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Computational fishing of new DNA methyltransferase inhibitors from natural products

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ABSTRACT

DNA methyltransferase inhibitors (DNMTis) have become an alternative for cancer therapies. However, only two DNMTis have been approved as anticancer drugs, although with some restrictions. Natural products (NPs) are a promising source of drugs. In order to find NPs with novel chemotypes as DNMTis, 47 compounds with known activity against these enzymes were used to build a LDA-based QSAR model for active/inactive molecules (93% accuracy) based on molecular descriptors. This classifier was employed to identify potential DNMTis on 800 NPs from NatProd Collection. 447 selected compounds were docked on two human DNA methyltransferase (DNMT) structures (PDB codes: 3SWR and 2QRV) using AutoDock Vina and Surflex-Dock, prioritizing according to their score values, contact patterns at 4 Å and molecular diversity. Six consensus NPs were identified as virtual hits against DNMTs, including 9,10-dihydro-12-hydroxygambogic, phloridzin, 2′,4′-dihydroxychalcone 4′-glucoside, daunorubicin, pyrromycin and centaurein. This method is an innovative computational strategy for identifying DNMTis, useful in the identification of potent and selective anticancer drugs.

1. Introduction

DNA methylation is a covalent biochemical modification defined as an epigenetic change important in the regulation of gene expression [1,2]. The progression of DNA methylation involves a cycle of demethylation, *de novo* methylation, and methylation maintenance, catalyzed by family enzymes known as DNA methyltransferases (DNMTs, EC#: 2.1.1.37) [3–5]. These are responsible of transferring a methyl group from S-adenosyl-L-methionine (SAM) to the carbon-5 position of cytosine in DNA. This mechanism has been proposed for several authors (Fig. 1) [6–9]. Currently, three types of cytosine-5 DNMTs have been identified, including two *de novo* DNA methyltransferases; DNMT3A and DNMT3B, which establish the methylation patterns during embryonic development in mammals and in differentiated cells [10,11]; and DNMT1, the most abundant and active of these enzymes responsible for copying the methylation pattern of DNA during cell division [12,13]. It has been shown that DNMT1 plays an important role in carcinogenesis [12,14], therefore, these targets are of particular interest to search for specific inhibitors [15–17].

The inhibition of DNMTs activity has been presented as a possible pathway to reactivate genes silenced by methylation of their promoters in different diseases, including cancer [1,12,18]. The relationship between the hypermethylation of promoter of tumor suppressor genes and cancer development has been clearly demonstrated [3,4,19], suggesting DNMTs as promising drug targets for the discovery of new and more potent/selective anticancer drugs [20]. To date, several DNMT inhibitors (DNMTis) of different structural classes have been published; basically categorized as nucleoside DNMTis and non-nucleoside analog DNMTis, Fig. 2 [16,21]. DNMTis nucleosides, cytosine analogs, have been studied in several cancer types [22,23]. Most of these compounds that inhibit the activity of DNMT have been related with significant "off target" effects [24], a fact that has prevented their use with pharmacological purposes. However, two of them, azacitidine and decitabine, have been approved by FDA (Food and Drug Administration) for the treatment of myelodysplastic syndromes [25,26]. Moreover, non-nucleoside DNMTis, such as RG-108 [27], which was identified *via* virtual screening methods; and SGI-1027, a quinoline derivative, have been proposed as DNMTis [28,29]. However, the weak inhibitory activity of these compounds [30] indicates a need for the search of more effective inhibitors in the future.

Natural products (NPs) are a promissory source of drugs due to their molecular diversity and low toxicity. It is estimated that 60% of approved drugs are derived from natural sources [31–33]. To

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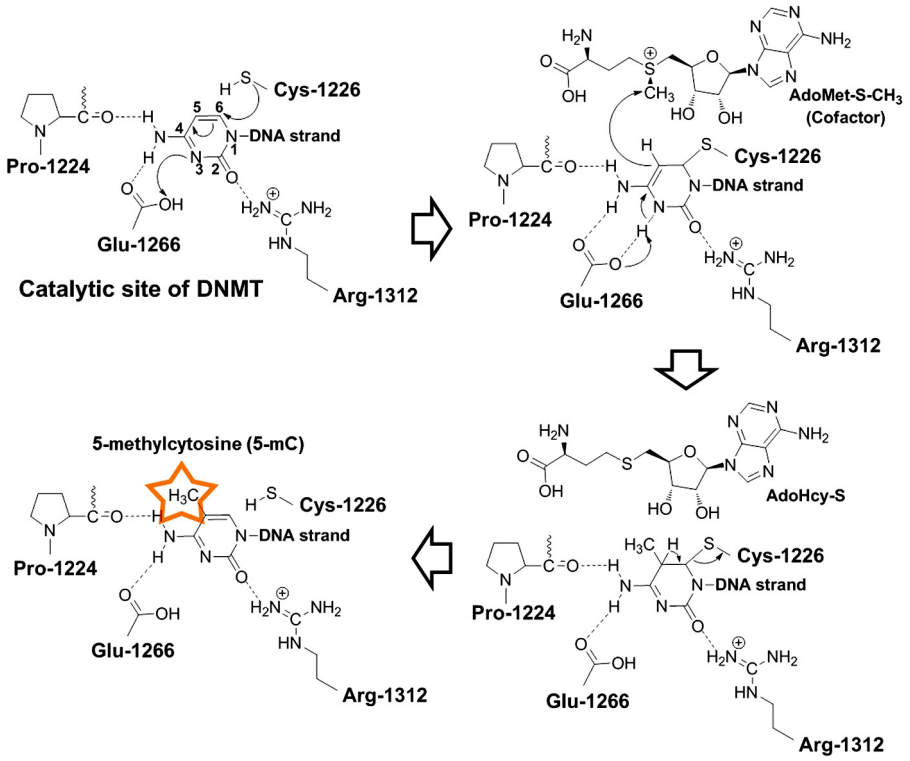

Fig. 1. Mechanism of cytosine DNA methylation catalyzed by DNMTs. DNMTs contain a conserved cysteine residue that attacks the C(6) atom of cytosine forming a covalent bond. A nucleophilic attack occurs on the methyl group of S-adenosyl-L-methionine (AdoMet), which is converted to S-adenosyl-L-homocysteine (AdoHcy-S). The last step comprises β-elimination across the C(5)—C(6) bond, releasing the enzyme.

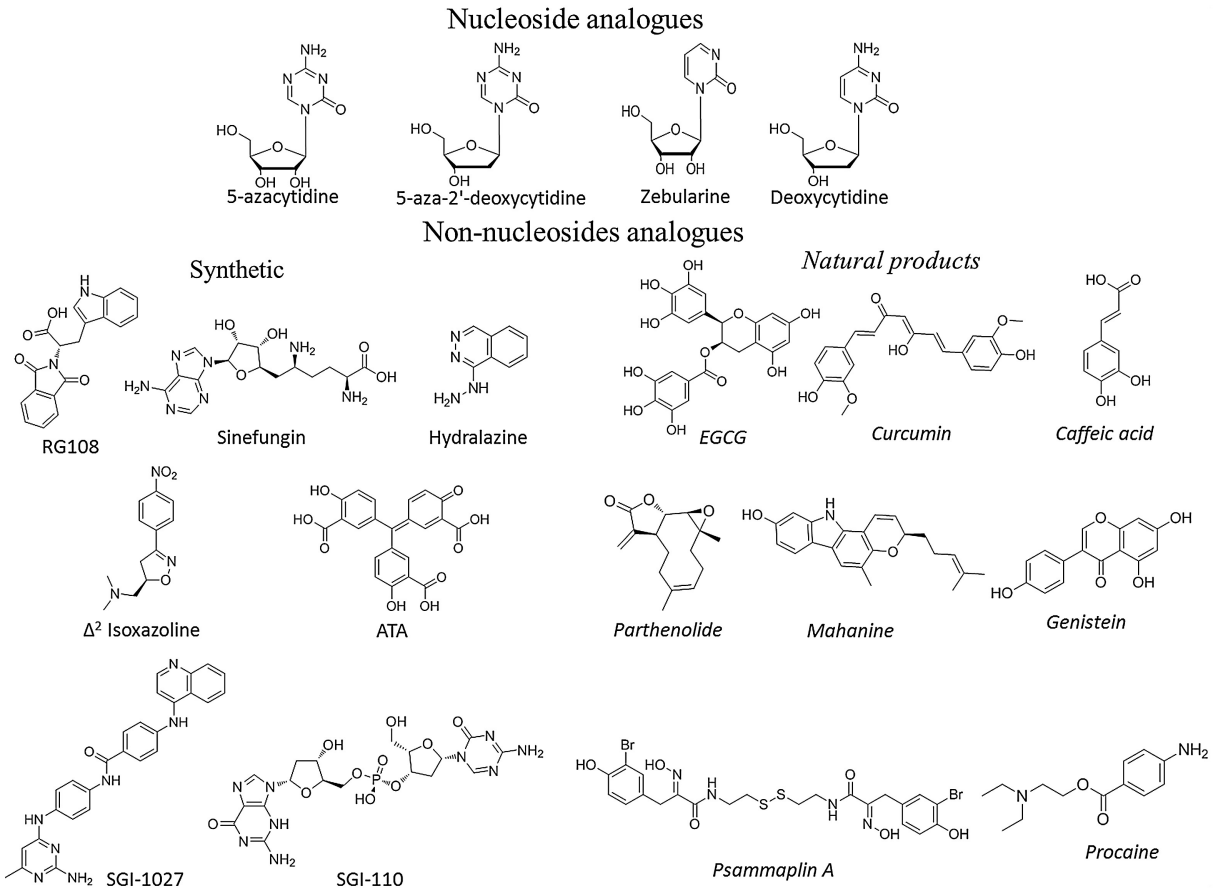

Fig. 2. Chemical structure of representative known nucleoside analogs and non-nucleoside DNMTis, classified as synthetic and natural products.