

In Silico Investigation of the Constituents of Aroeira Honey (*Astronium urundeuva*) and the Binding Affinity with Important Proteins of *M. leprae* and *M. tuberculosis*

Victor M. M. de Souza, Géssica E. do N. Costa, Rodrigo F. dos S. Silva, Ricardo M. Ramos and Ézio R. A. de Sá

Supplementary Material

Table 1S: Compounds identified in Aroeira honey.

Constituents	CID PubChem	REFERENCE
Quercetin	5280343	(JÚNIOR <i>et al</i> , 2022)
Quercetin- <i>O</i> -rhamnoside	*	(MĂRGĂOAN <i>et al</i> , 2021)
Quercetin 3-orutinoside (rutin)	5280805	(JÚNIOR <i>et al</i> , 2022)
Quercetin 3',3'-dimethyl ether	5316900	(MĂRGĂOAN <i>et al</i> , 2021)
Quercetin 7,3'-dimethyl ether	5280417	(MĂRGĂOAN <i>et al</i> , 2021)
Quercetin rhamnosyl- hexosyl-rhamnoside	*	(MĂRGĂOAN <i>et al</i> , 2021)
Agipenin	5280443	(MĂRGĂOAN <i>et al</i> , 2021)
Kaempferol	5280863	(MĂRGĂOAN <i>et al</i> , 2021)
Kaempferide	5281666	(MĂRGĂOAN <i>et al</i> , 2021)
Isorhamnetin	5281654	(MĂRGĂOAN <i>et al</i> , 2021)
Galangin	5281616	(MĂRGĂOAN <i>et al</i> , 2021)
Genistein	5280961	(MĂRGĂOAN <i>et al</i> , 2021)
Myricetin	5281672	(MĂRGĂOAN <i>et al</i> , 2021)
Methyl anthranilate	8635	(MĂRGĂOAN <i>et al</i> , 2021)
Catechin	9064	(MĂRGĂOAN <i>et al</i> , 2021)
Epicatechin	72276	(MĂRGĂOAN <i>et al</i> , 2021)
Pinobanksin	73202	(MĂRGĂOAN <i>et al</i> , 2021)
Pinocembrin	68071	(MĂRGĂOAN <i>et al</i> , 2021)
Chrysin	5281607	(MĂRGĂOAN <i>et al</i> , 2021)
Acacetin	5280442	(MĂRGĂOAN <i>et al</i> , 2021)
Luteolin	5280445	(MĂRGĂOAN <i>et al</i> , 2021)
Baicalein	5281605	(MĂRGĂOAN <i>et al</i> , 2021)
Hesperetin	72281	(MĂRGĂOAN <i>et al</i> , 2021)
Naringenin	439246	(MĂRGĂOAN <i>et al</i> , 2021)
Eriodictyol	440735	(MĂRGĂOAN <i>et al</i> , 2021)
5-Methoxy pinobanksin	*	(MĂRGĂOAN <i>et al</i> , 2021)
<i>P</i> -Hydroxybenzoic acid	135	(MĂRGĂOAN <i>et al</i> , 2021)
Vanilic acid	8468	(MĂRGĂOAN <i>et al</i> , 2021)

Phenylacetic acid	999	(MĂRGĂOAN <i>et al</i> , 2021)
L- β -phenyllactic acid	444718	(MĂRGĂOAN <i>et al</i> , 2021)
Dl- β -phenyllactic acid	3848	(MĂRGĂOAN <i>et al</i> , 2021)
Dl- <i>p</i> -hydroxyphenyllactic acid	9378	(MĂRGĂOAN <i>et al</i> , 2021)
Gentisic acid	3469	(MĂRGĂOAN <i>et al</i> , 2021)
Rosmarinic acid	5281792	(MĂRGĂOAN <i>et al</i> , 2021)
Phenyllactic acid	1303	(MĂRGĂOAN <i>et al</i> , 2021)
Lumichrome	5326566	(MĂRGĂOAN <i>et al</i> , 2021)
Caffeic acid	689043	(MĂRGĂOAN <i>et al</i> , 2021)
Caffeic acid phenethyl ester	637542	(MADEIRA, 2021)
<i>p</i> -Coumaric acid	637540	(MADEIRA, 2021)
<i>O</i> -coumaric acid	637541	(MĂRGĂOAN <i>et al</i> , 2021)
<i>M</i> -coumaric acid	445858	(MĂRGĂOAN <i>et al</i> , 2021)
Ferulic acid	444539	(MĂRGĂOAN <i>et al</i> , 2021)
Cinnamic acid	444539	(MĂRGĂOAN <i>et al</i> , 2021)
Trans-cinnamic acid	637540	(MĂRGĂOAN <i>et al</i> , 2021)
2-Hydroxycinnamic acid	717531	(MĂRGĂOAN <i>et al</i> , 2021)
3,4-Dimethoxycinnamic acid	444539	(MĂRGĂOAN <i>et al</i> , 2021)
Trans-cinnamic acid	736186	(MĂRGĂOAN <i>et al</i> , 2021)
Isoferulic acid	637775	(MĂRGĂOAN <i>et al</i> , 2021)
Sinapic acid	10742	(MĂRGĂOAN <i>et al</i> , 2021)
Syringic acid	370	(JÚNIOR <i>et al</i> , 2022)
Gallic acid	8468	(MĂRGĂOAN <i>et al</i> , 2021)
Vanillic acid	5281855	(MĂRGĂOAN <i>et al</i> , 2021)
Ellagic acid	135	(MĂRGĂOAN <i>et al</i> , 2021)
<i>P</i> -Hydroxybenzoic acid	7420	(MĂRGĂOAN <i>et al</i> , 2021)
3-Hydroxybenzoic acid	135	(MĂRGĂOAN <i>et al</i> , 2021)
4-Hydroxybenzoic acid	7478	(MĂRGĂOAN <i>et al</i> , 2021)
4-Methoxybenzoic acid	72	(MĂRGĂOAN <i>et al</i> , 2021)
Protocatechuic acid	70164	(MĂRGĂOAN <i>et al</i> , 2021)
Methyl syringate	162221887	(MĂRGĂOAN <i>et al</i> , 2021)
Monogalloyl glucose	10364	(MĂRGĂOAN <i>et al</i> , 2021)

Carvacrol	6989	(MĂRGĂOAN <i>et al</i> , 2021)
Thymol	1794427	(MĂRGĂOAN <i>et al</i> , 2021)
Chlorogenic acid	72277	(MĂRGĂOAN <i>et al</i> , 2021)
Epigallocatechin	65064	(MĂRGĂOAN <i>et al</i> , 2021)
Epigallocatechin gallate	445154	(MĂRGĂOAN <i>et al</i> , 2021)
Resvaratrol	1303	(MĂRGĂOAN <i>et al</i> , 2021)
Phenyllactic acid	24888569	(MĂRGĂOAN <i>et al</i> , 2021)
2-cis,4-trans-abscisic acid	*	(MĂRGĂOAN <i>et al</i> , 2021)
2-trans,4-trans-Abscisic acid	5281614	(MĂRGĂOAN <i>et al</i> , 2021)
Fisetin	65084	(MĂRGĂOAN <i>et al</i> , 2021)
Gallocatechin	65084	(MĂRGĂOAN <i>et al</i> , 2021)

Font: Authors, 2024.

Table 2S: Results from the first battery of predictions.

COMPOUND	GI	BBB	P-gp	Lipinski	Carcino mause	Carcino Rat
Abscisic Acid	High	Yes	No	Yes	Negative	Positive
Caffeic Acid	High	No	No	Yes	Negative	Positive
p-coumaric acid	High	Yes	No	Yes	Negative	Positive
Phenylacetic acid	High	Yes	No	Yes	Negative	Negative
Succinic Acid	High	No	No	Yes	Negative	Positive
Vanillic Acid	High	No	No	Yes	Negative	Positive
Crysin	High	Yes	No	Yes	Negative	Negative
2-Hydroxyquinoline	High	Yes	No	Yes	Positive	Positive
Syringaldehyde	High	Yes	No	Yes	Negative	Positive
Quercetin	High	No	No	Yes	Negative	Positive
Rutin	Low	No	No	No	Negative	Negative
Quercetin 3,3'-dimethyl ether	High	No	No	Yes	Negative	Positive
Quercetin 7,3'-dimethyl ether	High	No	No	Yes	Negative	Positive
Apigenin	High	No	No	Yes	Negative	Positive
Kaempferol	High	No	No	Yes	Negative	Positive
Kaempferide	High	No	No	Yes	Negative	Positive
Isorhamnetin	High	No	No	Yes	Negative	Positive
Galangin	High	No	No	Yes	Negative	Negative
Genistein	High	No	No	Yes	Negative	Positive
Myricetin	Low	No	No	Yes; 1 violation: NHorOh>5.	Negative	Positive
Methyl anthranilate	High	Yes	No	Yes	Negative	Positive
Catechin	High	No	Yes	Yes	Negative	Negative
Epicatechin	High	No	Yes	Yes	Negative	Negative
Pinobanksin	High	No	No	Yes	Negative	Negative
Pinocembrin	High	Yes	No	Yes	Negative	Negative

Chrysin	High	Yes	No	Yes	Negative	Negative
Acacetin	High	No	No	Yes	Positive	Positive
Luteolin	High	No	No	Yes	Negative	Positive
Baicalein	High	No	No	Yes	Negative	Positive
Hesperetin	High	No	Yes	Yes	Negative	Positive
Naringenin	High	No	Yes	Yes	Negative	Positive
Eriodictyol	High	No	Yes	Yes	Negative	Positive
<i>P</i> -Hydroxybenzoic acid	High	Yes	No	Yes	Negative	Negative
Vanillic acid	High	No	No	Yes	Negative	Positive
Phenylacetic acid	High	Yes	No	Yes	Negative	Negative
L- β -phenyllactic acid	High	Yes	No	Yes	Negative	Negative
Dl- β -phenyllactic acid	High	Yes	No	Yes	Negative	Negative
Dl- <i>p</i> -hydroxyphenyllactic acid	High	No	No	Yes	Negative	Negative
Gentisic acid	High	No	No	Yes	Negative	Positive
Rosmarinic acid	High	No	No	Yes	Negative	Positive
Phenyllactic acid	High	Yes	No	Yes	Negative	Negative
Lumichrome	High	No	No	Yes	Positive	Negative
Caffeic acid	High	No	No	Yes	Negative	Positive
Acacetin	High	No	No	Yes	Positive	Negative
Luteolin	High	No	No	Yes	Negative	Positive
Baicalein	High	No	No	Yes	Negative	Positive
Hesperetin	High	No	Yes	Yes	Negative	Positive
Naringenin	High	No	Yes	Yes	Negative	Positive
Eriodictyol	High	No	Yes	Yes	Negative	Negative
<i>P</i> -Hydroxybenzoic acid	High	Yes	No	Yes	Negative	Negative
Vanillic acid	High	No	No	Yes	Negative	Positive
Phenylacetic acid	High	Yes	No	Yes	Negative	Positive
L- β -phenyllactic acid	High	Yes	No	Yes	Negative	Negative
Dl- β -phenyllactic acid	High	Yes	No	Yes	Negative	Positive
Dl- <i>p</i> -hydroxyphenyllactic acid	High	No	No	Yes	Negative	Positive
Gentisic acid	High	No	No	Yes	Negative	Positive
Rosmarinic acid	High	No	No	Yes	Negative	Positive
Phenyllactic acid	High	Yes	No	Yes	Negative	Positive
Lumichrome	High	No	No	Yes	Positive	Positive
Caffeic acid	High	No	No	Yes	Negative	Positive
Caffeic acid phenethyl ester	High	Yes	No	Yes	Negative	Negative
<i>p</i> -Coumaric acid	High	Yes	No	Yes	Negative	Positive
<i>O</i> -coumaric acid	High	Yes	No	Yes	Negative	Positive

<i>M</i> -coumaric acid	High	Yes	No	Yes	Negative	Negative
Ferulic acid	High	Yes	No	Yes	Negative	Positive
Cinnamic acid	High	Yes	No	Yes	Negative	Positive
Trans-cinnamic acid	High	Yes	No	Yes	Negative	Positive
2-Hydroxycinnamic acid	High	Yes	No	Yes	Negative	Negative
3,4-Dimethoxycinnamic acid	High	Yes	No	Yes	Negative	Positive
Trans-cinnamic acid	High	Yes	No	Yes	Negative	Positive
Isoferulic acid	High	Yes	No	Yes	Negative	Positive
Sinapic acid	High	No	No	Yes	Negative	Positive
Syringic acid	High	No	No	Yes	Negative	Positive
Gallic acid	High	No	No	Yes	Negative	Positive
Vanillic acid	High	No	No	Yes	Negative	Positive
Ellagic acid	High	No	No	Yes	Negative	Positive
<i>P</i> -Hydroxybenzoic acid	High	Yes	No	Yes	Negative	Negative
3-Hydroxybenzoic acid	High	Yes	No	Yes	Negative	Positive
4-Hydroxybenzoic acid	High	Yes	No	Yes	Negative	Negative
4-Methoxybenzoic acid	High	Yes	No	Yes	Negative	Negative
Protocatechuic acid	High	No	No	Yes	Negative	Positive
Methyl syringate	High	Yes	No	Yes	Negative	Negative
Monogalloyl glucose	X	X	X	X	X	X
Carvacrol	High	Yes	No	Yes	Negative	Negative
Thymol	High	Yes	No	Yes	Negative	Negative
Chlorogenic acid	Low	No	No	Yes; 1 violation: NhorH>5.	Negative	Negative
Galocatechin	High	No	No	Yes; 1 violation: NhorH>5.	Negative	Negative
Epigallocatechin	High	No	No	Yes; 1 violation: NhorH>5.	Negative	Negative
Epigallocatechin gallate	Baixa	No	No	No; 2 violations: NorO>10, NhorOH>5.	Negative	Positive
Resvaratrol	High	Yes	No	Yes	Negative	Negative
Phenyllactic acid	High	Yes	No	Yes	Negative	Negative
2-cis,4-trans-abscisic acid	X	X	X	X	X	X
Fisetin	High	No	No	Yes	Negative	Positive

Font: SWISSADME, 2024. PREADMET, 2024.

Table 3S: Pharmacological predictions of the compounds with the best scores.

COMPOUND	LogS (ESOL)	Water Solubility	Lipinski	BBB	Carcino Mouse	Carcino Rat	Caco2	MDCK
Caffeic Acid	-1.89	Very Soluble	Yes	No	Negative	Positive	21.1076	109.433
Succinic Acid	-0.00	Very Soluble	Yes	No	Negative	Positive	15.5793	8.5114
Vanillic Acid	-2.02	Soluble	Yes	No	Negative	Positive	19.9363	29.0612
Quercetin	-3.16	Soluble	Yes	No	Negative	Positive	3.4129	13.3528
Quercetin 3,3'-dimethyl ether	-4.25	Moderately Soluble	Yes	No	Negative	Positive	2.99677	28.016
Quercetin 7,3'-dimethyl ether	-4.10	Moderately Soluble	Yes	No	Negative	Positive	2.22065	24.5132
Rhamnazin	-4.10	Moderately Soluble	Yes	No	Negative	Positive	5.09497	18.5427
Apigenin	-3.94	Soluble	Yes	No	Negative	Positive	10.5468	44.302
Kaempferol	-3.31	Soluble	Yes	No	Negative	Positive	9.57744	29.6119
Kaempferide	-3.51	Soluble	Yes	No	Negative	Positive	9.33535	27.3621
Isorhamnetin	-3.36	Soluble	Yes	No	Negative	Positive	4.93924	23.8308
Genistein	-3.72	Soluble	Yes	No	Negative	Positive	5.74714	39.4329
Luteolin	-3.71	Soluble	Yes	No	Negative	Positive	4.53973	36.5205
Baicalein	-4.03	Moderately Soluble	Yes	No	Negative	Positive	1.28026	101.909
Hesperetin	-3.62	Soluble	Yes	No	Negative	Positive	7.00371	24.4527
Naringenin	-3.49	Soluble	Yes	No	Negative	Negative	10.5211	44.6354

Eriodictyol	-3.26	Soluble	Yes	No	Negative	Positive	4.5336	35.5683
Gentisic acid	-2.23	Soluble	Yes	No	Negative	Positive	18.3041	51.49
Rosmarinic acid	-3.44	Soluble	Yes	No	Negative	Positive	20.7246	0.20263
Lumichrome	-2.63	Soluble	Yes	No	Positive	Negative	6.46142	228.515
Sinapic Acid	-2.16	Soluble	Yes	No	Negative	Positive	19.854	270.199
Syringic acid	-1.84	Very Soluble	Yes	No	Negative	Positive	18.8327	29.7007
Gallic acid	-1.64	Very Soluble	Yes	No	Negative	Positive	13.8492	9.53976
Vanillic acid	-2.02	Soluble	Yes	No	Negative	Positive	19.9363	29.0612
Ellagic acid	-2.94	Soluble	Yes	No	Negative	Positive	20.4888	17.2974
Protocatechuic acid	-1.86	Very Soluble	Yes	No	Negative	Positive	18.3046	23.6995
Fisetin	-3.35	Soluble	Yes	No	Negative	Positive	9.57535	68.1923
Galangin	-3.46	Soluble	Yes	No	Negative	Negative	3.70589	79.4051
Catechin	-2.22	Soluble	Yes	No	Negative	Negative	0.65696	44.3849
Epicatechin	-2.22	Soluble	Yes	No	Negative	Negative	0.65696	44.3849
Pinobanksin	-2.95	Soluble	Yes	No	Negative	Negative	3.69179	66.137
Dl- <i>p</i> -hydroxyphenyllact acid	-1.29	Very Soluble	Yes	No	Negative	Negative	21.1076	255.863

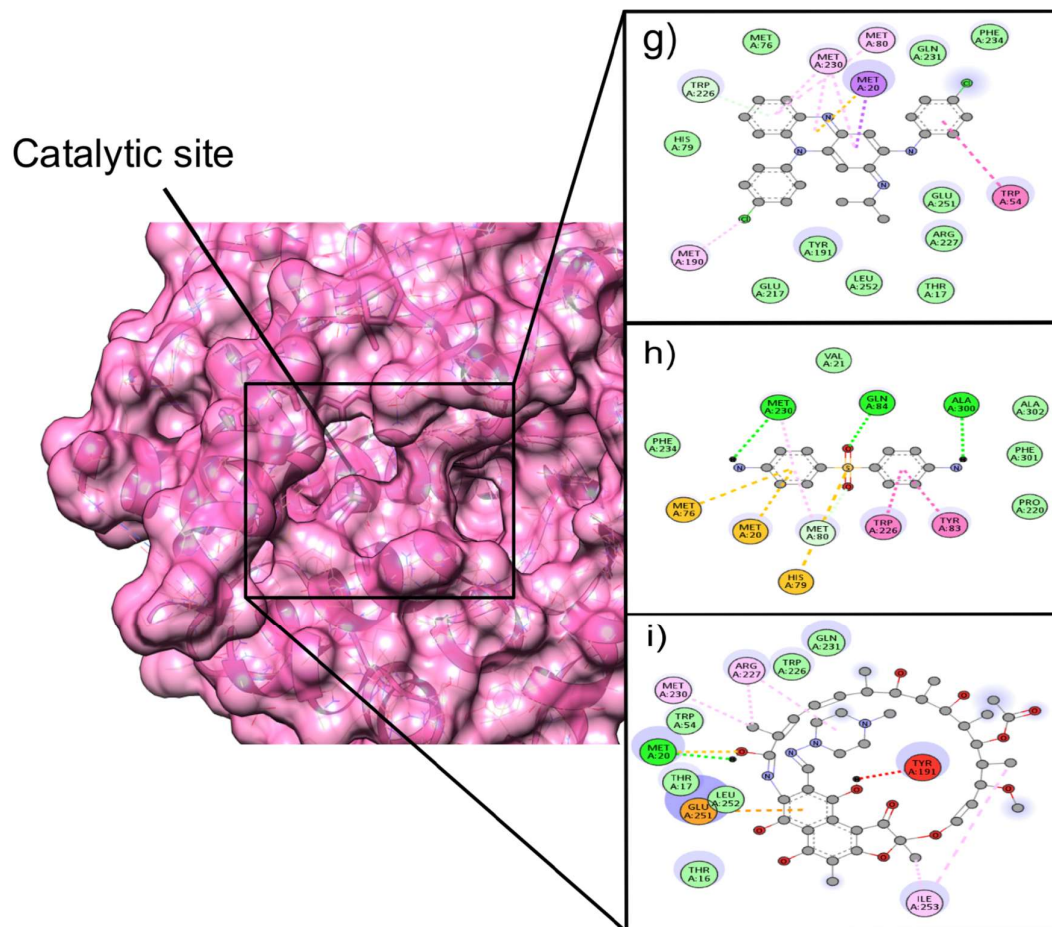
(continues)

COMPOUND	TA100_10RL I	TA100_N A	TA1535_10RL I	TA1535_N A	CYP3A 4	HIA	TESTE AMES
Caffeic Acid	Negative	Positive	Positive	Positive	Inhibitor	82.301	Mutagen
Succinic Acid	Negative	Negative	Positive	Negative	Inhibitor	54.538	Mutagen
Vanillic Acid	Positive	Positive	Positive	Negative	No	85.369	Mutagen
Quercetin	Negative	Positive	Negative	Negative	Inhibitor	63.485	Mutagen
Quercetin 3,3'- dimethyl ether	Negative	Positive	Negative	Negative	Inhibitor	87.828	Mutagen
Quercetin 7,3'- dimethyl ether	Negative	Positive	Negative	Negative	Inhibitor	87.825	Mutagen
Rhamnazin	Negative	Positive	Negative	Negative	Inhibitor	87.828	Mutagen
Apigenin	Positive	Negative	Negative	Negative	Inhibitor	88.122	Mutagen
Kaempferol	Negative	Positive	Negative	Negative	Inhibitor	79.439	Mutagen
Kaempferide	Negative	Positive	Negative	Negative	Inhibitor	88.192	Mutagen
Isorhamnetin	Negative	Positive	Negative	Negative	Inhibitor	78.347	Mutagen
Genistein	Positive	Positive	Negative	Negative	Inhibitor	88.122	Mutagen
Luteolin	Negative	Positive	Negative	Negative	Inhibitor	79.427	Mutagen
Baicalein	Negative	Positive	Negative	Negative	Inhibitor	88.105	Mutagen
Hesperetin	Negative	Positive	Negative	Negative	Inhibitor	87.192	Mutagen
Naringenin	Positive	Positive	Negative	Negative	Inhibitor	87.318	Mutagen
Eriodictyol	Negative	Positive	Negative	Negative	Inhibitor	77.430	Mutagen
Gentisic acid	Negative	Positive	Positive	Positive	Inhibitor	74.750	Mutagen
Rosmarinic acid	Negative	Negative	Negative	Positive	Inhibitor	62.487	Mutagen
Lumichrome	Negative	Negative	Negative	Negative	No	94.527	Mutagen
Sinapic Acid	Negative	Negative	Positive	Positive	No	88.553	Mutagen
Syringic acid	Negative	Negative	Positive	Negative	No	82.027	Mutagen

Gallic acid	Negative	Positive	Positive	Negative	Inhibitor	53.696	Mutagen
Vanillic acid	Positive	Positive	Positive	Negative	No	85.369	Mutagen
Ellagic acid	Negative	Positive	Positive	Negative	Inhibitor	61.395	Mutagen
Protocatechuic acid	Negative	Positive	Positive	Negative	Inhibitor	74.749	Mutagen
Fisetin	Negative	Positive	Negative	Negative	Inhibitor	79.431	Mutagen
Galangin	Positive	Positive	Negative	Negative	Inhibitor	88.122	Mutagen
Catechin	Negative	Positive	Negative	Negative	Inhibitor	66.707	Mutagen
Epicatechin	Negative	Positive	Negative	Negative	Inhibitor	66.707	Mutagen
Pinobanksin	Positive	Positive	Negative	Negative	Inhibitor	87.607	Mutagen
Dl- <i>p</i> -hydroxyphenyllactic acid	Positive	Negative	Positive	Positive	No	90.758	Mutagen

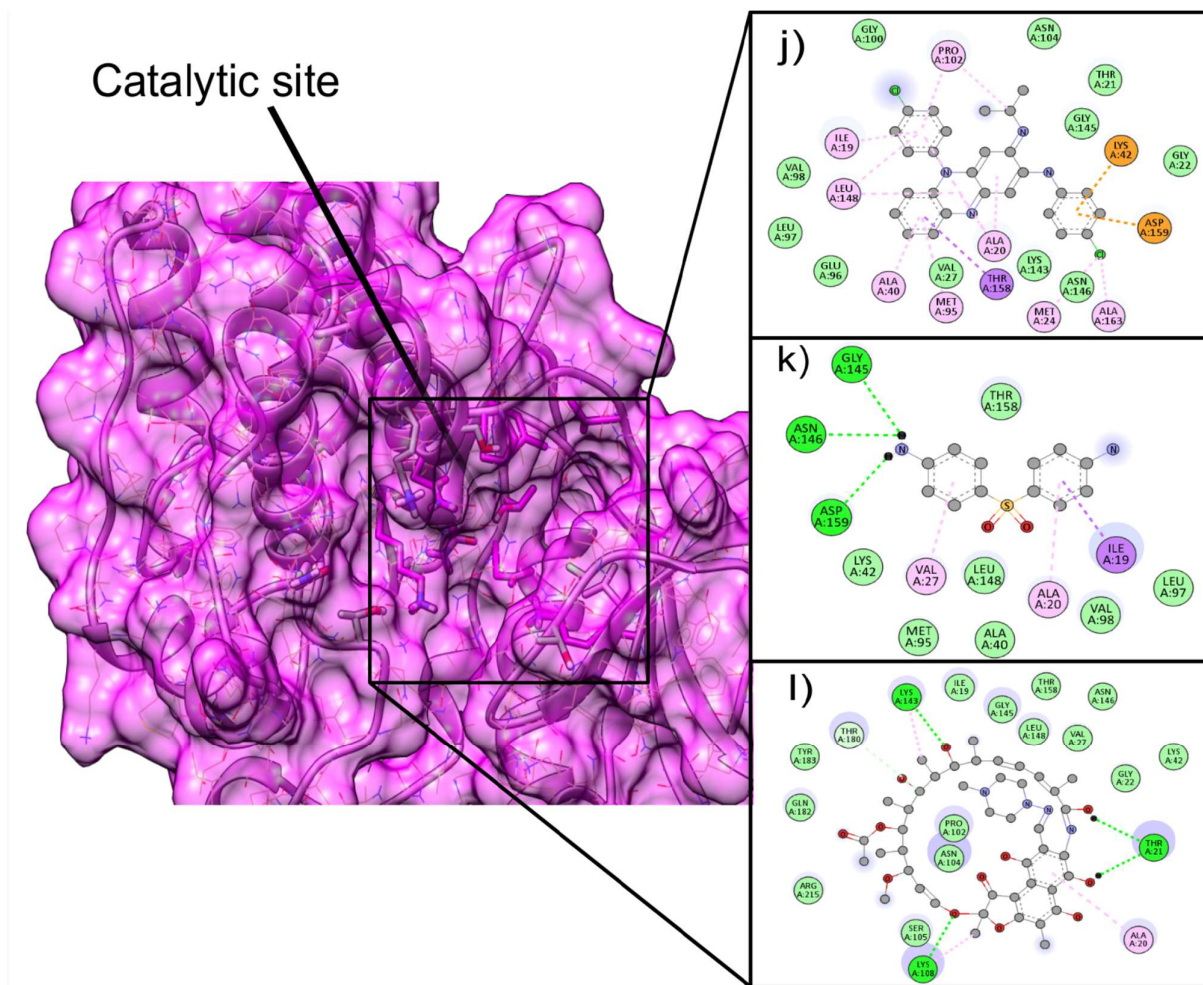
Font: SWISSADME, 2024. PREADMET, 2024.

Figure 1S: Maps of interactions of the control drugs **(g)** Clofazimine, **(h)** Dapsone, and **(i)** Rifampicin on the ML2640c protein (PDB ID:2UYO).



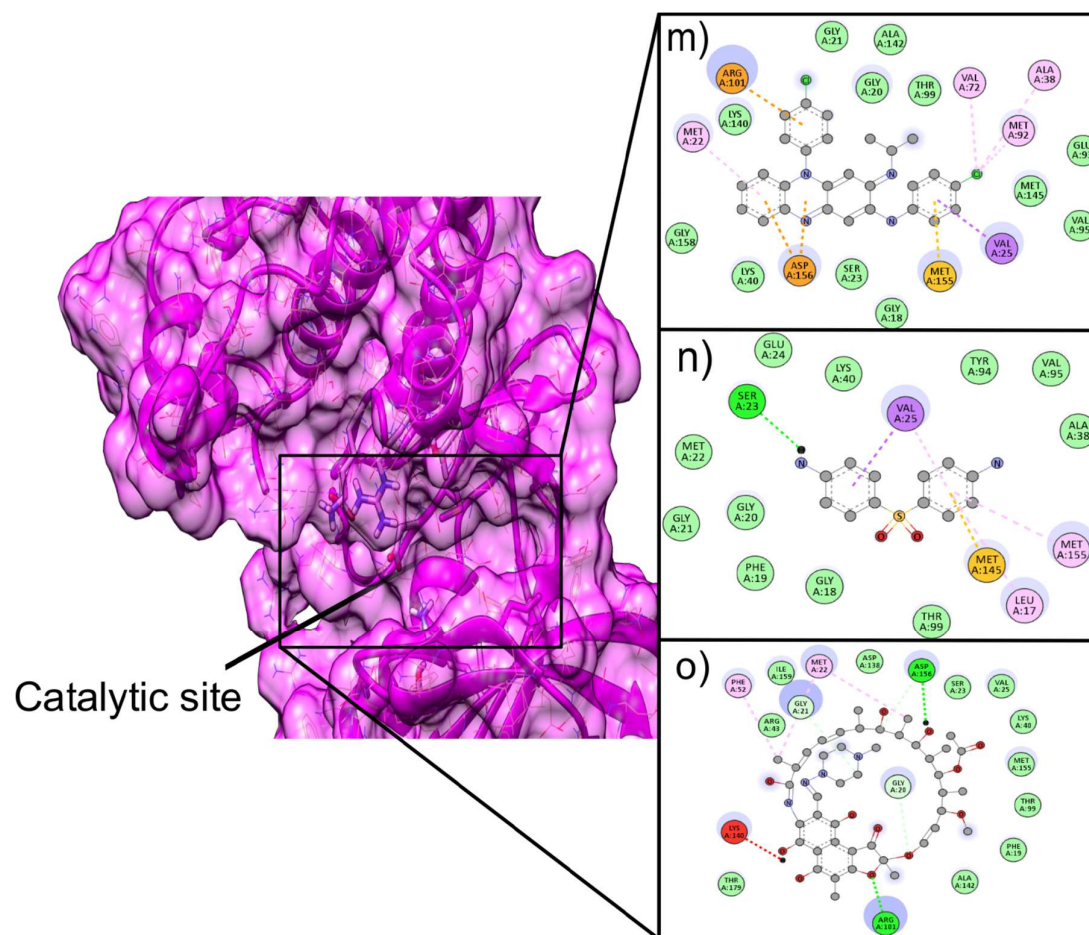
The ligands were omitted within the catalytic site to avoid possible errors in image interpretation. The highlighted location represents the exact coordinates of the ligand coupling defined by CavityPlus.

Figure 2S: Maps of interactions of the control drugs (j) Clofazimine, (k) Dapsone and (l) Rifampicin on the PknA protein (PDB ID: 4OW8).



The ligands were omitted within the catalytic site to avoid possible errors in image interpretation. The highlighted location represents the exact coordinates of the ligand coupling defined by CavityPlus.

Figure 3S: Maps of interactions of the control drugs (m) Clofazimine, (n) Dapsone, and (o) Rifampicin on the PknB protein (PDB ID: 1MRU).



The ligands were omitted within the catalytic site to avoid possible errors in image interpretation. The highlighted location represents the exact coordinates of the ligand coupling defined by CavityPlus.