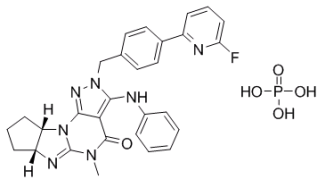
Data Sheet

Product Name:	ITI214
Cat. No.:	HY-12501A
CAS No.:	1642303-38-5
Molecular Formula:	$C_{29}H_{29}FN_7O_5P$
Molecular Weight:	605.56
Target:	Phosphodiesterase (PDE)
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO: ≥ 30 mg/mL



BIOLOGICAL ACTIVITY:

ITI–214 is a picomolar PDE1 inhibitor with excellent selectivity against other PDE family members and against a panel of enzymes, receptors, transporters, and ion channels, exhibits potent PDE1 inhibitory activity (Ki = 58 pM).
IC50 value: 58 pM (Ki)
Target: PDE1
in vitro: ITI–214 exhibits picomolar inhibitory potency for PDE1, demonstrates excellent selectivity against all other PDE families. ITI214 exhibits excellent selectivity over other PDE family
members. For instance, the Ki values of ITI214 against recombinant full–length human PDE1A, PDE1B, and PDE1C are 33 pM, 380 pM, and 35 pM, respectively. ITI214 is profiled in a panel of enzymes, receptors, transporters, and ion channels from Caliper at 10 μM, which is over 170000 times higher than its Ki for PDE1, and demonstrates good selectivity. [1]
in vivo: ITI214 possesses a good overall profile with balanced physicochemical properties, excellent potency and selectivity, and good pharmacokinetics. ITI214 is found to significantly enhance memory performance in the test with a minimum effective dose of 3 mg/kg. [1]

PROTOCOL (Extracted from published papers and Only for reference)

Enzyme assay [1] Phosphodiesterases 1A, 1B, 1C, 2A, 3B, 4A, 5A, 7B, 8A, 9A, 10A, and 11A were generated from full–length human recombinant clones. PDE1 and PDE6 were isolated from bovine brain and bovine retina, respectively. PDE assays were performed in a reaction medium containing 10 mM Tris–HCl (pH 7.2), 10 mM MgCl2, 0.1% BSA, and 45 nM Fl–cGMP or Fl–cAMP, respectively. This level of substrate is significantly lower than Km values for PDE enzymes and so measured IC50 values are essentially Ki values. Immobilized metal affinity fluorescence polarization (IMAP) assays were carried out for 15 min at room temperature and terminated by addition of binding reagent. Reaction mixture for assay of PDE1 activity also contained 30 μM CaCl2 and 10 U/mL calmodulin. The reaction mixture for assay of PDE2 contained 2 μM cGMP. Fluorescent–labeled cGMP (Fl–cGMP) was used as the substrate in the assays for PDE1, PDE1A, PDE1B, PDE1C, PDE5A, PDE6, and PDE9A, while fluorescent–labeled cAMP (Fl–cAMP) was used as the substrate for PDE2A, PDE3B, PDE4A, PDE7B, PDE8A, PDE10A, and PDE11A. Ki values were calculated using nonlinear regression software, fitting a four–parameter one–site dose–response model. Animal administration [1] Different groups of adult, male Sprague–Dawley rats (200–250 g, N = 7 rats/dose/test substance) were injected acutely via the intraperitoneal route with either vehicle solution or a test substance in the vehicle solution (2 mL/kg volume) at a range of concentrations. Sixty (60) min later they were placed in an open field apparatus containing two identical objects. The treated rats were allowed to explore the open field for a 6 min period, referred to as the T1 training session. The animals were then returned to their home cages. Twenty–four hours later the rats were again placed in the open field apparatus for a second 6 min test session (the T2 test session), then returned to their home cages. During T2 one of the objects present in the open field was identical to that present during T1 (i.e., the familiar object), while the other was replaced by a new object (i.e., the novel object). Objects and their placement into the open field were varied across rats to

avoid positional biases. To control for possible odor cues the objects were cleaned with a 10% ethanol solution at the end of each trial and the floor of the open field wiped down to eliminate possible scent/trail markers. During the test phase, the novel object was also wiped down prior to testing so that the objects would all have the same odor. The rats were videotaped during the T1 and T2 period to ensure accuracy and reliability in the scoring of the behavior. The videotapes were subsequently scored by two impartial observers who were blind to drug conditions for the time (in sec) spent by each animal in physical contact (exploration) with the novel and familiar objects. The mean (with SEM) time (sec) spent by drug–treated and vehicle–treated rats with each object was calculated. A two–way analysis of variance (ANOVA) was conducted followed by a posthoc Dunnett's comparison of each dose level to vehicle. A difference of $p < 0.05$ was considered statistically significant.

References:

[1]. Lawrence Wennogle. Novel uses. From PCT Int. Appl. (2014), WO 2014145617 A2 20140918.

[2]. Peng Li , et al. Salt crystals. From PCT Int. Appl. (2013), WO 2013192556 A2 20131227.

[3]. Allen A. Fienberg, et al. Organic compounds. From PCT Int. Appl. (2010), WO 2010132127 A1 20101118.

[4]. Li P, et al. Discovery of Potent and Selective Inhibitors of Phosphodiesterase 1 for the Treatment of Cognitive Impairment Associated with Neurodegenerative and Neuropsychiatric Diseases. J Med Chem. 2016 Feb 11;59(3):1149–64.

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