In silico prediction of physicochemical, pharmacokinetic and toxicological properties of sulforaphane

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Introduction

- Cancer - a major cause of morbidity and mortality worldwide
- Different disturbed signaling pathways
- Effective therapy is lacking
- Phytochemicals, such as sulforaphane (SFN), are receiving great attention
- Data on the toxic potential of chemically synthesized SFN and its toxicological profile are very limited

The aim of this study was to conduct *in silico* prediction of physicochemical and pharmacokinetic properties for the targeted molecule, sulforaphane, in order to better understand its toxicological potential

Method

- SwissADME (http://www.swissadme.ch/) - physicochemical and pharmacokinetic properties assessment
- mcule (https://mcule.com/; Toxicity checker tool) - assessment of toxic properties based on structure
- ADMETlab 2.0 (https://admetmesh.scbdd.com/) – physicochemical, pharmacokinetic and toxic properties assessment

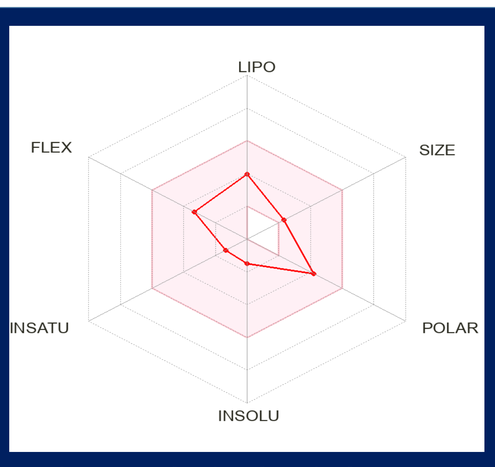

Figure 1. Physicochemical properties of sulforaphane (SwissADME)

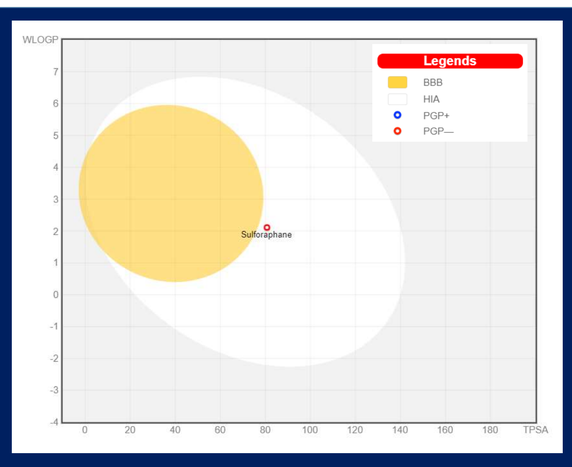

Figure 2. Pharmacokinetics of sulforaphane (SwissADME)

Table I The results obtained from SwissADME and ADMETlab 2.0 analysis - Pharmacokinetics, Druglikeness, Medicinal chemistry

SwissADME		ADMETlab 2.0	
Pharmacokinetics			
GI absorption	High	/	
BBB permeant	No	**medium**	
P-gp substrate	No	No	
CYP1A2 inhibitor	No	No	
CYP2C19 inhibitor	No	**Yes**	
CYP2C9 inhibitor	No	No	
CYP2D6 inhibitor	No	No	
CYP3A4 inhibitor	No	No	
Druglikeness			
Lipinski	Yes	Lipinski Rule	Accepted
Ghose	Yes	Pfizer Rule	Accepted
Veber	Yes	GSK Rule	Accepted
Egan	Yes	**Golden Triangle**	**Rejected**
Muegge	**No; 1 violation: MW<200**	**QED**	**0.274**
Medicinal chemistry			
PAINS	0 alert	PAINS	0 alert
Brenk	**2 alerts: imine_1, thiocarbonyl_group**	**ALARM NMR Rule**	**1 alert**
Leadlikeness	**No; 1 violation: MW<250**	**BMS Rule**	**1 alert**
Synthetic accessibility	3.07	Synthetic accessibility	4.972

Results

- SFN was in the optimal range for lipophilicity, size, polarity, solubility, saturation and flexibility – **good oral bioavailability** (**Fig. 1.)**
- The passive human gastrointestinal absorption (HIA) – high (**Fig 2**.)
- The differences between results obtained from SwissADME and ADMETlab 2.0 analysis regarding **pharmacokinetics, druglikeness, medicinal chemistry** are shown in **Table I**.
- **Toxicity prediction analysis** and **Tox21 Pathway analysis** are shown in Table 2. (ADMETlab 2.0), shown in **Table II**.
- **Toxic matching rules:** SFN contains potential promiscuous substructure (mcule, Toxicity checker tool), shown in **Fig.3.**
- **Toxicophore rules:** ADMETlab 2.0 indicated alerts for Genotoxic Carcinogenicity (2), NonGenotoxic Carcinogenicity (1), Skin Sensitization (3), Aquatic Toxicity (2). SFN has MedChem unfriendly status and potentially toxic substructures (SureChEMBL Rule and FAF-Drugs4 Rule)

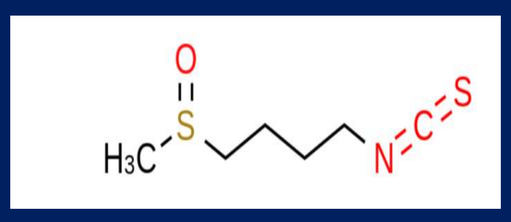

Figure 3. Sulforaphane contains potential promiscuous substructure (mcule, Toxicity checker tool)

Table III Clearance and the half-life of sulforaphane (ADMETlab 2.0)

Excretion	
CL	6.775 ml/min/kg
T1/2	0.729 (< 3 hours)

Table II.Toxicity prediction analysis and **Tox21 Pathway analysis** (ADMETlab 2.0)

Tox21 Pathway		Toxicity	
Androgen receptor	---	hERG Blockers	---
Androgen receptor ligand-binding domain	--	Human hepatotoxicity	--
Aryl hydrocarbon Receptor	+++	Drug induces liver injury	-
Aromatase	+	AMES Toxicity	++
Estrogen receptor	-	Rat Oral Acute Toxicity	+++
Estrogen receptor lignad-binding domain	---	Maximum recommended daily dose	--
Peroxisome proliferator receptor gamma	--	Skin Sensitization	+
Antioxidant response element	+++	Carcinogencity	++
ATPase family AAA domain-containing protein	---	Eye Corrosion	+++
Heat shock factor response element	+++	Eye Irritation	+++
Mitochondrial membrane potential	++	Respiratory Toxicity	+++
tumor suppressor protein p53	-		

Conclusions

- **This *in silico* study reported significant variability in prediction of physicochemical and pharmacokinetic properties as well in toxicological potential of SFN**
- **Larger-scale of *in silico* and toxicity studies are necessary to further examine its toxicological profile**

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