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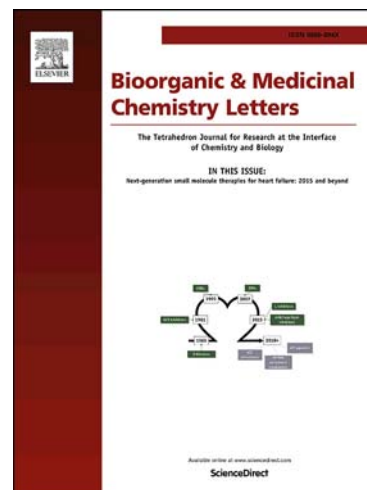
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**Covalent inhibitors of nicotinamide N-methyltransferase (NNMT) provide evidence for target engagement challenges *in situ***

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**Abstract**

Nicotinamide N-methyltransferase (NNMT) catalyzes the N-methylation of nicotinamide using S-adenosyl-L-methionine (SAM) as a methyl donor and, through doing so, can modulate cellular methylation potential to impact diverse epigenetic processes. NNMT has been implicated in a range of diseases, including cancer and metabolic disorders. Potent, selective, and cell-active inhibitors would constitute valuable probes to study the biological functions and therapeutic potential of NNMT. We previously reported the discovery of electrophilic small molecules that inhibit NNMT by reacting with an active-site cysteine residue in the SAM-binding pocket. Here, we have used activity-based protein profiling (ABPP)-guided medicinal chemistry to optimize the potency and selectivity of NNMT inhibitors, culminating in the discovery of multiple alpha-chloroacetamide ( $\alpha$ CA) compounds with sub- $\mu$ M IC<sub>50</sub> values *in vitro* and excellent proteomic selectivity in cell lysates. However, these compounds showed much weaker inhibition of NNMT in cells, a feature that was not shared by off-targets of the  $\alpha$ CAs. Our results show the potential for developing potent and selective covalent inhibitors of NNMT, but also highlight challenges that may be faced in targeting this enzyme in cellular systems.

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