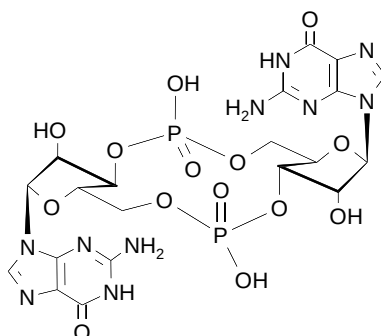


Technical Information about c-diGMP

Bacterial second messenger

Update: July 5, 2016 нд



Abbreviation:

c-diGMP

Formula	CAS No.	Molecular Weight	UV	BIOLOG Cat. No.
C ₂₀ H ₂₄ N ₁₀ O ₁₄ P ₂ (for free acid)	[61093-23-0]	690.4 (for free acid)	λ _{max} 253 nm / ε 23700 / pH 7	C 057

Name: Cyclic diguanosine monophosphate / cyclic bis (3' → 5') diguanylic acid / cyclic diguanylate / c-di-GMP

Description: In c-diGMP two 5'-GMP units are connected to form a cyclic structure.

Properties: c-diGMP is a near ubiquitous bacterial second messenger that was found to be involved in a wide variety of physiological processes such as biofilm formation, motility, and virulence in multiple bacteria. The c-diGMP metabolite pGpG (Cat. No. P 023) and the structurally related bacterial second messenger c-diAMP are offered as well (Cat. No. C 088).

Specification: Crystallized or lyophilized sodium salt. Please keep in mind that equal amounts of the compound may look different in volume. 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}.

Purity: Typical analysis is better than 98% (HPLC / UV / 253 nm). The product is not sterile and has not been tested for endotoxins.

Solubility: c-diGMP has excellent solubility in water and aqueous buffers. Please rinse tube walls carefully and preferably use ultrasonic or vortex to achieve total and uniform mixing. When opening the tube please make sure that no substance is lost within the cap.

HPLC Applications: c-diGMP can easily form aggregates in water sometimes leading to complex HPLC elution profiles. However, Hyodo et al. (2005) reported c-diGMP monomer formation upon addition of NaCl to a final concentration of > 154 mM (0.9%), resulting in highly reproducible HPLC analytics of the compound. **Reference:** Hyodo, M.; Sato, Y.; Hayakawa, Y.; Karaolis, D.K., *Nucleic Acids Symp. Ser. (Oxf.)*, **49**, 117 - 118 (2005): "Chemical Behavior of Bis(3'-5')diguanylic Acid in Aqueous Solutions"

Stability and Storage: c-diGMP 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: 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!

Selected References for c-diGMP:

Li, W.; Cui, T.; Hu, L.; Wang, Z.; Li, Z.; He, Z.-G., *Nat. Commun.*, **6**, 8330. doi (2015): "Cyclic Diguanylate Monophosphate Directly Binds to Human Siderocalin and Inhibits its Antibacterial Activity"

Gundlach, J.; Dickmanns, A.; Schröder-Tittmann, K.; Neumann, P.; Kaesler, J.; Kampf, J.; Herzberg, C.; Hammer, E.; Schwede, F.; Kaefer, V.; Tittmann, K.; Stülke, J.; Ficner, R., *J.Biol.Chem.*, **290**, 3069 - 3080 (2015): "Identification, Characterization, and Structure Analysis of the Cyclic di-AMP-binding PII-like Signal Transduction Protein DarA"

Hanson, M.C.; Crespo, M.P.; Abraham, W.; Moynihan, K.D.; Szeto, G.L.; Chen, S.H.; Melo, M.B.; Mueller, S.; Irvine, D.J., *J. Clin. Invest.*, **125**, 2532 - 2546 (2015): "Nanoparticulate STING Agonists are Potent Lymph Node-targeted Vaccine Adjuvants"

Sureka, K.; Choi, P.H.; Precit, M.; Delince, M.; Pensinger, D.A.; Huynh, T.N.; Jurado, A.R.; Goo, Y.A.; Sadilek, M.; Iavarone, A.T.; Sauer, J.-D.; Tong, L.; Woodward, J.J., *Cell*, **158**, 1389 - 1401 (2014): "The Cyclic Dinucleotide c-diAMP is an Allosteric Regulator of Metabolic Enzyme Function"

Lolicato, M.; Bucchi, A.; Arrigoni, C.; Zucca, S.; Nardini, M.; Schroeder, I.; Simmons, K.; Aquila, M.; DiFrancesco, D.; Bolognesi, M.; Schwede, F.; Kashin, D.; Fishwick, C.W.; Johnson, A.P.; Thiel, G.; Moroni, A., *Nat. Chem. Biol.*, **10**, 457 - 462 (2014): "Cyclic Dinucleotides bind the C-linker of HCN4 to Control Channel cAMP Responsiveness"

Sundriyal A.; Massa, C.; Samoray, D.; Zehender, F.; Sharpe, T.; Jenal, U.; Schirmer, T., *J. Biol. Chem.*, **289**, 6978 - 6990 (2014): "Inherent Regulation of EAL Domain-catalyzed Hydrolysis of Second Messenger Cyclic di-GMP"

Yi, G.; Brendel, V.P.; Shu, C.; Li, P.; Palanathan, S.; Kao, C.C., *PLoS One*, **8**, e77846 (2013): "Single Nucleotide Polymorphisms of Human STING Can Affect Innate Immune Response to Cyclic Dinucleotides"

Schaap, P., *IUBMB Life*, **65**, :897-903 (2013): "Cyclic Di-Nucleotide Signaling Enters the Eukaryote Domain"

Ho, C.L.; Chong, K.S.J.; Oppong, J.A.; Chuah, M.L.C.; Tan, S.M.; Liang, Z.-X., *JACS*, **135**, 566 - 569 (2013): "Visualizing the Perturbation of Cellular Cyclic di-GMP Levels in Bacterial Cells"

Stelitano, V.; Giardina, G.; Paiardini, A.; Castiglione, N.; Cutruzzolà, F.; Rinaldo, S., *PLoS ONE*, **8**, e74920 (2013): "C-di-GMP Hydrolysis by *Pseudomonas aeruginosa* HD-GYP Phosphodiesterases: Analysis of the Reaction Mechanism and Novel Roles for pGpG"

Danilchanka O.; Mekalanos J.J., *Cell*, **154**, 962 - 970 (2013): "Cyclic Dinucleotides and the Innate Immune Response"

Abdul-Sater, A.A.; Tattoli, I.; Jin, L.; Grajkowski, A.; Levi, A.; Koller, B.H.; Allen, I.C.; Beaucage, S.L.; Fitzgerald, K.A.; Ting, J.P.; Cambier, J.C.; Girardin, S.E.; Schindler, C., *EMBO Rep.*, **14**, 900 - 906 (2013): "Cyclic-di-GMP and Cyclic-di-AMP Activate the NLRP3 Inflammasome"

Gao, X.; Mukherjee, S.; Matthews, P.M.; Hammad, L.A.; Kearns, D.B.; Dann, C.E. 3rd, *J. Bacteriol.*, **195**, 4782 - 4792 (2013): "Functional Characterization of Core Components of the *Bacillus subtilis* Cyclic-di-GMP Signaling Pathway"

Gentner, M.; Allan, M.G.; Zaehring, F.; Schirmer, T.; Grzesiek, S., *J. Am. Chem. Soc.*, **134**, 1019 - 1029 (2012): "Oligomer Formation of the Bacterial Second Messenger c-di-GMP: Reaction Rates and Equilibrium Constants Indicate a Monomeric State at Physiological Concentrations"

Sharma, I.M.; Dhanaraman, T.; Mathew, R.; Chatterji, D., *Biochemistry*, **51**, 5443 - 5453 (2012): "Synthesis and Characterization of a Fluorescent Analogue of Cyclic Di-GMP"

Abdul-Sater, A.A.; Grajkowski, A.; Erdjument-Bromage, H.; Plumlee, C.; Levi, A.; Schreiber, M.T.; Lee, C.; Shuman, H.; Beaucage, S.L.; Schindler, C., *Microbes Infect.*, **14**, 188 - 197 (2012): "The Overlapping Host Responses to Bacterial Cyclic Dinucleotides"

Davies, B.W.; Bogard, R.W.; Young, T.S.; Mekalanos, J.J., *Cell*, **149**, 358 - 370 (2012): "Coordinated Regulation of Accessory Genetic Elements Produces Cyclic Di-Nucleotides for *V. Cholerae* Virulence"

Chen, Z.-H.; Schaap, P., *Nature*, **488**, 680 - 683 (2012): "The Prokaryote Messenger c-di-GMP Triggers Stalk Cell Differentiation in *Dictyostelium*"

Düvel, J.; Bertinetti, D.; Möller, S.; Schwede, F.; Morr, M.; Wissing, J.; Radamm, L.; Zimmermann, B.; Genieser, H.-G.; Jänsch, L.; Herberg, F.W.; Häussler, S., *J. Microbiol. Methods.*, **88**, 229 -236 (2012): "A Chemical Proteomics Approach to Identify c-di-GMP Binding Proteins in *Pseudomonas aeruginosa*"

Ebensen, T.; Libanova, R.; Schulze, K.; Yevsa, T.; Morr, M.; Guzmán C.A., *Vaccine*, **29**, 5210 - 5220 (2011): "Bis-(3',5')-cyclic Dimeric Adenosine Monophosphate: Strong Th1/Th2/Th17 Promoting Mucosal Adjuvant"

Abdul-Sater, A.A.; Grajkowski, A.; Erdjument-Bromage, H.; Plumlee, C.; Levi, A.; Schreiber, M.T.; Lee, C.; Shuman, H.; Beaucage, S.L.; Schindler, C., *Microbes Infect.*, **14**, 188 - 197 (2011): "The Overlapping Host Responses to Bacterial Cyclic Dinucleotides"

Newell, P.D.; Boyd, C.D.; Sondermann, H.; O'Toole, G.A., *PLoS Biol.*, **9** (2011): "A c-di-GMP Effector System Controls Cell Adhesion by Inside-Out Signaling and Surface Protein Cleavage"

Navarro, M.V.A.S.; Newell, P.D.; Krasteva, P.V.; Chatterjee, D.; Madden, D.R.; O'Toole, G.A.; Sondermann, H., *PLoS Biol.*, **9** (2011): "Structural Basis for c-di-GMP-Mediated Inside-Out Signaling Controlling Periplasmic Proteolysis"

- Matilla, M.A.; Travieso, M.L.; Ramos, J.L.; Ramos-Gonzales, M.I., *Environmental Microbiol.*, **13**, 1745 - 1766 (2011): "Cyclic Diguanylate Turnover Mediated by the Sole GGDEF/EAL Response Regulator in *Pseudomonas putida*: its Role in the Rhizosphere and an Analysis of its Target Processes"
- Johnson, J.G.; Murphy, C.N.; Sippy, J.; Johnson, T.J.; Clegg, S., *J. Bacteriol.*, **193**, 3453 - 3460 (2011): "Type 3 Fimbriae and Biofilm Formation are Regulated by the Transcriptional Regulators MrkHI in *Klebsiella Pneumoniae*"
- Gomelsky, M., *Mol. Microbiol.*, **79**, 562 - 565 (2011): "cAMP, c-di-GMP, c-di-AMP and now cGMP: Bacteria use Them All!"
- Smith, K.D.; Shanahan, C.A.; Moore, E.L.; Simon, A.C.; Strobel, S.A., *Proc. Natl. Acad. Sci. USA*, **108**, 7757 - 7762 (2011): "Structural Basis of Differential Ligand Recognition by Two Classes of bis-(3'-5')-cyclic Dimeric Guanosine Monophosphate-binding Riboswitches"
- Smith, K.D.; Strobel, S.A., *Biochem. Soc. Trans.*, **39**, 647 - 651 (2011): "Interactions of the c-di-GMP Riboswitch with its Second Messenger Ligand"
- Spangler, C.; Kaever, V.; Seifert, R., *J. Pharmacol. Exp. Ther.*, **336**, 234 - 241 (2011): "Interaction of the Diguanylate Cyclase YdeH of *Escheria Coli* with 2', (3')-Substituted Purine and Pyrimidine Nucleotides"
- Oppenheimer-Shaanan, Y.; Wexselblatt, E.; Katzhendler, J.; Yavin, E.; Ben-Yehuda, S., *EMBO Rep.*, **12**, 594 - 601 (2011): "c-di-AMP Reports DNA Integrity During Sporulation in *Bacillus subtilis*"
- Libanova, R.; Ebensen, T.; Schulze, K.; Bruhn, D.; Nörder, M.; Yevsa, T.; Morr, M.; Guzman, C.A., *Vaccine*, **28**, 2249 - 2258 (2010): "The Member of the Cyclic Di-Nucleotide Family Bis-(3', 5')-Cyclic Dimeric Inosine Monophosphate Exerts Potent Activity as Mucosal Adjuvant"
- Kanazawa, T.; Ren, S.; Maekawa, M.; Hasegawa, K.; Arisaka, F.; Hyodo, M.; Hayakawa, Y.; Ohta, H.; Masuda, S., *Biochemistry*, **49**, 10647 - 10655 (2010): "Biochemical and Physiological Characterization of a BLUF Protein-EAL Preprotein Complex Involved in Blue Light-Dependent Degradation of Cyclic Diguanylate in the Purple Bacterium *Rhodopseudomonas Palustris*"
- Tagliabue, L.; Maciag, A.; Antoniani, D.; Landini, P., *FEMS Immunol. Med. Microbiol.*, **59**, 477 - 484 (2010): "The yddV-dos Operon Controls Biofilm Formation through the Regulation of Genes Encoding Curli Fibers' Subunits in Aerobically Growing *Escherichia Coli*"
- Tchigvintsev, A.; Xu, X.; Singer, A.; Chang, C.; Brown, G.; Proudfoot, M.; Cui, H.; Flick, R.; Anderson, W.F.; Joachimiak, A.; Galperin, M.Y.; Savchenko, A.; Yakunin, A.F., *J Mol Biol.*, **402**, 524 - 538 (2010): "Structural Insight into the Mechanism of c-di-GMP Hydrolysis by EAL Domain Phosphodiesterases"
- Chen, W.X.; Patel, G.B.; Yan, H.B.; Zhang, J.B., *Hum. Vaccin.*, **6**, 706 - 714 (2010): "Recent Advances in the Development of Novel Mucosal Adjuvants and Antigen Delivery Systems"
- Harmsen, M.; Yang, L.; Pamp, S.J.; Tolker-Nielsen, T., *FEMS Immunol. Med. Microbiol.*, **59**, 253 - 268 (2010): "An Update on *Pseudomonas Aeruginosa* Biofilm Formation, Tolerance, and Dispersal"
- Spangler, C.; Böhm, A.; Jenal, U.; Seifert, R.; Kaever, V., *J. Microbiol. Methods*, **81**, 226 - 231 (2010): "A Liquid Chromatography-coupled Tandem Mass Spectrometry Method for Quantitation of Cyclic Di-guanosine Monophosphate"
- Malone, J.G.; Jaeger, T.; Spangler, C.; Ritz, D.; Spang, A.; Arrieumerlou, C.; Kaever, V.; Landmann, R.; Jenal, U., *PLOS Pathogenes*, **6**, 1 - 17 (2010): "YfiBNR Mediates Cyclic di-GMP Dependent Small Colony Variant Formation and Persistence in *Pseudomonas Aeruginosa*"
- Ching, S.M.; Tan, W.J.; Chua, K.L.; Lam, Y., *Bioorg. Med. Chem.*, **18**, 6657 - 6665 (2010): "Synthesis of Cyclic Di-nucleotidic Acid as Potential Inhibitors Targeting Diguanylate Cyclase"
- Antoniani, D.; Bocci, P.; Maciag, A.; Raffaelli, N.; Landini, P., *Appl. Microbiol. Biotechnol.*, **85**, 1095 - 1104 (2010): "Monitoring of Diguanylate Cyclase Activity and of Cyclic-Di-GMP Biosynthesis by Whole-Cell Assays Suitable for High-Troughput Screening of Biofilm Inhibitors"
- Baird, N.J.; Kulshina, N.; Ferré-D'Amare, A.R., *RNA Biology*, **7**, 328 - 332 (2010): "Riboswitch function- Flipping the Switch or Tuning the Dimmer?"
- Kitanishi, K.; Kobayashi, K.; Kawamura, Y.; Ishigami, I.; Ogura, T.; Nakajima, K.; Igarashi, J.; Tanaka, A.; Shimizu, T., *Biochemistry*, **49**, 10381 - 10393 (2010): "Important Roles of Tyr43 at the Putative Heme Distal Side in the Oxygen Recognition and Stability of the Fe(II)-O₂ Complex of YddV, a Globin-Coupled Heme-Based Oxygen Sensor Diguanylate Cyclase"
- Rao, F.; See, R.Y.; Zhang, D.; Toh, D.C.; Ji, Q.; Liang, Z.-X., *J. Biol. Chem.*, **285**, 473 - 482 (2010): "YybT is a Signaling Protein that Contains a Cyclic Dinucleotide Phosphodiesterase Domain and a GGDEF Domain with ATPase Activity"
- Hengge, R., *Nat. Rev. Microbiol.*, **7**, 263 - 273 (2009): "Principles of c-di-GMP Signalling in Bacteria"
- Lai, T.-H.; Kumagai, Y.; Hyodo, M.; Hayakawa, Y.; Rikihisa, Y., *J Bacteriol.*, **191**, 693 - 700 (2009): "The *Anaplasma Phagocytophilum* PleC Histidine Kinase and PleD Diguanylate Cyclase Two-Component System and Role of Cyclic Di-GMP in Host Cell Infection"

Hu, D.L.; Narita, K.; Hyodo, M.; Hayakawa, A.; Karaolis, D.K.R., *Vaccine*, **27**, 4867 - 4873 (2009): "C-di-GMP as a Vaccine Adjuvant Enhances Protection Against Systemic Methicillin-resistant Staphylococcus Aureus (MRSA) Infection"

Yan, H.; Wang, X.; KuoLee, R.; Chen, W., *Bioorg. Med. Chem. Lett.*, **18**, 5631 - 5634 (2008): "Synthesis and Immunostimulatory Properties of the Phosphorothioate Analogues of c-di-GMP"

Sudarsan, N.; Lee, E.R.; Weinberg, Z.; Moy, R.H.; Kim, J.N.; Link, K.H.; Breaker, R.R., *Science*, **321**, 411 - 413 (2008): "Riboswitches in Eubacteria Sense the Second Messenger Cyclic di-GMP"

Waters, C.A.; Lu, W.Y.; Rabinowitz, J.D.; Bassler, B.L., *J. Bacteriol.*, **190**, 2527 - 2536 (2008): "Quorum Sensing Controls Biofilm Formation in *Vibrio Cholerae* through Modulation of cyclic-di-GMP Levels and Repression of vpsT"

Guvener, Z.T.; Harwood, C.S.; Herberg, F.W., *Mol. Microbiol.*, **66**, 1459 - 1473 (2007): "Subcellular Location Characteristics of the *Pseudomonas Aeruginosa* GGDEF Protein, WspR, Indicate that it Produces cyclic-diGMP in Response to Growth on Surfaces"

Karaolis, D.K.R.; Means, T.K.; Yang, D.; Takahashi, M.; Yoshimura, T.; Muraille, E.; Philpott, D.; Schroeder, J.T.; Hyodo, M.; Hayakawa, Y.; Talbot, B.G.; Brouillette, E.; Malouin, F., *J. Immunol.*, **178**, 2171 - 2181 (2007): "Bacterial c-di-GMP is an Immunostimulatory Molecule"

Kim, Y.K.; McCarter, L.L., *J. Bacteriol.*, **189**, 4094 - 4107 (2007): "ScrG, a GGDEF-EAL Protein, Participates in Regulating Swarming and Sticking in *Vibro parahaemolyticus*"

Cotter, P.A.; Stibitz, S., *Curr. Opin. Microbiol.*, **10**, 17 - 23 (2007): "C-di-GMP Mediated Regulation of Virulence and Biofilm Formation"

Simm, R.; Lusch, A.; Kader, A.; Andersson, M.; Römling, U., *J. Bacteriol.*, **189**, 3613 - 3623 (2007): "Role of EAL-containing Proteins in Multicellular Behavior of *Salmonella enterica* Serovar Typhimurium"

Mendez-Ortiz, M.M.; Hyodo, M.; Hayakawa, Y.; Membrillo-Hernandez, J., *J. Biol. Chem.*, **281**, 8090 - 8099 (2006): "Genome-wide Transcriptional Profile of *Escherichia coli* in Response to High Levels of the Second Messenger 3', 5'- cyclic Diguanylic Acid"

Zhang, Z.; Kim, S.; Gaffney, B. L.; Jones, R.A., *J. Am. Chem. Soc.*, **128**, 7015 - 7024 (2006): "Polymorphism of the Signaling Molecule c-di-GMP"

Gjermansen, M.; Ragas, P.; Tolker-Nielsen, T., *FEMS Microbiol. Lett.*, **265**, 215 - 224 (2006): "Proteins with GGDEF and EAL Domains Regulate *Pseudomonas Putida* Biofilm Formation and Dispersal"

Ryan, R.P.; Fouhy, Y.; Lucey, J.F.; Dow, J.M., *J. Bacteriol.*, **188**, 8327 - 8334 (2006): "Cyclic Di-GMP Signaling in Bacteria: Recent Advances and New Puzzles"

Camilli, A.; Bassler, B.L., *Science*, **311**, 1113 - 1116 (2006): "Bacterial Small-Molecule Signaling Pathways"

Christen, M.; Christen, B.; Folcher, M.; Schauerte, A.; Jenal, U., *J. Biol. Chem.*, **280**, 30829 - 30837 (2005): "Identification and Characterization of a Cyclic di-GMP-specific Phosphodiesterase and Its Allosteric Control by GTP"

Hoffmann, L.; D'Argentino, D.A.; MacCross, M.J.; Zhang, Z.; Jones, R.A.; Miller, S.I., *Nature*, **436**, 1171 - 1175 (2005): "Aminoglycoside Antibiotics Induce Bacterial Biofilm Formation"

Tamayo, R.; Tischler, A.D.; Camilli, A., *J. Biol. Chem.*, **280**, 33324 - 33330 (2005): "The EAL Domain Protein VieA is a Cyclic Diguanylate Phosphodiesterase"

Römling, U.; Gomelsky, M.; Galperin, M.Y., *Mol. Microbiol.*, **5**, 629 - 639 (2005): "C-di-GMP: the Dawning of a Novel Bacterial Signalling System"

Karaolis, D.K.R.; Cheng, K.; Lipsky, M.; Elnabawi, A.; Catalano, J.; Hyodo, M.; Hayakawa, Y.; Raufman, J.-P., *Biochem. Biophys. Res. Comm.*, **329**, 40 - 45 (2005): "3', 5'-cyclic Diguanylic Acid (c-di-GMP) Inhibits Basal and Growth Factor-stimulated Human Colon Cancer Cell Proliferation"

Simm, R.; Morr, M.; Kader, A.; Nimtz, M.; Römling, U., *Mol. Microbiol.*, **53**, 1123 - 1134 (2004): "GGDEF and EAL Domains Inversely Regulate Cyclic Di-GMP Levels and Transition from Sessility to Motility"

D'Argenio, D.A. & Miller, S.I., *Microbiology*, **150**, 2497 - 2502 (2004): "Cyclic di-GMP as a Bacterial Second Messenger"

Ross, P.; Mayer, R.; Benziman, M., *Microbiol. Rev.*, **55**, 35 - 58 (1991): "Cellulose Biosynthesis and Function in Bacteria"

Amikam, D.; Benziman, M., *J. Bacteriol.*, **171**, 6649 - 6655 (1989): "Cyclic Diguanylic Acid and Cellulose Synthesis in *Agrobacterium tumefaciens*"

Ross, P.; Weinhouse, H.; Aloni, Y.; Michaeli, D.; Weinberger-Ohana, P.; Mayer, R.; Braun, S.; de Vroom, E.; van der Marel, G. A.; van Boom, J. H.; Benziman, M., *Nature*, **325**, 279 - 281 (1987): "Regulation of Cellulose Synthesis in *Acetobacter xylinum* by Cyclic Diguanylic acid"