Supplementary information

Estimation of omipalisib metabolic stability in the human liver microsomes employing ultra-fast UPLC-MS/MS approach: Greenness evaluation with the in-silico study for structural alarms and metabolic lability

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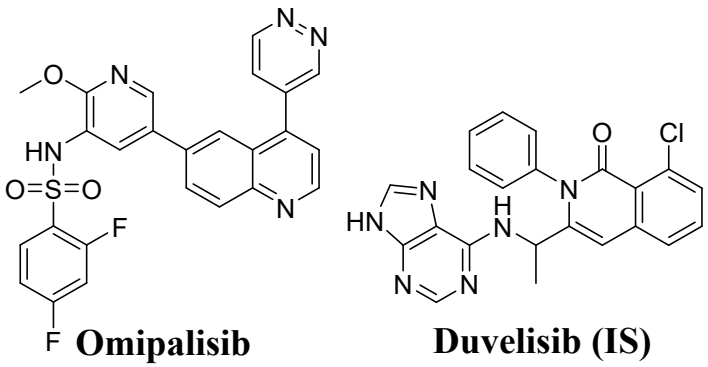
In-silico ADME profiling of OMP

The ADME characteristics of OMP were calculated using its SMILES representation COC1=C(C=C(C=N1)C2=CC3=C(C=CN=C3C=C2)C4=CN=NC=C4)NS(=O)(=O)C5=C(C=C(C=C5)F)F on the SwissADME platform. An evaluation was conducted to examine the tendency of OMP to exhibit drug-like characteristics by examining its ADME properties. The log p score generated by the SwissADME procedure suggests that OMP exhibits a moderate degree of water solubility (Log S = -5.42). The expected pharmacokinetic profile for GIT absorption reveals minimal absorption; though, permeability across the blood-brain barrier is not yet recognized. The valuation of drug similarity meets the criteria set forth by Lipinski (one violation: MW>500), Veber, and Muegge [1, 2]; however, it does not conform to the Ghose recommendations (two violations: MW>480, WLOGP>5.6) and the Egan criteria (one violation: WLOGP>5.88) [3]. The proposed bioavailability score is 0.55. The Log Kp mark, indicative of skin permeability, is computed at -7.03 cm/s. The suggested mechanism of OMP action comprises the inhibition of specific CYP450 sub enzymes, namely CYP2D6, CYP2C9, and CYP3A4, as well as P-glycoprotein, that functions as a substrate. The statement indicates that EST does not show inhibitory effects on other CYP450 sub enzymes, comprising CYP2C19 and CYP1A2. Fig. 2 exhibits the ADME radar map for OMP, with applicable data listed in Table 1.

Figures:



Omipalisib Molecular Weight: 505.50

Duvelisib (IS) Molecular Weight: 416.87

Fig. S1. The chemical structure of omipalisib and duvelisib (IS).

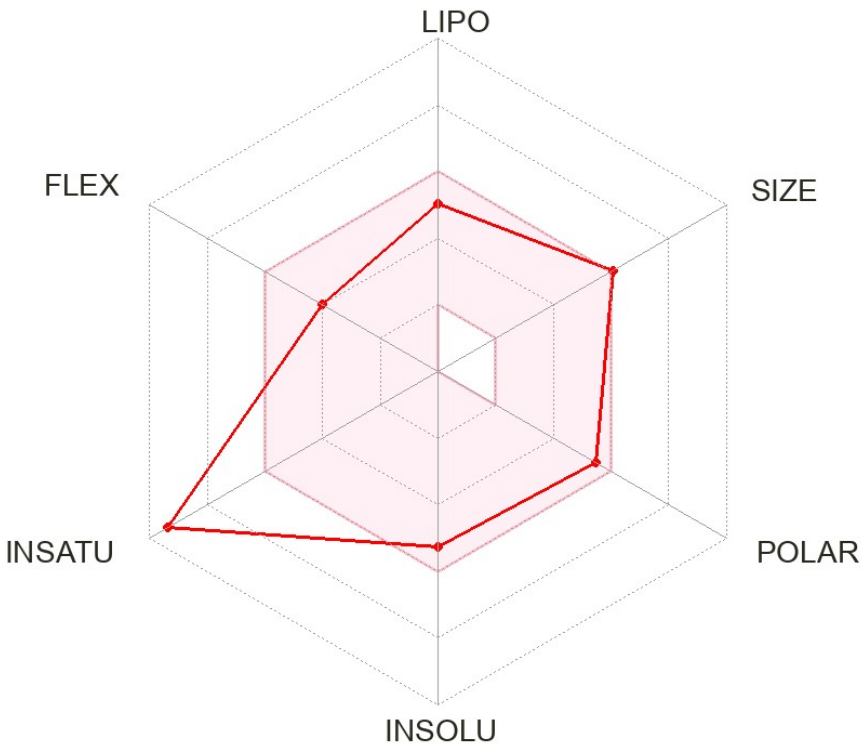


Fig. S2. Saturation (INSATU): carbons fraction in sp^3 hybridization 0.04; Molecular weight (SIZE): 505.50 g/mol; Polarity (POLAR): TPSA 115.34 $Å^2$; Flexibility (FLEX): Solubility (INSOLU): log S ≤ 10.61; 6 rotatable bonds. Lipophilicity (LIPO) is determined as XLOGP3 = +3.32. The OMP ADME radar chart was done applying the in-silico SwissADME online software.

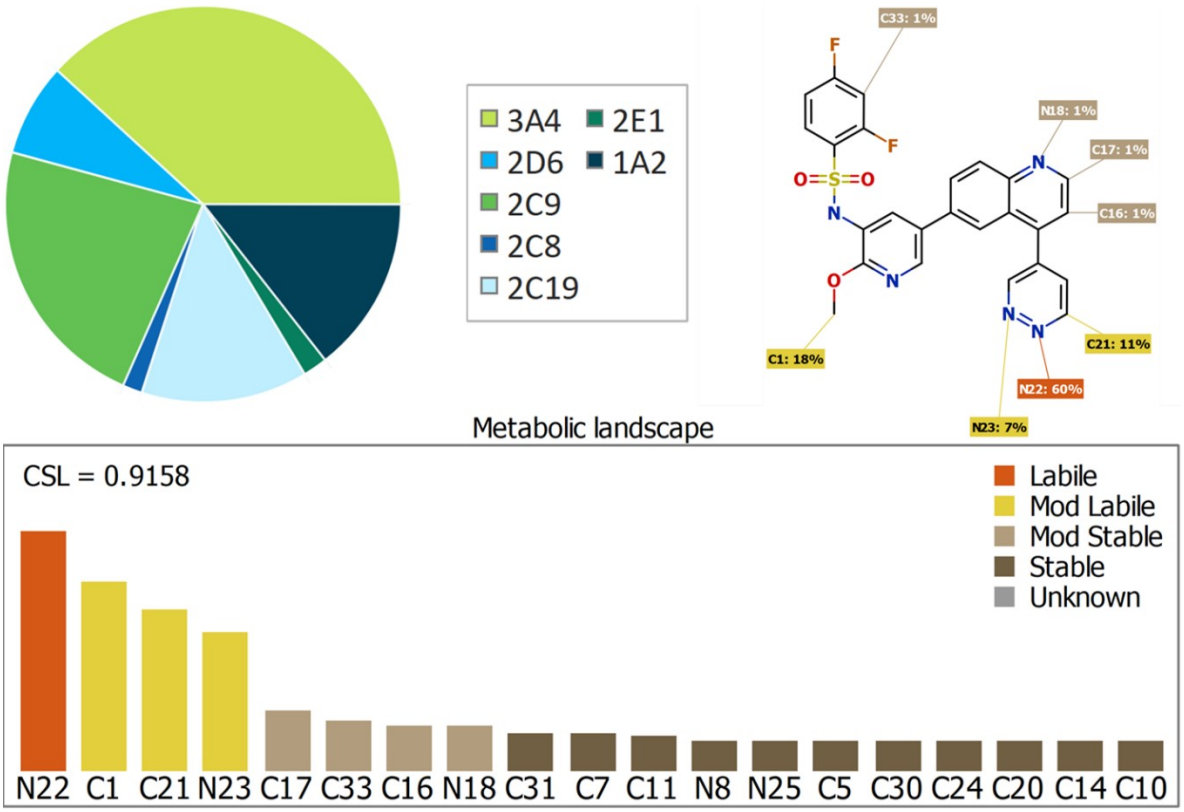


Fig. S3. The CSL value of 0.9158 designates that OMP displays a high susceptibility to metabolism. The outcomes were estimated applying the P450 software.

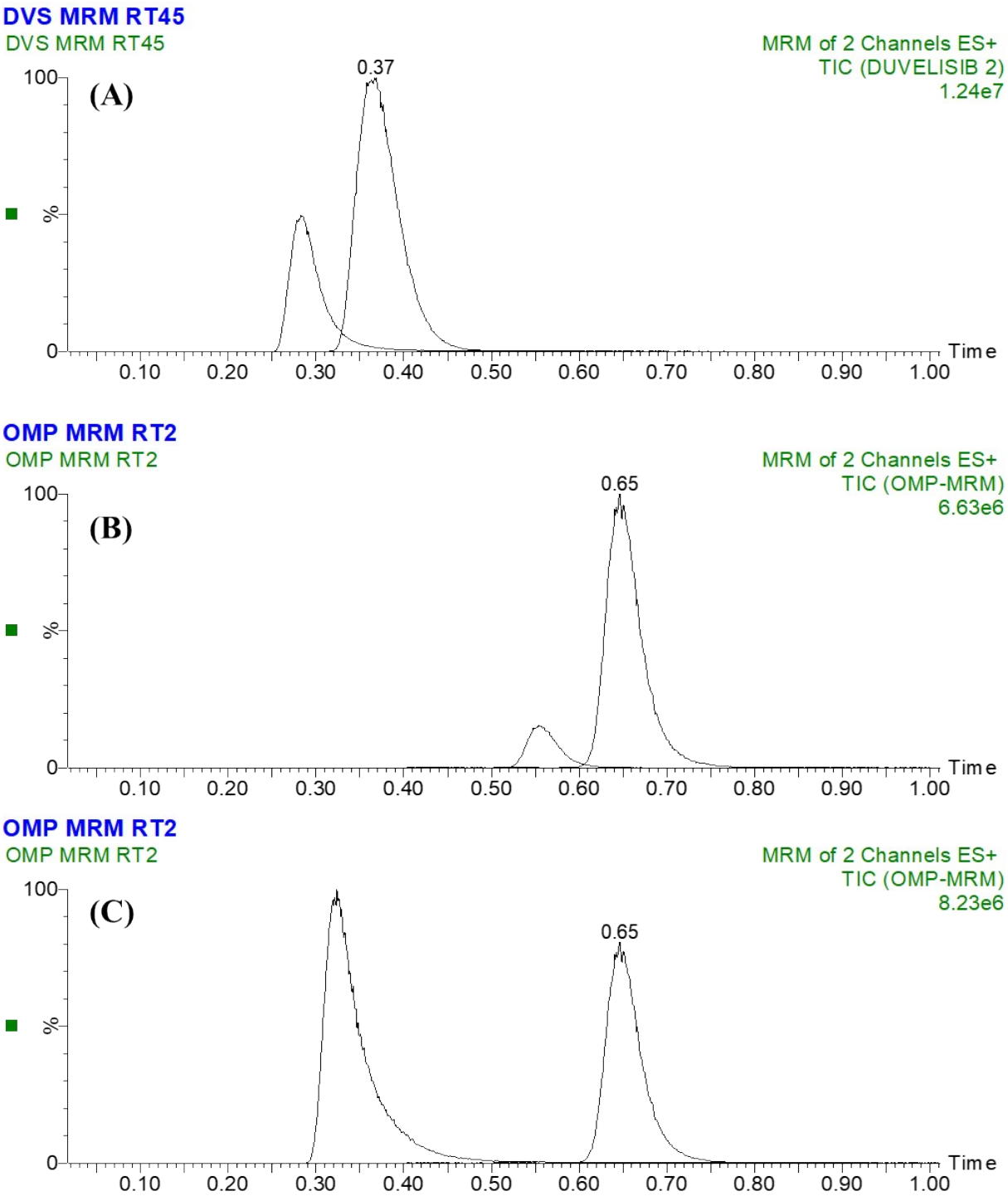


Fig. S4. Chromatographic separation of OMP and DUV using HILIC DIOL column (**A**), imidazole column (**B**) and Eclipse Plus C8 column (**C**).

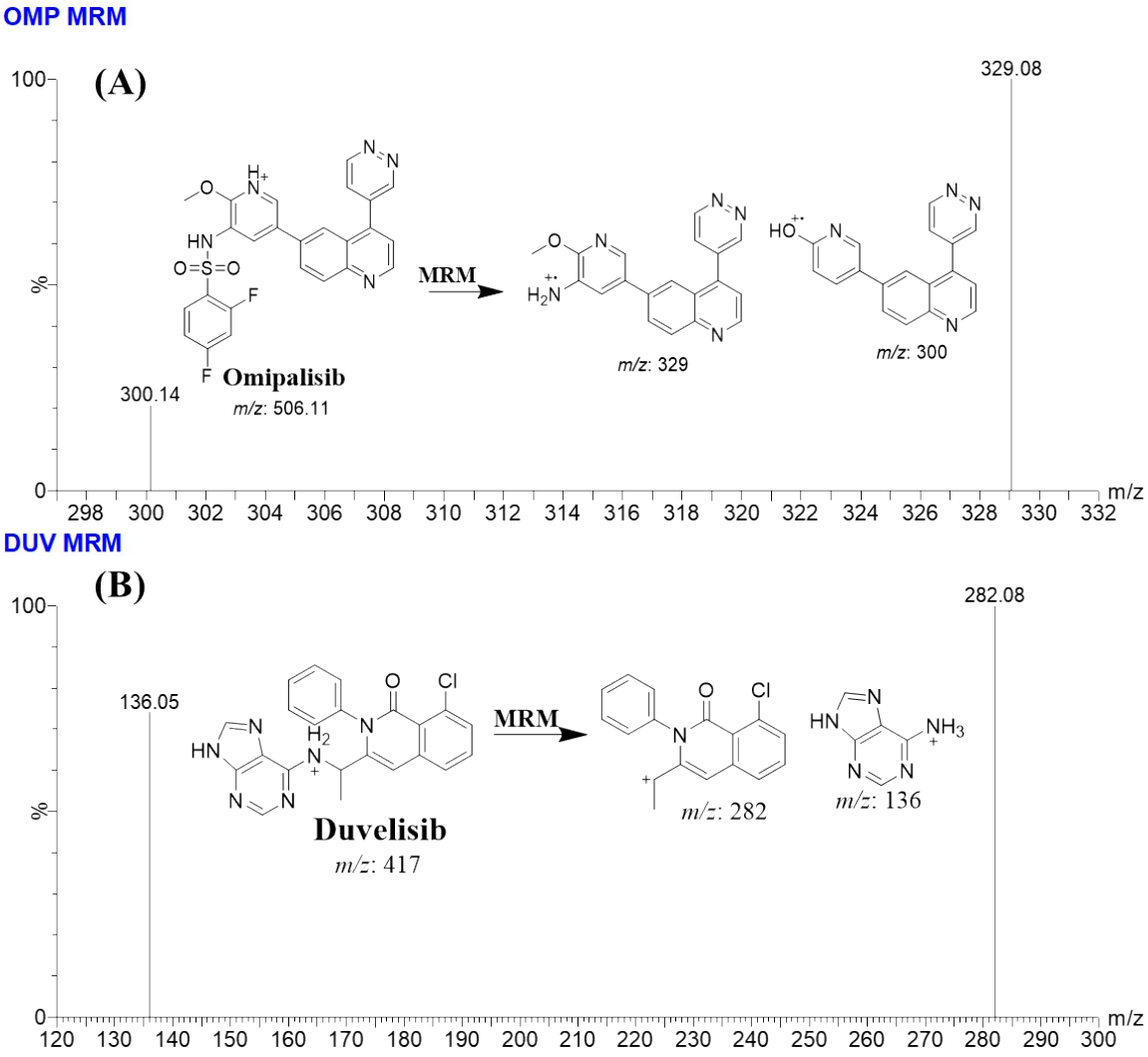


Fig. S5. MS spectrum of OMP (**A**) and MS spectrum of DUV as IS (**B**) attained applying MRM mass detector mode. The proposed fragmentation patterns are displayed.

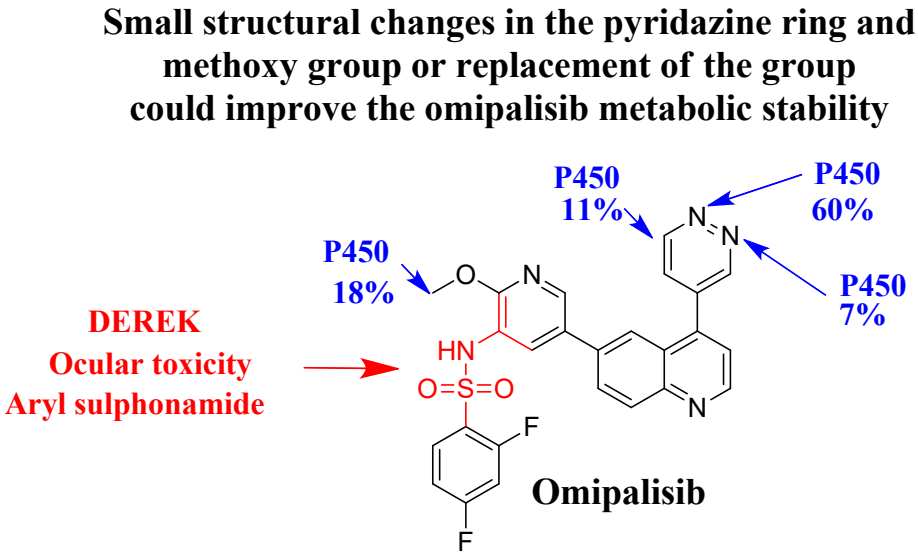


Fig. S6. The OMP structure displaying the WhichP450 metabolic locations marked in blue color that the pyridazine ring and methoxy group (marked in blue color) are accountable for OMP's metabolic lability, although OMP DEREK alert predictions (red color) reveal that Aryl sulphonamide moiety is anticipated for ocular toxicity.

Tables:

Table S1. The ADME features of omipalisib were assessed applying the SwissADME tool that is freely accessible.

Physicochemical characteristics		**Water Solubility**	
Heavy atoms num.	36	Solubility	2.87e-03 mg/mL; 5.69^{-6} mol/L
Formula	$C_{25}H_{17}F_2N_5O_3S$	Log S (ESOL)	-5.25
Rotatable bonds num.	6	Class	Moderately soluble
Molecular weight	505.50 g/mol	Solubility	1.93e-03 mg/mL; 3.82^{-6} mol/L
Num. of arom. heavy atoms	28	Log S (Ali)	-5.42
Fraction Csp3	0.04	Class	Moderately soluble
		Solubility	1.23e-08 mg/mL; 2.44^{-11} mol/L
Num. of H-bond donors	1	Class	Insoluble
Num. of H-bond acceptors	9	Log S (SILICOS-IT)	-10.61
TPSA	115.34 Å²	**Medicinal Chemistry**	
Molar Refractivity	129.52	Leadlikeness	No; 1 violation: MW>350
Lipophilicity		Synthetic accessibility	3.57
Log Po/w (XLOGP3)	3.32	Brenk	0 alert
Log Po/w (WLOGP)	6.57	PAINS	0 alert
Log Po/w (iLOGP)	3.08	**Pharmacokinetics**	
Log Po/w (MLOGP)	2.67	P-gp substrate	No
Log Po/w (SILICOS-IT)	4.28	GI absorption	Low
Consensus Log Po/w	3.98	Permeant to BBB	No
Druglikeness		CYP2D6 inhibition	Yes
Ghose	No; 2 violations: LOGP>5.6, MW>480	CYP1A2 inhibition	No
Lipinski	Yes; 1 violation: MW>500	Skin permeation (Log Kp)	-7.03 cm/s
Egan	No; 1 violation: WLOGP>5.88	CYP2C19 inhibition	No
Muegge	Yes	CYP2C9 inhibition	Yes
The score of bioavailability	0.55	CYP3A4 inhibition	Yes
Veber	Yes		

Table S2. The twelve characteristics of the greenness assessment of the UPLC-MS/MS methodology.

Standards	Mark	Weight
1. Utilize straight approaches of analysis to circumvent the necessity for sample treatment.	0.3	2
2. The targets are to accomplish a low size of sample and just the right samples number.	0.75	2
3. Whenever feasible, it is advisable to conduct observations on site.	0.0	2
4. The integration of operational procedures and analytical approaches lead to conserving energy and a reduction in reagent usage.	1.0	2
5. One should choose automated and miniaturized approaches.	0.5	2
6. Avoidance of derivatization is recommended.	1.0	2
7. It is important to prevent the beginning of a considerable analytical waste volume and verification that suitable measures are in place for its control.	0.79	2
8. Methods that analyze many analytes or parameters simultaneously are favored over methods that analyze one analyte at a time.	1.0	2
9. Energy consumption should be reduced.	0.0	2
10. It is sensible to arrange reagents that are originated from natural resources.	0.5	2
11. It is important to remove or substitute toxic reagents.	0.8	2
12. The level of safety for operators should be enhanced.	0.6	2

References

1. I. Muegge, *Medicinal Research Reviews*, 2003, **23**, 302-321.
2. M. Motiwale, H. Verma, O. Silakari and B. Sapra, *Computational Drug Delivery: Molecular Simulation for Pharmaceutical Formulation*, 2024, 39.
3. M. W. Attwa, A. S. Abdelhameed and A. A. Kadi, *Medicina*, 2024, **60**, 1914.