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In-silico analysis and pharmacophore modeling of anticancer HDAC-Topo dual inhibitor

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INTRODUCTION

Cancer

A condition in which abnormal cells divide uncontrollably and destroy body tissue (Wu et al., 2006)

In 2020 nearly 10 million people died because of cancer, making cancer a prime cause of worldwide death

Anticancer drugs

•Anti-cancer drugs or treatments are the methods to prevent or stop cancer from developing (Taghipour et al., 2022)

Chemotherapy, Immunotherapy, Surgery, Hormonal treatments, Radiotherapy, Hyperthermia, Bone marrow transplant

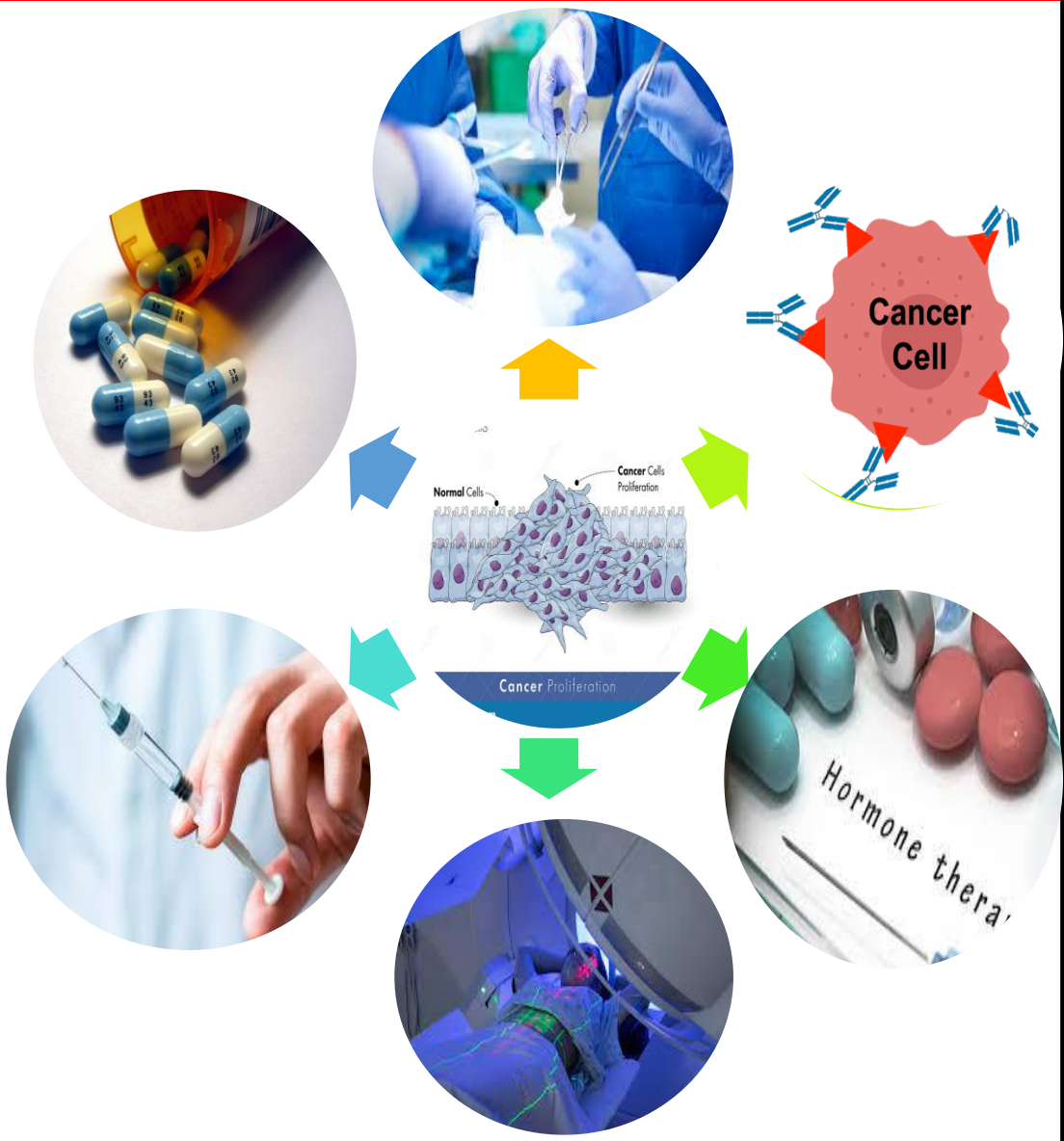


Fig 1. Different anti-cancer therapies

INTRODUCTION

HDACs

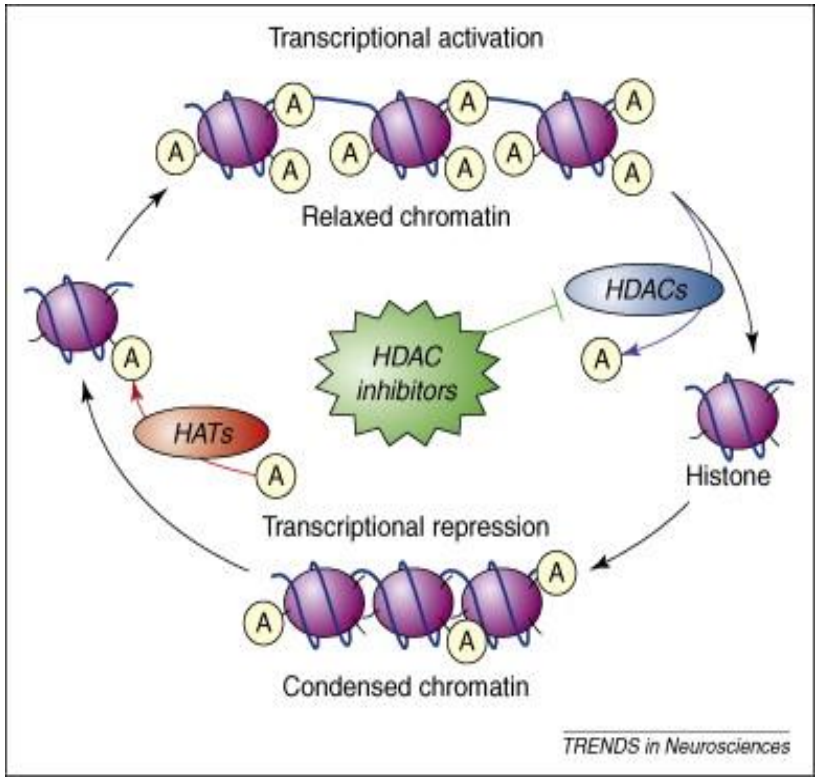


Fig 2. Function of HDACs

Topoisomerase

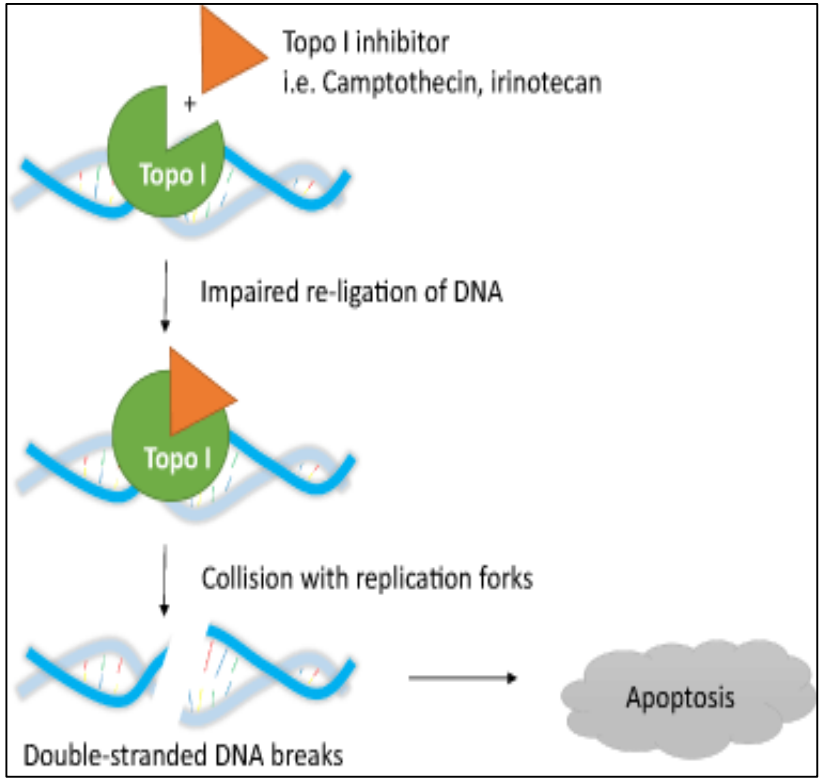


Fig 3. Function of TOPO Inhibitors

Dual targeting

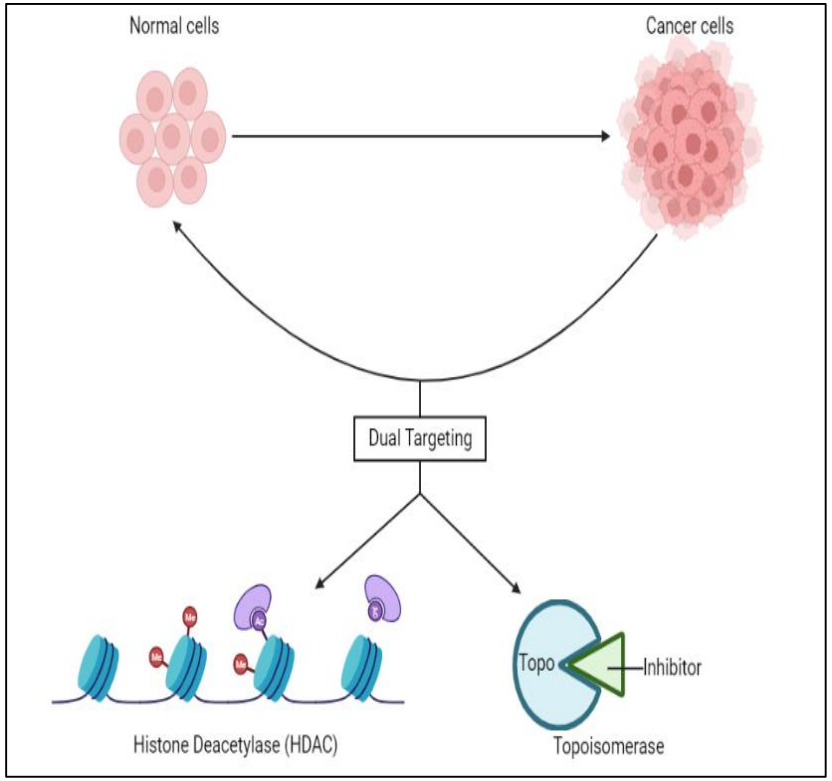


Fig 4. Dual targeting of HDAC and Topo in cancer cells

(Created using biorender)

INTRODUCTION

Virtual screening and Drug discovery

- **PRX-00023 (Phase IIb)- Major depression**
- **PRX-03140 (Phase IIb)-Alzheimer's disease**
- **SC12267 (Phase IIa)- Rheumatoid arthritis**
- **Cevoglitazar (Phase II)- PPAR- α / γ dual agonist**
- **DMP450 (Phase II)- Inhibitor of HIV-1 protease**

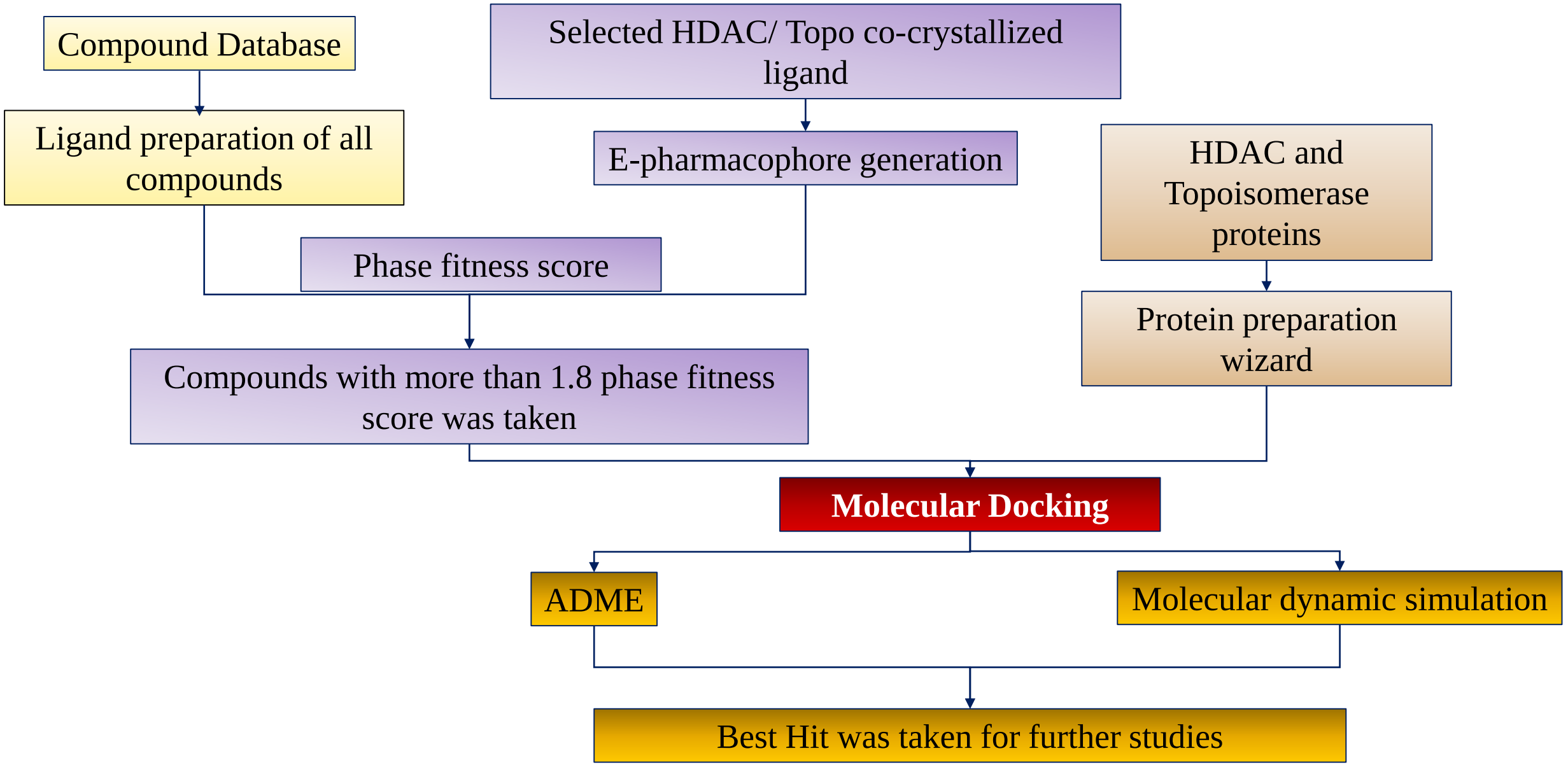
"*In-silico*"

In silico methods include databases, quantitative structure-activity relationships, pharmacophores, homology models and other molecular modeling approaches, machine learning, data mining, network analysis tools and data analysis tools that use a computer.

AIM/OBJECTIVE

To design a potent HDAC-TOPO dual-inhibitor by pharmacophore modelling, virtual screening and molecular docking techniques

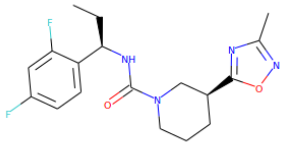
METHODOLOGY



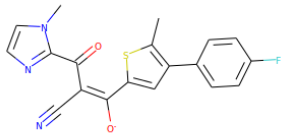
METHODOLOGY

Ligand preparation and E-pharmacophore generation

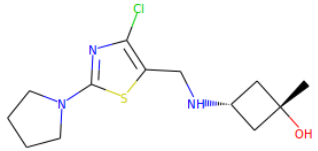
Selection of database



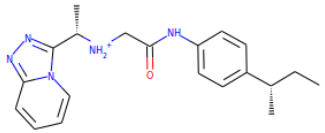
MCULE



Maybridge



Zinc2700



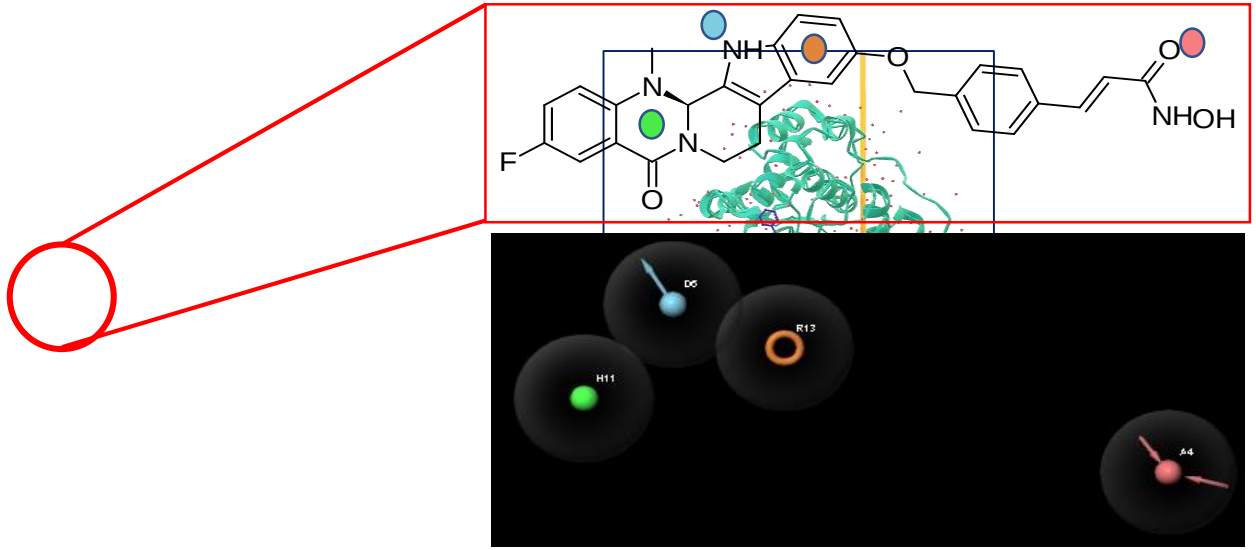
Target oncology

Lig prep module

LigPrep produces a single, low-energy, 3D structure with correct chiralities for each successfully processed input structure.

Literature proved
HDAC/topo inhibitor

Phase module



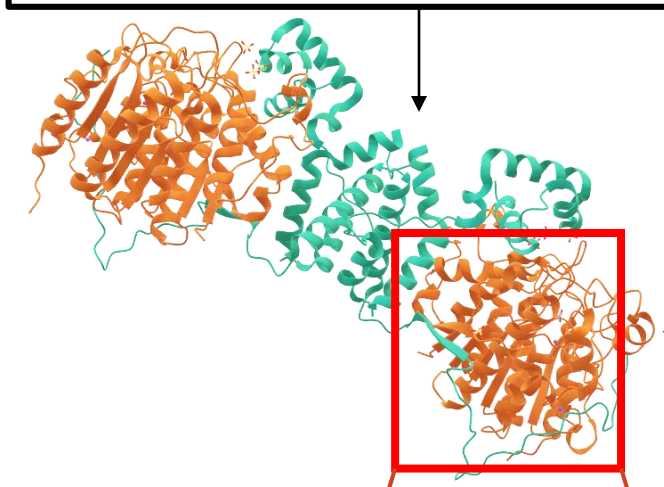
E-pharmacophore Hypothesis generation

Compounds with more than 1.8 phase score

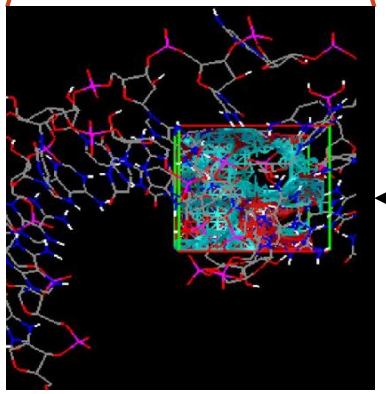
Molecular docking

Protein Preparation

Retrieve Protein structures using PDB ID



Protein energy Minimization and Optimization



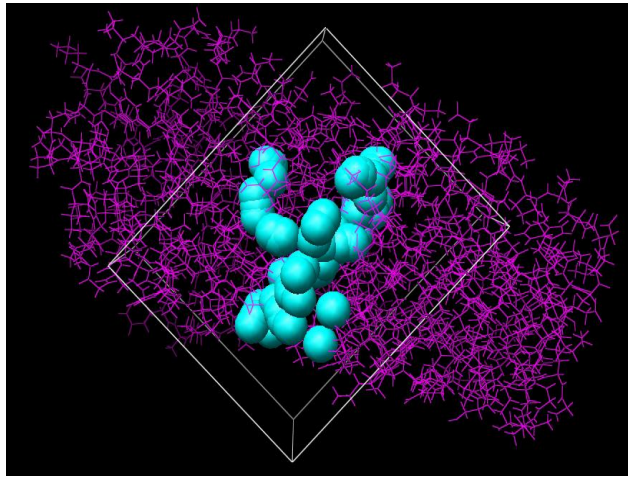
Grid Box Formation

Table 1. PDB ID of all the proteins which is used for docking

HDAC Isoforms	PDB ID
HDAC1	4BXK
HDAC2	4LY1
HDAC3	4A69
HDAC4	2VQJ
HDAC5	-*
HDAC6	3PHD
HDAC7	3ZNR
HDAC8	1T69
HDAC9	-*
HDAC10	6UII
HDAC11	-*

*Protein modeling using SWISS model

Topoisomerase	PDB ID
Topo 1	1EJ9
Topo 1	1SC7
Topo 2	5GWK
Topo 2	4G0U



RESULTS

Table 2. Docking score of best-hit compounds from all the databases against all HDAC isoforms and Topo 1 and 2 (kcal/mol)

Database	Compound Name	HDAC1	HDAC2	HDAC3	HDAC4	HDAC5	HDAC6	HDAC7	HDAC8	HDAC9	HDAC10	HDAC11	Topo1	Topo2
Target oncology	1060 (1A)	-0.565	-4.733	1.857	-4.16	-1.04	-1.354	-2.371	-3.091	-2.62	NA	NA	NA	-6.995
Maybridge	19098 (1B)	-2.339	-7.521	-0.667	-7.433	-2.977	-3.192	-7.201	-10.204	-4.054	-7.534	-4.365	-5.016	-9.834
	24579 (1C)	-2.188	-9.867	-2.002	-9.002	-4.794	-4.402	-7.433	-9.975	-4.785	-4.417	-5.897	-6.86	-8.446
	20086 (1D)	-4.286	-9.475	-7.179	-8.805	-3.984	-4.344	-7.924	-8.253	-5.323	-6.232	-9.871	-9.165	-13.192
zinc	40112 (1E)	-1.81	-11.5	-0.647	-6.869	-4.219	-1.52	-7.437	-11.18	-4.212	-6.342	-4.017	-7.243	-9.6
	36784 (1F)	-4.221	-10.585	-2.961	-6.768	-6.665	-3.531	-8.146	-10.15	-6.123	-6.615	-5.349	-7.603	-11.026
	49437 (1G)	-3.828	-7.918	-3.136	-7.605	-6.236	-3.688	-7.994	-5.861	-6.008	-7.064	-5.923	-9.495	-11.692
	55229 (1H)	-3.407	-7.239	-4.109	-9.244	-3.765	-5.37	-9.04	-5.44	-5.522	-6.503	-8.291	-9.512	-12.467
MCULE	95352 (1I)	-2.084	-6.014	-2.029	-6.844	-3.112	-3.038	-6.241	-6.338	-3.497	-6.091	-6.981	-6.206	-6.599
	82539 (1J)	-1.775	-8.514	-1.541	-6.343	-2.442	-3.375	-6.879	-8.916	-2.63	-7.686	-5.113	-3.907	-6.049
	32563 (1K)	-2.744	-7.921	-2.029	-8.228	-4.048	-4.903	-7.515	-9.16	-4.051	-7.612	-5.323	-6.272	-7.117
	SAHA	-2.04	-12.07	-2.23	-8.12	-3.93	-3.91	-8.19	-9.99	-2.90	-8.80	-7.49	NA	NA
	Etoposide	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-8.57
	Topothecan	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-8.02	NA

RESULT

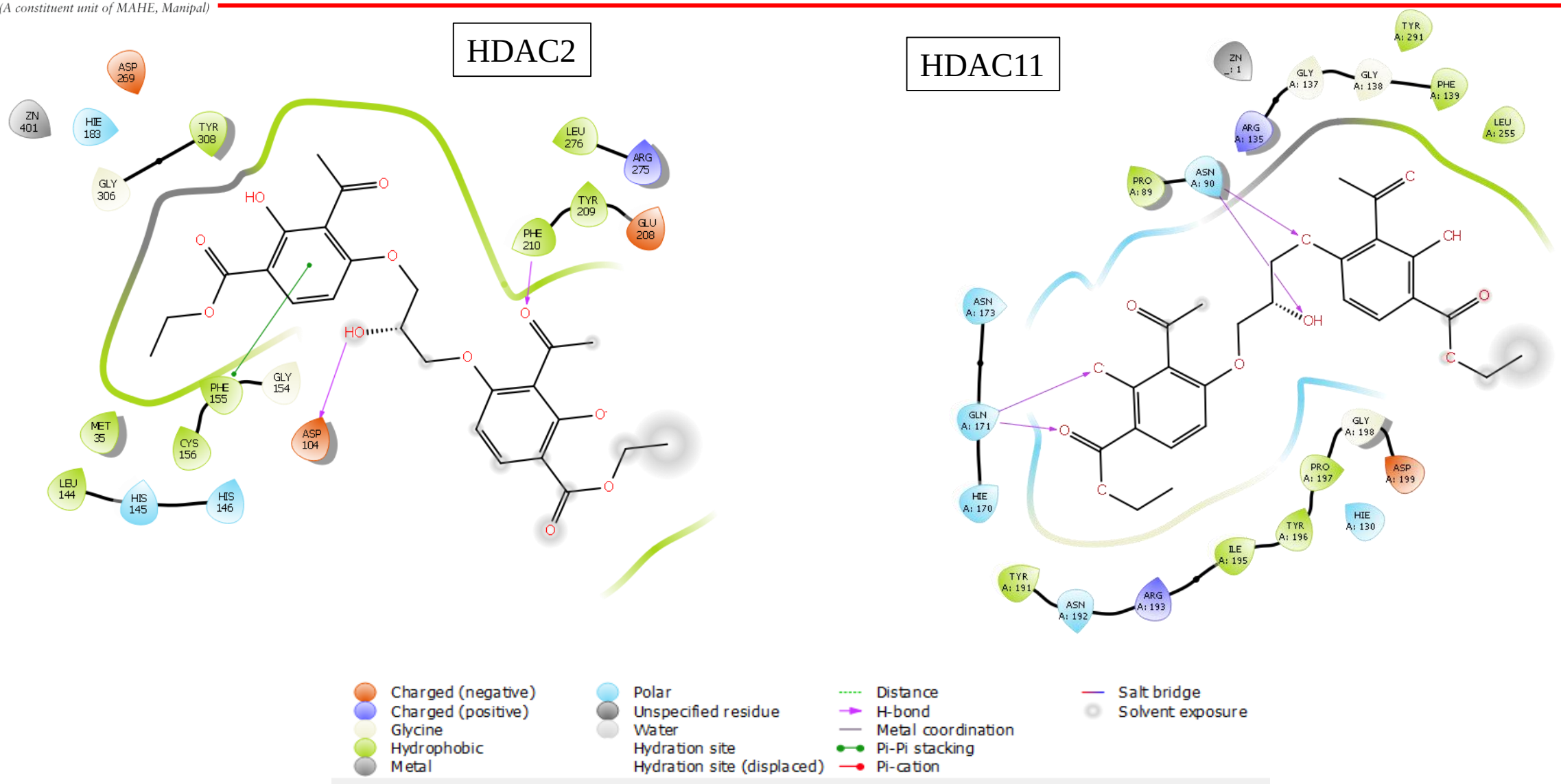


Fig 6. Ligand interaction diagram of compound 1D against HDAC 2 and 11

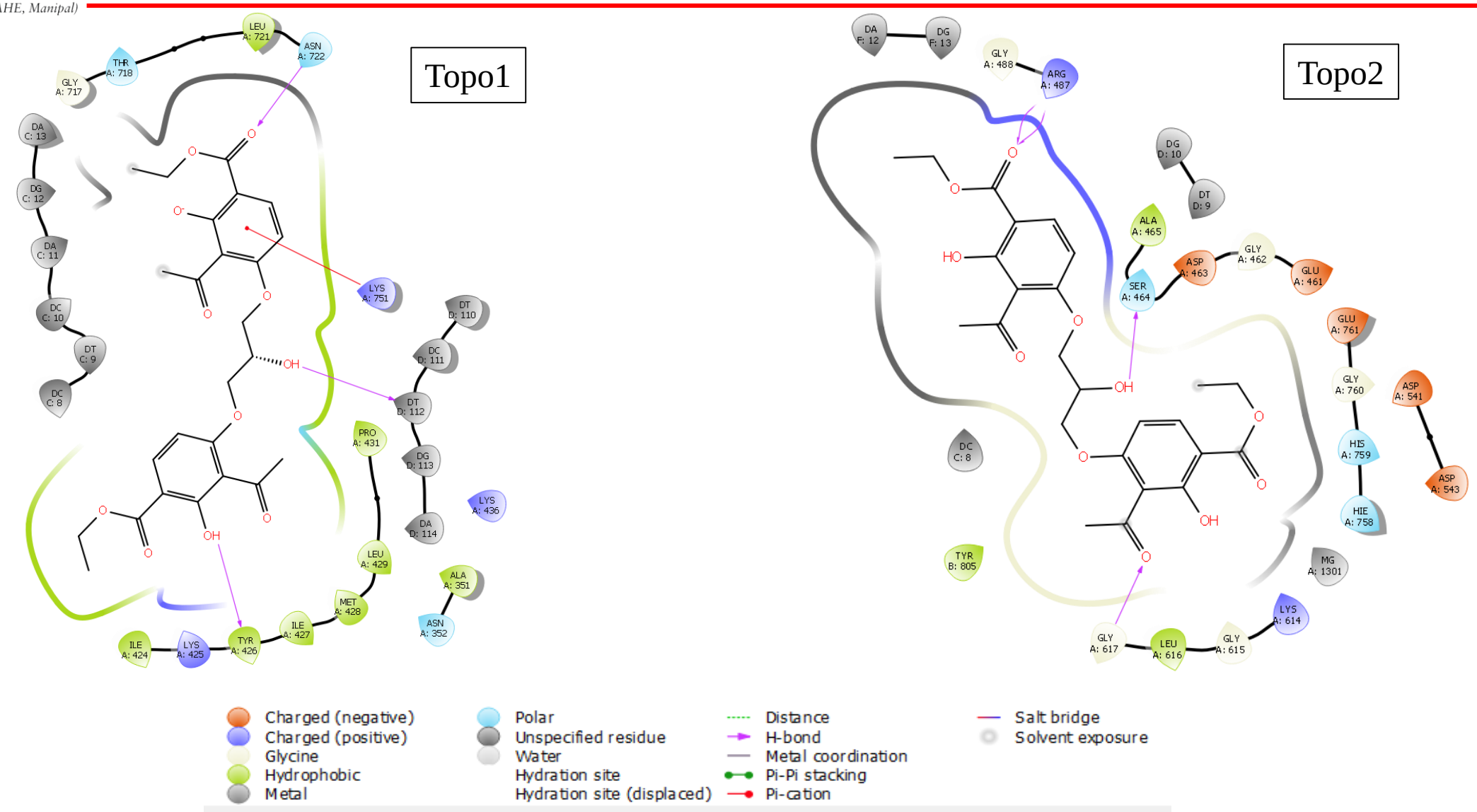


Fig 7. Ligand interaction diagram of compound 1D against Topo proteins

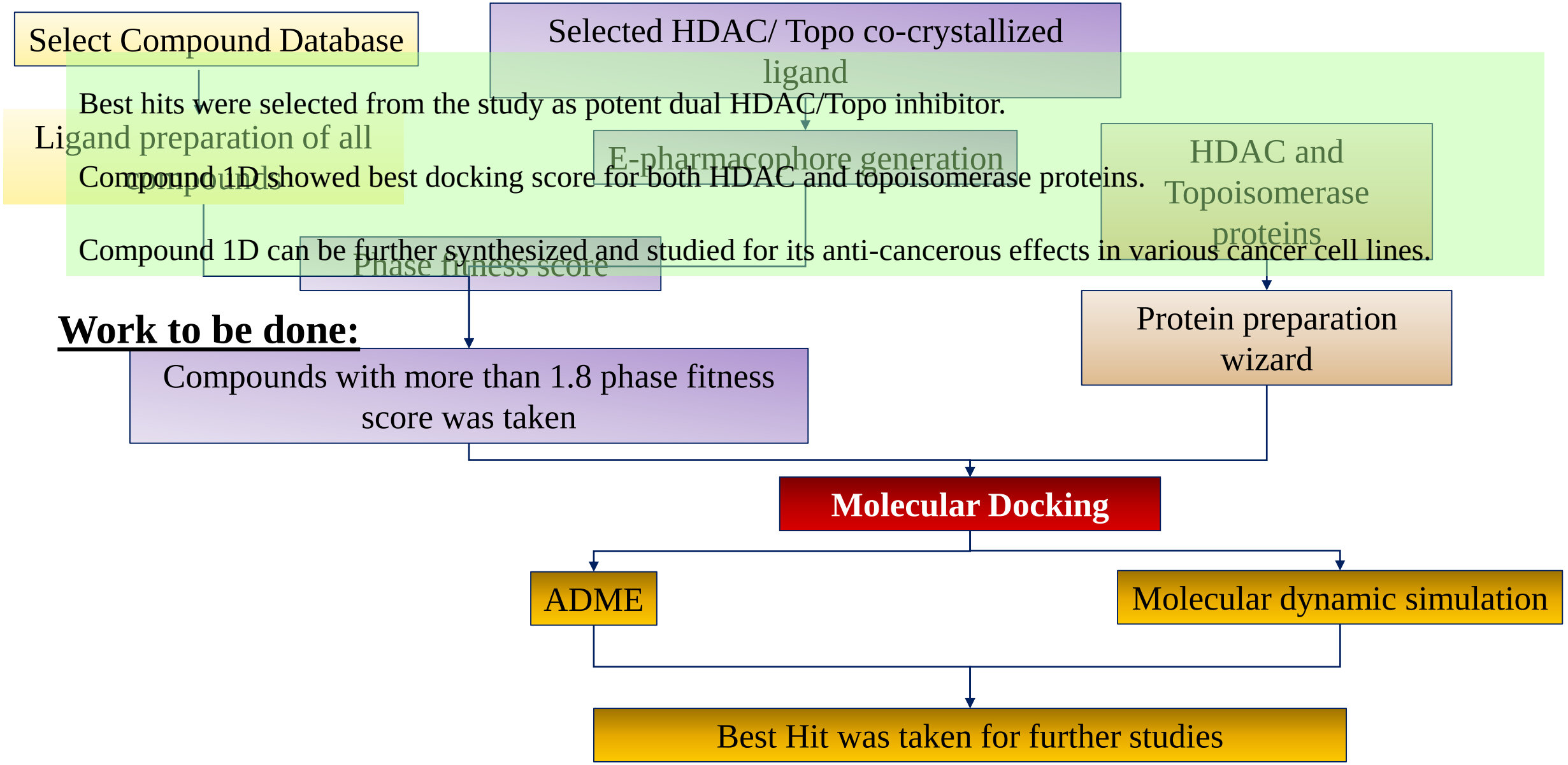
CONCLUSION

Best hits were selected from the study as potent dual HDAC/Topo inhibitor.

Compound 1D showed best docking score for both HDAC and topoisomerase proteins.

Compound 1D can be further synthesized and studied for its anti-cancerous effects in various cancer cell lines.

Work to be done:



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6. Wu, H. C., Chang, D. K., & Huang, C. T. (2006). Targeted therapy for cancer. *J Cancer Mol*, *2*, 57-66.

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Thank You