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Acetoxymethyl Esters:

Highly Membrane-permeant Precursors of Cyclic Nucleotides and their Analogues

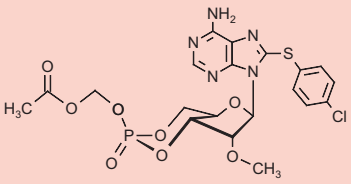
Introduction

Cyclic nucleotides and their analogues have a negatively charged phosphate group which confers extreme hydrophilicity, reducing their membrane permeability or making them membrane-impermeable. This hydrophilicity prevents endogenously formed cyclic nucleotides from leaking out of cells. However, it can also make experimental extracellular application difficult or ineffective.
One approach for generating lipophilic and membrane-permeant derivatives involves masking the negative charge of a cyclic nucleotide by esterification of its cyclic phosphate with an acetoxymethyl group. The compound is reversibly converted into an uncharged and lipophilic derivative that can cross the cell membrane.

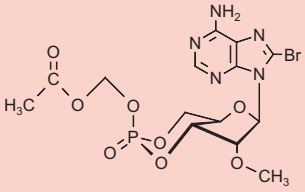
Inside the cell, the bioactivatable acetoxymethyl ester is hydrolyzed by endogenous esterases. This causes the cyclic nucleotide to revert to its biologically active form with acetic acid and formaldehyde released as by-products of the conversion.

BIOLOG offers highly membrane-permeant acetoxymethyl esters of PKA- or Epac-specific cAMP analogues that can be used to distinguish between both signalling pathways, and a control compound for acetoxymethyl ester applications.

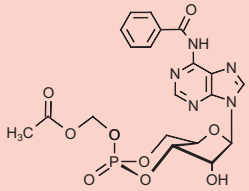
Ref.: Schultz et al., *Mol. Pharmacol.*, **46**, 702 - 708 (1994): "Membrane-permeant Derivatives of cyclic AMP Optimized for High Potency, Prolonged Activity, or Rapid Reversibility" • Schultz et al., *J. Biol. Chem.*, **268**, 6316 - 6322 (1993): "Acetoxymethyl Esters of Phosphates, Enhancement of the Permeability and Potency of cAMP"



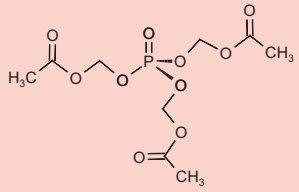
8-pCPT-2'-O-Me-cAMP-AM
Cat. No. C 051
Metabolically activatable, highly membrane-permeant Epac agonist



8-Br-2'-O-Me-cAMP-AM
Cat. No. B 028
Metabolically activatable, highly membrane-permeant Epac agonist



6-Bnz-cAMP-AM
Cat. No. B 079
Metabolically activatable, highly membrane-permeant PKA agonist



PO_4-AM_3
Cat. No. P 030
Control compound for acetoxymethyl ester applications

8-pCPT-2'-O-Me-cAMP-AM
C 051-01, 1 µmol/~0.6 mg
C 051-05, 5 x 1 µmol

8-(4-Chlorophenylthio)-2'-O-methyladenosine-3',5'-cyclic monophosphate, acetoxymethyl ester; purity > 97% HPLC for mixture of isomers.

Extremely membrane-permeant precursor of the specific Epac agonist 8-pCPT-2'-O-Me-cAMP (Cat. No. C 041). After permeation and metabolic activation by esterases the active compound is released.

Ref.: Vliem et al., *ChemBioChem*, **9**, 2052-2054 (2008) • Chepurny et al., *J. Biol. Chem.*, **284**, 10728-10736 (2009) • Dzhura et al., *J. Physiol.*, **588**, 4871-4889 (2010)

8-Br-2'-O-Me-cAMP-AM
B 028-01, 1 µmol/~0.5 mg
B 028-05, 5 x 1 µmol

8-Bromo-2'-O-methyladenosine-3',5'-cyclic monophosphate, acetoxymethyl ester; purity > 97% HPLC for mixture of isomers.

Extremely membrane-permeant precursor of the specific Epac agonist 8-Br-2'-O-Me-cAMP (Cat. No. B 022). After permeation and metabolic activation by esterases the active compound is released. 8-Br-2'-O-Me-cAMP-AM is suitable for a newly developed improved FRET protocol for measurements of intracellular cAMP concentrations and kinetics.

Ref.: Börner et al., *Nature Protocols*, **6**, 427-438 (2011)

6-Bnz-cAMP-AM
B 079-01, 1 µmol/~0.5 mg
B 079-05, 5 x 1 µmol

N^6-Benzoyladenosine-3',5'-cyclic monophosphate, acetoxymethyl ester; purity > 97% HPLC for mixture of isomers.

Extremely membrane-permeant precursor of the specific PKA agonist 6-Bnz-cAMP (Cat. No. B 009). After permeation and metabolic activation by esterases the active compound is released. 6-Bnz-cAMP-AM does not activate Epac and thus can be used as an Epac-negative control.

Ref.: Leech et al., *Islets*, **2**, 72-81 (2010) • Dzhura et al., *J. Physiol.*, **588**, 4871-4889 (2010)

PO_4-AM_3
P 030-003, 0.33 µmol/~0.1 mg
P 030-015, 5 x 0.33 µmol

Phosphate tris(acetoxymethyl)-ester; purity > 95% (MS); 0.33 µmol of PO_4-AM_3 correspond to 1 µmol of a cyclic nucleotide-acetoxymethyl ester.

Membrane-permeant prodrug of inorganic phosphate. After permeation and metabolic activation by esterases the highly polar inorganic phosphate (PO_4^{3-}) is released. In addition, the acetoxymethyl ester groups liberate acetic acid and formaldehyde, two metabolites with potential biological functions. Therefore, PO_4-AM_3 is recommended as a control reagent in nucleotide-acetoxymethyl ester applications to test for side effects of acetic acid and formaldehyde.

Ref.: Kelley et al., *Islets*, **1**, 260-265 (2009) • Dzhura et al., *J. Physiol.*, **588**, 4871-4889 (2010)

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