The novel phosphodiesterase 9A inhibitor BI 409306 increases cyclic guanosine monophosphate levels in the brain, promotes synaptic plasticity and enhances memory function in rodents

Holger Rosenbrock, Riccardo Giovannini, Gerhard Schänzle, Eliza Koros, Frank Runge, Holger Fuchs, Anelise Marti, Klaus G. Reymann, Ulrich H. Schröder, Ernesto Fedele, Cornelia Dorner-Ciossek

*The Journal of Pharmacology and Experimental Therapeutics*
**Supplementary Figure S1** Concentration-activity curve for inhibition of PDE9A by BI 409306 determined by a SPA

Data are expressed as mean (±SD). N=8 dilutions from 4 experiments.

PDE9A, phosphodiesterase 9A; SD, standard deviation; SPA, scintillation proximity assay
### Supplementary Table S1

**Potency and selectivity of BI 409306 for non-PDE targets**

| Target pathway | Target | Inhibition of binding<sup>a</sup> with BI 409306 10 µM |
|----------------|--------|---------------------------------------------------|
| Acetylcholine  | M<sub>1</sub> receptor | <50 %    |
| Acetylcholine  | M<sub>2</sub> receptor | <50 %    |
| Acetylcholine  | M<sub>3</sub> receptor | <50 %    |
| Acetylcholine  | M<sub>4</sub> receptor | <50 %    |
| Acetylcholine  | M<sub>5</sub> receptor | <50 %    |
| Acetylcholine  | nAChR | <50 %    |
| Acetylcholine  | α<sub>1</sub> nAChR (bungarotoxin) | <50 %    |
| Acetylcholine  | α<sub>4</sub>β<sub>2</sub> nAChR (cytisine) | <50 %    |
| Acetylcholine  | α<sub>7</sub> nAChR (bungarotoxin) | <50 %    |
| Acetylcholine  | α<sub>7</sub> nAChR (methyllycaconitine) | <50 %    |
| Acetylcholine  | Choline transporter | <50 %    |
| Adenosine      | A<sub>1</sub> receptor | <50 %    |
| Adenosine      | A<sub>2a</sub> receptor | <50 %    |
| Adenosine      | A<sub>3</sub> receptor | <50 %    |
| Androgen       | Androgen receptor (testosterone) | <50 %    |
| Bradykinin     | B<sub>1</sub> receptor | <50 %    |
| Bradykinin     | B<sub>2</sub> receptor | <50 %    |
| Calcium channel| L-Type VGCC (benzothiazepine) | <50 %    |
| Calcium channel| L-Type VGCC (dihydropyridine) | <50 %    |
| Calcium channel| N-Type VGCC | <50 %    |
| Cannabinoid    | CB<sub>1</sub> receptor | <50 %    |
| Cannabinoid    | CB<sub>2</sub> receptor | <50 %    |
| Dopamine       | D<sub>1</sub> receptor | <50 %    |
| Dopamine       | D<sub>2</sub> receptor long splice variant | <50 %    |
| Dopamine       | D<sub>2</sub> receptor short splice variant | <50 %    |
| Dopamine       | D<sub>3</sub> receptor | <50 %    |
| Dopamine       | D<sub>4.2</sub> receptor variant | <50 %    |
| Dopamine       | D<sub>4.4</sub> receptor variant | <50 %    |
| Dopamine       | D<sub>4.7</sub> receptor variant | <50 %    |
| Dopamine       | D<sub>5</sub> receptor | <50 %    |
| Dopamine       | Dopamine transporter | <50 %    |
| Endothelin     | ET<sub>a</sub> receptor | <50 %    |
| Endothelin     | ET<sub>b</sub> receptor | <50 %    |
| Estrogen       | ER<sub>α</sub> receptor | <50 %    |
| GABA           | GABA<sub>A</sub> receptor (flunitrazepam) | <50 %    |
| GABA           | GABA<sub>A</sub> receptor (muscimol) | <50 %    |
| GABA           | Hippocampal GABA<sub>A</sub> receptor (Ro-15-1788) | <50 %    |
| GABA           | Cerebellar GABA<sub>A</sub> receptor (Ro-15-1788) | <50 %    |
| GABA           | GABA<sub>A</sub> receptor (TBOB) | <50 %    |
| GABA           | GABA<sub>A</sub> receptor (TBPS) | <50 %    |
| GABA           | GABA<sub>B</sub> receptor (non-selective) | <50 %    |
| GABA           | GABA<sub>B</sub>1a receptor subunit | <50 %    |
| GABA           | GABA<sub>B</sub>1b receptor subunit | <50 %    |
| GABA           | GABA transporter | <50 %    |
| Glucocorticoid | Glucocorticoid receptor | <50 %    |
| Glutamate      | Kainate receptor | <50 %    |
| Glutamate      | NMDA receptor (agonism) | <50 %    |
| Compound          | Receptor/Transporter                  | % Inhibition |
|-------------------|--------------------------------------|-------------|
| Glutamate         | NMDA receptor (glycine)              | <50 %       |
| Glutamate         | NMDA receptor (phencyclidine)        | <50 %       |
| Glutamate         | NMDA receptor (polyamine)            | <50 %       |
| Glycine           | Strychnine-sensitive receptor        | <50 %       |
| Glycine           | Glycine transporter                  | <50 %       |
| G-protein coupled receptor | GPR103 receptor                   | <50 %       |
| Histamine         | H₁ receptor                          | <50 %       |
| Histamine         | H₂ receptor                          | <50 %       |
| Histamine         | H₃ receptor                          | <50 %       |
| Imidazoline       | I₂ receptor (central)                | <50 %       |
| Leukotriene       | CysLT₁ receptor                     | <50 %       |
| Melatonin         | MT₁ receptor                         | <50 %       |
| Monoamine         | Monoamine transporter                | <50 %       |
| Neuropeptide Y    | Y₁ receptor                          | <50 %       |
| Neuropeptide Y    | Y₂ receptor                          | <50 %       |
| Norepinephrine    | α₁a receptor                         | <50 %       |
| Norepinephrine    | α₁b receptor                         | <50 %       |
| Norepinephrine    | α₁d receptor                         | <50 %       |
| Norepinephrine    | α₂a receptor                         | <50 %       |
| Norepinephrine    | β₁ receptor                          | <50 %       |
| Norepinephrine    | β₂ receptor                          | <50 %       |
| Norepinephrine    | Norepinephrine transporter           | <50 %       |
| Opioid            | δ receptor                           | <50 %       |
| Opioid            | κ receptor                           | <50 %       |
| Opioid            | μ receptor                           | <50 %       |
| Phorbol ester     | Phorbol ester                       | <50 %       |
| Platelet activating factor | Platelet activating factor | <50 %       |
| Potassium channel | K<sub>ATP</sub> channel             | <50 %       |
| Potassium channel | hERG channel                        | <50 %       |
| Prostanoid        | EP4 receptor                         | <50 %       |
| Purinergic        | P<sub>₂x</sub> receptor              | <50 %       |
| Purinergic        | P<sub>₂y</sub> receptor              | <50 %       |
| Phosphodiesterase | Phosphodiesterase (rolipram)         | <50 %       |
| Serotonin         | 5-HT<sub>₁a</sub> receptor          | <50 %       |
| Serotonin         | 5-HT<sub>₁b</sub> receptor          | <50 %       |
| Serotonin         | 5-HT<sub>₂a</sub> receptor          | <50 %       |
| Serotonin         | 5-HT<sub>₂b</sub> receptor          | <50 %       |
| Serotonin         | 5-HT<sub>₂c</sub> receptor          | <50 %       |
| Serotonin         | 5-HT<sub>₃</sub> receptor           | <50 %       |
| Serotonin         | 5-HT<sub>₄</sub> receptor           | <50 %       |
| Serotonin         | 5-HT<sub>₅a</sub> receptor          | <50 %       |
| Serotonin         | 5-HT<sub>₆</sub> receptor           | <50 %       |
| Serotonin         | Serotonin transporter                | <50 %       |
| Sigma             | σ₁ receptor                          | <50 %       |
| Sigma             | σ₂ receptor                          | <50 %       |
| Sodium channel    | Receptor site 2                      | <50 %       |
| Tachykinin        | NK₁ receptor                         | <50 %       |
| Thyroid hormone   | Thyroid hormone                      | <50 %       |

*aInhibition of binding of the endogenous ligand, or the drug or ligand shown in brackets.

5-HT, 5-hydroxytryptamine; A, adenosine; B, bradykinin; CB, cannabinoid; CysLT, cysteinyl leukotriene; D, dopamine; EP, prostaglandin E; ER, estrogen receptor; ET, endothelin;
GABA, γ-aminobutyric acid; GPR103, G-protein coupled receptor 103; H, histamine; hERG, human ether-a-go-go-related gene; I, imidazoline; K_{ATP}, ATP-sensitive potassium channel; M, muscarinic; MT, melatonin; nAChR, nicotinic acetylcholine receptor; NK, neurokinin; NMDA, N-methyl-D-aspartate; P, purine; PDE, phosphodiesterase; VGCC, voltage-gated calcium channel