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In Silico Pharmacological Prediction of Capitavine, Buchenavianine and Related Flavonoid Alkaloids †

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Abstract: Flavonoid alkaloids represent interesting subgroup of alkaloid family. Several plants containing flavonoid alkaloids are used in the folk medicine for the treatment of various diseases. Interesting biological properties of flavonoid alkaloids make them attractive candidates for lead compounds in drug discovery. Capitavine, or 5,7-dihydroxy-6-(1-methylpiperidin-2-yl)flavone and related compounds belong to piperidine-flavonoid alkaloids, possessing a piperidine ring connected to the C6-position of flavonoid skeleton, while buchenavianine is C8 piperidine-bonded analog. Capitavine derivatives were isolated mainly from *Buchenavia capitata,* buchenavianine derivatives are present mainly in *B. macrophylla*. It was found, the chloroform extract of the leaves of *B. capitata* showed anti-HIV activity. The biological activity of capitavine and buchenavianine derivatives needs to be investigated within the perspective of their pharmacokinetic properties and the toxicity, which are important factors in finding potential drug candidate. The present in silico study using SwissADME, Osiris and Molinspiration softwares showed, studied capitavine-derived flavonoid alkaloids exhibit considerable bioactivity for GPCR ligand (0.12 to 0.20), as enzyme inhibitor (0.17 to 0.22) and as nuclear receptor ligand (0.07 to 0.28). All compounds exhibit good gastrointestinal absorption and low risk of being irritants, tumorigenic or to have reproductive effect. The risk of mutagenicity was calculated for two compounds related to buchenavianine and at this point the role of 5-methoxy group appears to be crucial for the low risk of mutagenicity.

Keywords: capitavine; buchenavianine; flavonoid alkaloid; Molinspiration; swissADME; Osiris

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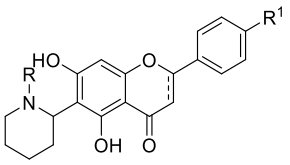
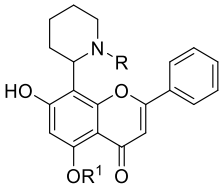
1. Introduction

Capitavine **1** (Figure 1) is a flavonoid alkaloid from the seeds of *Buchenavia capitata* Eichler, Combretaceae [1,2]. Two other capitavine derivatives: 4′-hydroxycapitavine **3** and 2,3-dihydro-4′-hydroxycapitavine **4** were also isolated from the same plant, while *N*-demethylcapitavine **2** and 2,3-dihydrocapitavine **5**, respectively were found only in the fruits of *Buchenavia macrophylla* Eichler [3]. Buchenavianine **6** (Figure 1) is the major alkaloid from the leaves of *B. macrophylla.* Similar alkaloids, namely *O*-demethylbuchenavianine **7**, *N*-demethylbuchenavianine **8** and *N*,*O*-bisdemethylbuchenavianine **9** have been isolated from the fruits of *B. macrophylla* [3]. Capivatine-related compounds belong to piperidine-flavonoid alkaloids, possessing a piperidine ring connected to the C6-position of flavonoid skeleton. On the other hand, structurally similar buchenavianine and its derivatives are C8 piperidine-bonded analogs. Biological activity evaluation of the chloroform extract of the leaves of *B. capitata* was accomplished by Beutler et al. [4]. The results show a potential anti-HIV activity of *B. capitata* constituents and *O*-demethylbuchenavianine **7** was supposed to be the most active component. In general, natural products and their structural analogs represent a rich

source of pharmacologically important substances. However, drug discovery is a challenge due to the isolation, structure elucidation and biological activity screening of a large number of structures. Therefore, various in silico tools have been created. SwissADME, Osiris and Molinspiration (SOM) analysis enables to access the pharmacokinetic profile of the synthesized molecules and their toxicity [5,6].





1 Capitavine: R = CH_3, R^1 = H, C_2=C_3
2 *N*-Demethylcapitavine: R = R^1 = H, C_2=C_3
3 4´-Hydroxycapitavine: R = CH_3, R^1 = OH, C_2=C_3
4 2,3-Dihydrocapitavine: R = CH_3, R^1 = H, C_2-C_3
5 2,3-Dihydro-4´-Hydroxycapitavine: R = CH_3, R^1 = OH, C_2-C_3

6 Buchenavianine: R = R^1 = R = CH_3
7 *O*-Demethylbuchenavianine: R = CH_3, R^1 = H
8 *N*-Demethylbuchenavianine: R = H, R^1 = CH_3
9 N,*O*-Bis(demethyl)buchenavianine: R = R^1 = H

Figure 1. Capivatine **1**, buchenavianine **6** and related flavoalkaloids.

2. Material and Methods

Molinspiration Cheminformatics [7] was used for the calculation of molecular properties (logP, TPSA, number of H-bond donors and acceptors) and prediction of bioactivity score for the most important drug targets (GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease or enzyme inhibitor). SwissADME software [8] was used for the pharmacokinetic parameters calculations, mainly gastrointestinal absorption, blood-brain barrier permeation, the assessment of whether a compound is a substrate or non-substrate of P-gp, the interactions of the molecule with the cytochrome P450 or the skin permeability (Log Kp). The druglikeness score using five different methods (Lipinski, Ghose, Veber, Egan and Muegge), the bioavailability score, PAINS and Brenk structural alerts, leadlikeness and synthetic accessibility were calculated. Osiris property Explorer [9] was used to calculate the toxicity risk (mutagenicity, tumorigenicity, irritating effects and reproductive effects) of flavonoid alkaloids **1–9,** exprimed in semaphore colors.

3. Results and Discussion

3.1. Molinspiration

Lipinski's rule of five [10] is a computational method for developing tools to design orally active compounds and selecting drug molecules for further development According to Lipinski's rule only a molecule with MW ≤ 500, LogP ≤ 5, number of H-donors (OH, NH) ≤ 5 and number of H-acceptors (O, N) ≤ 10 could be a good drug candidate. Moreover Verber at all. [11] observed, compounds with TPSA ≤ 140 Å and number of the rotatable bonds ≤ 10 have good oral bioavailability. All flavonoid alkaloids **1-*9*** are in accordance with both Lipinski's and Verber's rules (Table 1).

Results of Molinspiration bioactivity score prediction suggest that studied flavonoid alkaloids should exhibit considerable bioactivity towards GPCR ligands, nuclear receptor ligands or as the kinase and other enzyme inhibitors, which is exprimed by the positive bioactivity score values (Table 1). Calculated GPCR, NRL and EI scores of C2–C3 hydrogenated capitavines **4** and **5** reached high values (0.20–0.28).

Table 1. Physiochemical properties and boactivity scores of **1–9** calculated using Molinspiration software.

No.	logP	TPSA	MW	nA/nD	rot	GPCR	ICM	KI	NRL	PI	EI
1	4.23	73.91	351.40	5/2	2	0.12	0.02	0.06	0.07	−0.05	0.17
2	3.09	82.69	337.38	5/3	2	0.09	−0.01	0.06	0.12	−0.04	0.21
3	3.75	94.13	367.40	6/2	2	0.13	0.03	0.07	0.12	−0.05	0.18
4	3.68	70.00	353.42	5/2	2	0.20	−0.10	−0.27	0.23	0.07	0.20
5	3.20	90.23	369.42	6/3	2	0.20	−0.09	−0.24	0.28	0.07	0.20
6	4.51	62.91	365.43	5/1	3	0.15	−0.10	0.12	0.06	−0.10	0.11
7	4.23	73.91	351.40	5/1	2	0.18	−0.05	0.14	0.12	−0.05	0.18
8	3.36	71.70	351.40	5/2	3	0.12	−0.14	0.12	0.11	−0.10	0.14
9	3.09	82.69	337.38	5/3	2	0.16	−0.08	0.15	0.17	−0.04	0.22

LogP—Octanol-water partition coefficient; **TPSA**-topological polar surface area; **MW**-molecular weight; **nA**—number of hydrogen bond acceptors (O, N); **nD**—number of hydrogen bond donors (OH, NH); **rot**—number of rotatable bonds; **GPCR**—GPCR ligand; **ICM**—ion channel modulator; **KI**—kinase inhibitor; **NRL**—nuclear receptor ligand; **PI**—protease inhibitor; **EI**—enzyme inhibitor.

3.2. SwissADME

SwissADME predictions given in Table 2 show that all studied flavonoid alkaloids **1–9** exhibit high gastrointestinal absorption (GIA). Blood-brain barriers (BBB) permeation is predicted for five compounds (**1**, **4**, **6–8**) and compounds **2, 3, 5** and **9** are unable to cross BBB.

Table 2. The SwissADME calculations of **1-9.**

No	GIA	BBB	P-gpS	CYP	Lipinski	Ghose	Veber	Egan	Muegge	PAINS	Brenk	LL	SA	$LogK_p$	BA
1	H	Y	Y	Y,Y,Y,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.69	−5.79	0.55
2	H	N	Y	Y,Y,Y,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.58	−5.68	0.55
3	H	N	N	N,N,Y,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.72	−5.89	0.55
4	H	Y	Y	N,N,N,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.73	−6.00	0.55
5	H	N	Y	N,N,N,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.81	−6.25	0.55
6	H	Y	Y	N,N,N,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.95	−6.24	0.55
7	H	Y	Y	N,N,N,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.83	−6.00	0.55
8	H	Y	Y	N,Y,N,Y,Y	Y	Y	Y	Y	Y	1	0	N	3.84	−6.49	0.55
9	H	N	Y	N,N,N,Y,N	Y	Y	Y	Y	Y	1	0	N	3.73	−6.25	0.55

Y—yes; **N**—no; **GIA**—gastrointestinal absorption; **BBB**—blood brain barrier permeation; **P-gpS**—P-glycoprotein substrate; **CYP**—cytochrome P450 (1A2, 2C19, 2C9, 2D6, 3A4) inhibitors; **PAINS**—pan assay interference structures; **Brenk**—structural alert by Brenk; **LL**—leadlikeness; **SA**—synthetic accessibility; **$LogK_p$**—skin permeation (cm/s) ; **BA**—bioavailability score.

The SwissADME enables prediction simultaneously of two key ADME parameters—the passive gastrointestinal absorption (GIA) and blood-brain barrier (BBB) permeation via the "Boiled egg" graphical model, which exprimes dependance of WLOGP [12] and TPSA (for lipophilicity and apparent polarity) [13]. As it is shown in Figure 2, four studied compounds (**1, 4, 6, 8**) are placed in the "yolk" area, representing physicochemical space for highly probable BBB permeation. The white area represents the physicochemical space for highly probable GIA absorption with four compounds (**2, 3, 5, 9**). Studied compounds were predicted to be substrates of P-glycoprotein (P-gp), except *N*-demethylcapitavine **2.** Inhibition of P-gp can increase drug absorption and bioavailability and thus therapeutic effects of the drug [14]. The results are shown at the boiled egg model that allows the graphical output for P-gp substrates (blue dots) and P-gp non-substrates (red dots).

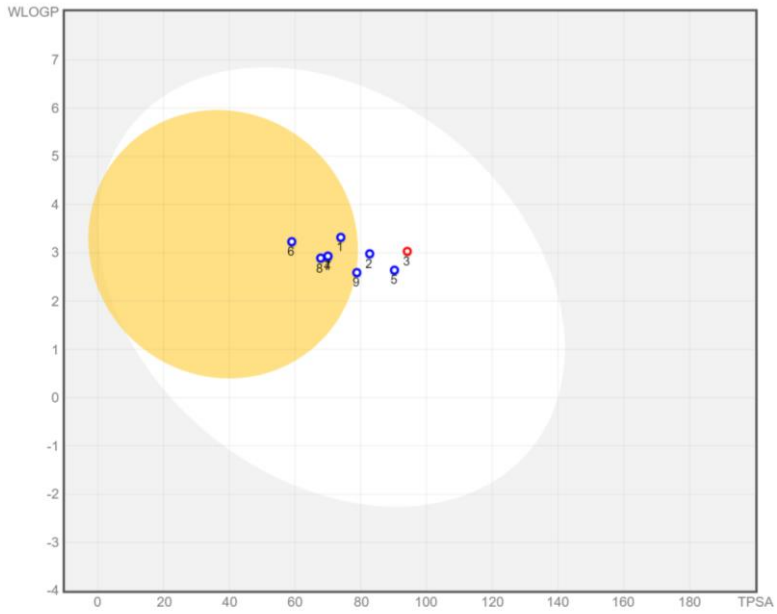


Figure 2. Prediction of passive diffusion of **1–9** through GIA and BBB by "boiled egg" model (yolk—BBB permeation; white—GIA; blue dots—P-gp substrate; red dot—P-gp non-substrate).

The study of potential drug interactions with cytochrome P450 isoenzymes is an important factor in drug design [15]. The SwissADME calculations have shown all studied flavonoid alkaloids are inhibitors of at least one CYPs. When compounds are predicted potential inhibitors of three or more CYPs (**1, 2, 3, 8**), they are predicted to be at risk of increased toxicity. All flavonoid alkaloids **1–9** are predicted not to be lead-like structures mostly due to the MW > 350 [16]. PAINS structural alert [17], associated with Mannich base (due to the structural unit N-C-C-C-OH) was calculated for all compounds.

3.3. Osiris

Calculations of toxicity risk prediction using Osiris software showed (Table 3), all compounds **1–9** exhibit low risk in three categories—irritation, tumorigenicity and reproductive effects. The high risk of being mutagenic was calculated for two buchenavianine-related alkaloids **7** and **9**

Table 3. OSIRIS toxicity risk, druglikeness and drug score calculations of **1-9**.

No	MUT	TUM	IRR	REP	DL	DS
1	++	++	++	++	3.52	0.70
2	++	++	++	++	0.52	0.63
3	++	++	++	++	3.68	0.79
4	++	++	++	++	4.12	0.79
5	++	++	++	++	4.06	0.81
6	++	++	++	++	3.57	0.71
7	-	++	++	++	3.52	0.46
8	++	++	++	++	0.61	0.59
9	-	++	++	++	0.52	0.38

MUT—mutagenicity; TUM—tumorigenicity; IRR—irritant; RE—reproductive effect; DL—druglikeness; DS—drug score. (++)—low toxicity risk; (-)—high toxicity risk.

Structures **7** and **9** possess 5-hydroxy group, while buchenavianines **6** and **8** are 5-methoxy derivatives. It seems, the role of 5-methoxy group appears to be crucial for the low risk of mutagenicity however more calculations should be accomplished to confirm

it. Drug score and druglikeness values were also calculated (Table 3). Drug score indicates the potential of a compound to be a drug. Moderate values of drug score were calculated for **7** and **9** (associated with high mutagenicity risk), other structures exhibit good drug score values.

4. Conclusions

Results of SOM analysis (SwissAdme/Osiris/Molinspiration) of capivatine and buchenavianine derived flavonoid alkaloids show studied compounds obey Lipinski rule of five and exhibit high bioactivity score to the drug targets: GPCR and nuclear receptor ligands, kinase and other enzyme inhibitors, that should indicate multiple mechanisms of the physiological action of studied compounds. All compounds have good intestinal absorption, five of them are expected to permeat BBB, but only one is expected not to be P-gp substrate. All compounds are considered non-toxic, except two 5-hydroxy-substituted buchenavianine derivatives with possible mutagenic effect.

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