



# Regioselective enzymatic undecylenoylation of 8-chloroadenosine and its analogs with biomass-based 2-methyltetrahydrofuran as solvent

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## HIGHLIGHTS

- Use of MeTHF as a promising alternative to THF for enzymatic acylation.
- Much better enzyme performance in MeTHF than in other media.
- Excellent regioselectivities (94–>99%) of the enzymatic approach for nucleosides acylation.
- Revealing nucleoside substrate recognition of *Penicillium expansum* lipase for the first time.

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## ABSTRACT

2-Methyltetrahydrofuran (MeTHF), a biomass-derived compound, is a promising medium for biocatalysis and organometallic reactions. The regioselective acylation of 8-chloroadenosine (8-Cl-Ado) and its analogs was carried out in MeTHF with immobilized *Penicillium expansum* lipase. The lipase displayed more than twofold higher catalytic activity and much better thermostability in MeTHF than in other organic solvents and co-solvent systems. The optimum reaction medium, enzyme dosage, molar ratio of viny ester to nucleoside and reaction temperature for the enzymatic acylation of 8-Cl-Ado were MeTHF, 25 U/mL, 7.5 and 35 °C, respectively, under which the desirable 5'-O-undecylenoyl-8-Cl-Ado was obtained with a yield of 95% and a regioselectivity of >99% in 3 h. In addition, the lipase catalyzed regioselective undecylenoylation of other purine nucleosides, producing 5'-undecylenic acid esters with moderate to high yields (63–94%) and excellent 5'-regioselectivities (94–>99%). Use of biomass-derived solvents might open up novel opportunities for sustainable and greener biocatalytic processes.

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## 1. Introduction

Purine nucleoside analogs represent an important class of cytotoxic agents with high immunosuppressive and anti-tumor activities (Robak et al., 2006). For instance, 8-chloroadenosine (8-Cl-Ado), an active metabolite of its 3',5'-cyclic monophosphate (8-Cl-cAMP), is efficacious against multiple myeloma cells (Gandhi et al., 2001); and 2-chloroadenosine (2-Cl-Ado) exerted strong cytotoxicity against human prostate cancer cells (Bellezza et al., 2008). Like other purine nucleosides, these nucleoside analogs are unstable *in vivo* and readily degraded to metabolites with low activities such as 8-chloroinosine and 8-chloroadenine by adenosine deaminase and phosphorylase, respectively (Langeveld et al., 1992; Wang et al., 2000). In addition, nucleoside drugs usually suffer from severe side effects as well as low oral

bioavailability because of their high polarity and low intestinal permeability (Li et al., 2008a). In contrast, ester derivatives of nucleosides do not exhibit the drawbacks of their parent compounds; for example, valganciclovir, a monoester derivative of ganciclovir, has been approved to be the antiviral alternative to ganciclovir by the US Food and Drug Administration (De Clercq and Field, 2006). However, regioselective acylation of nucleosides remains a tedious task because of the presence of multiple active hydroxyl and/or amino groups. The use of biocatalysts enables the modification of such compounds, due to the enzymes' exquisite regioselectivity, simplicity of use, mild reaction conditions, and environmentally friendly nature (Li et al., 2010).

2-Methyltetrahydrofuran (MeTHF) has emerged as an alternative to the commonly used analog – THF, and has been increasingly applied in various organic reactions due to its favorable properties (Pace et al., 2011, 2012; Robert et al., 2008). For example, the higher boiling point of MeTHF (80 vs. 66 °C for THF) could significantly reduce solvent evaporation during the reaction, and MeTHF has much higher tolerance toward HCl than THF (Aycok, 2007). In

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