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New potential inhibitors molecules of the envelope protein from dengue virus type 2

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INTRODUCTION & AIM

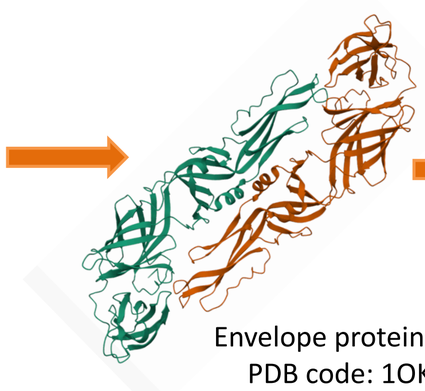
By 2024, 14.1 million cases of dengue were reported around the world, folding the amount of 2023.

Dengue is an orphan disease caused by the dengue virus (DENV), it's transmitted by mosquitoes such as *Aedes aegypti*, which has one of the highest reproductive rates and is more susceptible to the DENV-2 serotype.

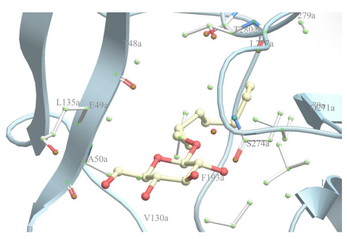
Scientific studies indicate that the envelope protein (EP) could be inhibited avoiding the viral fusion and interrupting the replication.

AIM: Design new drug candidates molecules for the treatment of DENV-2.

Mosquitoe *Aedes aegypti*



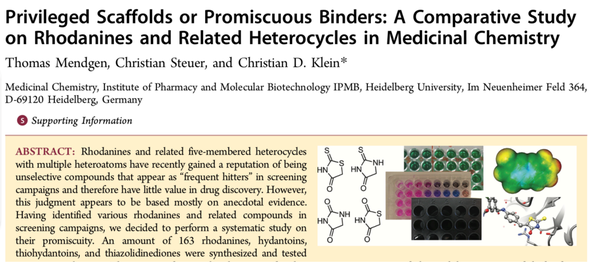
Envelope protein (EP)
PDB code: 1OKE



Chain A active site of EP

METHOD

The base molecule was selected by searching for active chemical structures in ChEMBL from a study of 163 molecules.



Privileged Scaffolds or Promiscuous Binders: A Comparative Study on Rhodanines and Related Heterocycles in Medicinal Chemistry

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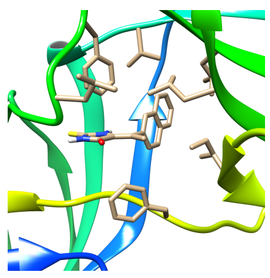
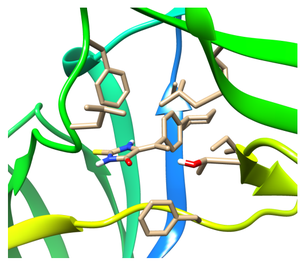
Supporting Information

ABSTRACT: Rhodanines and related five-membered heterocycles with multiple heteroatoms have recently gained a reputation of being unselective compounds that appear as "frequent hitters" in screening campaigns and therefore have little value in drug discovery. However, this judgment appears to be based mostly on anecdotal evidence. Having identified various rhodanines and related compounds in screening campaigns, we decided to perform a systematic study on their promiscuity. An amount of 163 rhodanines, hydantoins, thiohydantoins, and thiazolidinediones were synthesized and tested

Molecular docking was performed using Autodock-Vina 1.1.2 a box with 30 by size, coordinates (x = -10.418, y =79.48, z = 46.224) and exhaustiveness of 8. The molecules with the highest activity were 36 and 136 with -8 and -9.2 respectively.

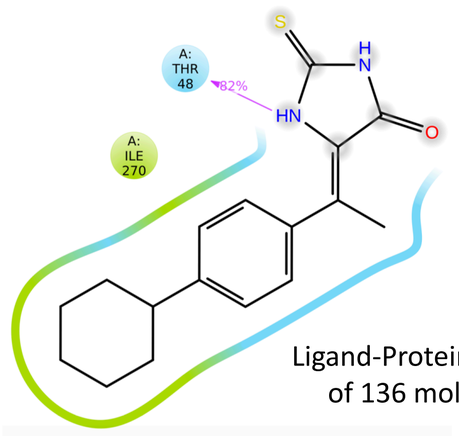


Molecular docking of 36 molecule.



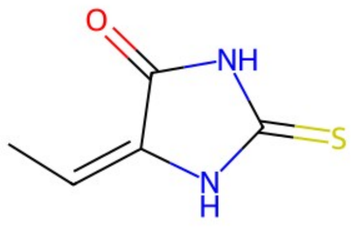
Molecular docking of 136 molecule.

Both molecules were subjected to molecular dynamics by Mestro Viewer- Schrödinger the molecule 136 exhibited a better affinity, binding the amino acid THR48 of EP through the pharmacophore alpha-ethylidene thiohydantoin.



Ligand-Protein contact of 136 molecule.

The pharmacophore alpha-ethylidene thiohydantoin was used for the virtual screening in Zinc20 database and found 1233 bioisosteres.

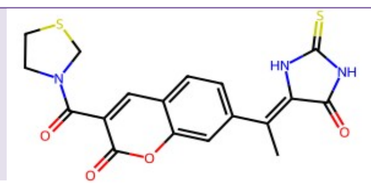
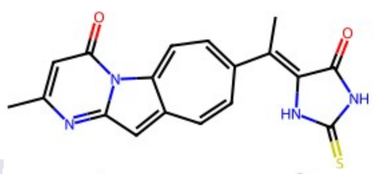
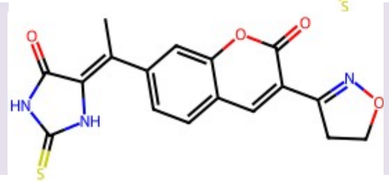
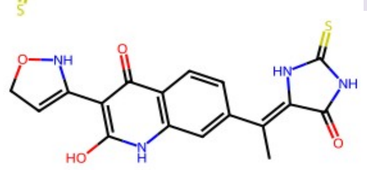


Pharmacophore alpha-ethylidene thiohydantoin

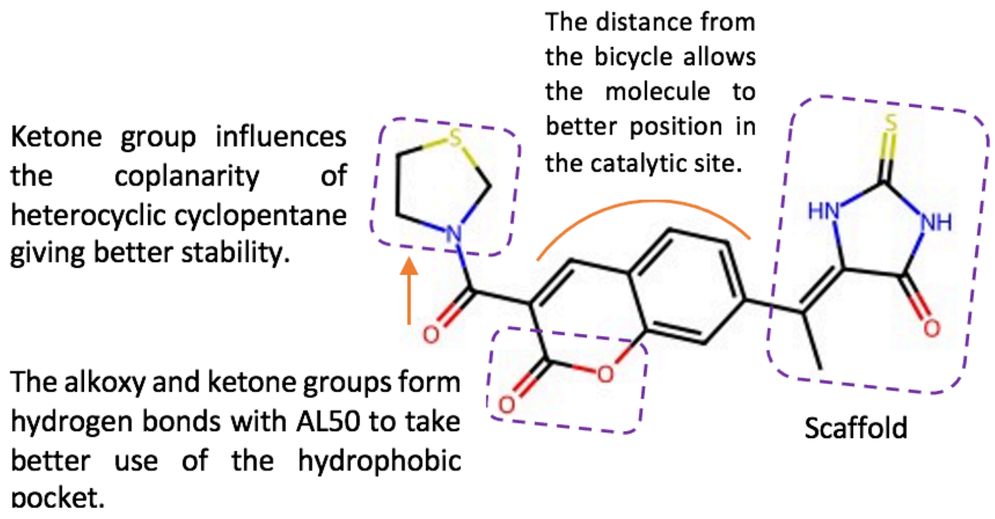
Molecular docking was performed using Autodock-Vina 1.1.2 with the same box and coodinates. The molecules with the highest activity were 1104,1101,1154 and 872.

RESULTS & DISCUSSION

Table 1. Molecules with the best biological activity and physicochemical properties.

Number	MW (g/mol)	LogP	TPSA (Å²)	Molecule	Biological activity
1104	401.46	2.05	149.04		-10.8
1101	350.39	1.96	107.59		-10.5
1154	355.37	1.92	125.02		-10.2
872	370.38	1.15	147.57		-10.1

Structural chemical analysis of molecule 1104 refers to the greater activity due to the ketone group because it influences the coplanarity of the heterocyclic cycloplentane, making better use of the pocket of the catalytic site of EP and is stabilized by forming hydrogen bonds with AL50. Molecule 1101 presents a tricyclic ring that can be located in the catalytic site similar to molecule 1104, it presents acidic amines and a carboxyl group that can form hydrogen bonds with amino acid residues of the protein. Molecule 1154 also maintains the distance like the base molecule 136; however, it is substituted by a bicycle from which a ketone bridge is formed as in molecule 1104, this bridge also influences the coplanarity of the 4,5-dihydro-1,2-oxazole heterocycle and in turn the stability of nitrogen or oxygen to form hydrogen bonds with the amine functional group of AL50. For molecule 872 the bioisosteric substitutions respect the volume and distance to be occupied from the active site pocket, and like molecule 1154, it has the 4,5-dihydro-1,2-oxazole heterocycle that is being affected by the carboxyl group of the netx heterocycle separated by a carbon-carbon bond, this can increase its activity since it prevents the increase in activation energy in the hydrophobic pocket. The physicochemical properties show similarities for all the compounds.



SAR of molecule 1104

CONCLUSION

Four novel compounds of promising activity against envelope protein of dengue virus type 2 where found.

FUTURE WORK / REFERENCES

1. Mendgen T, Steuer C, Klein CD. Privileged scaffolds or promiscuous binders: a comparative study on rhodanines and related heterocycles in medicinal chemistry. J Med Chem [Internet]. 2012;55(2):743–53. Available from: http://dx.doi.org/10.1021/jm201243p
2. Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry, 31(2), 455-461.