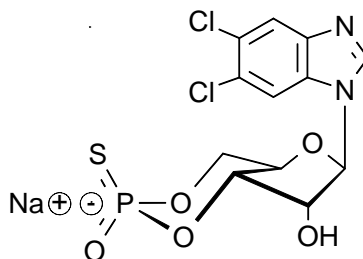


Technical Information about Sp-5,6-DCI-cBIMPS

Potent membrane-permeant and PDE-resistant activator of cAMP-dependent protein kinases

Update: November 16, 2007 AI



Abbreviation: **Sp-5,6-DCI-cBiMPS**

Formula	CAS No.	Molecular Weight	UV	BIOLOG Cat. No.
C ₁₂ H ₁₀ Cl ₂ N ₂ O ₅ PS·Na	[120912-54-1]	419.2	λ _{max} 254 nm / ε 6400 / pH 7	D 014

Name: 5, 6- Dichloro-1- β- D- ribofuranosylbenzimidazole- 3', 5'- cyclic monophosphorothioate, Sp- isomer (Sp-5,6-DCI-cBIMPS)

Description: Sp-5,6-DCI-cBIMPS is an analogue of the parent second messenger cyclic AMP in which the adenine moiety is replaced by a highly lipophilic modified benzimidazole ring system. In addition, the axial one of the two exocyclic oxygen atoms in the cyclic phosphate moiety is modified by sulfur.

Legal information: Synthesis and distribution protected under patent DE 3802865.4 licensed to BIOLOG Life Science Institute.

Properties: Sp-5,6-DCI-cBIMPS is a rationally designed activator of cAMP-dependent protein kinase (cAK) with considerably improved properties compared to its parent compound Sp-cAMPS:

- **Potent activator of cAMP-dependent protein kinase,**
- **very high lipophilicity and excellent membrane permeability, useful for intact cells while still soluble in aqueous solvents,**
- **very high metabolic stability towards all cyclic nucleotide- responsive phosphodiesterases examined so far,**
- **site selective activator of the cAK isozymes with strong preference for cAK type II (Dostmann et al. 1990),**
- **suitable partner for synergistic activation of cAK II by pairs of cAMP analogs** (please ask for respective information),
- **excellent selectivity for cAK vs. cGK,**
- **replaces the still widely used but unsatisfactory 8-CPT-cAMP (Sandberg et al. 1991) and dibutyryl cAMP.**

Summing up Sp-5,6-DCI-cBIMPS is a potent activator of the cAK isozymes with special preference for cAK type II. Due to its high lipophilicity and metabolic stability it has excellent membrane permeability and is especially of interest when working with intact cells.

Specification: Crystallized or lyophilized sodium salt. Other salt forms of Sp-5,6-DCI-cBIMPS are available upon request. Equal concentrations of Sp-5,6-DCI-cBIMPS can appear very different in volume due to sensitivity of the lyophilized form to humidity. The compound can even contract to small volume droplets. Normally the product is located in the conical bottom of the tube. Micromolar quantities are determined by UV at λ_{max}. BIOLOG also offers the corresponding Rp-isomer (Rp-5,6-DCI-cBIMPS; Cat. No. D 013) and the parent sulfur-free 5,6-DCI-cBIMP (Cat. No. D 011).

Purity: Typical analysis is better than 99% (HPLC / UV / 254 nm). The product is not sterile and has not been tested for endotoxins.

Stability and Storage: Sp-5,6-DCI-cBIMPS has sufficient stability at room temperature and does not need special care during handling or shipment. Nevertheless, we recommend that the compound should be stored in the freezer, for longer storage periods preferably in freeze-dried form.

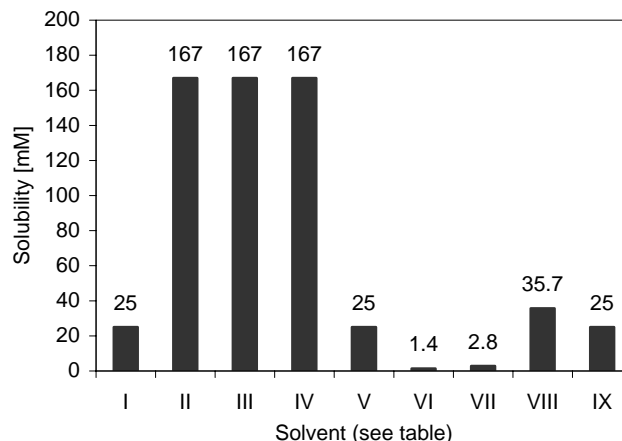
Toxicity and Safety: Since cyclic AMP has multiple tasks in every organism it is very likely that lipophilic cAMP analogues will interfere with many cell regulation processes *in vivo*. However, due to the rather small quantities to work with no health hazards have been reported. Nevertheless please keep in mind that the *in vivo* properties of this compound are not sufficiently characterized up to now. Avoid skin contact or ingestion and allow only trained personnel to handle the product.

Our products are designed, developed and sold for research purposes only. They are intended for *in vitro* and nonhuman *in vivo* laboratory applications. Any other use requires approval of health authorities.

Not for drug, household or related uses!

Solubility: Detailed information on the solubility of Sp-5,6-DCI-cBIMPS in water and various buffers are listed in the solubility chart below. Concentrations have been tested at ambient temperatures and can be considered as minimum concentrations obtainable. When opening the tube please make sure that no substance is lost within the cap. Please rinse tube walls carefully and preferably use ultrasonic or vortex to achieve total and uniform mixing.

No.	Solvent	Solubility [mM]
I	H ₂ O	25
II	DMSO	167
III	DMF	167
IV	Ethanol 96%	167
V	Methanol	25
VI	PBS, pH 7.4	1.4
VII	100 mM Na ₂ HPO ₄ , pH 7.0	2.8
VIII	25 mM Hepes/NaOH, pH 7.2	35.7
IX	25 mM Tris/HCl, pH 7.4	25



Selected References for Sp-5,6-DCI-cBIMPS: Sp-5,6-DCI-cBIMPS was synthesized in order to develop optimized cAMP agonists with respect to PDE stability and membrane permeability. For a comprehensive and updated list please visit our website (<http://www.biolog.de>).

Pfitzer, G.; Lubomirov, L.T.; Reimann, K.; Gagov, H.; Schubert, R., *J. Muscle Res. Cell Motil.*, **27**, 445 – 454 (2006). "Regulation of the Crossbridge Cycle in Vascular Smooth Muscle by cAMP Signalling"

Kwong, K.; Lee, I.Y., *J. Physiol.*, **564**, 437 - 450 (2005): "Prostaglandin E-2 Potentiates a TTX-resistant Sodium Current in Rat Capsaicin-sensitive Vagal Pulmonary Sensory Neurons"

Harrison, R.A.P., *Mol. Reprod. Dev.*, **67**, 337 - 352 (2004): "Rapid PKA-catalysed Phosphorylation of Boar Sperm Proteins Induced by the Capacitating Agent Bicarbonate"

Nguyen, G.H.; French, R.; Radhakrishna, H., *Cell Signal.*, **16**, 1141 - 1151 (2004): "Protein Kinase A Inhibits Lysophosphatidic Acid Induction of Serum Response Factor via Alterations in the Actin Cytoskeleton"

Kloss, S.; Srivastava, R.; Mulsch, A., *Mol. Pharmacol.*, **65**, 1440 - 1451 (2004): "Down-regulation of Soluble Guanylyl Cyclase Expression by Cyclic AMP is Mediated by mRNA-stabilizing Protein HuR"

Murthy, K.S., *Neurochem. Int.*, **45**, 845 - 851 (2004): "Modulation of Soluble Guanylate Cyclase Activity by Phosphorylation"

Fricke, K.; Heitland, A.; Maronde, E., *Endocrinology*, **145**, 4940 - 4947 (2004): "Cooperative Activation of Lipolysis by Protein Kinase A and Protein Kinase C Pathways in 3T3-L1 Adipocytes"

Harayama, H.; Sasaki, K.; Miyake, M., *Mol. Reprod. Dev.*, **69**, 194 - 204 (2004): "A Unique Mechanism for cyclic Adenosine 3', 5'-monophosphate-induced Increase of 32-kDa Tyrosine-phosphorylated Protein in Boar Spermatozoa"

Makarevich, A.V.; Sirotkin, A.V.; Genieser, H.-G., *Anim. Reprod. Sci.*, **81**, 125 - 136 (2004). "Action of Protein Kinase A Regulators on Secretory Activity of Porcine Granulosa Cells in Vitro"

Kopperud, R.; Krakstad, C.; Selheim, F.; Doeskeland, S. O., *FEBS Lett.*, **546**, 121 - 126 (2003): "cAMP Effector Mechanisms. Novel Twists for an 'Old' Signaling System"

Harayama, H., *J. Androl.*, **24**, 831 - 842 (2003): "Viability and Protein Phosphorylation Patterns of Boar Spermatozoa Agglutinated by Treatment with a Cell-permeable Cyclic Adenosine 3', 5'-Monophosphate Analog"

Harayama, H.; Okada, K.; Miyake, M., *J. Androl.*, **24**, 91 - 99 (2003): "Involvement of Cytoplasmic Free Calcium in Boar Sperm: Head-to-head Agglutination Induced by a Cell-Permeable Cyclic Adenosine Monophosphate Analog"

Mutafova-Yambolieva, V.N.; Smyth, L.; Bobalova, J., *Cardiovasc. Res.*, **57**, 217 - 224 (2003): "Involvement of Cyclic AMP-mediated Pathway in Neural Release of Noradrenaline in Canine Isolated Mesenteric Artery and Vein"

Jang, E.K.; Azzam, J.E.; Dickinson, N.T.; Davidson, M.M.L.; Haslam, R.J., *Brit. J. Haematol.*, **117**, 664 - 675 (2002): "Roles for Both Cyclic GMP and Cyclic AMP in the Inhibition of Collagen-induced Platelet Aggregation by Nitroprusside"

Christensen, A.E.; de Rooij, J.; Kopperud, R.; Nilsen, O.K.; Dao, K.K.; Schwede, F.; Bos, J.L.; Genieser, H.-G.; Døskeland, S.O., Abstracts of the 13th Protein Kinase Symposium, Oslo/Norway, 2002: "Comparison of the cAMP Binding Sites of EPAC-1 and cAMP-Kinase"

Wollert, K.C.; Fiedler, B.; Gambaryan, S.; Smolenski, A.; Heineke, J.; Butt, E.; Trautwein, C.; Lohmann, S.M.; Drexler, H., *Hypertension*, **39**, 87 - 92 (2002): "Gene Transfer of cGMP-dependent Protein Kinase I Enhances the Antihypertrophic Effects of Nitric Oxide in Cardiomyocytes"

- Vargas, G.; Lucero, M.T., *J. Membr. Biol.*, **188**, 115 - 125 (2002): "Modulation by PKA of the Hyperpolarization-activated Current (I_h) in Cultured Rat Olfactory Receptor Neurons"
- Popp, R.; Brandes, R.P.; Ott, G.; Busse, R.; Fleming, I., *Circ. Res.*, **90**, 800 - 806 (2002): "Dynamic Modulation of Interendothelial Gap Junctional Communication by 11, 12-Epoxyeicosatrienoic Acid"
- Han, J.; Kim, N.; Kim, E.; Ho, W.-K.; Earm, Y.E., *J. Biol. Chem.*, **276**, 22140 - 22147 (2001): "Modulation of ATP-sensitive Potassium Channels by cGMP-dependent Protein Kinase in Rabbit Ventricular Myocytes"
- von der Weid, P. Y.; Zhao, J.; Ven Helden, D. F., *Am. J. Physiol.-Heart Circul. Physiol.*, **280**, H2707 - H2716 (2001): "Nitric Oxide Decreases Pacemaker Activity in Lymphatic Vessels of Guinea Pig Mesentery"
- Maurice, N.; Tkatch, T.; Meisler, M.; Sprunger, L.K.; Surmeier, D.J., *J. Neurosci.*, **21**, 2268 - 2277 (2001): "D₁/D₅ Dopamine Receptor Activation Differentially Modulates Rapidly Inactivating and Persistent Sodium Currents in Prefrontal Cortex Pyramidal Neurons"
- Lubomirov, L.; Gagov, H.; Petkova-Kirova, P.; Duridanova, D.; Kalentchuk, V.U.; Schubert, R., *Br. J. Pharmacol.*, **134**, 1564 - 1570 (2001): "Urocortin Relaxes Rat Tail Arteries by a PKA-mediated Reduction of the Sensitivity of the Contractile Apparatus for Calcium"
- Murthy, K.S., *Biochem. J.*, **360**, 199 - 208 (2001): "Activation of Phosphodiesterase 5 and Inhibition of Guanylate Cyclase by cGMP-dependent Protein Kinase in Smooth Muscle"
- Maronde, E.; Wicht, H.; Tasken, K.; Genieser, H.G.; Olcese, J.; Korf, H.W., *J. Pineal Res.*, **27**, 170 - 182 (1999): "CREB Phosphorylation and Melatonin Biosynthesis in the Rat Pineal Gland: Involvement of cyclic AMP-dependent Protein Kinase Type II"
- Ruth, P., *Pharmacol. Ther.*, **82**, 355 - 372 (1999): "Cyclic GMP-Dependent Protein Kinases: Understanding in vivo Functions by Gene Targeting"
- Cantrell, A. R.; Tibbs, V. C.; Westenbroek, R. E.; Scheuer, T.; Catterall, W. A., *J. Neurosci.*, **19**, 1 - 6 (1999): "Dopaminergic Modulation of Voltage-Gated Na⁺ Current in Rat Hippocampal Neurons Requires Anchoring of cAMP-Dependent Protein Kinase"
- Singh, A.K.; Tasken, K.; Walker, W.; Frizzell, R.A.; Watkins, S.C.; Bridges, R.J.; Bradbury, N.A., *Am.J. Physiol.*, **275**, C562 - C570 (1998): "Characterization of PKA Isoforms and Kinase-dependent Activation of Chloride Secretion in T84 Cells"
- Cheng, X.-J.; Höög, J.-O.; Nairn, A.C.; Greengard, P.; Aperia, A., *Am. J. Physiol.*, **273**, C1981 - C1986 (1997): "Regulation of Rat Na⁺, K⁺-ATPase Activity by PKC is Modulated by State of Phosphorylation of Ser-943 by PKA"
- Weissinger, E.; Eissner, G.; Grammer, C.; Fackler, S.; Haefner, B.; Yoon, L.S.; Lu, K.S.; Bazarow, A.; Sedivy, J.M.; Mischak, H.; Kolch, W., *Mol. Cell. Biol.*, **17**, 3229 - 3241 (1997): "Inhibition of the Raf-1 Kinase by Cyclic AMP Agonists Causes Apoptosis of v-abl-Transformed Cells"
- Torgersen, K.M.; Vaage, J.T.; Levy, F.O.; Hansson, V.; Rolstad, B.; Tasken, K., *J. Biol. Chem.*, **272**, 5495 - 5500 (1997): "Selective Activation of cAMP-Dependent Protein Kinase Type I Inhibits Rat Natural Killer Cell Cytotoxicity"
- Schubert, R.; Serebryakov, V.N.; Mewes, H.; Hopp, H.H., *Amer. J. Physiol.*, **41**, H1147 - H1156 (1997): "Iloprost Dilates Rat Small Arteries - Role of K-ATP- and K-CA-Channel Activation by cAMP-Dependent Protein Kinase"
- Maronde, E.; Middendorff, R.; Telgmann, R.; Müller, D.; Hemmings, B.; Tasken, K.; Olcese, J., *J. Neurochem.*, **68**, 770 - 777 (1997): "Melatonin Synthesis in the Bovine Pineal Gland is Regulated by Type II Cyclic AMP-Dependent Protein Kinase"
- Johnson, B.D.; Brousal, J.P.; Peterson, B.Z.; Gallombardo, P.A.; Hockerman, G.H.; Lai, Y.; Scheuer, T.; Catterall, W.A., *J. Neurosci.*, **17**, 1243 - 1255 (1997): "Modulation of the Cloned Skeletal Muscle L-Type Ca²⁺ Channel by Anchored cAMP-Dependent Protein Kinase"
- Tenor, H.; Hatzelmann, A.; Church, M.K.; Schudt, C.; Shute, J.K., *Br. J. Pharmacol.*, **118**, 1727 - 1735 (1996): "Effects of Theophylline and Rolipram on Leukotriene C₄ (LTC₄) Synthesis and Chemotaxis of Human Eosinophils from Normal and Atopic Subjects"
- Murphy-Ullrich, J. E.; Pallero, M.A.; Boerth, N.; Greenwood, J.A.; Lincoln, T.M.; Cornwell, T.L., *J. Cell Sci.*, **109**, 2499 - 2508 (1996): "Cyclic GMP-dependent Protein Kinase is Required for Thrombospondin and Tenascin mediated Focal Adhesion Disassembly"
- Azula, F.J.; Alzola, E.S.; Conde, M.; Trueba, M.; Macarulla, J.M.; Marino, A., *Mol. Pharmacol.*, **50**, 367 - 379 (1996): "Thrombin-stimulated Phospholipase C Activity is Inhibited Without Visible Delay by a Rapid Increase in the Cyclic GMP Levels Induced by Sodium Nitroprusside"
- Holen, I.; Gordon, P.B.; Stroemhaug, P.E.; Seglen, P.O., *Eur. J. Biochem.*, **236**, 163 - 170 (1996): "Role of cAMP in the Regulation of Hepatocytic Autophagy"
- Raman, I.M.; Tong, G.; Jahr, C.E., *Neuron* **16**, 415 - 421 (1996): "β-Adrenergic Regulation of Synaptic NMDA Receptors by cAMP-Dependent Protein Kinase"
- Fehmann, H.C.; Jiang, J.W.; Pitt, D.; Schweinfurth, J.; Göke, B., *Pancreas*, **13**, 273 - 282 (1996): "Ligand-induced Regulation of Glucagon-like Peptide-I Receptor Function and Expression in Insulin-secreting β Cells"

References cited in this Technical Information:

Sandberg, M.; Butt, E.; Nolte, C.; Fischer, L.; Halbrügge, M.; Jahnsen, T.; Genieser, H.-G.; Jastorff, B.; Walter, U., *Biochem. J.*, **279**, 521 - 527 (1991): "Characterization of Sp-5,6-dichloro-1-β-D-ribofuranosylbenzimidazole-3',5'-monophosphorothioate (Sp-5,6-DCI-cBIMPS) as a Potent and Specific Activator of cyclic AMP-dependent Protein Kinase in Cell Extracts and Intact Cells"

Dostmann, W.R.G.; Taylor, S.S.; Genieser, H.-G.; Jastorff, B.; Døskeland, S.O.; Øgreid, D., *J. Biol. Chem.*, **265**, 10484 - 10491 (1990): "Probing the Cyclic Nucleotide Binding Sites of cAMP-dependent Protein Kinase I and II with Analogs of Adenosine 3',5'-Cyclic Phosphorothioates"