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# Thiazolopyrimidine as a Promising Anticancer Pharmacophore: *In Silico* Drug Design, Molecular Docking and ADMET Prediction Studies

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

pharmaceuticals MDPI

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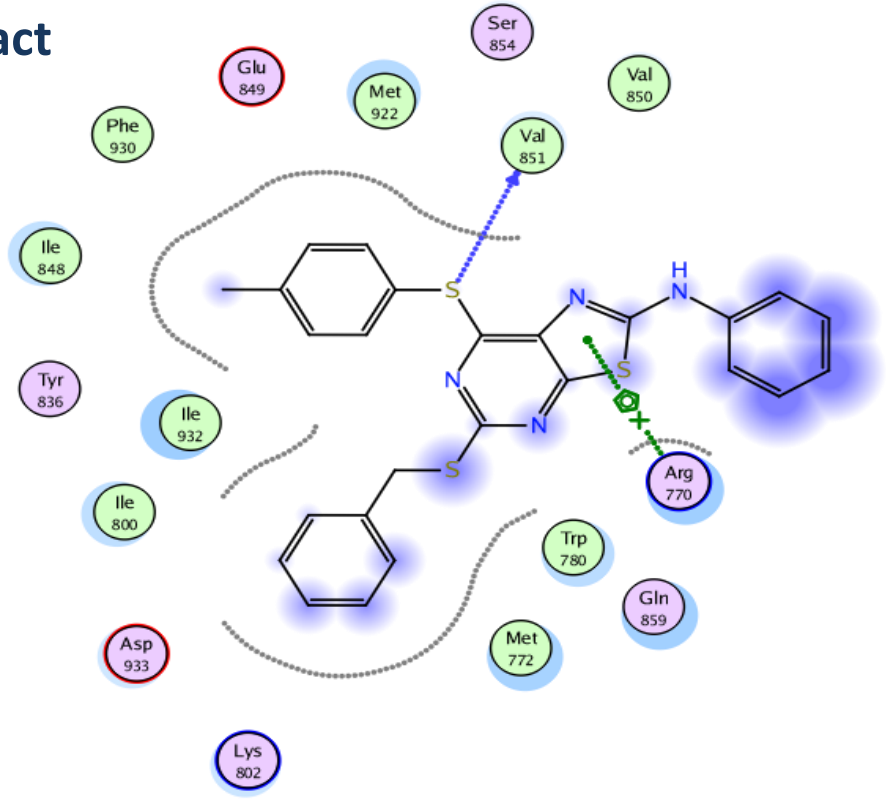
# Thiazolopyrimidine as a Promising Anticancer Pharmacophore: *In Silico* Drug Design, Molecular Docking and ADMET Prediction Studies

## Graphical Abstract




**Interaction of Compound 7 with PI3K**

**Abstract:**

Thiazolopyrimidines are designed to act as bio-isosteric analogues of purine nucleus. They proved to show a wide range of biological activities; such as anticancer, anti-inflammatory, antifungal, antiviral and antitubercular activity.

In this study, a literature survey was performed to elect the most active thiazolopyrimidine-containing scaffolds; acting as anticancer agents; to be subjected to extensive computational studies in order to explore the possible credible mode of their anticancer activity. First, drug-likeness was investigated for the most active derivatives, followed by molecular docking study against CDK, VEGFR and PI3K enzymes to assess their binding energy and propose the mode of action. Then, contact preference and surface mapping studies were carried out to explain the presence of remarkable affinity of certain analogues towards a specific enzyme, in addition to providing more information about their activity. Finally, physicochemical properties, Lipinski's rule and ADMET prediction studies were applied to predict the best route of administration and to suggest the pharmacokinetics of the most promising candidates.

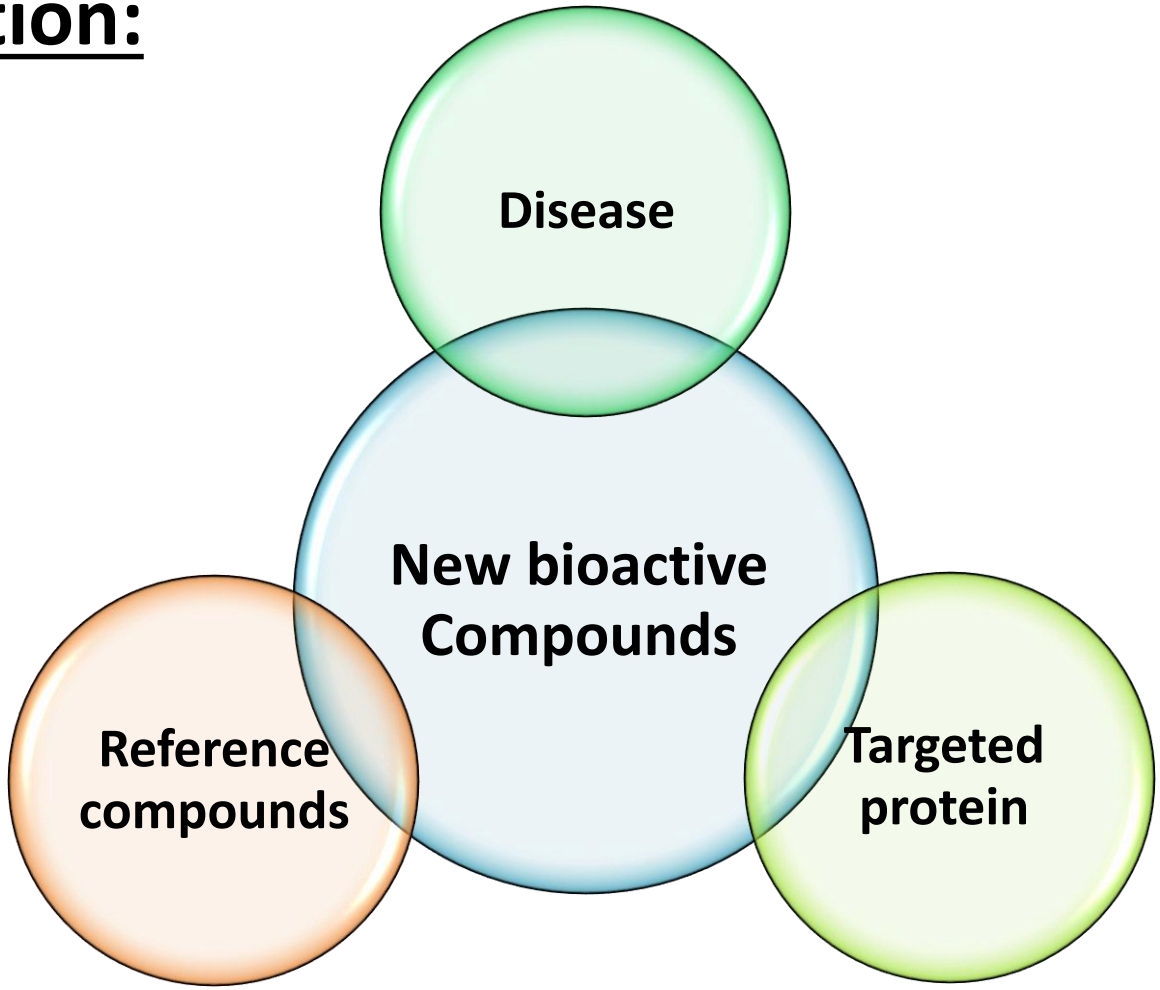
**Keywords:** Thiazolopyrimidines, Anticancer , ADMET prediction, computational studies, molecular docking.

# Introduction:

## *In silico* drug design goals

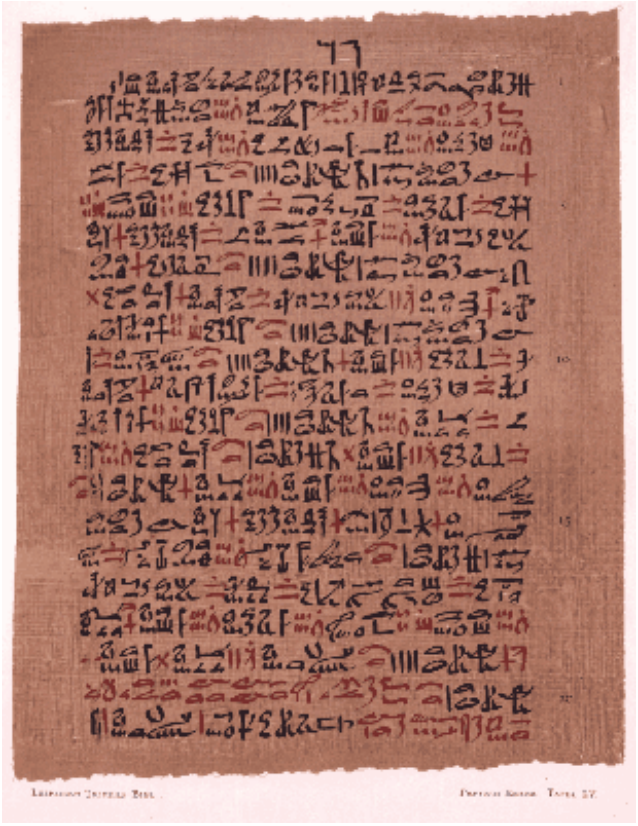
- Understanding Drug-receptor interaction .
- Discovery of potential new lead compound.
- Optimization the activity of the new lead derivative .
- Save time and money.
- Less trial and error .

# Introduction:



# Introduction:

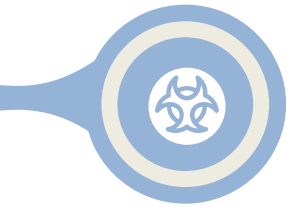
## The disease is Cancer



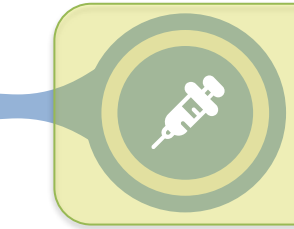
a) R.L. Siegel *et.al*/ CA. Cancer J. Clin. 71 (2021) 7

# Cancer Treatments

Surgery



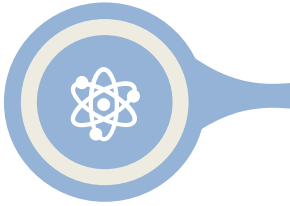
Radiation therapy



Chemotherapy

Immunotherapy

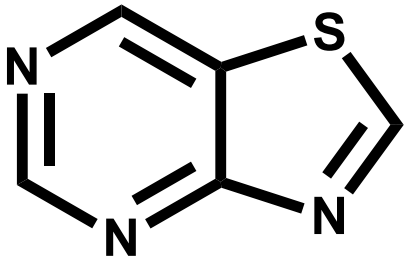
Hormonal therapy



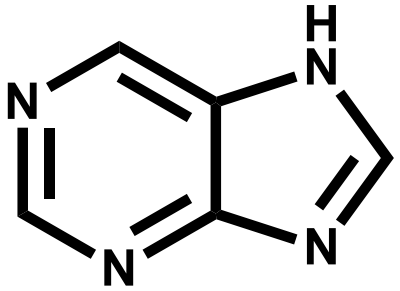
Stem cells transplant

Precision Medicine

# The Reference Compounds (Thiazolo[4,5-d]pyrimidines)



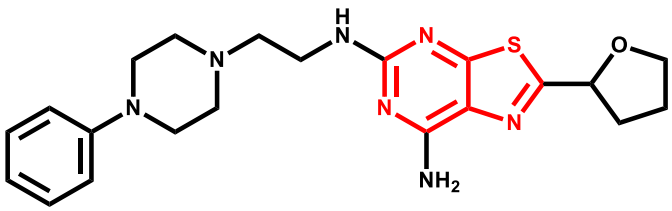

**Thiazolo[4,5-d]pyrimidines**




**Purine**

a) B. Kuppast *et.al* Eur J Med Chem 4 (2016)

# The Reference Compounds: Thiazolo[4,5-d]pyrimidines



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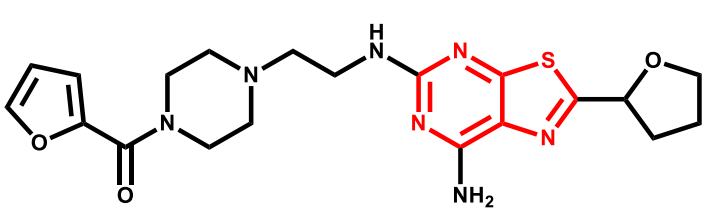

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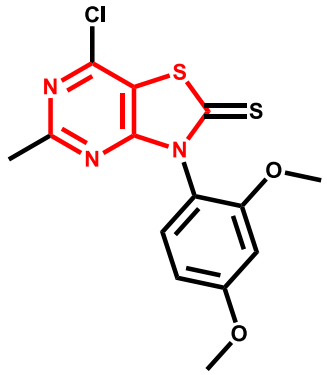

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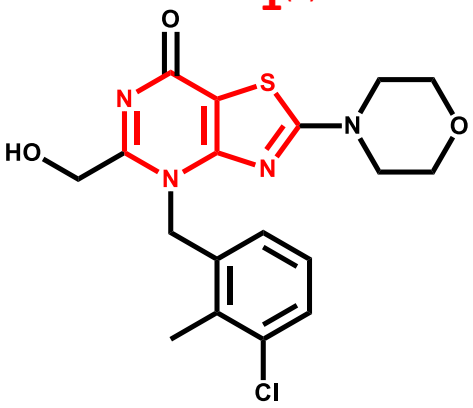
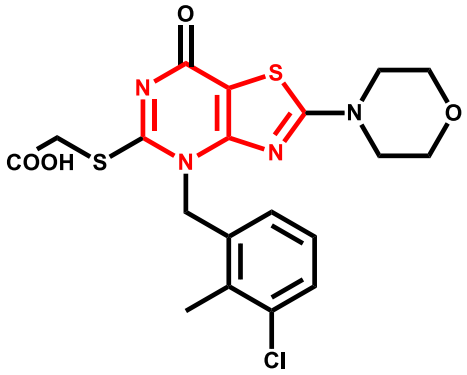


**4**(c)



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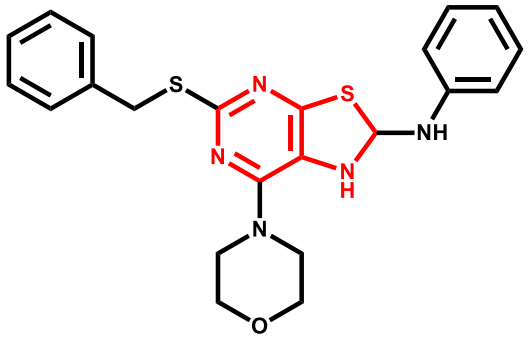


**6**(d)

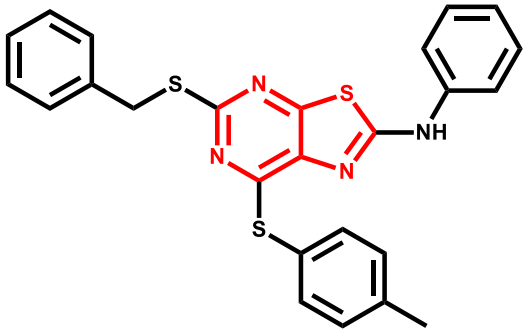
a) F Varano *et.al* Pharmaceuticals 13 (8) (2020)

b) S. Mohamed *et.al* bioorg med chem J. 28 (17) (2020)

c) H. Lin *et.al* *Med Chem Lett* 3 (2012)

d) Z.-H. Li *et.al* EJ Med Chem. (135) (2017)

# The Reference Compounds: Thiazolo[4,5-d]pyrimidines



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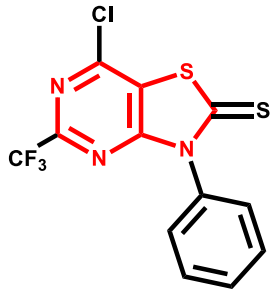

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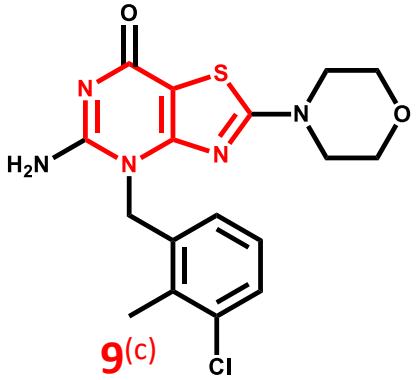

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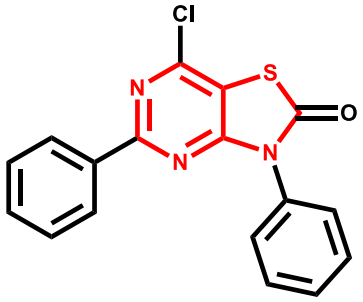


**10**(d)

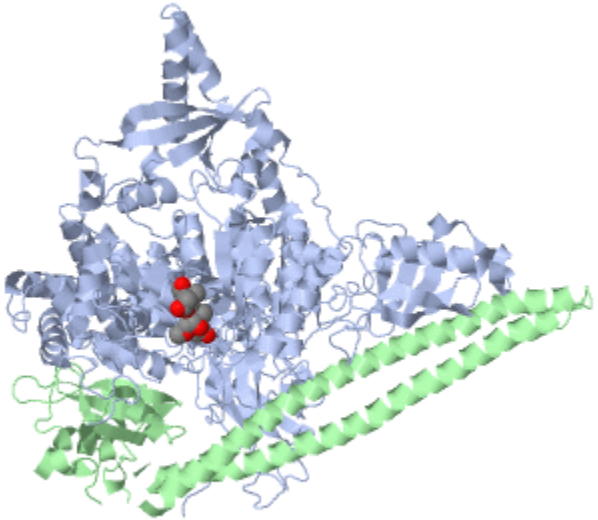
a) Z.-H. Li *et.al* EJ Med Chem. (138) (2017)

b) L. Becan *et.al* Pharmaceuticals 15, 92 (2022)

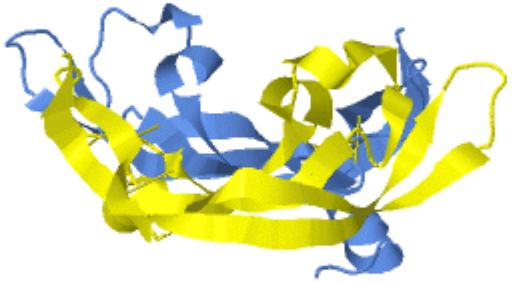
c) H. Lin *et.al* *Med Chem Lett* 3 (2012)

d) L. Becan *et.al* Med Chem Res (2013)

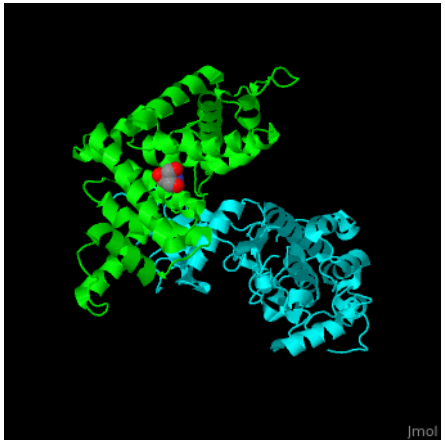
# Targeted Protein



PI3K[(a)]



VEGFR-2[(B)]



CDK-1[(C)]

a) P. Furet *et.al* Bioorg. Med. Chem. Lett. 23 (2013)

b) K. Okamoto Li *et.al* *ACS Med. Chem. Lett. 6* (2015)

c) E. Schneider *et.al* PNAS 110 (2013)

# Aim of the study

- It is a preliminary study to review the pre-synthesized thiazolo[4,5-d] pyrimidines derivatives as anticancer agents.
- The reported anticancer compounds will be selected and assessed computationally by molecular docking study against PI3K, VEGFR-2, CDK1 enzymes to suggest their mechanism of action.
- Also, contact preference and surface mapping studies will be done to support the results.
- Finally, drug likeness and physicochemical properties will be predicted to suggest the best route of administration and the pharmacokinetics of the most promising candidates.

## Results and discussion

## 1. Molecular Docking Study

1. The first study that showed the complex between **PI3Kα** and Alpelisib selected as the docking model (PDB code: 4JPS)[(a)]
2. The second study showed the complex between **VEGFR-2** and Sorafenib selected as the docking model (PDB code: 3WZE)[(b)]
3. The third study showed the complex between **CDK1** and compound A selected as the docking model (PDB code: 4F7N)[(c)]

- Docking interaction energy (kcal/mol) is shown in the next table.

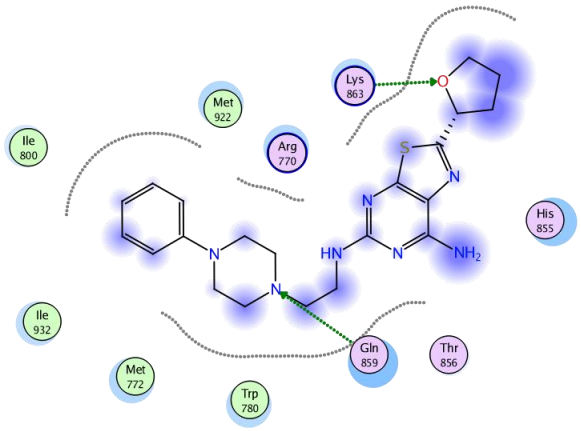
a) P. Furet *et.al* Bioorg. Med. Chem. Lett. 23 (2013)

b) K. Okamoto Li *et.al* *ACS Med. Chem. Lett. 6* (2015)

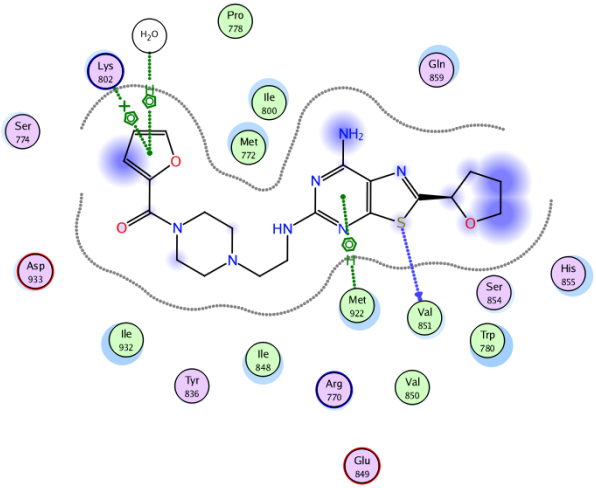
c) E. Schneider *et.al* PNAS 110 (2013)

| Compound No. | Docking interaction energy (kcal/mol) | | |
|---|---|---|---|
| | PI3K | VEGFR-2 | CDK1 |
| 1 | - 7.27 | - 8.61 | - 5.99 |
| 2 | - 7.42 | - 8.27 | - 6.56 |
| 3 | - 6.21 | - 6.13 | - 5.85 |
| 4 | - 4.80 | - 6.34 | - 6.87 |
| 5 | - 6.84 | - 7.79 | - 7.25 |
| 6 | - 7.96 | - 7.36 | - 6.76 |
| 7 | - 8.71 | - 7.24 | - 6.97 |
| 8 | - 5.97 | - 5.20 | - 5.35 |
| 9 | - 6.25 | - 6.56 | - 6.70 |
| 10 | - 7.02 | - 5.63 | - 6.05 |
| Alpelisib | - 8.10 | NA | NA |
| Sorafenib | NA | - 8.1 | NA |
| Compound A | NA | NA | - 9.61 |

## 2D interaction with PI3K




1

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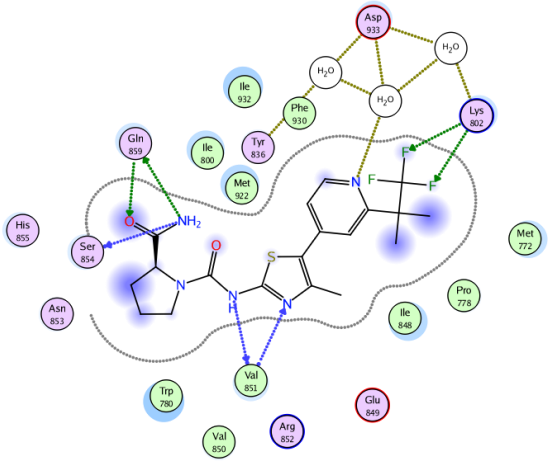
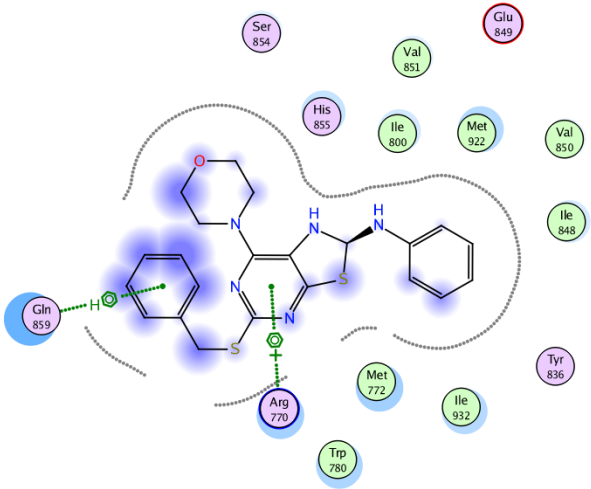



Alpelisib

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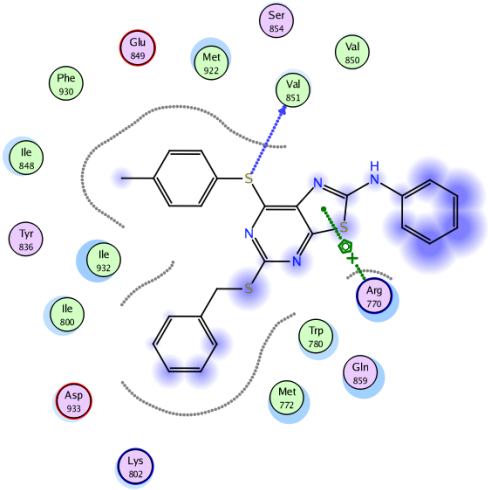
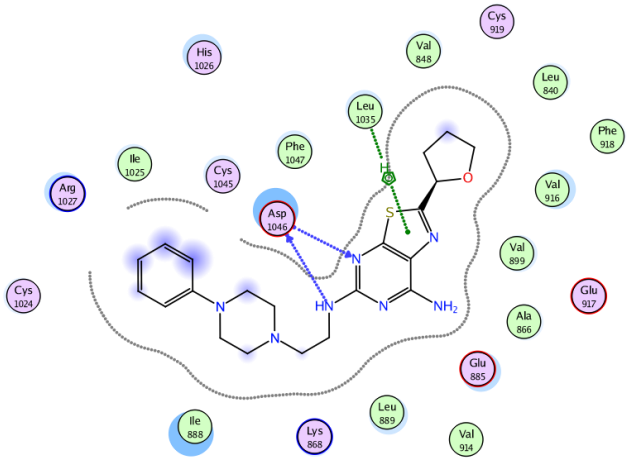



7

## 2D interaction with VEDFR-2

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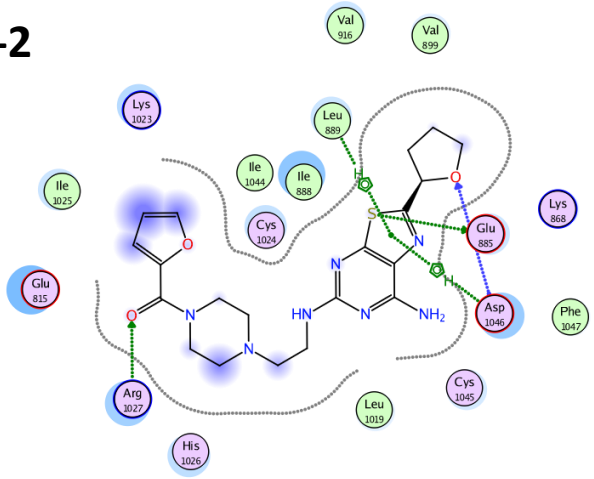


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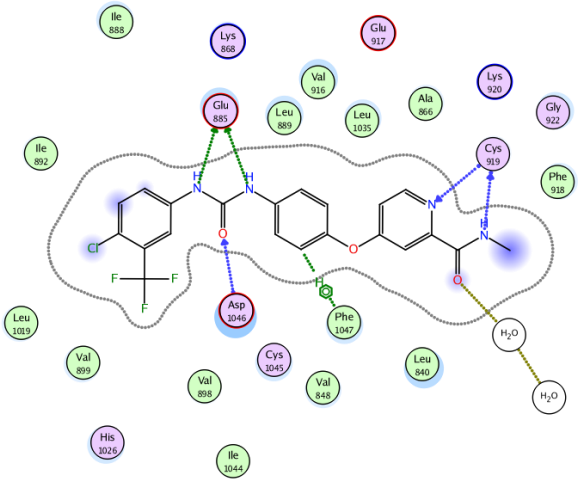
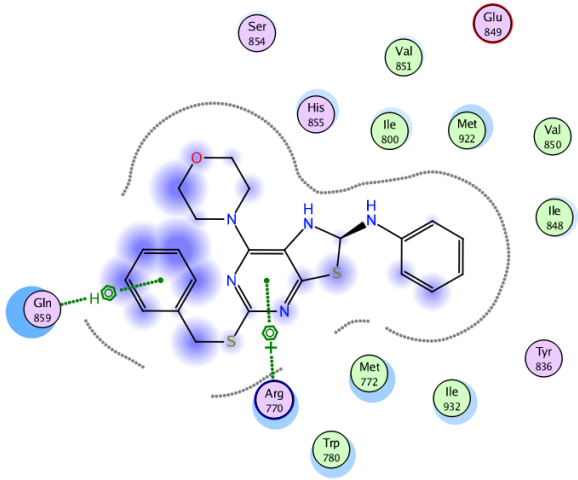



**Sorafenib**

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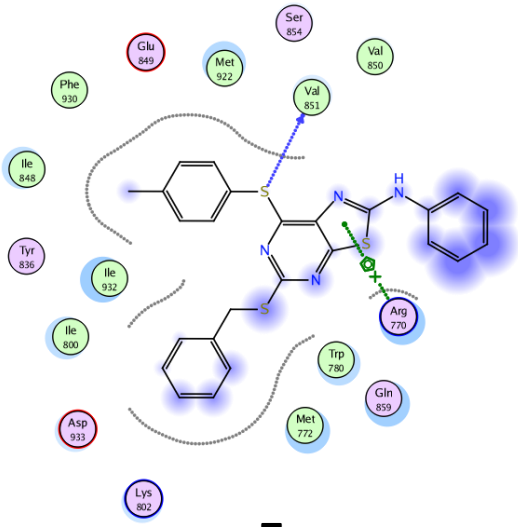
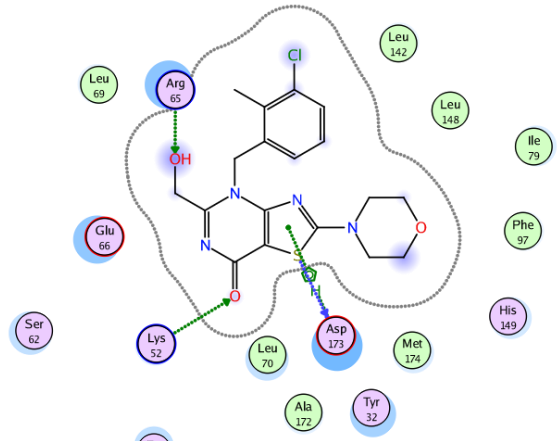



**7**

## 2D interaction with CDK1

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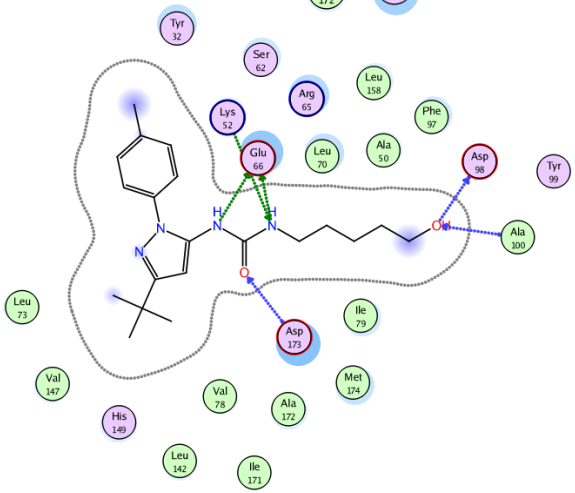
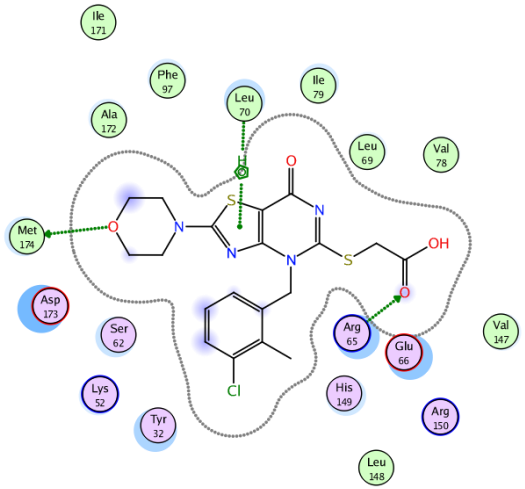



Comp A

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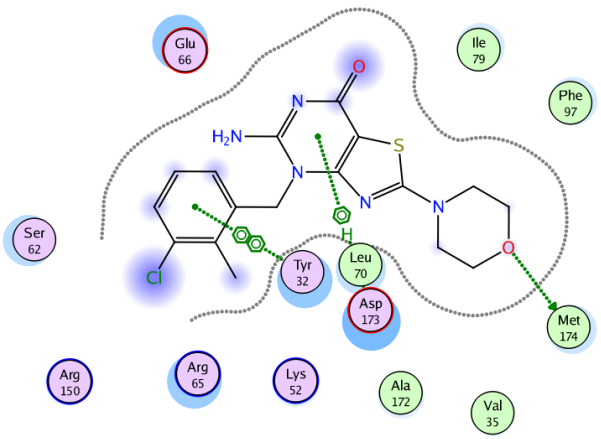


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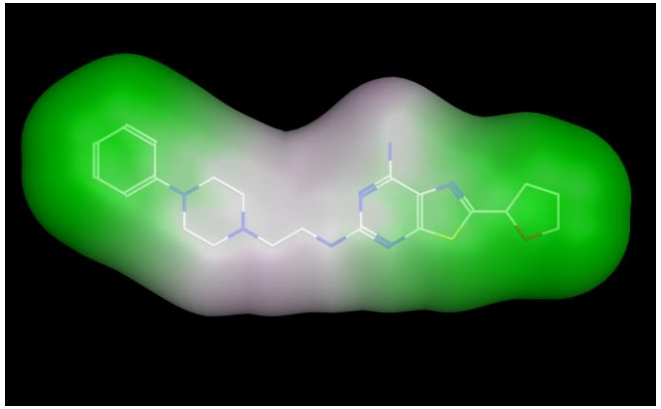
## Results and discussion

### 2. Surface Mapping

Surface mapping is a second evaluation phase that confirms that binders of the most active chemicals, comparable to those of the PI3K and VEGFR-2 enzymes

## Surface Mapping



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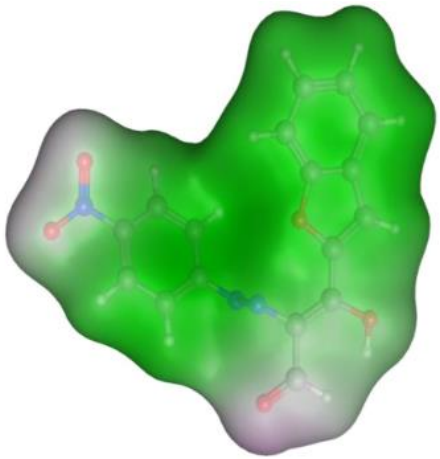
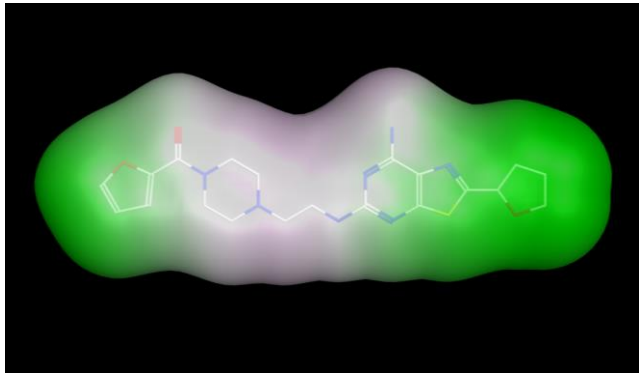


Alpelisib



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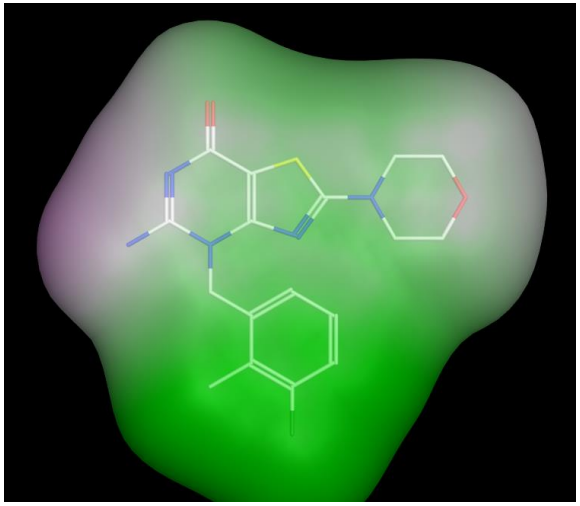

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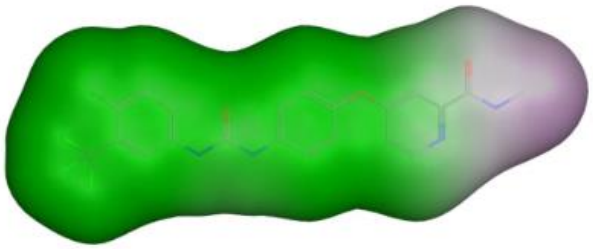
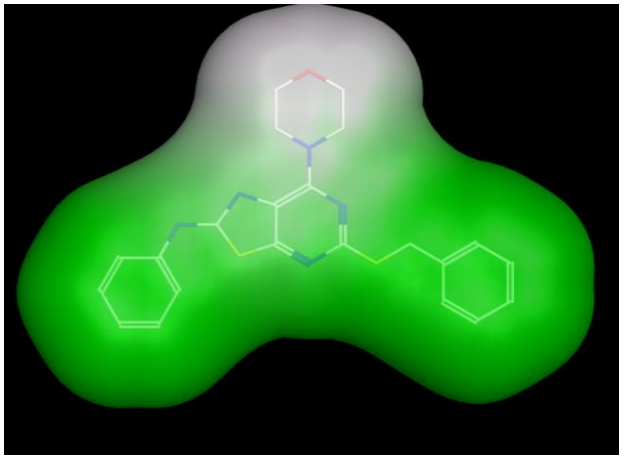


Sorafenib

Pink: hydrophilic,
White: neutral,
Green: hydrophobic.



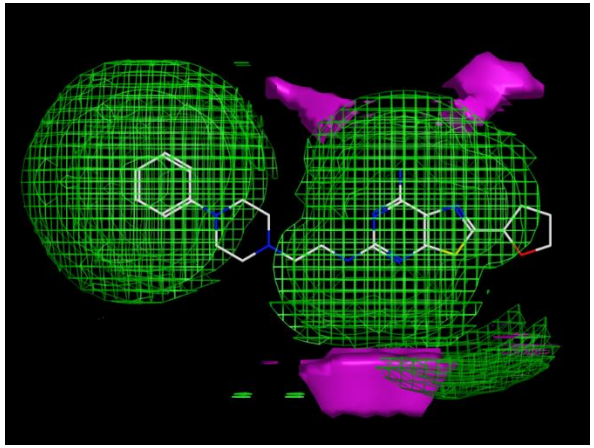
7

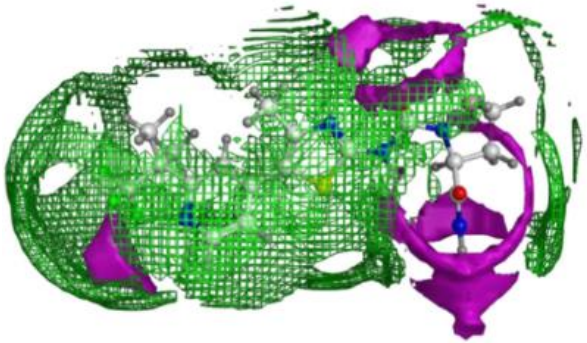
## Results and discussion

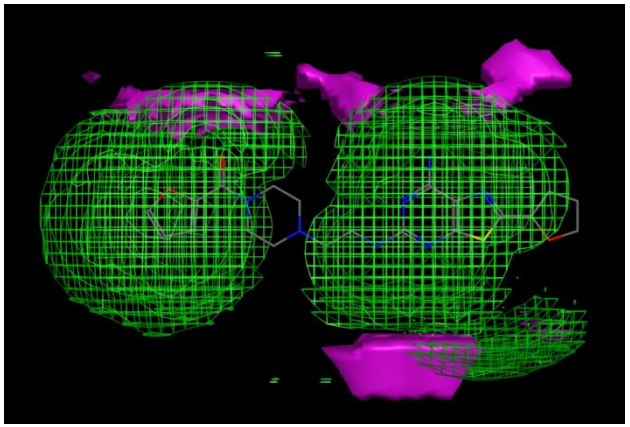
## 3. Contact Preference

- Contact statistics application aim is to calculate, from the 3D atomic coordinates of ligand, the best positions for hydrophobic and hydrophilic ligand atoms.
- Moreover, it includes the interactions between the chemical components of the ligands and the protein microenvironment surrounding them.

Contact Preference



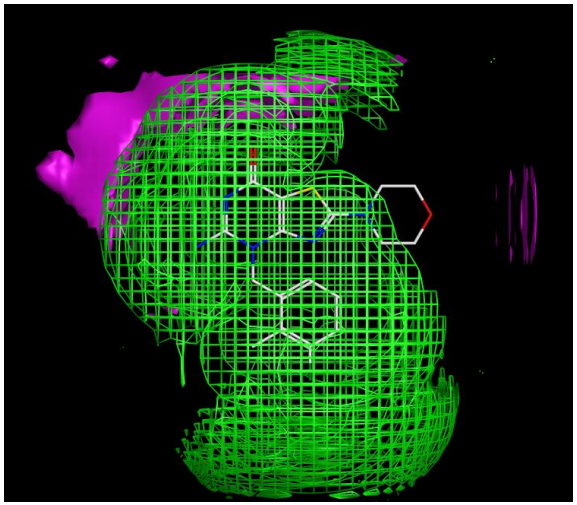


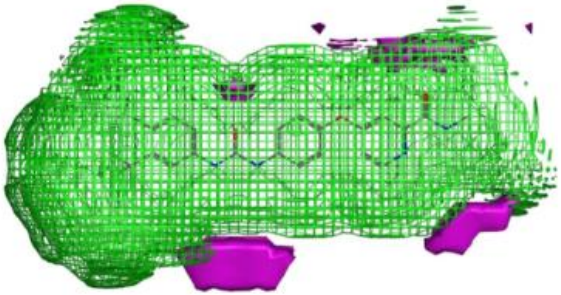


1

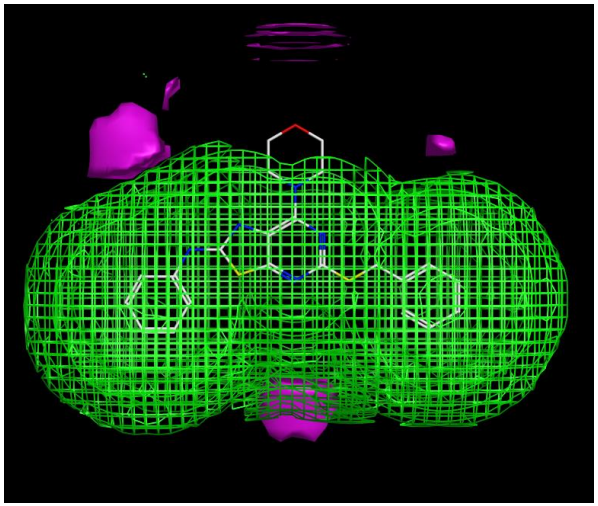
Alpelisib

2





Sorafenib



Hydrophobic: green,
Hydrophilic: purple

6

7

## Results and discussion

## 4. Drug likeness, physicochemical properties, Lipinski's rule and ADMET prediction

- The drug-likeness of a compound is a key criterion in screening drug candidates towards drug targets in living beings.
- The pharmaceutical activity of a drug in humans is evaluated using a set of guidelines, known as Lipinski's rule of five (RO5).
- According to Lipinski's RO5, a compound possesses good permeability across the cell membrane if log P value does not exceed five, the number of hydrogen bond donors and acceptors does not exceed 5 and 10 respectively, and the molecular mass should be less than 500 g/mol.
- To be an orally active drug, a compound should have good agreement with Lipinski's rule

| Comp. No. | Log S[a] | TPSA[b] | MW[c] | M log P[d] | nRB[e] | nHBA[f] | nHBD[g] | nVio[h] |
|---|---|---|---|---|---|---|---|---|
| 1 | -4.22 | 120 | 425.55 | 3.66 | 6 | 5 | 2 | 0 |
| 2 | -3.43 | 150.88 | 433.52 | 3.43 | 7 | 7 | 2 | 0 |
| 4 | -4.08 | 108 | 406.89 | 2.78 | 4 | 5 | 1 | 0 |
| 5 | -5.03 | 151 | 466.96 | 3.03 | 6 | 6 | 1 | 0 |
| 6 | -5.86 | 112.9 | 437.58 | 3.64 | 6 | 3 | 2 | 0 |
| 7 | -7.95 | 129 | 472.65 | 4.91 | 7 | 3 | 1 | 1 |
| 9 | -4.12 | 114.51 | 391.88 | 1.97 | 3 | 4 | 1 | 0 |
| Alpelisib | -4.42 | 129 | 441.5 | 2.95 | 4 | 8 | 2 | 0 |

[a] Solubility parameter., [b] Topological polar surface area (Å$^2$). , [c] Molecular weight (g/mol), [d] Lipophilicity parameter, [e] Number of rotatable bond, [f] Number of hydrogen bond acceptors, [g] Number of hydrogen bond donor, [h] Number of violations to Lipinski's rule of five.

## Conclusions

- Bulk substitution at pyrimidine ring can significantly increase the activity.
- Substitution at position 2 on thiazole can increase binding activity with PI3K, VEGFR-2 and CKD1.
- All selected compounds showed a good explanation for their binding through their surface mapping and contact preference studies.
- In drug likeness study, compounds 1,2,4,5,6,7 and 9 had good drug-likeness with acceptable physicochemical properties and can be taken orally.


Thank you