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Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA
pharmaceuticals MDPI

Design of new derivatives of dimedone molecules using QSAR and Docking molecular

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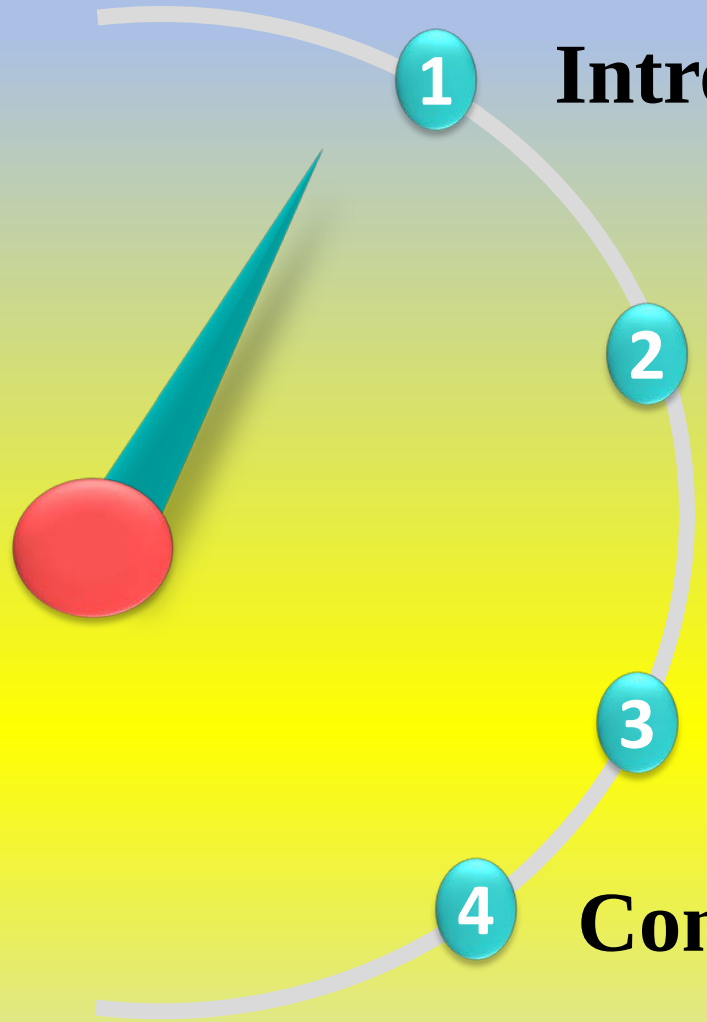
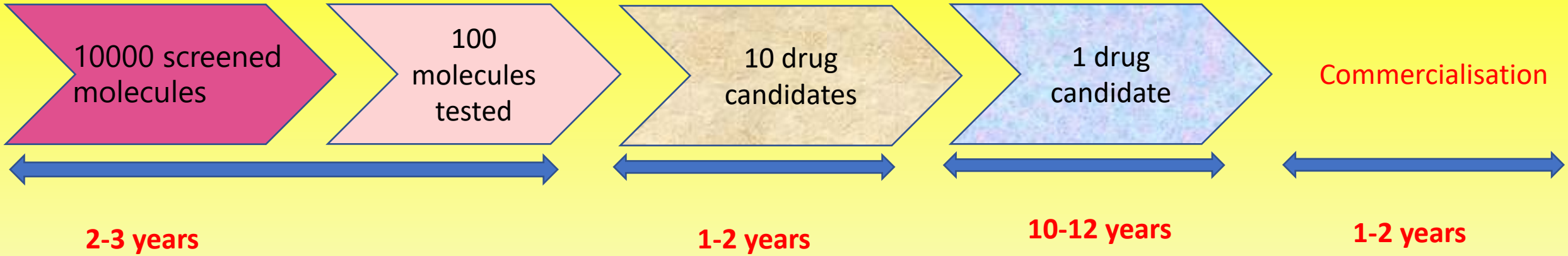
Outline



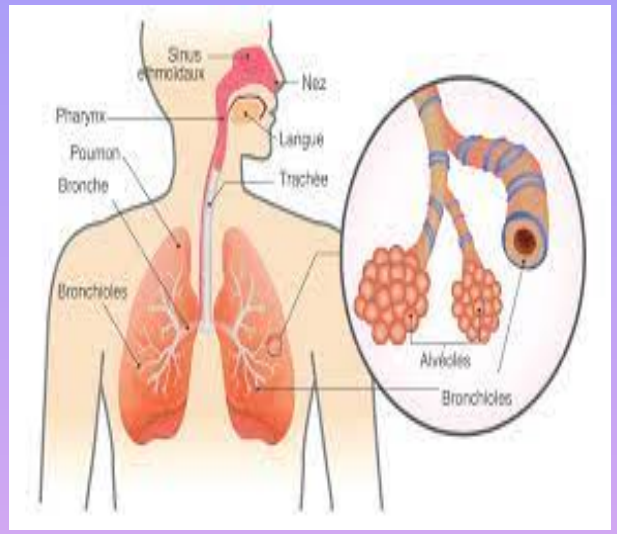
1. Introduction
2. Generality of 2D-QSAR study and Molecular Docking studies
3. Simulation Results
4. Conclusion

1-Introduction

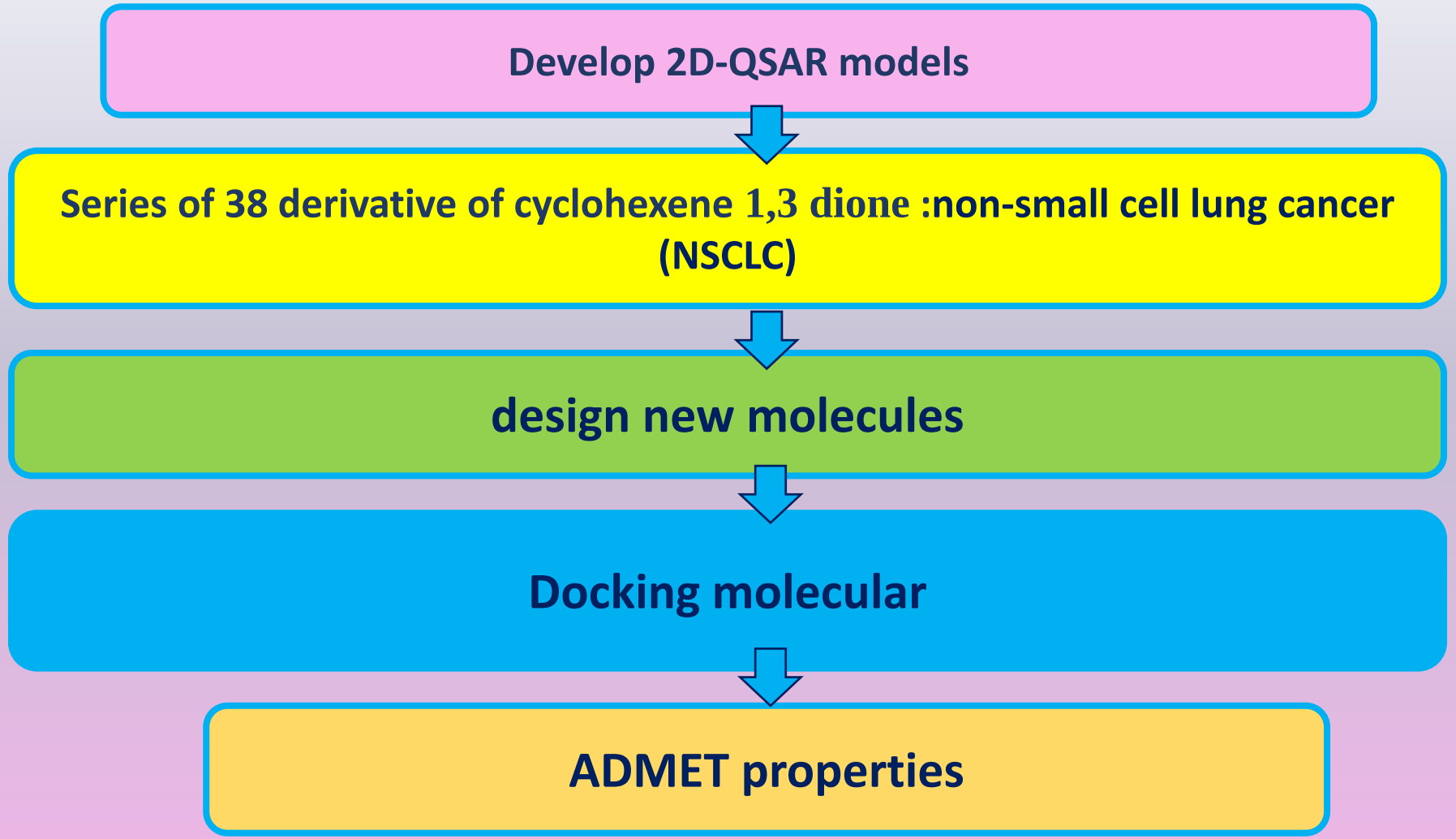


The pharmaceutical industry is oriented towards new research methods based on molecular modeling, which permit to predict the biological activity and pharmacokinetics of compounds before synthesis

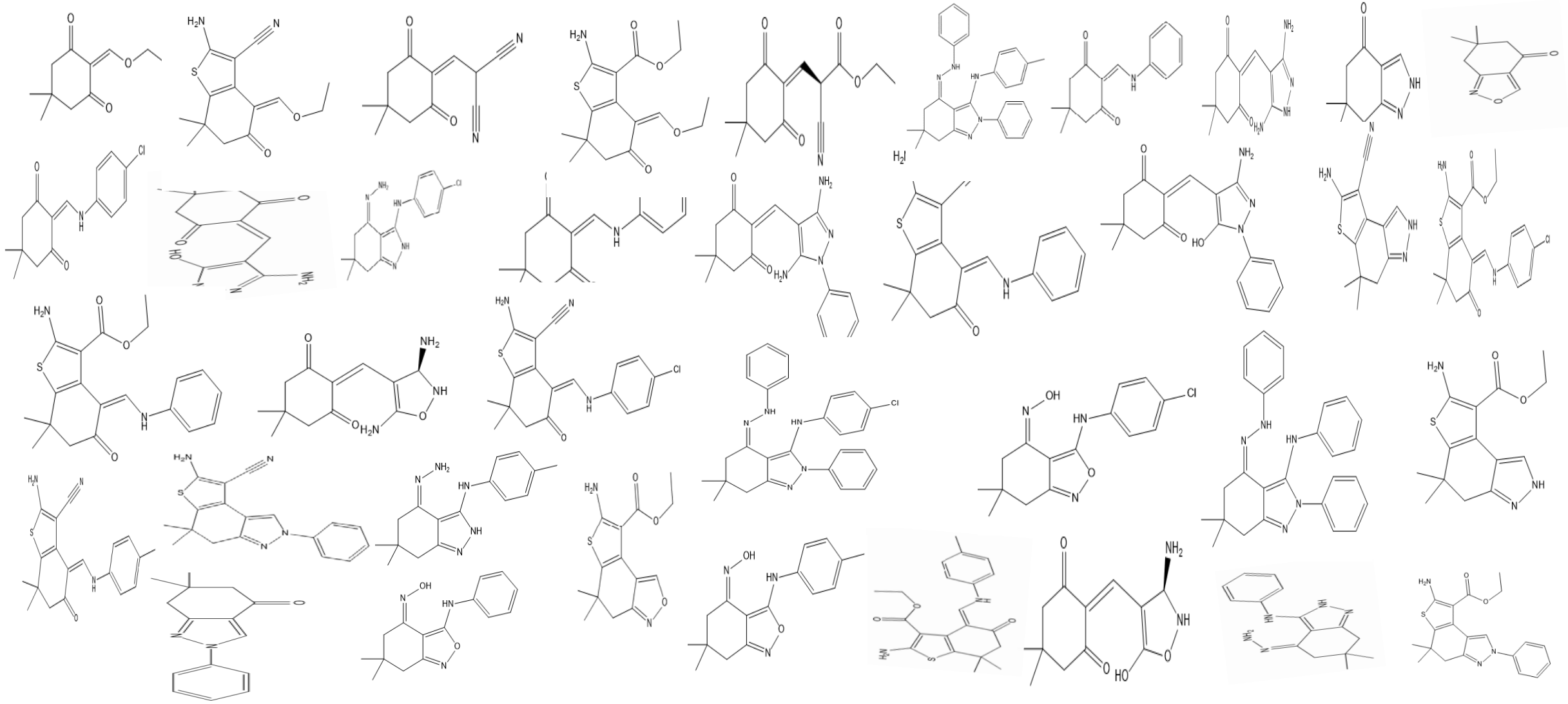
Cancer is considered the leading cause of death worldwide



(NSCLC) accounts for 85% of lung cancers

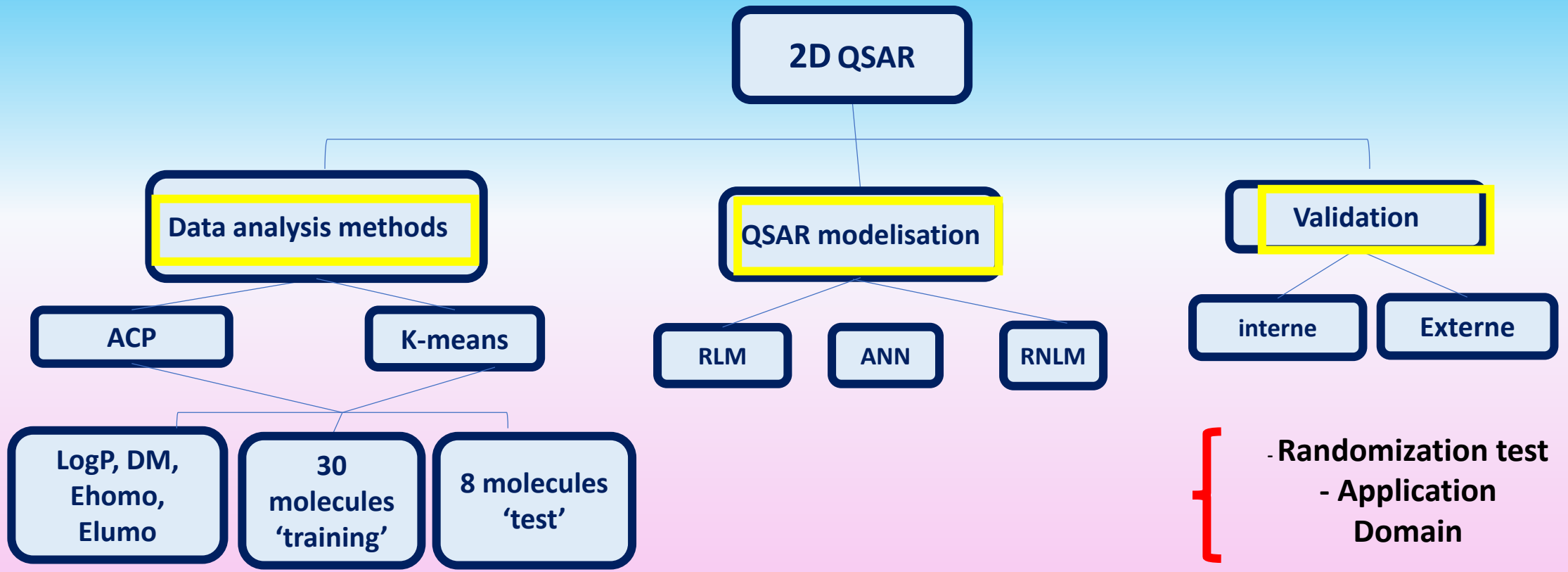

Develop 2D-QSAR models
Series of 38 derivative of cyclohexene 1,3 dione :non-small cell lung cancer (NSCLC)
design new molecules
Docking molecular
ADMET properties

cyclohexene 1,3 dione series *

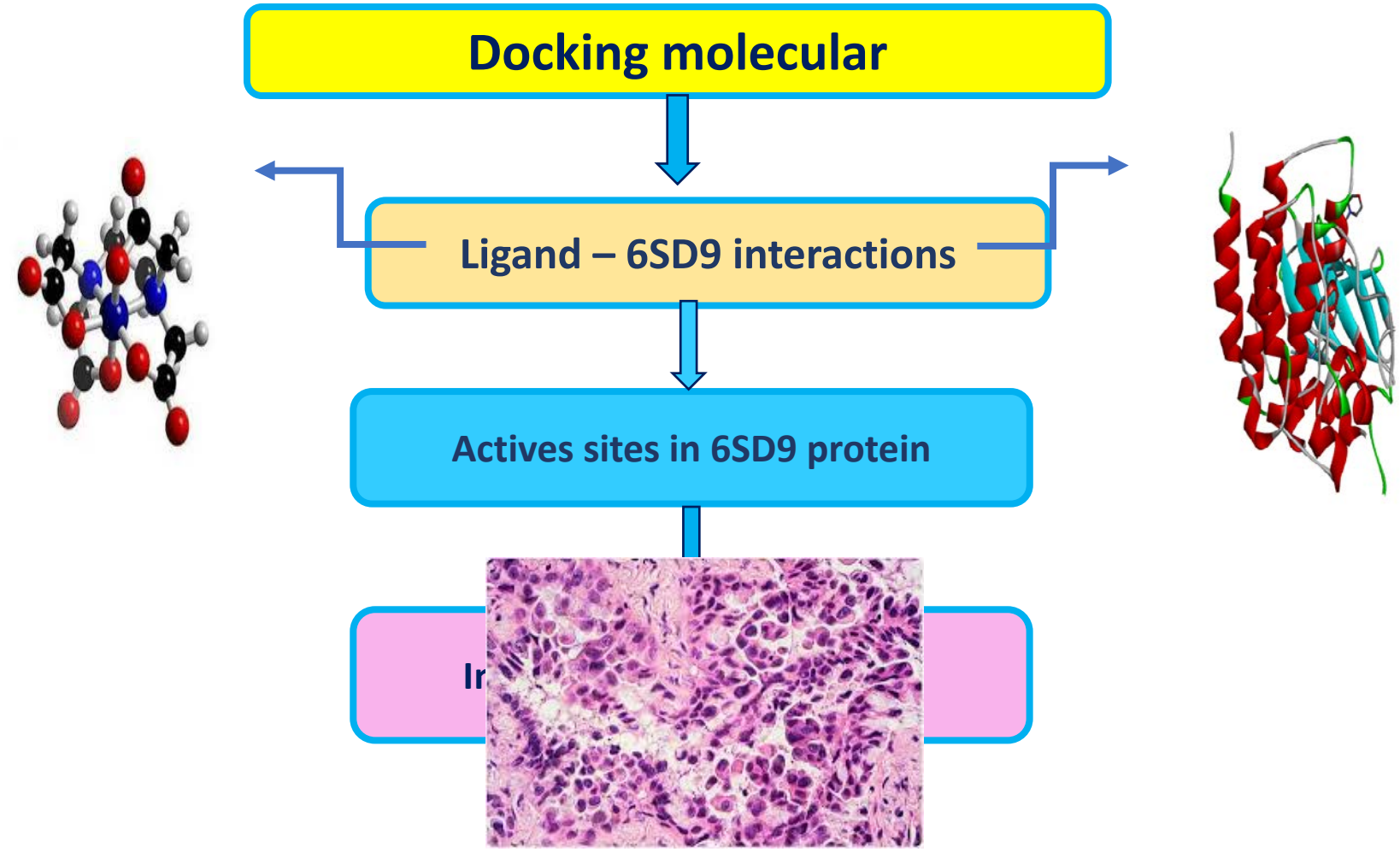


*: Rafat Milad Mohareb,2020 Medicinal Chemistry Research

2- 2D-QSAR and Molecular Docking studies



2- 2D QSAR and Molecular Docking studies



3-Simulation Results

Table1: Coefficient values of QSAR models

	Parameters	MLR	MNLR	ANN
Training	R	0,95	0,995	0,994
	R^2	0,91	0,991	0,99
	R^2_{cv}	0,85	0,82	0,989
	MCE	0,004	0,001	4,7 10^-4
test	R	0,966	0,9984	0,976
	R^2test	0,934	0,997	0,954
	MCE	3,5 10^-4	2,6 10^-4	1,4 10^-4

3-Simulation Results

Residual limits= ±2.5

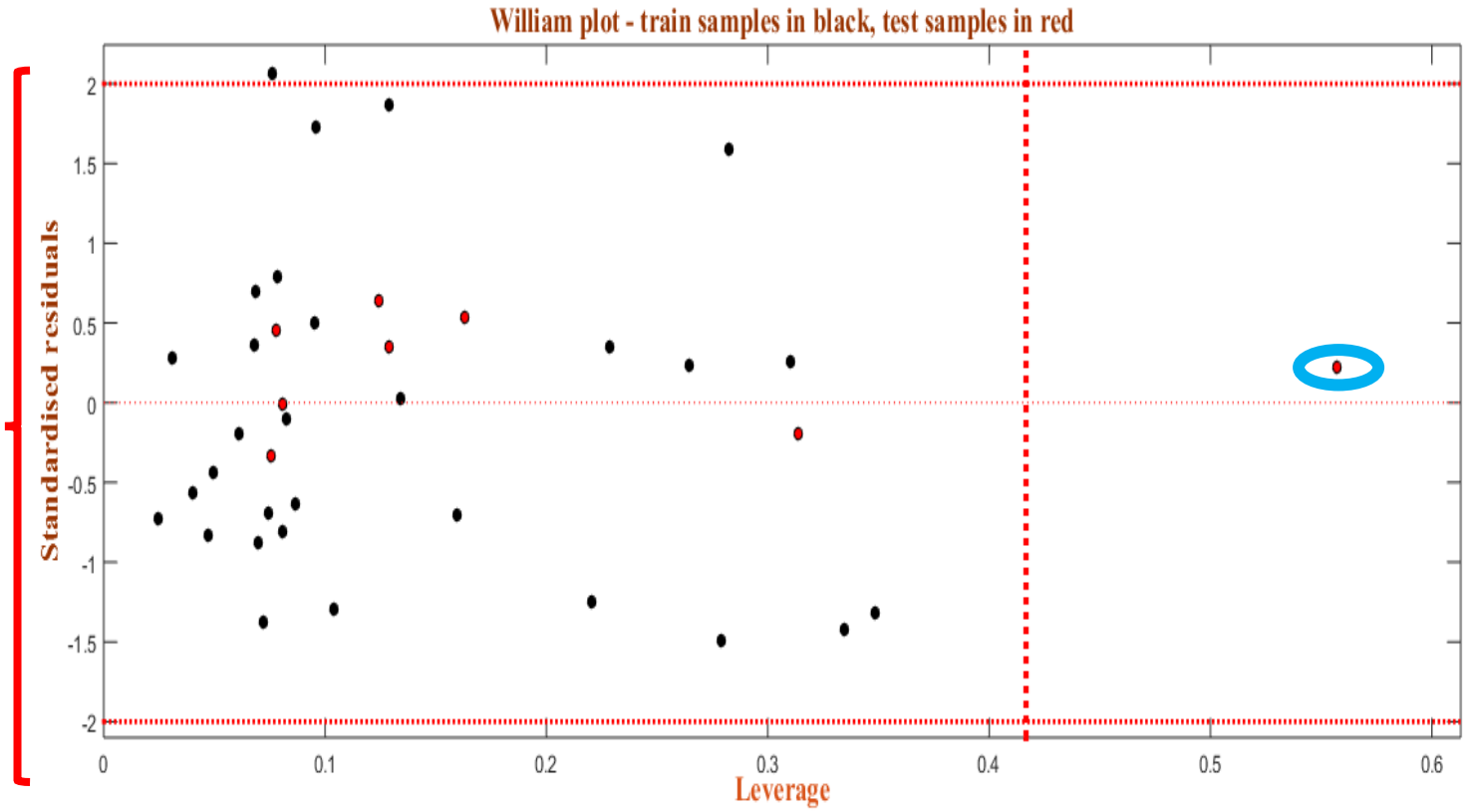


Figure1: Williams graph of the leverage-standardized residue for the pIC50 MLR model (with h = 0.416 and residual limits = ±2.5).

3-Simulation Results

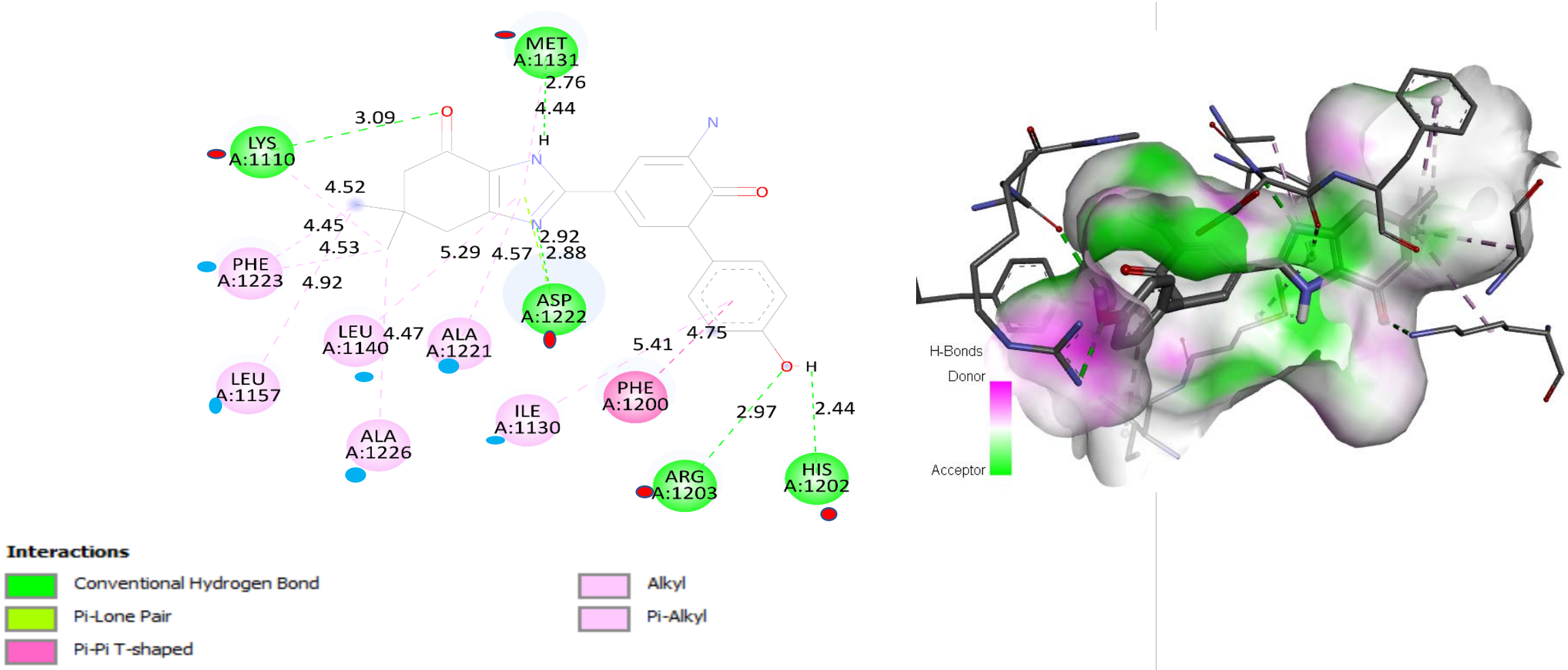
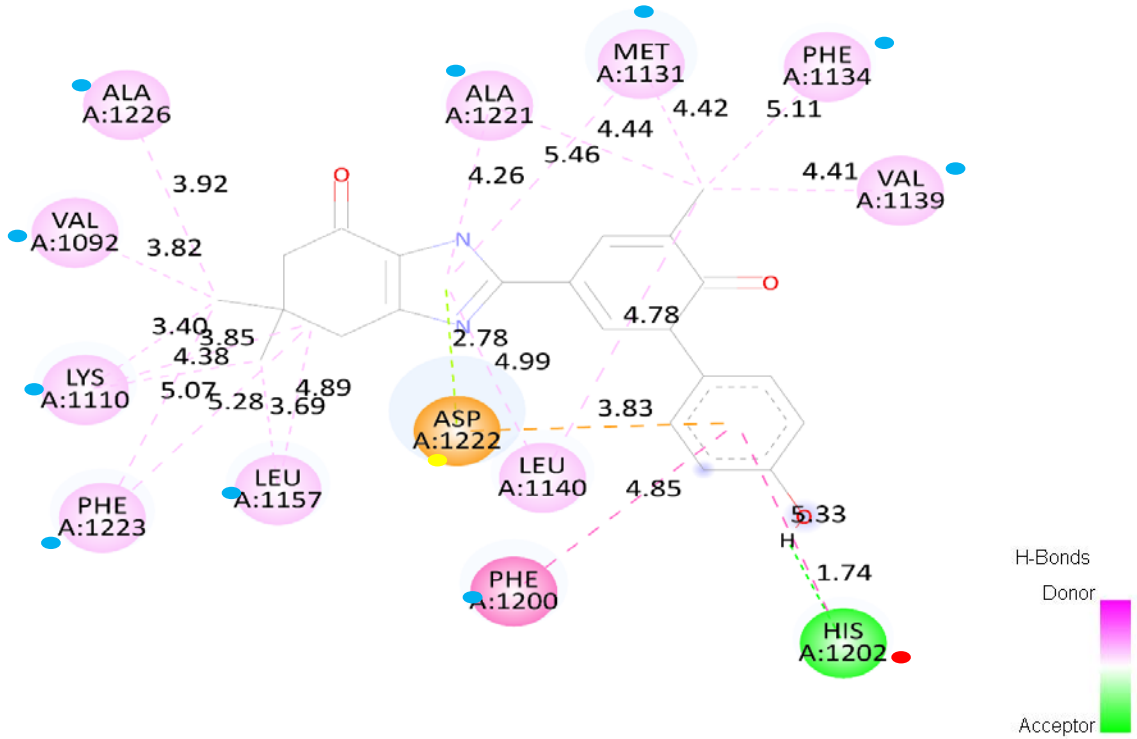
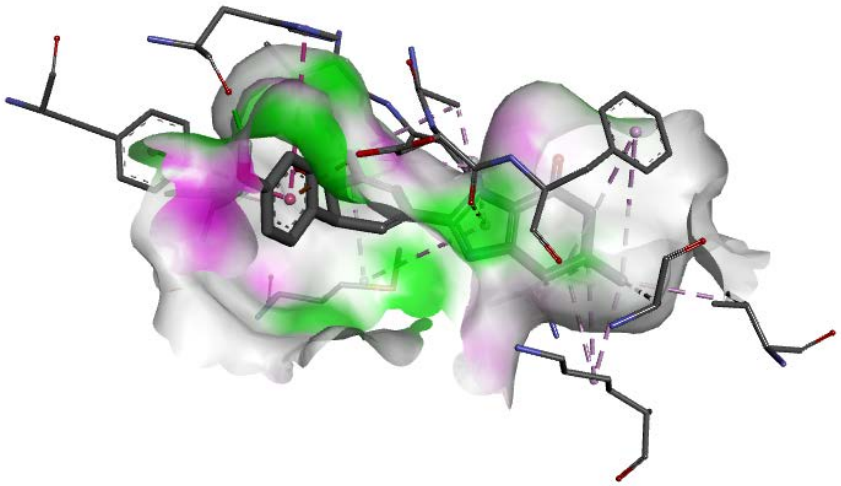


Figure 2: 2D -3D representation of the interactions between the active sites of 6SD9 and ligand 2

3-Simulation Results





Interactions

- Conventional Hydrogen Bond
- Pi-Anion
- Pi-Lone Pair
- Pi-Pi T-shaped
- Alkyl
- Pi-Alkyl

Figure 3: 2D -3D representation of the interactions between the active sites of 6SD9 and ligand 13

3-Simulation Results

➢Evaluation of drug-likeness properties

Table 3. Drug-like evaluation of the proposed molecules.

Entry	ABS	TPSA(A^2)	n-ROTB	MW	LogP	n-OHN acceptors	n-OHNH donors	Lipinski's violations	Veber Violations	Egan Violation	S.A
Rule	-	<140	<10	<500	<=5	<10	<5	<=1	<=1	<=1	0<S.A<10
X2	High	109,07	2	363,41	2,72	4	3	Yes	Yes	Yes	4.2
X13	High	83,05	2	362,42	1,75	4	2	Yes	Yes	Yes	4,22
Abbreviations	ABS: Absorption, TPSA: Topological Polar Surface Area, n-ROTB: Number of Rotatable Bonds, MW: Molecular Weight, Log P: logarithm of partition coefficient of compound between n-octanol and water, n-ONHN acceptors: Number of hydrogen bond acceptors, n-OHNH donors: Number of hydrogen bonds donors, S.A: Synthetic accessibility.										

3-Simulation Results

Table4: Predicted ADMET properties of the designed compounds

	Model	Unit	Predictive values		
			Foretinib	Ligand 2	Ligand 13
Absorption	Intestinal (human) absorption	Numeric (% Absorbed)	95.561	78.809	83.42
Distribution	VDss Unbound fraction Permeability of the BBB CNS permeability	Numeri (log L/kg) Digital (Fu) Digital (log BB) Numeric (PS log)	0.549 0.346 -1.848 -3.502	0.54 0.227 -0.944 -2.374	0.649 0.118 -0.751 -0.051
Metabolism	Substrate CYP2D6 CYP3A4 Inhibitors CYP1A2 CYP2C19 CYP2C9 CYP2D6 CYP3A4	Category(yes/no)	Not Yes No No No Yes No	No No No No No No No	Yes Yes Yes Yes No Yes Yes
Excretion	Total clearance	Digital (log mL min^{-1} kg^{-1})	1.048	0.779	0.819
Toxicity	AMSE toxicity	Category(yes/no)	No	Yes	No

4-Conclusion

- In this work, we developed 2 models 2D QSAR for cyclohexene 1,3 dione derivatives series for non-small cell lung cancers.
- We have designed 16 molecules based on the molecule that has the highest biological activity.
- Among the 16 molecules designed, two molecules with high activities but a single molecule that respects the properties of drug likness and ADMET.
- This molecule ‘13’ can be considered as a drug after conducting additional in vivo and in vitro investigations before the clinical trial procedure.

Thank you for your attention