Chemoinformatic-Based Pharmacophore Modeling of Non-nucleoside Inhibitors of DNA Methyltransferase 1

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Background

DNA methylation is an epigenetic modification involving the addition of methyl group at the C-5 position of a cytosine residue. This process plays a key role in mammal development and in cancer cell growth. The methylation process is mediated by an enzymatic family called DNA methyltransferases (DNMTs).

Justification

The number of DNMT inhibitors reported in the literature is growing. However, to date is not known the structural diversity and chemical space coverage quantitatively or at least relative to other known compounds collections properties. From this analysis we identified the best compounds with biological activity against this DNMT1, which in turn served as the basis for studies of molecular docking and pharmacophore modeling.

Methodology

- It was built and cured a database DNMT inhibitors (DNMT) from four sources , three public databases and inhibitors information in scientific literature (265 ChEMBL, HEMD 106 , 337 Binding Database and 47 Literature) .
- Cured public databases : approved drugs (**Ap**) , compounds in clinical trials (**Cli**), an inhibitors collection (**In**) and a focused library of epigenetic inhibitors (**Epi**)
- Comparison and analysis through six physicochemical properties (**HBA , HBD , SlogP, MW , RB, TPSA**) , molecular fingerprints (**GpiDAPH3 , MACCS keys , TGD , ECFP4 and 6**) and scaffolds (**cyclic systems**) .
- Molecular docking by ICM protocol of the selected compounds was performed.
- The best scoring conformations were selected to perform **PLIF**(Protein Ligand Interaction Fingerprints) calculations and develop of pharmacophore model (**MOE**).
- The models were validated by DNMT data base and a conformational library. Through the result obtained in every search we construct the confusion matrix and ROC space to select the best model to be a DNMT1 inhibitor query.
- Preliminary test through pharmacophore based virtual screening on approved drugs and anticancer compounds databases to confirm the selectivity a sensitivity of the modes.

Results

Physicochemical properties (PCP)

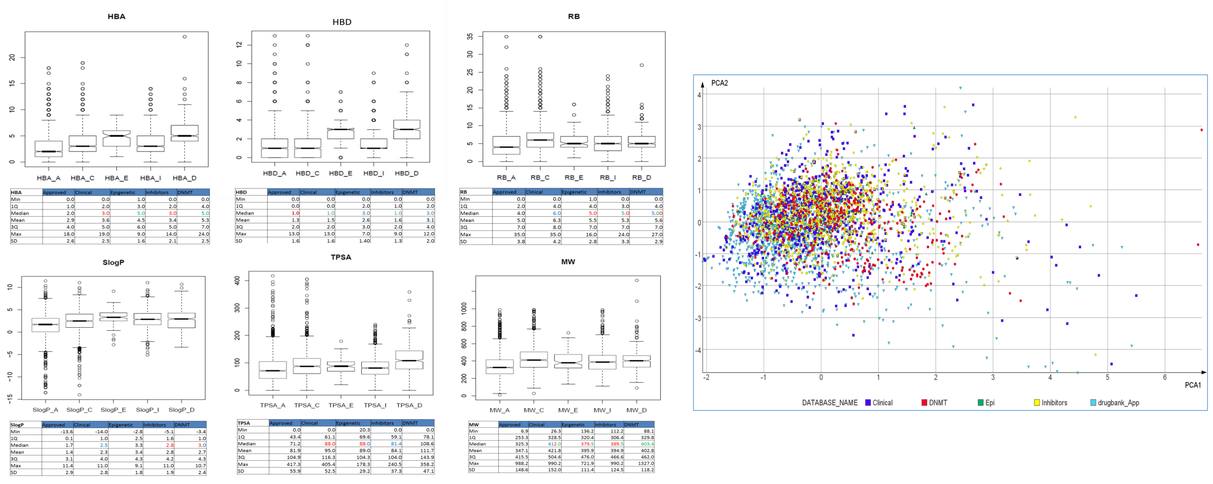

Fig1. Notch boxplots and distributions of the six physicochemical properties for each of the databases studied. Principal Component Analysis for the six physicochemical properties for each databases.

Scaffolds

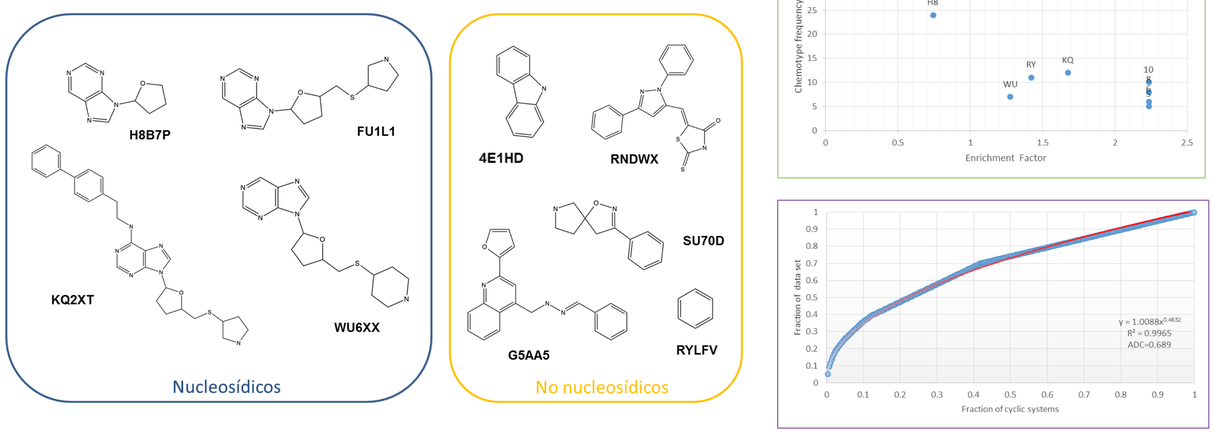

Fig2. Nucleoside and non-nucleoside cyclic systems obtained through MEQI software. Frequency vs enrichment factor chart and cyclic systems retrieval curve (CSR)

Fingerprints

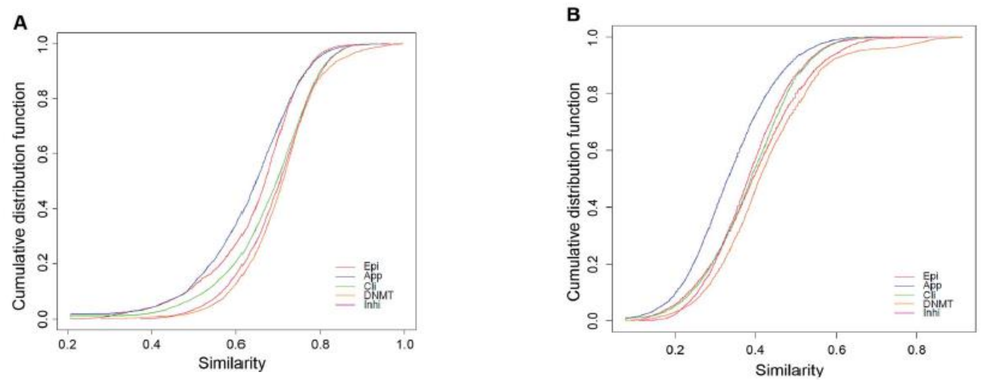

Fig3. CDF of the databases studied regard TGD (A) and MACCS keys (B)

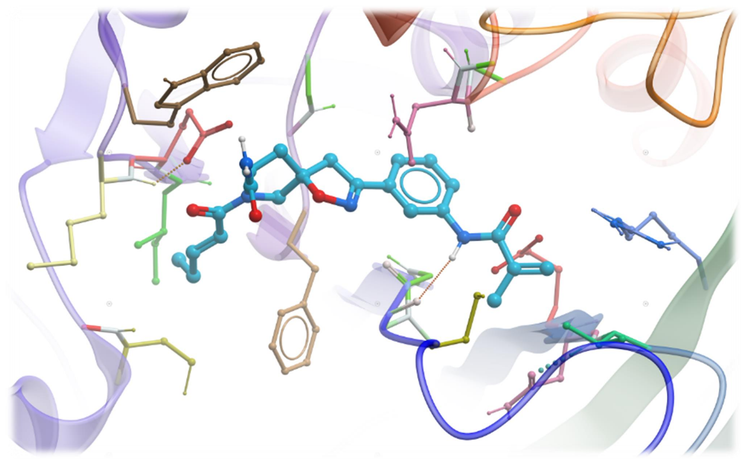

Fig4. Molecular docking of the best enrichment factor and frequency scaffold (SU70D).

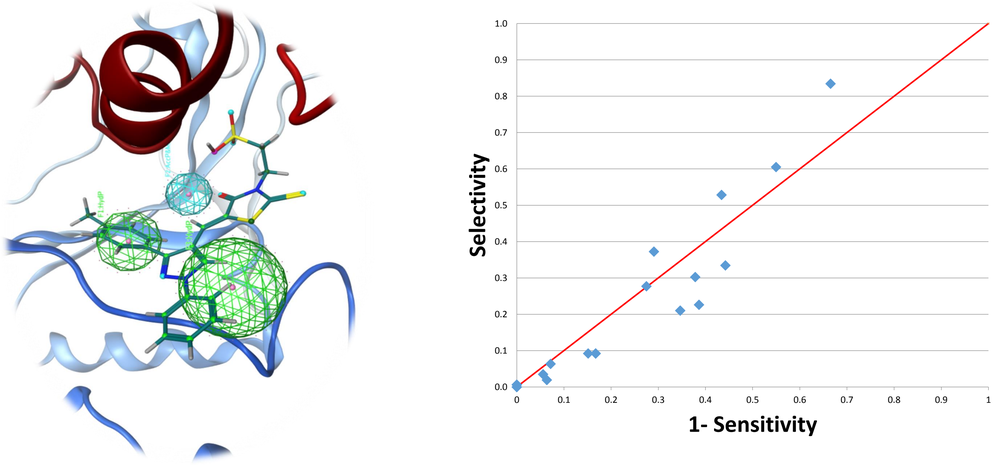

Fig5. Best pharmacophore model according to ROC space.

Model	Hits	PM > 600 compounds	Specificity	Selectivity
RN_All	2304	254	+	-
SU3_All	761	178	-	+

Data set	RN_All Hits	SU3_All Hits
AOD_Plate4825	72	34
AODIV_Plate1 and 2	52	28
ApprovedOncDrugs_5_PlateMap_AOD	67	33

Fig6. Preliminary pharmacophore based virtual screening on approved drugs database from Drug Bank (1490) and approved oncology drugs data sets plates from National Cancer Institute U.S.A.(119,114 and 95)

Conclusions

PFQ. The distributions found in the reference databases and reported in published works are similar. The PCP of Epi and DNMT are statistically similar , as well as Ap, Cli and In. Property space is mainly occupied by Ap and In and all other collections are contained in this space. DNMT compounds and Epi occupy similar subspaces but DNMT covers some areas not occupied by Epi .

***FingerPrints*.**The best performances fingerprint are TGD and MACCS keys. Diversity is in the order : Ap > In> Cli > DNMT > Epi .

Scaffolds.We found most often nucleoside cyclic systems but the non-nucleoside compounds have a higher enrichment factor (EF). High EF molecules are potential privileged scaffolds DNMT1 inhibitors.

Docking. We obtain the best scoring poses for each of the scaffolds with higher frequency and EF in the substrate and cofactor site through ICM software.

Pharmacophore. Different pharmacophore models for each scaffold conformation were obtained and validated by ROC space. The selected models showed a good performance in the preliminary virtual screening search of compounds with anticancer properties within the approved drugs database.

Acknowledgements

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