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In Silico Studies of Biological Activity and Toxicity of Naturally Occurring Buchenavianines †

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Abstract

Buchenavianine, or 7-hydroxy-5-methoxy-8-(1-methylpiperidin-2-yl)flavone along with its related compounds *O*-Demethylbuchenavianine, *N*-demethylbuchenavianine and *N*,*O*-bis(dimethyl)buchenavianine belong to the class of piperidine-flavonoid alkaloids, possessing a piperidine ring connected to the C8-position of the flavonoid skeleton. Buchenavianine derivatives have been primarily isolated from *Buchenavia macrophylla* and also found in *B. capitata.* Studies have suggested that buchenavianines may possess anti-inflammatory, antioxidant, anti-HIV and anticancer properties. Understanding the biological activity of buchenavianine derivatives is crucial for assessing their potential as drug candidates considering factors such as pharmacokinetic and toxicity. The present study focuses on the in silico prediction of antibacterial, antiviral and antifungal activities using the AntiBac-pred, antiVir-pred and AntiFun-pred tools available on the Way2drug platform. Results are presented as confidence values indicating the likehood of inhibitory or non-inhibitory effects against specific pathogens (bacteria, viruses or fungi). The calculations suggest that natural buchenavianines under investigation are likely to exhibit antibacterial activity with confidence values ranging from 0.4980 to 0.3390 even against resistant bacterial strains. Antifungal activity was predicted with confidences of 0.1250–0.0274 while calculations of antiviral activity resulted in high confidence values of 0.8739 to 0.7500 highlighting their potential as antiviral agents. Toxicity assessments of buchenavianine derivatives were conducted using ProTox 3.0 software. The results indicate that all compounds would be non-toxic with a low probability of neurotoxicity and a high probability of respiratory toxicity.

Keywords: buchenavianine; AntiBac-pred; AntiVir-pred; Anti-Fun-pred; ProTox 3.0

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1. Introduction

The genus *Buchenavia* distributed in Central America is a rich source of pharmacologically significant flavonoid alkaloids, that are currently being investigated for their potential medicinal properties, such as anti-inflammatory, antioxidant, antifungal and antimicrobial effects [1–4]. Buchenavianine **1** (Figure 1) is the main alkaloid found in *B. macrophylla* leaves and is also present in *B. capitata* [3]. *O*-Demethylbuchenavianine **2** is found in both species while *N*-demethylbuchenavianine 3 and *N*,*O*-bis(dimethyl)buchenavianine **4** have been isolated from the leaves and fruits of *B. macrophylla* [5]. Biological

activity evaluation of the chloroform extract of the leaves of *B. capitata* was conducted by Beutler et al. [6] who discovered potential anti-HIV activity of constituents of *B. capitata*. *O*-Demethylbuchenavianine **7** was identified as the most active component. *N*-Demethylbuchenavianine and buchenavianine were later found to be moderately active on inhibiting cyclin-dependent kinases [7].

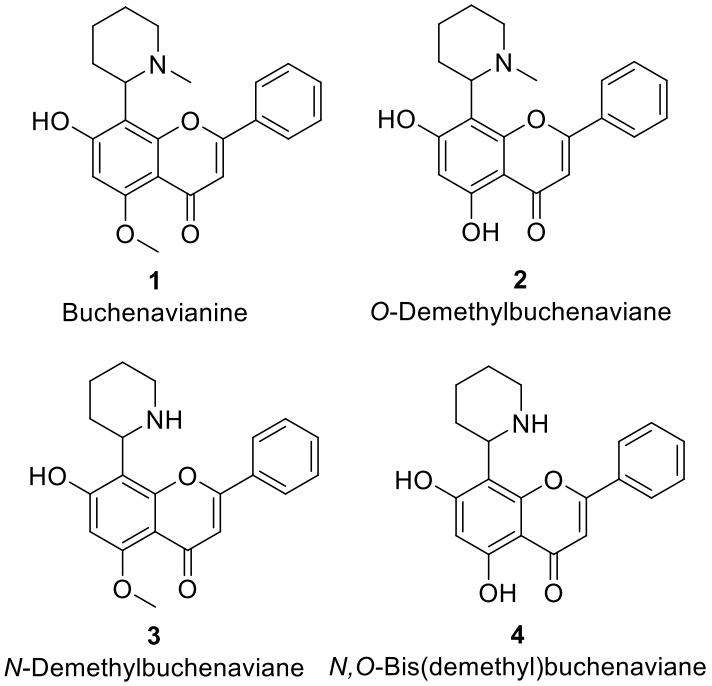

Figure 1. Buchenavianine **1** and related natural flavoalkaloids **2**–**4**.

Although natural products are a rich source of pharmacologically important substances, the process of drug discovery is challenging due to the isolation, structure elucidation and biological activity screening required. To address these challenges, various in silico tools have been developed. This work represents a continuation of our research on in silico calculations of the biological activity and toxicity of buchenavianines. AntiBac-pred [8] antiVir-pred [9] and AntiFun-pred [10] are tools of the Way2drug platform [11] which enable consideration of antibacterial, antiviral or antifungal properties of a particular structure. Toxicity calculations of buchenavianine derivatives were done using ProTox 3.0 software [12] and discussed in comparison with previously obtained calculations [13] using Osiris software [14].

2. Material and Methods

AntiBac-Pred [8] enables the prediction of growth inhibitors or non-inhibitors on 353 different bacterial strains. AntiVir-pred [9] was used to calculate antiviral activity against virues and predict protein targets. AntiFun-pred [10] was developed to calculate antifungal activity against specific funghi. The score for each compound is expressed as confidence value, indicating the probable inhibitory/non-inhibitory effect against specific bacteria. The higher the confidence value, the more accurate the prediction, and compounds with positive confidence values are considered to be active.

ProTox 3.0 [11] was used to calculate the toxicity risk (hepatotoxicity; neurotoxicity; nephrotoxicity; respiratory toxicity; cardiotoxicity; carcinogenity; immunotoxicity; cytotoxicity) of buchenavianines **1**–**4**. The prediction is expressed in red or green colors indicating activity or inactivity of compound towards the particular toxicity target. The more intense the color, the more probable the binding of the toxicity target is. Probability is also

expressed as a numerical value (0.0–1.0). ProTox 3.0 also includes information on the toxicity class and predicted median lethal dose (LD_{50}) in mg/kg weight.

3. Results and Discussion

3.1. AntiBac-Pred, AntiVir-Pred and Anti-Fun-Pred Calculations

Results of antibacterial activity predictions via tools of the Way2drug platform are given in Table 1. Calculations using AntiBac-pred showed the best confidence in antibacterial activity for N-demethylbuchenavianine **3** and *N*,*O*-bis(demethyl)buchenavianine **4** against resistant strain of *Mycobacterium ulcerans.* Compound **4** is predicted to be effective against 17 strains with a confidence level of up to 0.3.

Table 1. Prediction of **a**ntibacterial, antiviral and antifungal activity of **1**–**4**.

No.	AntiBac-Pred			AntiVir-Pred				AntiFun-Pred	
	Best cfd	Strain	No. > 0.3 Best cfd	Virus	Target	cfd HIV-2	Protein Target	Best cfd	Funghus
1	0.3488	res. *S. simulans*	3 0.8192			0.2855		0.0274	*T. mentagrophytes*
2	0.3390	res. *S. simulans*	3 0.8739	SARS-	replicase pol-	0.3919	HIV-2 integrase	0.1032	*C. dubliniensis*
3	0.4961	res. *M. ulcerans*	15 0.7500	COV 2	yprotein 1ab	0.3449		-	-
4	0.4980	res. *M. ulcerans*	17 0.8126			0.4575		0.1250	*C. dubliniensis*

cfd—confidence; res.—resistant.

In terms of potential antiviral activity, all derivatives **1**–**4** demonstrated high levels of confidence (0.8739-0.7500) against the SARS-COV2 virus, while confidences for anti-HIV activity were lower (0.4575-0.2855). The most potent antiviral activity was predicted for compounds **2** and **4**, which aligns quite well with experimental results [6].

Finally, all studied buchenavianines **1**–**4** were predicted to posess antifungal activity with low confidence values ranging from 0.1250 to 0.0274. No one fungal target for compound **3** was found.

3.2. ProTox 3.0 Calculations of Toxicity

Calculations of toxicity prediction using ProTox 3.0 (Table 2) indicated that compounds **1**–**4** have a low probability of exhibiting nephrotoxicity, cardiotoxicity; carcinogenity, mutagenicity or cytotoxicity. However, there is a high probability of respiratory toxicity and neurotoxicity for all studied compounds. Nephrotoxic effects were predicted for two buchenavianine-related alkaloids **3** and **4** and a risk of immunotoxicity for buchenavianine **1**. ProTox 3.0 calculated LD_{50} of 161 mg/kg assigned a toxicity class 3 to all compounds.

Table 2. ProTox 3.0 toxicity calculations of **1**–**4** in comparison with previously published results using OSIRIS [14].

	Osiris				Pro-Tox 3.0								
No.	MUT	TUM	IRR	RE	HEP	NEU	NEP	RES	CRD	CRC	IM	MUT	CYT
1	++	++	++	++	0.91	0.59	0.56	0.94	0.81	0.58	0.85	0.50	0.62
2	−	++	++	++	0.87	0.61	0.53	0.94	0.77	0.57	0.60	0.51	0.68
3	++	++	++	++	0.80	0.57	0.61	0.81	0.52	0.3	0.90	0.59	0.64
4	−	++	++	++	0.78	0.56	0.58	0.83	0.62	0.64	0.99	0.55	0.57

MUT—mutagenicity; TUM—tumorigenicity; IRR—irritant; RE—reproductive effect; (++)—low toxicity risk; (−)—high toxicity risk; HEP—hepatotoxicity; NEU—neurotoxicity; NEP—nephrotoxicity; RES—respiratory toxicity; CRD—cardiotoxicity; CRC—carcinogenity; IM—immunotoxicity; CYT—cytotoxicity, green color—inactive compound, red color—active compound.

Structures **1** and **3** possess a 5-methoxy group, while buchenavianines **2** and **4** are 5-hydroxy derivatives. In our previous research [13], it appeared that the presence of 5-methoxy group had an effect to the low risk of mutagenicity. However, calculations using the ProTox 3.0 tool did not confirm the importance of the 5-methoxy group for low mutagenicity.

4. Conclusions

The results of in silico calculations of buchenavianine derived flavonoid alkaloids show that the studied compounds exhibit positive confidence values as antibacterial, antiviral and antifungal agents, indicating that they should be considered active. High confidence values were calculated for antiviral activity, suggesting a higher accuracy of the prediction. All compounds are considered non-toxic in five categories (hepatotoxicity, cardiotoxicity; carcinogenity, mutagenicity and cytotoxicity), but they are expected to exhibit mainly neurotoxicity and respiratory toxicity.

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References

1. Silva,T.F.; Cavalcanti Filho, J.R.N.; Barreto Fonsêca, M.M.L.; Santos, N.M.D.; Barbosa da Silva, A.C.; Zagmignan, A.; Abreu, A.G.; Sant'Anna da Silva, A.P.; Lima, V.L.M.; Silva, N.H.D.; Dutra, L.M.; et al. Products derived from Buchenavia tetraphylla leaves have in vitro antioxidant activity and protect Tenebrio molitor larvae against Escherichia coli-induced injury. *Pharmaceuticals* **2020**, *13*, 46. https://doi.org/10.3390/ph13030046.
2. Ferreira, B.A.; da Silva, A.R.A.; Filbido, G.S.; Narita, I.M.P.; de Oliveira Pinheiro, A.P.; De Silva, D.D.C.; Nascimento, E.; Dalla Villa, R.; Narita, I.M.P. In vitro bioaccessibility of the bioactive compounds and minerals in the pulp and peel of Buchenavia tomentosa Eichler fruits and their antioxidant capacities. *Meas. Food* **2022**, *8*, 100064. https://doi.org/10.1016/j.meafoo.2022.100064.
3. Teodoro, G.R.; Brighenti, F.L.; Delbem, A.C.B.; Delbem, Á.C.B.; Khouri, S.; Gontijo, A.V.L.; Pascoal, A.C.; Salvador, M.J.; Koga-Ito, C.Y. Antifungal activity of extracts and isolated compounds from Buchenavia tomentosa on *Candida albicans* and non-albicans. *Future Microbiol.* **2015**, *10*, 917–927. https://doi.org/10.2217/fmb.15.20.
4. de Oliveira, Y.L.; Nascimento da Silva, L.C.; da Silva, A.G.; Macedo, A.J.; de Araújo, J.M.; Correia, M.T.; da Silva, M.V. Antimicrobial activity and phytochemical screening of Buchenavia tetraphylla (Aubl.) R. A. Howard (Combretaceae: Combretoideae). *Sci. World J.* **2012**, *2012*, 849302. https://doi.org/10.1100/2012/849302.
5. Gaur, R.; Gaur, J.; Kumar, N. Chemistry and Pharmacology of Naturally Occurring Flavoalkaloids. In *Medicinal Plants for Cosmetics, Health and Diseases*; CRC Press: Boca Raton, FL, USA, 2022; pp. 403–421. https://doi.org/10.1201/9781003108375-21.
6. Beutler, J.A.; Cardellina II, J.H.; McMahon, J.B.; Boyd, M.R.; Cragg, G.M. Anti-HIV and Cytotoxic Alkaloids from Buchenavia capitata. *J. Nat. Prod.* **1992**, *55*, 207–213. https://doi.org/10.1021/np50080a008.
7. Nguyen, T.B.; Lozach, O.; Surpateanu, G.; Wang, Q.; Retailleau, P.; Iorga, B.I.; Meijer, L.; Guéritte, F. Synthesis, Biological Evaluation, and Molecular Modeling of Natural and Unnatural Flavonoidal Alkaloids, Inhibitors of Kinases. *J. Med. Chem.* **2012**, *55*, 2811–2819. https://doi.org/10.1021/jm201727w.
8. AntiBac-pred. Available online: https://www.way2drug.com/antibac/ (accessed on 9 May 2025).
9. AntiVir-pred. Available online: https://www.way2drug.com/antivir/ (accessed on 13 May 2025).
10. AntiFun-pred. Available online: https://www.way2drug.com/antifun/ (accessed on 15 May 2025).
11. Way2drug. Available online: https://www.way2drug.com (accessed on).
12. ProTox 3.0. Available online: https://tox.charite.de/protox3/index.php?site=compound_input (accessed on 19 May 2025).

13. Gašparová, R.; Kabaňová, N. In Silico Pharmacological Prediction of Capitavine, Buchenavianine and Related Flavonoid Alkaloids. *Chem. Proc.* **2024**, *16*, 55. https://doi.org/10.3390/ecsoc-28-20222.
14. OSIRIS Property Explorer. Actelion Pharmaceuticals Ltd.: Allschwil, Switzerland, 2010. Available online: http://www.organic-chemistry.org/prog/peo/ (accessed on 5 June 2024).