sup>3</sup> H]AMPA	(+/-)AMPA Br	3.90E-8	5.45
Kainate	[ <sup>3</sup> H]Kainic acid	Kainic acid	1.12E-8	7.74
NMDA	[ <sup>3</sup> H]CGP 39653	NMDA	2.09E-6	6.54
NMDA-glycine	[ <sup>3</sup> H]MDL-105,519	MDL-105,519	6.37E-9	7.85
Glycine strychnine sensitive	[ <sup>3</sup> H]Strychnine	Strychnine Nitrate	1.71E-8	16.91
GABA A, agonist	[ <sup>3</sup> H]GABA	GABA	6.78E-9	10.13
GABA A, benzodiazepine	[ <sup>3</sup> H]Flunitrazepam	Clonazepam	1.31E-9	24.27
GABA B	[ <sup>3</sup> H]CGP 54626A	(+/-)Baclofen	1.01E-6	-2.73
Adenosine, nonselective	[ <sup>3</sup> H]NECA	NECA	2.90E-9	-8.56
Adrenergic, $\alpha$ 1	[ <sup>3</sup> H]7-MeOxy-Prazosin	Phentoramine	2.85E-9	-15.00
Adrenergic, $\alpha$ 2	[ <sup>3</sup> H]RX 821002	Phentoramine	2.39E-9	14.12
Adrenergic, $\beta$	[ <sup>3</sup> H]DHA	Alprenolol HCl	2.53E-9	12.31
Norepinephrine transporter	[ <sup>3</sup> H]Nisoxetine	Desipramine HCl	1.29E-9	6.34
Dopamine transporter	[ <sup>3</sup> H]WIN 35,428	GBR12909	2.26E-8	-9.48
Dopamine, nonselective	[ <sup>3</sup> H]Spiperone	Spiperone HCl	6.76E-10	-5.95
Histamine, H1	[ <sup>3</sup> H]Pyrilamine	Triplolidine HCl	5.53E-9	3.38
Histamine, H2	[ <sup>125</sup> I]Aminopotentidine	Tiotidine	7.12E-9	12.59
Histamine, H3	[ <sup>3</sup> H]N- $\alpha$ -MeHistamine	N- $\alpha$ -MeHistamine	7.91E-10	21.65
Melatonin	[ <sup>125</sup> I]2-Iodomelatonin	2-Iodomelatonin	7.31E-11	11.44
Serotonin, transporter	[ <sup>3</sup> H]Citalopram, N-Methyl	Imipramine HCl	1.52E-8	16.88
Serotonin, nonselective	[ <sup>3</sup> H]LSD	Methysergide maleate	8.23E-9	7.02

Muscarinic, M1 (human)	[ <sup>3</sup> H]Scoporamine, N-Methyl	(-)Scoporamine, MeBr	4.91E-11	4.78
Muscarinic, M2 (human)	[ <sup>3</sup> H]Scoporamine, N-Methyl	(-)Scoporamine, MeBr	1.36E-10	24.94
Muscarinic, nonselective CNS	[ <sup>3</sup> H]QNB	Atropine sulfate	3.29E-10	14.0
Muscarinic, nonselective, peripheral	[ <sup>3</sup> H]QNB	Atropine sulfate	1.83E-10	0.78
Nicotinic	[ <sup>3</sup> H]Epibatidine	(+/-)epibatidine	5.77E-11	4.10
Opiate, nonselective	[ <sup>3</sup> H]Naloxone	Naloxone HCl	1.93E-9	28.60
Sigma, nonselective	[ <sup>3</sup> H]DTG	Haloperidol	3.51E-9	35.41
Acetylcholinesterase	Acetylcholine	Eserine	9.68E-7	17.32
Choline acetyltransferase	[ <sup>14</sup> C]Acetyl Coenzyme	MNEP	2.08E-9	-10.79
Glutamic acid decarboxylase	[ <sup>14</sup> C]Glutamic acid	AminoOxy acetic acid	4.99E-10	9.32
MAO-A	[ <sup>14</sup> C]5HT	Ro 41-1049 HCl	6061E-9	24.94
MAO-B	[ <sup>14</sup> C]Phenylethylamine	Ro 16-6491 HCl	1.28E-8	-1.00
Estrogen	[ <sup>125</sup> I]3,17B-Estradiol, 16 $\alpha$	17-B-Estradiol	9.54E-11	6.17
Testosterone	[ <sup>3</sup> H]Methyltrienolone	Methyltrienolone	3.81E-9	25.86
Calcium, L	[ <sup>3</sup> H]Nitrendipine	Nifedipine	2.10E-10	9.83
Calcium, N	[ <sup>125</sup> I]Conotoxin GVIA	$\omega$ -Conotoxin GVIA	1.21E-11	16.00
Potassium, ATP sensitive	[ <sup>3</sup> H]Glibenclamide	Glibenclamide	3.05E-10	-5.45
Potassium, Ca <sup>2+</sup> activated, VI	[ <sup>125</sup> I]Apamin	Apamin	3.98E-11	-7.43
Potassium, Ca <sup>2+</sup> activated, VS	[ <sup>125</sup> I]Charibdotoxin	Charybdotoxin	6.10E-10	-16.79
Sodium, Site 1	[ <sup>3</sup> H]Saxitoxin	Tetrodotoxin	9.44E-9	12.68
Sodium, Site 2	[ <sup>3</sup> H]Batrachotoxin A 20- $\alpha$ -Benzo	Aconitine	8.06E-7	14.80
NOS	[ <sup>3</sup> H]NOARG	NOARG	3.29E-8	-8.02
Leukotriene B4	[ <sup>3</sup> H]LTB <sub>4</sub>	LTB <sub>4</sub>	5.07E-10	6.60

Leukotriene D4	[ <sup>3</sup> H]LTD <sub>4</sub>	LTD <sub>4</sub>	1.23E-9	3.59
Thromboxane A2	[ <sup>3</sup> H]SQ 29,548	Pinane-thromboxane	8.27E-8	-0.89
Corticotropin Releasing Factor	[ <sup>125</sup> I]Tyr0-oCRF	Tyr0-oCRF	3.66E-9	40.86
Oxytocin	[ <sup>3</sup> H]Oxytocin	Oxytocin	8.18E-9	26.39
Platelet Activating Factor, PAF	[ <sup>3</sup> H]Hexadecyl, PAF	C16 PAF	4.23E-9	-1.83
Thyrotropin Releasing Hormone, TRH	[ <sup>3</sup> H]-(3MeHis2)TRH	(3MeHis2)TRH	9.52E-8	0.49
Angiotensin II, AT1	[ <sup>125</sup> I]-(Sar1-Ile8) Angiotensin II	Angiotensin II	7.05E-9	0.51
Angiotensin II, AT2	[ <sup>125</sup> I]Thr4-Angiotensin II	Angiotensin II	3.72E-10	-1.08
Bradykinin, BK2	[ <sup>3</sup> H]Bradykinin	Bradykinin TFA	5.90E-10	-4.72
Cholecystokinin, CCK1	[ <sup>125</sup> I]CCK-8	CCK-8 (sulfated)	1.79E-11	21.13
Cholecystokinin, CCK2	[ <sup>125</sup> I]CCK-8	CCK-8 (sulfated)	1.19E-10	16.76
Endothelin, ET-A	[ <sup>125</sup> I]Endothelin-1	Endothelin-1	2.58E-10	-5.16
Endothelin, ET-B	[ <sup>125</sup> I]Endothelin-1	Endothelin-1	3.54E-10	11.58
Galanin	[ <sup>125</sup> I]Galanin	Galanin (Porcine)	4.21E-10	7.16
Neurokinin, NK1	[ <sup>3</sup> H]Substance P	Substance P	1.33E-8	7.50
Neurokinin, NK2 (Human)	[ <sup>125</sup> I]NKA	Neurokinin A	8.94E-10	10.11
Neurokinin, NK3	[ <sup>125</sup> I]Eledoisin	Eledoisin	7.21E-9	23.98
Vasoactive intestinal peptide	[ <sup>125</sup> I]VIP	VIP	5.82E-10	3.39
Vasopressin 1	[ <sup>3</sup> H]Vasopressin-1 antagonist	Arg8-Vasopressin	8.89E-9	-11.58

Experimental Procedure (performed by NovaScreen): Ligand binding assays were performed in extracts or membrane fractions obtained from various tissues and from cell lines expressing the respective targets. A radioactively labeled ligand specific for each target was added at a concentration approximately equivalent to the ligand's K<sub>d</sub>, and compound **6** was added at a concentration of 1.25 μM. In the negative controls no compound **6** as added. In the positive controls,

ligands with known  $K_i$ s for each target were added instead of compound **6** (listed as "reference compound" in the table). After incubation for a period of time sufficient to allow equilibrium binding, the ratio of bound and unbound radioactivity was measured. From this ratio the % inhibition of binding by compound **6** was determined. Data are the result of two experiments.

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