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Pharmacokinetics and Toxicological Profiling of Surfactin A: An In silico Approach

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Published: 4 December 2015

Abstract: Surfactin A, a cyclic lipopeptide from *Bacillus subtilis,* exhibited a wide spectrum therapeutic profile. But it's drug likeness has not been thoroughly assessed yet. Thus, the objective of the present work was to simulate it's drug likeness by predicting the pharmacokinetic and toxicological profiling parameters. ADME profiling was carried out by using StarDrop. Integrated Derek Nexus with StarDrop was used for the toxicological prediction against 40 toxicological end points. Metabolism of Surfactin A was modelled with three isoforms of cytochrome P450: 3A4, 2D6 and 2C9; and composite site lability (CSL) was analyzed. Only the alkyl regions in Surfactin A were found to be moderately labile to metabolism, indicating their tendency to get oxidized and form dealkylated Surfactin A. Toxicological prediction suggested that Surfactin A is not carcinogenic, mutagenic, teratogenic, hepatotoxic, neurotoxic, nephrotoxic and even clean for rest of the toxicological end points. Good human intestinal absorption (HIA) and poor blood brain barrier (BBB) crossing ability were also predicted for Surfactin A.

Keywords: Surfactin A; Cyclic Lipopeptide; ADMET; Drug Likeness; *Bacillus subtilis*

1. Introduction

Biosurfactants have potential industrial applications, for example, in digestion of persistent organic pollutants (POPs), as stabilizing agents in food processing and foam formation to name a few [1]. *Bacillus subtilis* yields a well known biosurfactant as secondary metabolite, Surfactin which exists in four isomeric forms viz. Surfactin A - D. Physiologically, it acts as anti-fibrin clotting agent, as an agent for cell lysis, anti-diabetic

adjuvant, anti-inflammatory agent etc [2-4]. But so far, its drug metabolism, pharmacokinetics and toxicological parameters have not be reported. In this study, we predict these features with the aid of computational tools.

2. Results and Discussion

Composite site lability of 0.9219 predicted the high rate of metabolism with 3A4 isoform of cytochrome P450 (**Table 1**). The CYP3A4 is the main isoform of P450 superfamily which resides majorly in the liver and is responsible for the metabolism of many drugs. Hence, the lability of surfactin with this isoform predicts the significant affinity. Interaction of surfactin A with CYP3A4 may increase/decrease its physiological effects which need to be assessed further. Amphiphillic nature of the surfactin A can be computed from its LogS and LogP values. Aliphatic elements like hydrocarbon side chain influence the hydrophobicity positively while the peptidal bonds have some negative influence on the hydrophobicity (**Figure 1**). Carboxyl group of aspartic acid and glutamic acid improved the solubility of surfactin A. Further, the tendency to get absorbed through human intestinal barrier and the inability to cross blood brain barrier makes it a potential candidate for oral and non-CNS drug.

Derek Nexus software predicted that the surfactin A doesn't have any potential site which can cause toxicity against any of the 40 tested toxicological end points.

Table 1. Drug Metabolism, Pharmacokinetics and Toxicological Profiling of Surfactin A, a cyclic lipopeptide.

Parameters	Surfactin A	Parameters	Surfactin A	Parameters	Surfactin A
Composite Site Lability against CYP3A4	0.9219	Mutagenicity in vitro	No report	Irritation (of the gastrointestinal tract)	No report
logS	2.459	Mutagenicity in vivo	No report	Irritation (of the respiratory tract)	No report
logS @ pH7.4	2.903	Photomutagenicity in vitro	No report	Irritation (of the skin)	No report
logP	3.11	alpha-2-mu-Globulin nephropathy	No report	Lachrymation	No report
logD	2.88	Anaphylaxis	No report	HERG channel inhibition in vitro	No report
2C9 pKi	4.858	Bladder urothelial hyperplasia	No report	Hepatotoxicity	No report
hERG pIC50	1.794	Cardiotoxicity	No report	Genotoxicity in vitro	No report
BBB log([brain]:[blood])	-0.6902	Cerebral oedema	No report	Genotoxicity in vivo	No report
BBB category	-	Chloracne	No report	Photogenotoxicit	No

				y in vitro	report
HIA category	+	Cholinesterase inhibition	No report	Photogenotoxicity in vivo	No report
P-gp category	yes	Cumulative effect on white cell count and immunology	No report	Chromosome damage in vitro	No report
2D6 affinity category	high	Cyanide-type effects	No report	Chromosome damage in vivo	No report
PPB90 category	high	High acute toxicity	No report	Photo-induced chromosome damage in vitro	No report
Developmental tox. category	Non-toxic	Methaemoglobinaemia	No report	Carcinogenicity	No report
Thyroid toxicity	No report	Nephrotoxicity	No report	Photocarcinogenicity	No report
Photoallergenicity	No report	Neurotoxicity	No report	Pulmonary toxicity	No report
Skin sensitisation	No report	Oestrogenicity	No report	Uncoupler of oxidative phosphorylation	No report
Occupational asthma	No report	Peroxisome proliferation	No report	Irritation (of the eye)	No report
Respiratory sensitisation	No report	Phospholipidosis	No report	Testicular toxicity	No report
Developmental toxicity	No report	Phototoxicity	No report	Ocular toxicity	No report

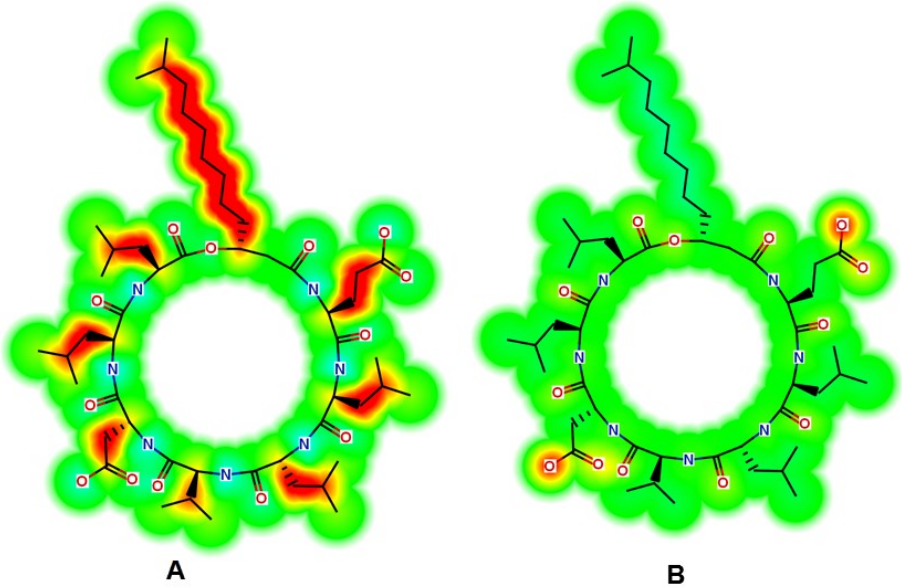

Figure 1. Responsible Structural Elements of Surfactin A. A: LogP and B: LogS @ pH 7.4. Green section: Neutral Region; Red section: Positively Influencing Elements; Yellow Section: Intermediary Infleuncing Elements; Blue Section: Negatively Influencing Elements.

3. Materials and Methods

Drug Metabolism & Pharmacokinetics

Drug metabolism and pharmacokinetics parameters were predicted using StarDrop (Optibrium Ltd., United Kingdom). Parameters studied were LogS, LogS@pH7.4, LogP, LogD, 2C9 pKi, hERG pIC50, BBB Log ([brain]:[blood]), BBB category, HIA category, P-gp category, 2D6 affinity category, PPB90 category, developmental toxicological category and composite site lability of these molecules on 3A4 isoform of cytochrome P450 [5-6].

Toxicological Studies

Derek Nexus module of LHASA Ltd. was used to calculate toxicological endpoints like carcinogenicity, photo-carcinogenicity, chromosome damage in vitro, chromosome damage in vivo, photo-induced chromosome damage in vitro, genotoxicity in vitro, genotoxicity in vivo, photogenotoxicity in vitro, photogenotoxicity in vivo, hepatotoxicity, irritation (of the eye), irritation (of the gastrointestinal tract), irritation (of the respiratory tract), irritation (of the skin), lachrymation, HERG channel inhibition in vitro, alpha-2-mu-globulin nephropathy, anaphylaxis, bladder urothelial hyperplasia, cardiotoxicity, cerebral oedema, chloracne, cholinesterase inhibition, cumulative effect on white cell count and immunology, cyanide-type effects, high acute toxicity, methaemoglobinaemia, nephrotoxicity, neurotoxicity, oestrogenicity, peroxisome proliferation, phospholipidosis, phototoxicity, pulmonary toxicity, uncoupler of oxidative phosphorylation, developmental toxicity, teratogenicity, testicular toxicity, ocular toxicity, mutagenicity in vitro, mutagenicity in vivo, photomutagenicity in vitro, thyroid toxicity, photoallergenicity, skin sensitization, occupational asthma and respiratory sensitization [5-6].

4. Conclusions

In this study, prediction of the drug metabolism, pharmacokinetic, and toxicological parameters were investigated for the well known biosurfactant, Surfactin A produced by *Bacillus subtilis*. Computataional tools predicted Surfactin A as a molecule, which can be studied and explored further for lead optimization.

Acknowledgments

Authors would like to express their thanks to Optibrium Ltd (U. K.) for providing trial version of StarDrop and Derek Nexus for the current study.

Author Contributions

RKS collected the data and prepared initial draft. AKD initialize the data, analyzed, and finalize the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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