

Abstract

The methylation of arginine residues is a prevalent post-translational modification, found on both nuclear and cytoplasmic proteins, catalyzed by the protein arginine N-methyltransferase (PRMT) family of enzymes. To date there have been only a few publications describing small-molecule chemical modulators of the PRMTs. In this thesis are report the synthesis of a number of compounds structurally related to arginine methyltransferase inhibitor 1 (AMI-1). The structural alterations that we made included: 1) the substitution of the sulfonic groups with the bioisosteric carboxylic groups; 2) the replacement of the ureidic function with a bisamidic and mixed urea-amidic moiety; 3) the introduction of a N-containing basic moiety; 4) the positional isomerization of the amino- hydroxynaphthoic moiety; and 5) bioisosteric substitution of naphthol with indol. The biological activity of these compounds has been assessed against a panel of arginine methyltransferases (fungal RmtA, hPRMT1, hCARM1, hPRMT3, hPRMT6) and lysine methyltransferase (SET7/9 and G9a) using histone and nonhistone proteins as substrates. Molecular modeling studies for a deep binding-mode analysis of test compounds were also performed. The bis-carboxylic acid derivatives **1b** and **7b** emerged as the most effective PRMT inhibitors, both in vitro and in vivo, being comparable or even better than the reference compound (**AMI-1**) and practically inactive against the lysine methyltransferase SET7/9. We also identified **33a** as the first powerful and selective activator of CARM-1.

Moreover an enantioselective α -amination of aryl oxindoles catalyzed by a dimeric quinidine has been developed. This procedure is general, broad in substrate scope, and affords the desired products in good yields with good to excellent enantioselectivities.