

ANTICANCER INHIBITORS OF *PLASMODIUM* PI4K AS POTENTIAL ANTIMALARIAL AGENTS

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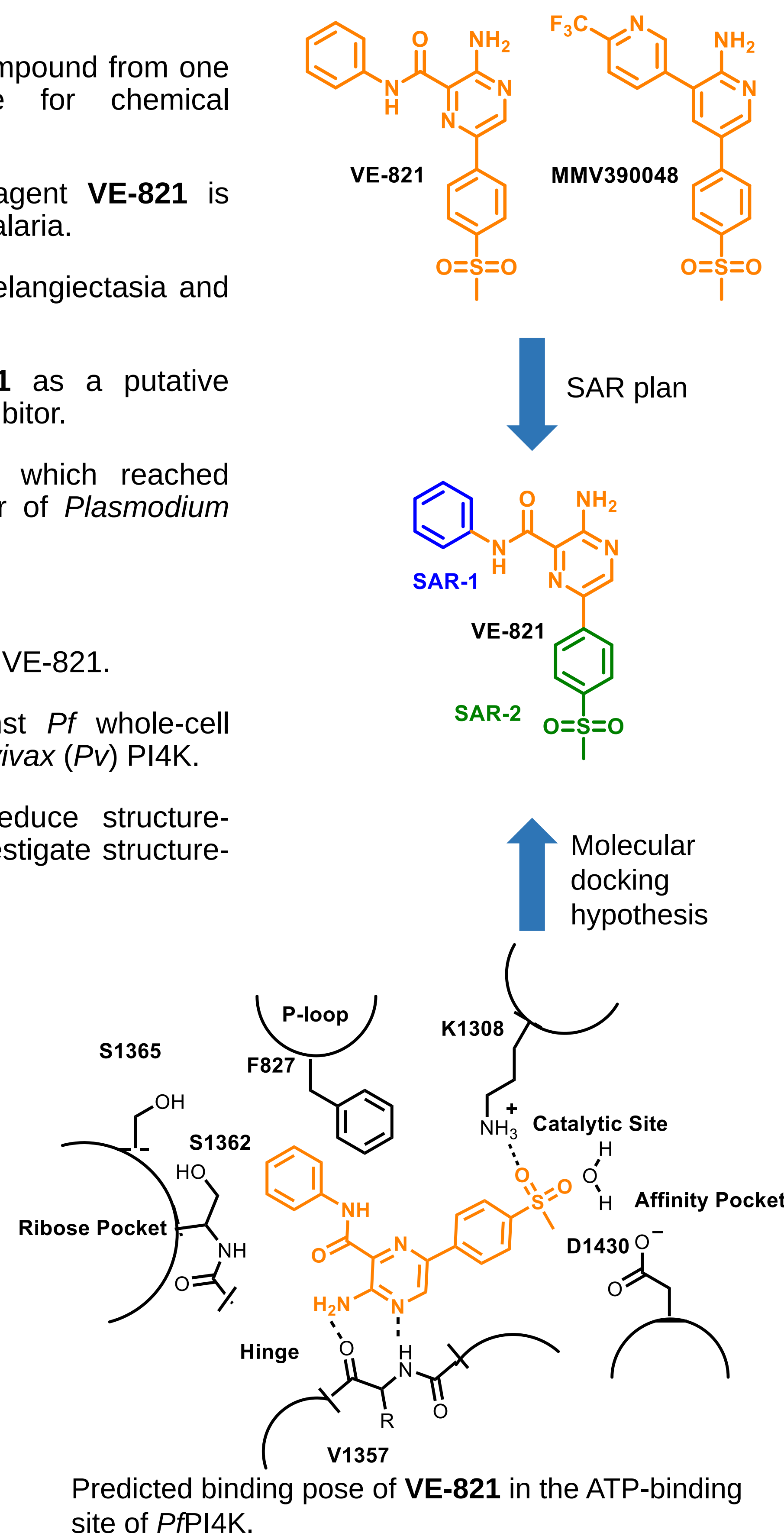
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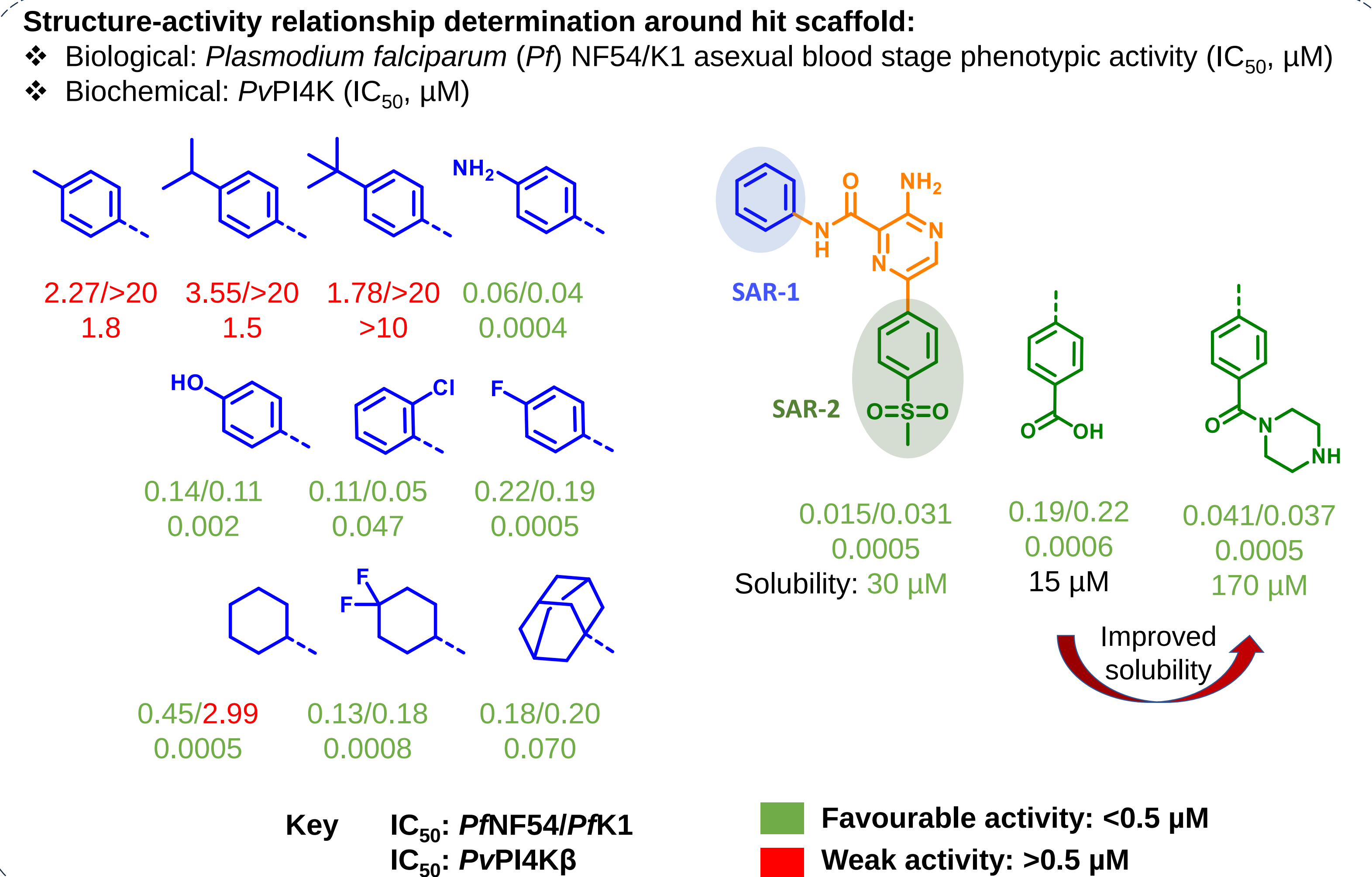
Background

- ❖ 95% of all cases of malaria infection that were reported in 2021 occurred in Africa.¹
- ❖ Drug repositioning refers to using a compound from one disease indication as a template for chemical optimisation against a new indication.
- ❖ In the current work the anticancer agent **VE-821** is investigated for repositioning against malaria.
- ❖ **VE-821** is a potent anticancer ataxia telangiectasia and Rad3-related kinase inhibitor (ATR).
- ❖ Kinobead screening identified **VE-821** as a putative phosphatidylinositol 4-kinase (PI4K) inhibitor.
- ❖ The antimalarial agent MMV390048, which reached Phase IIa clinical trials, is an inhibitor of *Plasmodium falciparum* (Pf) PI4Kβ.²
- ❖ The current objectives are to:
 1. Design and synthesise analogues of VE-821.
 2. Evaluate analogues *in vitro* against Pf whole-cell parasites and enzyme *Plasmodium vivax* (Pv) PI4K.
 3. Employ computational tools to deduce structure-activity relationships (SAR) and investigate structure-property relationships (SPR).

- PfPI4K hinge contains a HBD and a HBA at V1357, which were used as geometrical constraints for molecular docking experiments.³
- Thus, the phenyl substituent of the amide group of **VE-821** interacts with F827 and S1362.
- The methylsulfonylphenyl substituent interacts with the catalytic lysine K1308 through hydrogen bonding.



SAR and SPR Analyses



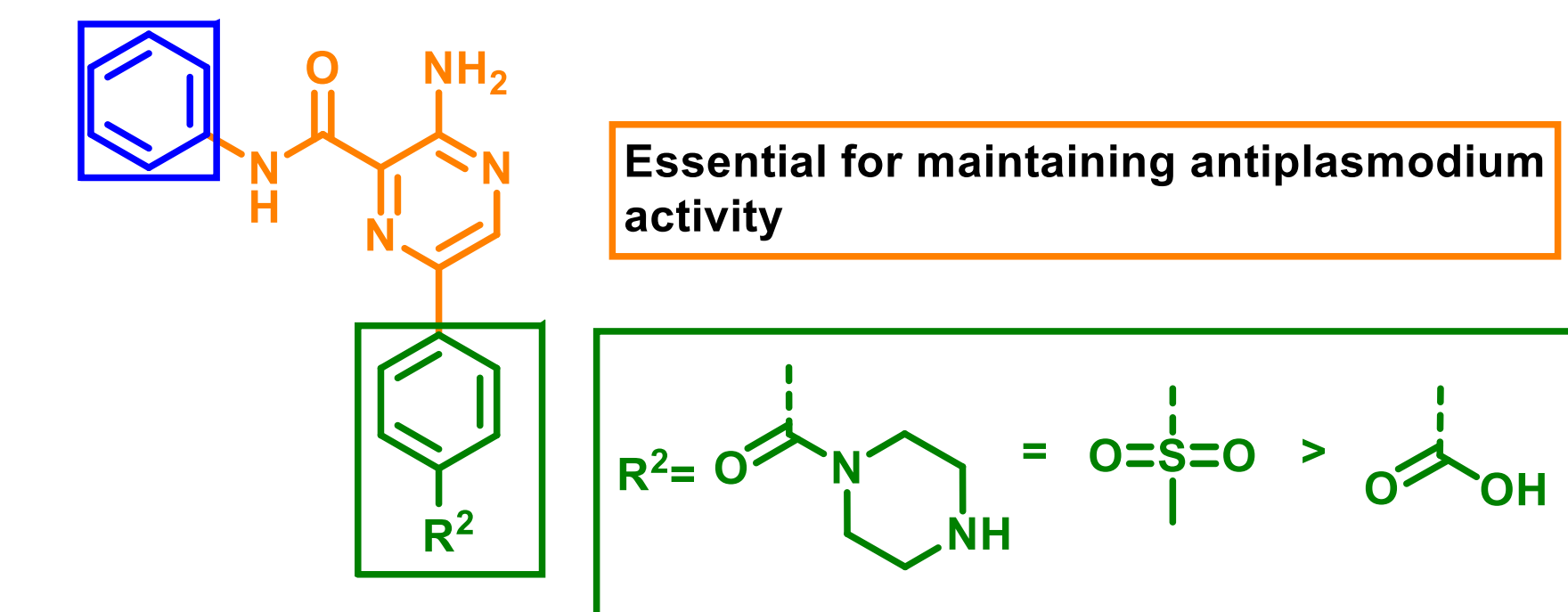
Evaluation of microsomal metabolic stability and *Homo sapiens* (Hs) off-targets:

	VE-821	NS-I	NS-L	MMV390048
Microsomal CL _{int, app} (mL/min/kg)	HLM <11.6 RLM <11.6 MLM <11.6	<11.6 <11.6 <11.6	<11.6 24.5 31.4	<11.6 <11.6 <11.6
HsPI4Kβ Selectivity Index, S.I.	1010	ND	3360	2290 ⁴
HsMINK1 S.I.	>20000	ND	1130	210 ⁴
HsMAP4K4 S.I.	5460	ND	890	240 ⁴

Conclusion and Future Work

- ✓ Electron-donating groups at SAR-1 are not tolerated with exceptions of the NH₂ and OH orthologues.
- ✓ Smaller electron-withdrawing substituents and substituents with a greater sp³ character at SAR-1 demonstrate comparable activities.
- ✓ The representative set of compounds of the **VE-821** series have good microsomal metabolic stability.
- ✓ The derivatives of **VE-821** poorly inhibit Hs orthologues.
- ✓ Evaluate frontrunner compounds for permeability and plasma protein binding to gain a better understanding of the frontrunner compounds' pharmacokinetic profile.

Phenyl ring sufficient for Van der Waals interactions
Bulkier electron withdrawing or donating groups result in loss in activity due to steric effects.



References

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