l-Carvone – prediction of potential absorption, distribution, metabolism and excretion

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Abstract. The compound carvone is a monoterpene oxygen derivative. It is presented by light yellow liquid. These compound characteristic a spicy smell and had a sweet taste. In the carvone observed two enantiomeric forms (S)-(+) and (R)-(-). It is used in perfumery and cosmetics, although it's considered a potential allergen. It's also used to flavor food and pharmaceutical products. The scope of these work was to predict different properties of *l*-carvone as physiochemical and lipophilic, water solubility, pharmacokinetics, drug likeness and pharmaceutical properties of the compound.

1 Introduction

Carvone is a monoterpene oxygen derivative. It occurs in two enantiomer forms that presented different biological properties. It is seen in caraway and dill fruits, and presented a spice odour. Its enantiomer [CAS 6485-40-1], (usually referred to as *l*-carvone). Usually in the mint leaves hold a Carvone that connected with mint odour, especially in leaves from spearmint (*Mentha spicata* L.) where it's most prevalent in its chemical composition [1-3]. Carvone and the oils contained in it are used to flavor food products, it is used in perfumery, cosmetics and aromatherapy.

Carvone isolated from essential oils has the following parameters: density at 20°C from 0.9603 to 0.9659, refractive index at 20°C from 1.4988 to 1.5003, boiling point between 230 and 231°C, polarization from +56 to +60° and from -57 to -62°, solubility in 50% ethanol 1:17, in 60% ethanol 1:4-5, in 70% ethanol 1:1.5-2 and purity over 98%. It has different solubility - it is insoluble in non-polar liquids, and it is soluble in polar liquids [3].

It has been established that carvone exhibits antimicrobial properties against various test cultures: in bacteria (+ and -) [4-6] yeasts and fungi [7-11], antioxidant activity [12, 13] and other biological properties, for example antinociceptive and anti-inflammatory [14, 15], antihyperglycemic [16], inflammatory [17], anaesthetic[18], pharmacological [19], *etc*. [20-25] due to which the essential oils containing it find a variety of applications.

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The essential oils of cumin and fennel fruits, of spearmint leaves and others that contain carvone are used in perfumery and cosmetics [1, 3]. However, there are studies that have found carvone, to be considered a potential allergen [26-30].

Essential oils containing carvone are also included in aromatic compositions used to flavour various foods [3].

The diverse application of essential oils containing carvone is a prerequisite for the study of some of their physicochemical properties, to establish their stability. Research has been conducted to determine various parameters – physicochemical (density, surface tension and refractive index), kinetic and thermodynamic (surface energy, surface heat capacity, reaction rate constant) of essential oil of spearmint and its main component carvone [11].

Prediction of some of its biological properties is the subject of this work.

2 Materials and methods

SwissADME (absorption, distribution, metabolism and excretion): By means of it, free access to various properties and predictive models necessary in determining physicochemical parameters and for evaluating pharmacokinetics is obtained [31].

The "Rule of Five" was used and other rules that are equal to the "Rule of Five" were proposed [32, 33].

Hopkins presented developed concepts [34] which eight physicochemical properties using 771 marketed oral drugs [34]. The QED is concept for ordinary drug-likeness rules [31].

3 Results and discussion

Some physicochemical parameters of *l*-carvone are presented in Table 1.

Table 1. Presentation of physicochemical properties in the compound (*l*-carvone).

MW (g/mol)	Num. heavy	Num. arom.	Fraction Csp^3	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	Molar refractivity	TPSA ($Å^2$)
150.22	11	0	0.50	1	1	0	47.32	17.07

Lipophilicity characteristics of *l*-carvone is presented in Table 2.

Table 2. Lipophilicity characteristics of the *l*-carvone.

iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
2.27	2.71	2.49	2.10	2.64	2.44

* Presentation of names according [31].

Log P data defines *l*-carvone as lipophilic. Two approaches to predict water solubility applying an ESOL model. (Solubility class: Log S Scale: Insoluble & lt; -10 weakly & lt; -6, moderately & lt; -4 soluble & lt; -2 very & lt; 0 & lt; high) presented according Ali et al. [24]. A third predictor has been developed from SILICOS-IT (Log S Scale: Insoluble & lt; - 10 weakly & lt; -6, moderately & lt; -4 soluble < -2 very & lt; 0 & lt; high), the linear coefficient was presented ($R^2 = 0.75$).

Water solubility characteristics of *l*-carvone are presented in Table 3. The *l*-carvone molecule has a high water solubility. For the prediction of passive absorption of the gastrointestinal tract, as well as in drug development, the BOILED-Egg model is used, which

is very rapid, spontaneous and, effective [36]. The molecules with a high absorption from the gastrointestinal tract is colored white, and this is most likely to penetrate the brain – in yellow [31]. It is known that between 50 and 90% of molecules with therapeutic properties from the five main isoforms of citral are biotransforate from cytochrome P450 (CYP) isoenzymes [37, 38].

Table 3. Characterization solubility of water in the *l*-carvone.

ESOL				Ali et al. [35]				SILICOS-IT			
Log *S*	Solubility		Class	Log *S*	Solubility		Class	Log *S*	Solubility		Class
	mg/ml	mol/L			mg/ml	mol/L			mg/ml	mol/L	
-2.41	5.81e-01	3.87e-03	S	-2.72	2.85e-01	1.90e-03	S	-2.16	1.04e+00	6.95e-03	S

Pharmacokinetics parameters of *l*-carvone are presented in Table 4. The data indicates a high level of absorption of the gastrointestinal tract and a high BBB, i.e. *l*-carvone is a non-substrate of P-gp, it is also a non-inhibitor of the cytochrome P450 isozymes. L-carvone is a compound with a weak permeability which is determined by the coefficient (Log Kp) [38]. Access to five different filters, are given by section SwissADME. The Lipinski et al. [39] filter the rule with different methods [32, 40-42]. The specific needs of the end-user with respect to the chemical space are formed by the different evaluations which allow a choice of diverse methods. A description of each rule violation appears in the output panel [31].

Table 4. Pharmacokinetics parameters of the *l*-carvone.

GI absorption	**BBB permeant**	**P-gp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**	**Log *Kp* (Skin Permeation) (cm/s)**
High	Yes	No	No	No	No	No	No	-5.29

Drug-likeness rule and Bioavailability score of *l*-carvone are presented in Table 5. *l*-Carvone presented rule in SwissADME, and according [43] the molecule is minimal. In the model of Brenk et al. [44] compounds are smaller hydrophobic with those obtained by "Lipinski's rule of 5" to extend the possibilities of optimization of lead. For example, lead optimization was developed by [45, 46] using method with molecular weight between 100 and 350 Da.

Table 5. Presentation of rule of Druglikeness and Bioavailability score in the *l*-carvone.

Lipinski et al. [20]	**Ghose et al. [32]**	**Veber et al. [40]**	**Egan et al. [41]**	**Muegge et al. [42]**	**Bioavailability score**
Yes; 0 violation	No; 1 violations MW < 160	Yes	Yes	No; 2 violation: MW < 200; Heteroatoms < 2	0.55

The medically important properties of *l*-carvone are presented in Table 6. No reaction alerts were observed for PAIN alert, but reaction alerts were observed for Brenk et al. [44].

Table 6. Medicinal chemistry properties of the compound (*l*-carvone).

Pains	**Brenk et al. [44]**	**Leadlikeness**	**Synthetic accessibility (SA)**
0 alert	1 alerts: isolated alkene	No; 1 violation: MW < 250	3.33

Therefore, there is some deviation in terms of its drug similarity. It is seen that the molecule is at the prediction site of BOILED-Egg (Fig. 1). The molecule *l*-carvone is seen as red point of P-gp (PGP).

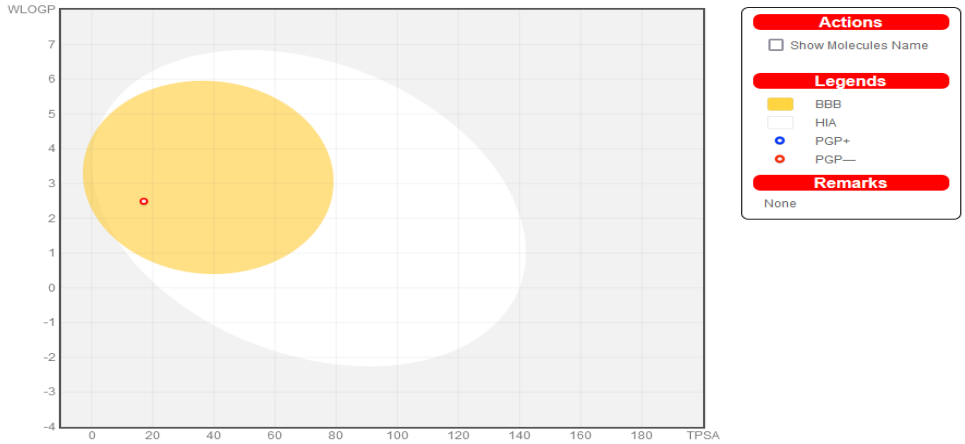

Fig. 1. Perceptive evaluation of passive gastrointestinal absorption (HIA) and Brain penetration (BBB) using BOILED-Egg (WLOGP vs TPSA).

l-Carvone was evaluated for drug-likeness by bioavailability radar (Fig. 2). For it six physicochemical properties including and Insaturation and Flexibiliti outline an optimum space (pink area) were predicted [31].

In Fig. 2 the Bioavailability Radar of the compound is presented, which is in the pink zone with small deviations in some parameters.

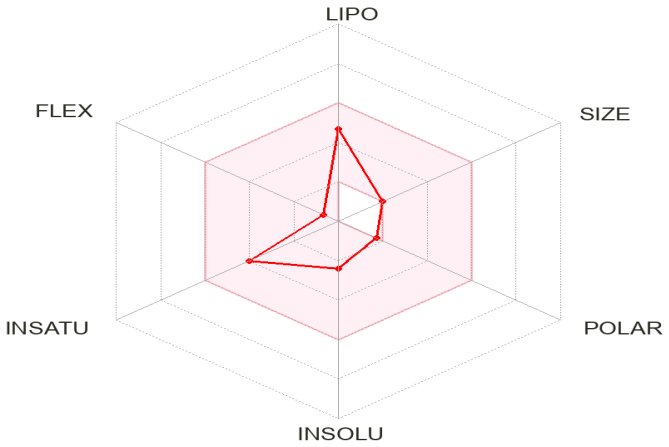

Fig. 2. Biavailability Radar schematic diagram of *l*-carvone.

4 Conclusion

In order to act as a drug, *l*-carvone must meet certain requirements that will allow the relevant biological events to take place. The SwissADME tool makes it possible to calculate medically important physicochemical, pharmacokinetic and other parameters of flavoring substances. This is important in the application of the aromatic component in the cosmetic and food products, subject to further research.

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