XXIX Symposium on Bioinformatics and Computed-Aided Drug Discovery

Expanding the epigenetic relevant chemical space: identification of DNA methyltransferase 1 activators.

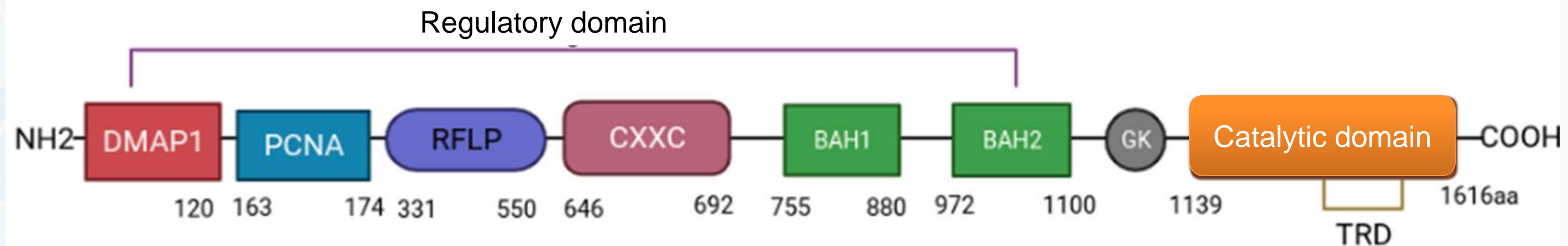BQD. Massyel M. Martínez-Cortés and Dr.

José L. Medina-Franco.

National Autonomous University of Mexico

September 19, 2023

DNA methyltransferases

- Regulate the DNA methylation process
- Family composed of 5 proteins: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L.
- The methylation process is through the transfer of the methyl group from S-adenosyl-methionine (SAM) to cytosine.
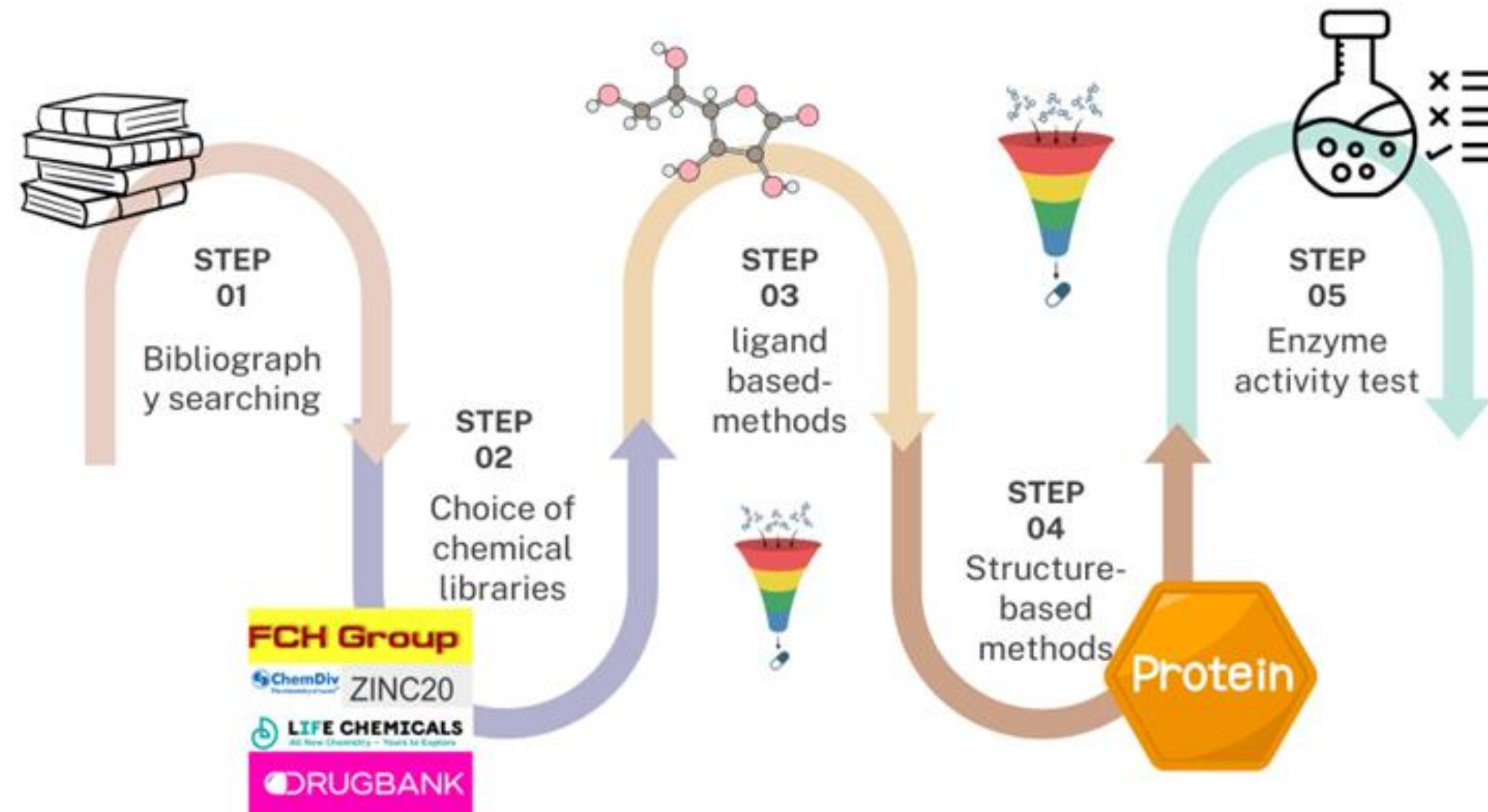
Importance of methylation

- Carcinogenesis is accompanied by a global loss in DNA methylation.
- Cancer hypomethylation may also cause genomic instability.
- Hypomethylated cells showed reduced proliferation rates, increased transcription of genes, reactivation of the inactive X-chromosome and abnormal nuclear morphologies.
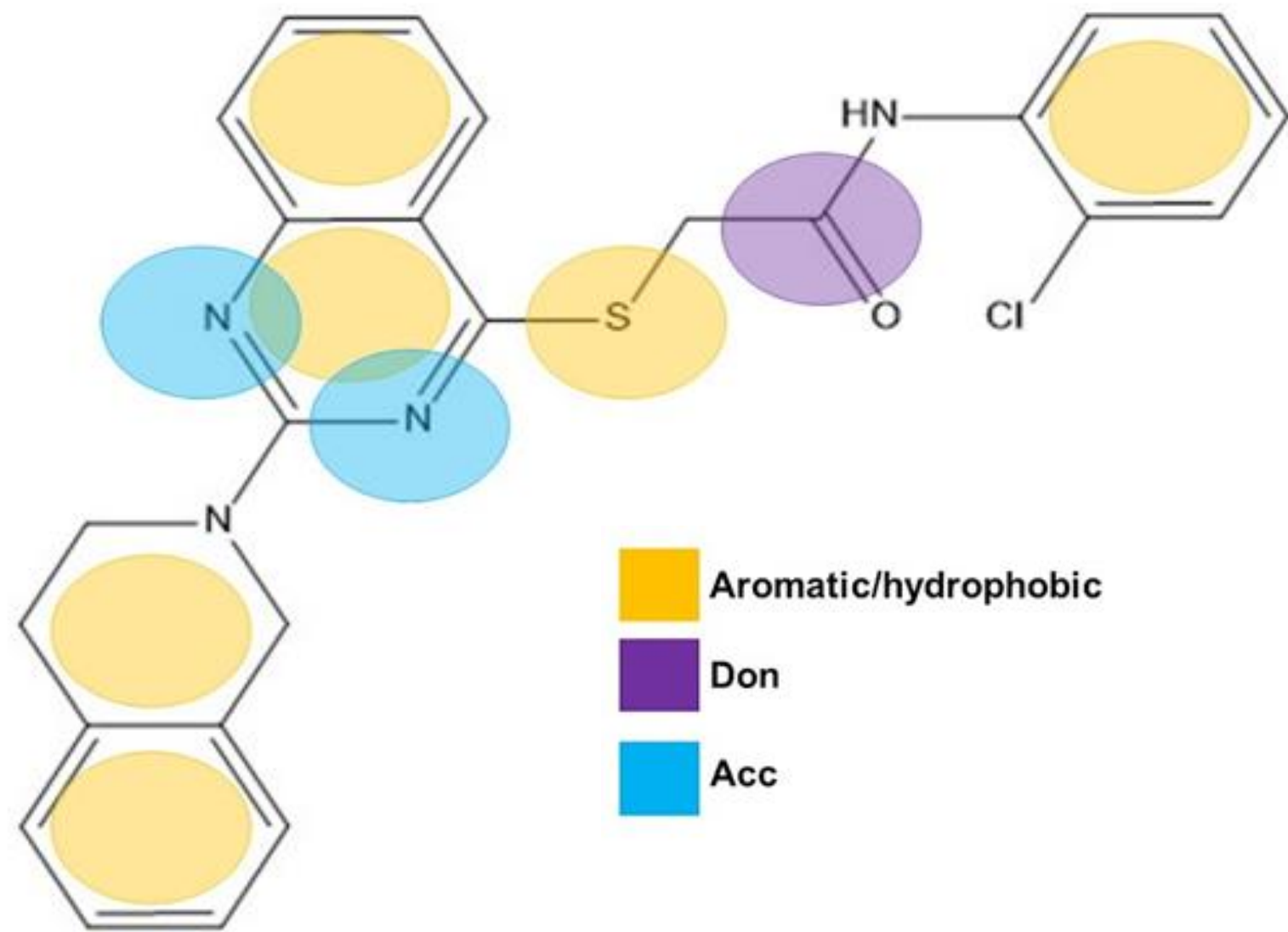
2
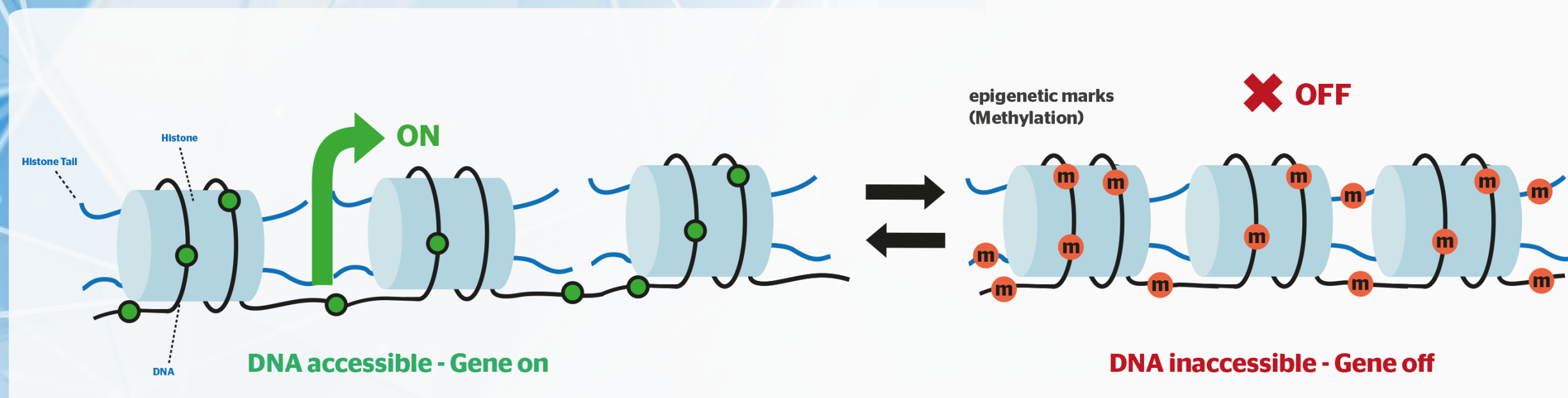
To identify compounds with the potential to enhance the catalytic activity of the DNA methyltransferase 1 enzyme (DNMT1), employing chemical libraries and computational tools.
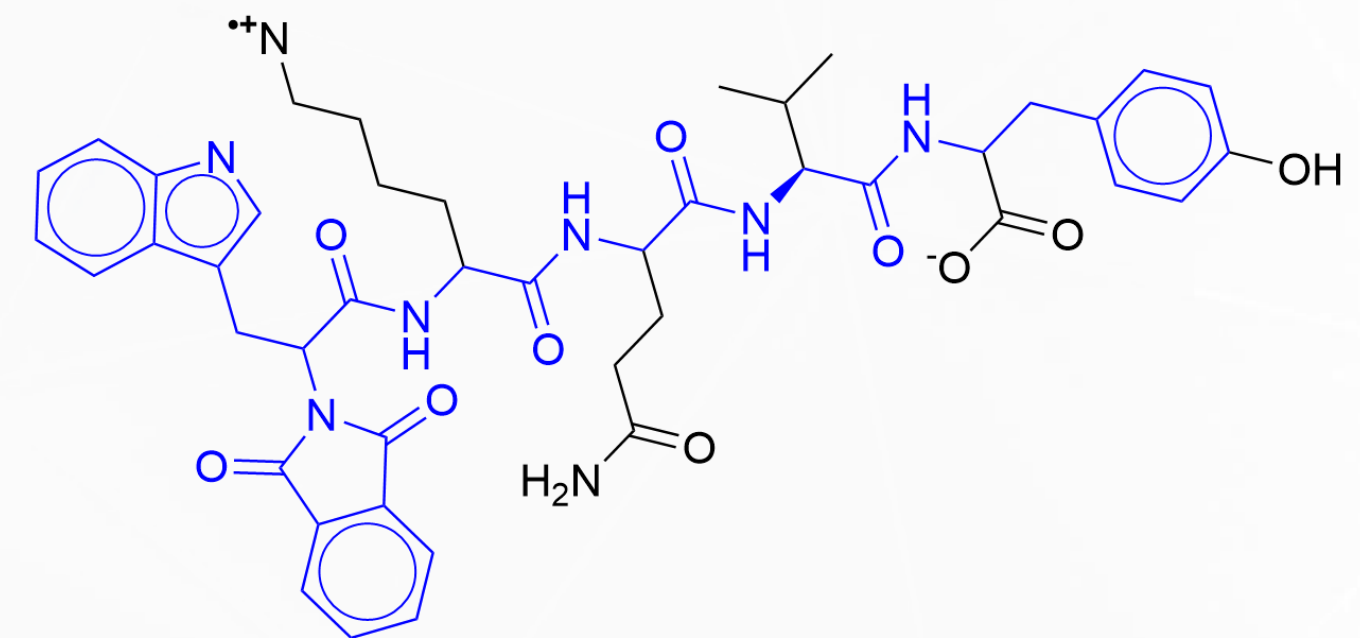

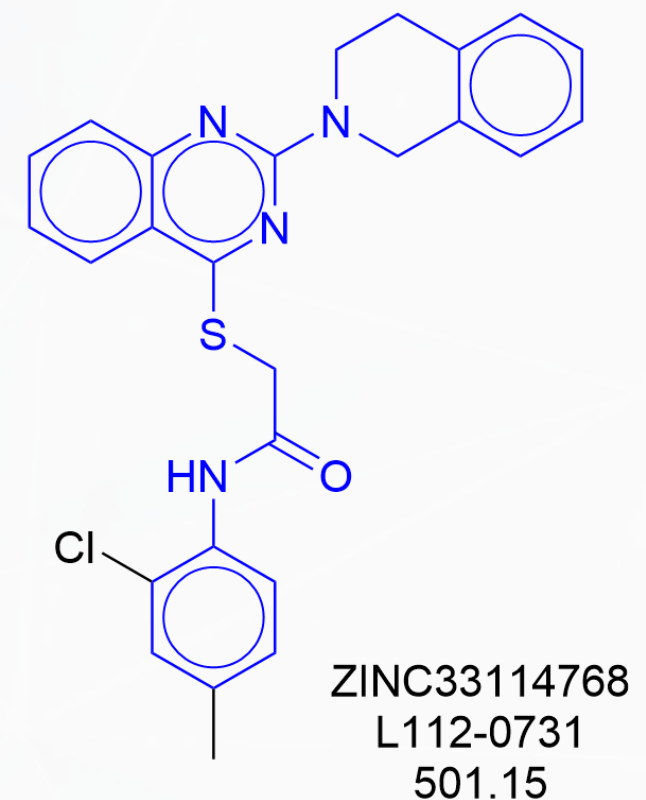STEP 01 Bibliography searching

STEP 02 Choice of chemical libraries

FCH Group
ChemDiv ZINC20
LIFE CHEMICALS
DRUGBANK

STEP 03 ligand based-methods

STEP 04 Structure-based methods

STEP 05 Enzyme activity test

Protein

Aromatic/hydrophobic

Don

Acc
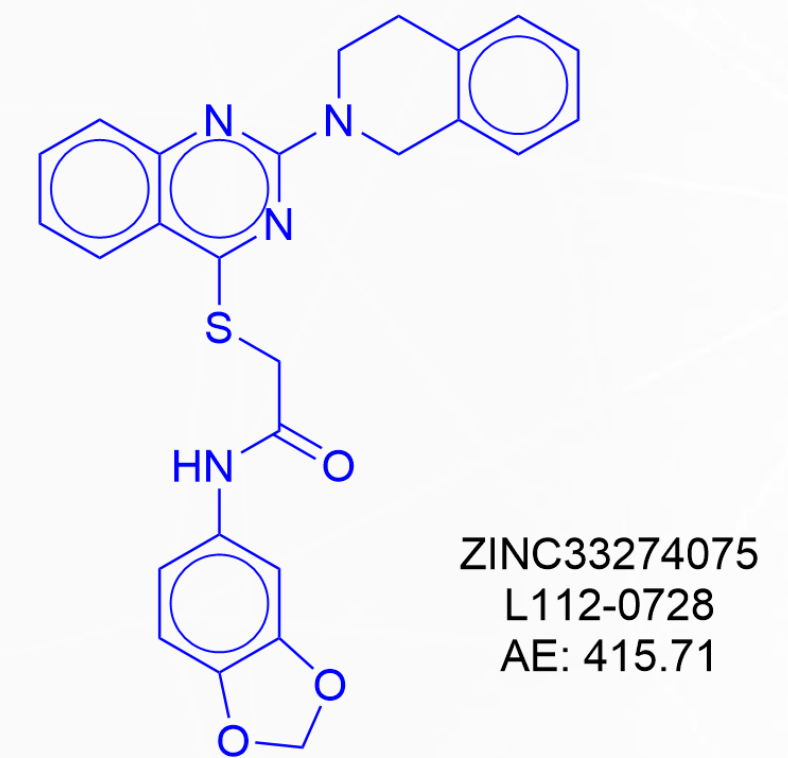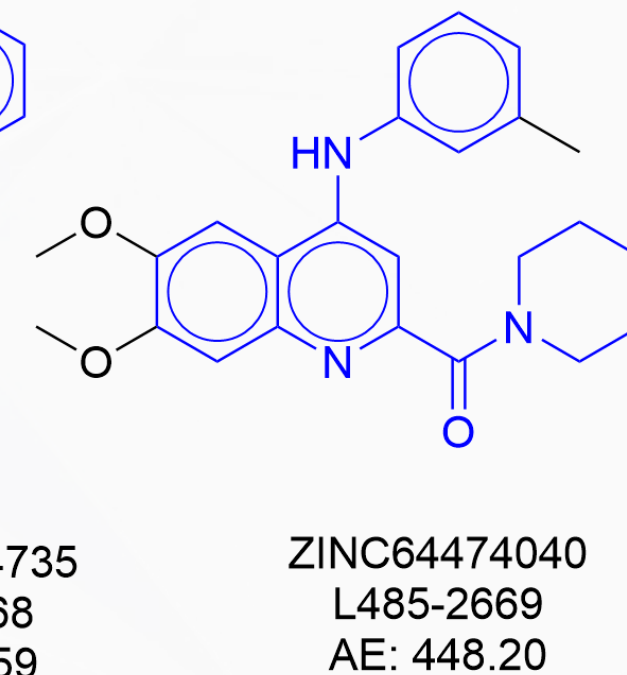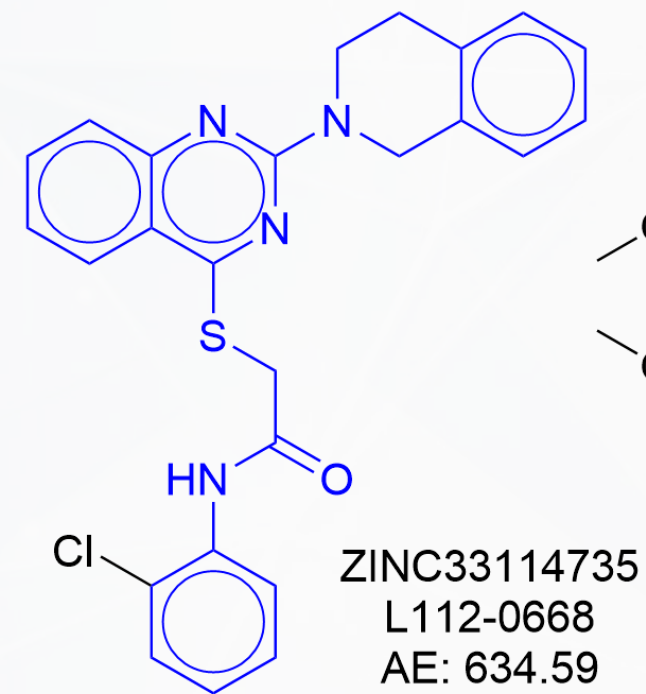
Molecules for the model: L112-0668, L112-0728, L485-2669, L112-0731 y RG108 KQVY.

The molecules described as high activating by their AE share similar functional groups and characteristics.

ZINC33114735
L112-0668
AE: 634.59

ZINC64474040
L485-2669
AE: 448.20

ZINC33274075
L112-0728
AE: 415.71

ZINC33114768
L112-0731
501.15

RG108-KQVY

Bemis and Murcko Scaffolds

International Journal of Peptide Research and Therapeutics 2022 28: 620

Martínez Liliam, 2023 Master's thesis in chemical sciences UNAM.

AE: Enzymatic activity . Unit of measure in % .

4

Results

| Compound	Percentage (± SD)
3909-9992	95.85 (±0.29)
C066-0242	94.04 (±6.09)
V011-9764	71.16 (±2.06)
ZINC33274076/ L112-0729	191.42 (±31.99)
ZINC64474058/ L485-2687	243.27 (±66.67)
ZINC64474109/L485-2777	672.64 (±88.85)
ZINC33114760/L112-0716	221.1 (±12.35)
ZINC33114754/ L112-0706	250.29 (±12.49)
ZINC33274072/ L0698	334.74 (±12.88)

■ Bemis and Murcko Scaffolds
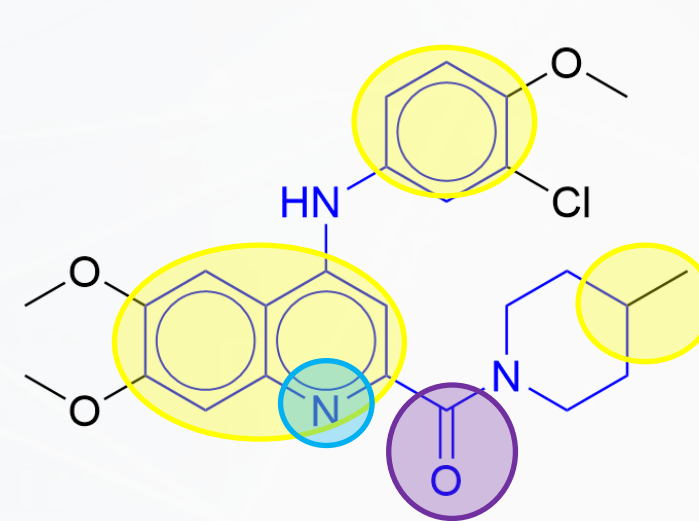
ZINC64474109
L485-2777
Similarity:
MACCS Keys: 0.98
ECFP6: 0.82
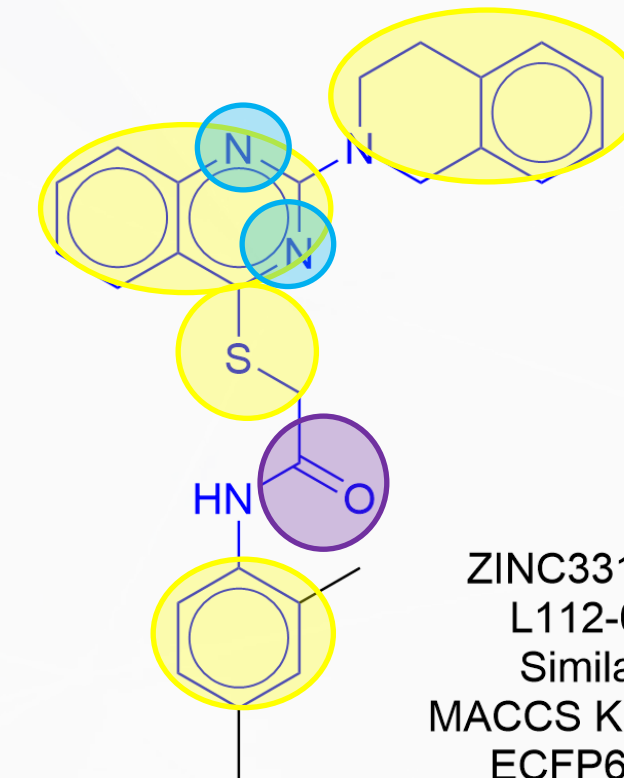
ZINC33114754
L112-0706
Similarity:
MACCS Keys: 0.90
ECFP6: 0.71
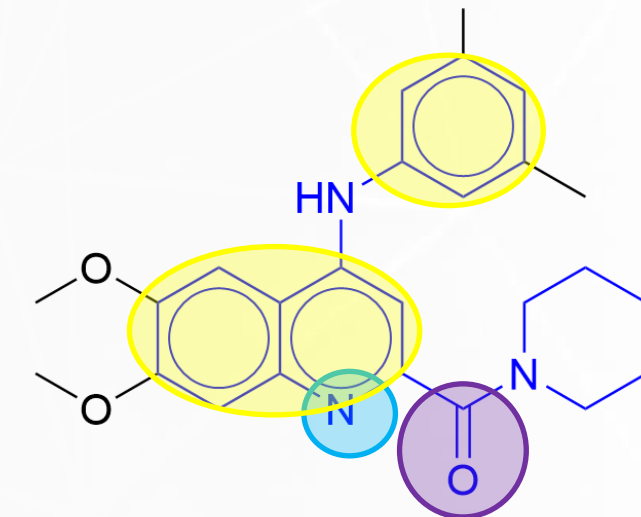
ZINC64474058
L485-2687
Similarity:
MACCS Keys: 1.00
ECFP6: 0.75

6 of 9 molecules are activators of DNMT1 enzyme.

01 Out of the nine molecules selected through fingerprint-based similarity, six activate the DNMT1 enzyme.

02 Notably, the most activating molecules do not possess all the pharmacophoric points.

03 The similarity values most pertinent to the molecules activity were those based on ECFP6 fingerprints.

04 Hit molecules share scaffolds with querys.

CONAHCYT

CVU1270111

PAPIIT

UNAM PAPIIT IN201321

DIFACQUIM GROUP

Question and Answer...

Thankyou for your attention!

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