Identification of novel DNA Methyltransferase 1 (DNMT1) inhibitors from focused databases

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INTRODUCTION

DNA methylation is associated with various diseases including psychiatric diseases, diseases of the immune system, and contributes to both the initiation and progression of various cancers. This reaction is mediated by a family of enzymes called DNA methyltransferases (DNMTs), including DNMT1. However, despite the importance of DNMT1, it has not been possible to develop drugs that allow its inhibition without potent cytotoxic effects. Thus, it is crucial to use cheminformatic tools to discover DNMT1 inhibitors that do not have cytotoxic effects.

AIM

Identification of novel DNA Methyltransferase 1 (DNMT1) inhibitors from focused databases that do not have the cytotoxic side effects current approved medications.

METHODOLOGY

1. Database selection

A code was made to establish a canonical SMILES for each compound and thus obtain its physicochemical properties. Afterwards, PUMA was used to perform an analysis of chemical space, scaffold diversity, and fingerprint similarity.

Focused libraries → OTAVA database

2. Selection of compounds

Molecular docking analysis and different machine learning methods including Epigenetic Target Profiler.

OTAVA database → 20 compounds

3. Assessment of selected compounds

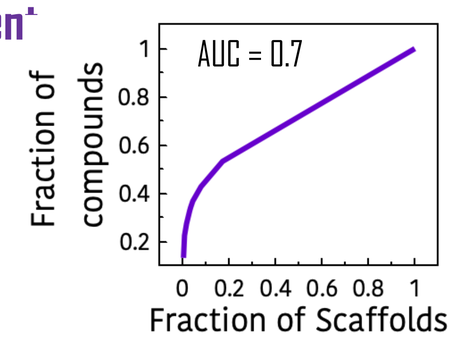
Selected compounds are currently being evaluated for their inhibitory activity against DNMT1.

20 compounds ⇢ Active compounds

RESULTS

Database assessmen*

97% of the compounds comply with the rules of Lipinski and Veber



M	399
N	226
Ns	187
N/M	57%
Ns/N	83%
P25	1%
P50	15%
P75	56%

Molecular docking

DNMT1: 4WXX
Autodock Vina

Average	-7.74
Standard deviation σ	0.94

* = Σcompounds > score
** = score + 0.5 ≥ compounds > score

Score	ΣCompounds*	Compounds**
-5	401	4
-5.5	397	16
-6	381	27
-6.5	354	52
-7	302	47
-7.5	255	91
-8	164	84
-8.5	80	51
-9	29	23
-9.5	6	5
-10	1	1

Machine Learning using fingerprints

Fingerprints used:
Morgan by Random Forest
RDK by SVM

RDK: Fingerprints

Morgan: Fingerprints		Positive	Negative
	Positive	9	19
	Negative	33	340

Toxicological Assessment

Currently compounds are being assessed for their cytotoxic activity as well as inhibitory activity

All compounds were studied using Toxtree 3.1 by the following protocols:

- Cramer Class
- Start Biodegradability
- DNA Binding Alerts
- Carcinogenicity (genotox and nongenotox) and mutagenicity rulebase by ISS

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