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ADME/drug-likeness properties of three vanillin-based Schiff bases

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

Marina D. Kostić [1], Vera M. Divac [2], and Jovana Marjanović [2]*

[1] Institute for Information technologies, University of Kragujevac, Jovana Cvijića bb, Kragujevac, Serbia
[2] Faculty of Science, University of Kragujevac, Radoja Domanovića 12, Kragujevac, Serbia
* Corresponding author: jovana.marjanovic@pmf.kg.ac.rs

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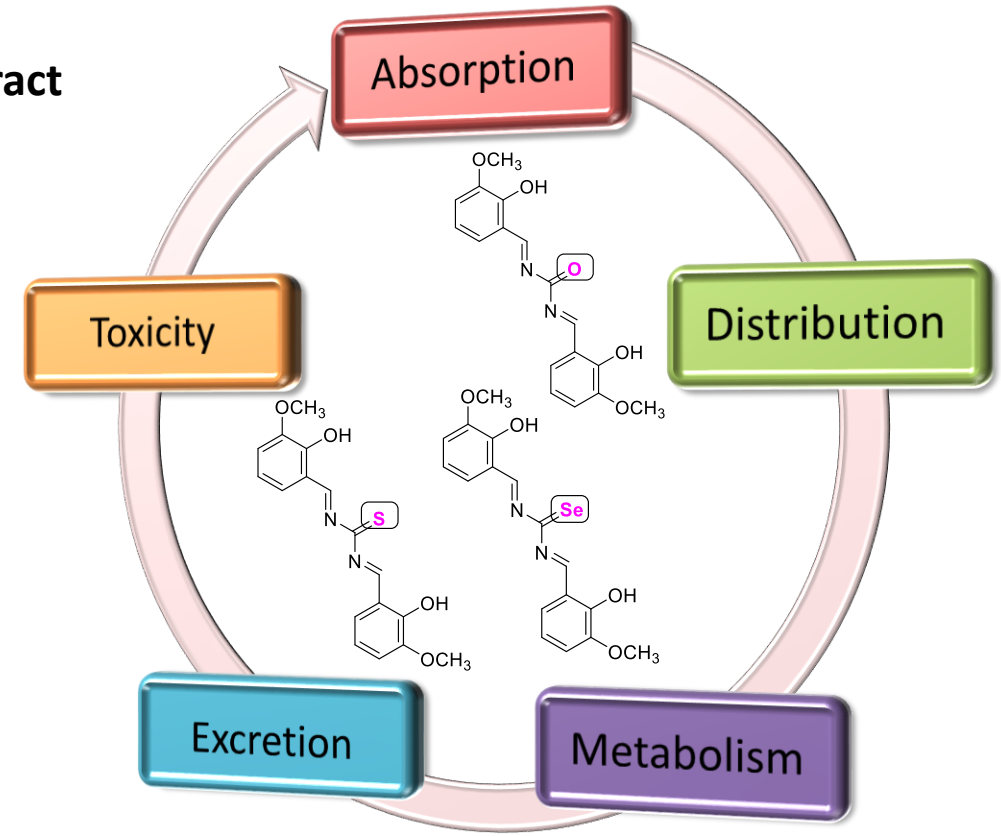
Graphical Abstract



Abstract: Herein we present the results obtained in the *in silico* ADME screening and drug-likeness evaluation of three Schiff bases based on vanillin aldehyde. As an amine counterpart, the selenourea, urea and thiourea were used. According to the obtained results, all three compounds have demonstrated optimal lipophilicity and moderate solubility necessary for the achievement of good bioavailability when administrated orally. Ii was also observed that all compounds have potential to be well absorbed into systematic circulation in the GIT (gastrointestinal tract), without possibility to cross blood-brain barrier. Taking into consideration the fact that the candidate drug should have limited inhibitory activity against CYP enzyme isoforms, the urea-based compound shown no potential to inhibit any of the five P450 isoforms. The target screening has indicated that the family of cytosolic proteins and enzymes were the most probable physiological targets for the screened compounds.

Keywords: ADME; Schiff bases; vanillin

Introduction

Schiff bases represent the condensation products of amines and aldehydes with an imine functionality present in their molecular scaffolds. They have been recognised as a molecules with broad range of promising biological properties, such as antimicrobial, antiviral and antibacterial[1]. In addition, they are also known as common enzyme intermediates. Taking into account the fact that the design and synthesis of potential drug candidates can be a time and cost process, the use of the application of different predictors for the determination of a potential drug's in vivo studies and properties necessary for the administration under physiological conditions, is today recognizable concept for the successful drug design and synthesis.

[1] A. Kajal, S. Bala, S. Kamboj, N. Sharma, V. Saini, Schiff Bases: A Versatile Pharmacophore, Journal of Catalysts, vol. 2013,https://doi.org/10.1155/2013/893512

Results and discussion

Herein we present the results obtained *in silico* ADME screening and drug-likeness evaluation of three Schiff bases based on vanillin aldehyde (Figure 1). As an amine counterpart, the urea (1), thiourea (2) and selenourea (3) were used.

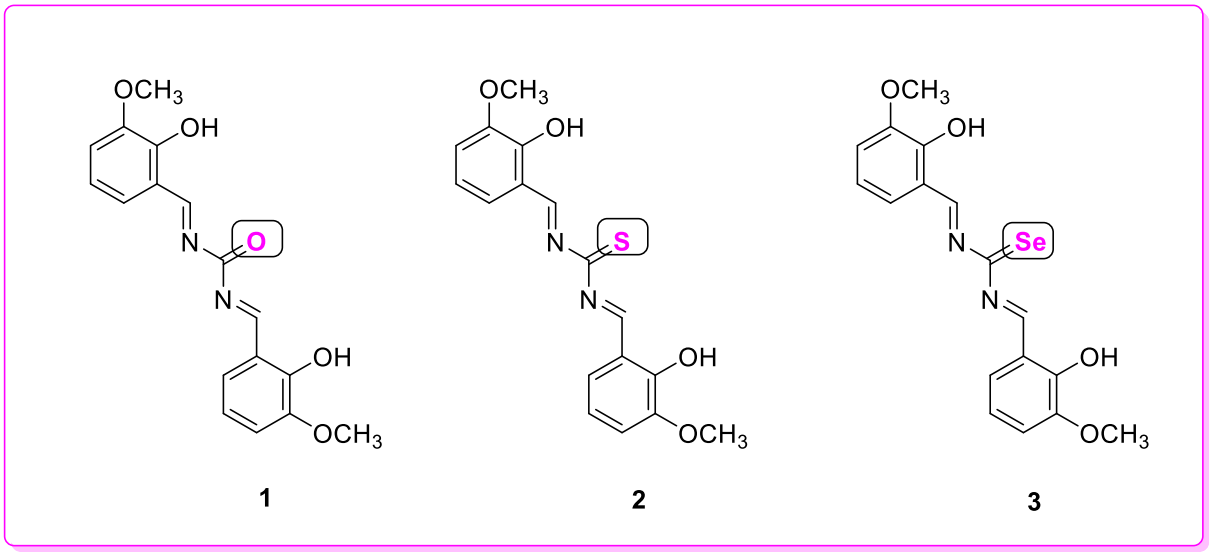


Figure 1. Vanilin-based Schiff bases

The SwissADME[2] online tool was used to evaluate pharmacokinetics, drug-likeness and other ADME properties and the obtained data are presented in Tables 1, 2 and 3.

Compound 1			
Physicochemical Properties		**Pharmacokinetics**	
Formula	$C_{17}H_{16}N_2O_5$	GI absorption	High
Molecular weight	328.32 g/mol	BBB permeant	No
Fraction Csp3	0.12	P-gp substrate	No
Num. rotatable bonds	6	CYP1A2 inhibitor	No
Num. H-bond acceptors	7	CYP2C19 inhibitor	No
Num. H-bond donors	2	CYP2C9 inhibitor	No
Molar Refractivity	90.5	CYP2D6 inhibitor	No
		CYP3A4 inhibitor	No
		Log Kp (skin permeation)	-6.59 cm/s
Lipophilicity		**Druglikeness**	
Log Po/w (iLOGP)	3.09	Lipinski	Yes; 0 violation
Log Po/w (XLOGP3)	2.41	Ghose	Yes
Log Po/w (WLOGP)	2.77	Veber	Yes
Log Po/w (MLOGP)	1.45	Egan	Yes
Log Po/w (SILICOS-IT)	3.27	Muegge	Yes
Log Po/w[b)]	2.6	Bioavailability Score	0.55
Water Solubility		**Medicinal Chemistry**	
Log S (ESOL)	-3.37	PAINS	0 alert
Solubility	1.41e-01 mg/ml ; 4.29e-04 mol/l	Brenk	1 alert: imine
Class	**Soluble**	Leadlikeness	Yes
Log S (Ali)	-4.17	Synthetic accessibility	2.97
Solubility	2.24e-02 mg/ml ; 6.81e-05 mol/l		
Class	**Moderately soluble**		
Log S (SILICOS-IT)	-4.13		
Solubility	2.43e-02 mg/ml ; 7.41e-05 mol/l		
Class	**Moderately soluble**		

Table 1. Predicted Drug-Likeness, Pharmacokinetic and other ADME properties calculated by SwissADME web tool for compound 1

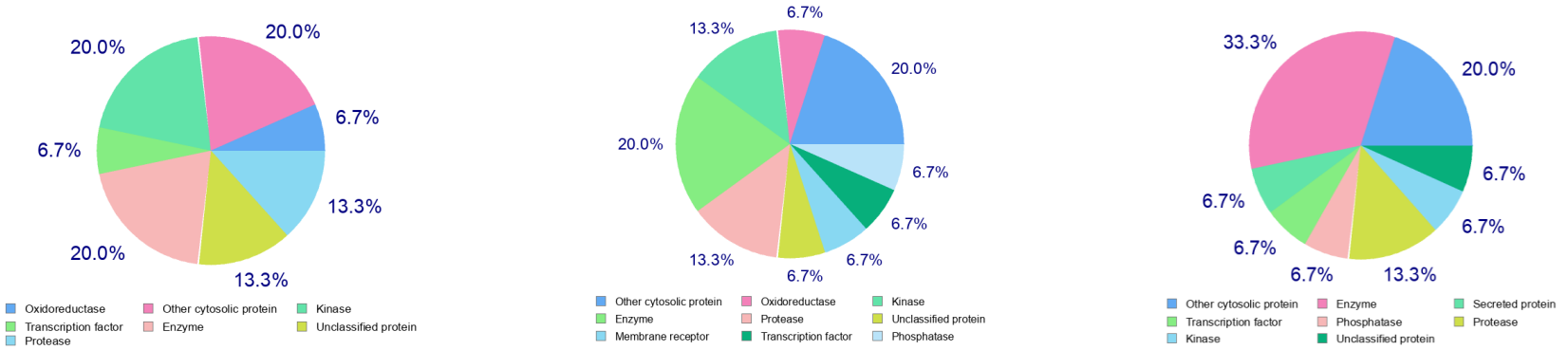
[2] A. Daina, O. Michielin, V. Zoete., SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, Sci Rep 7 (2017) 42717.

Compound 2			
Physicochemical Properties		**Pharmacokinetics**	
Formula	$C_{17}H_{16}N_2O_4S$	GI absorption	High
Molecular weight	344.38 g/mol	BBB permeant	No
Fraction Csp3	0.12662	P-gp substrate	No
Num. rotatable bonds	6	CYP1A2 inhibitor	Yes
Num. H-bond acceptors	6	CYP2C19 inhibitor	No
Num. H-bond donors	2	CYP2C9 inhibitor	Yes
Molar Refractivity	97.7	CYP2D6 inhibitor	No
		CYP3A4 inhibitor	Yes
		Log Kp (skin permeation)	-6.26 cm/s
Lipophilicity		**Druglikeness**	
Log Po/w (iLOGP)	3.03	Lipinski	Yes; 0 violation
Log Po/w (XLOGP3)	3.01	Ghose	Yes
Log Po/w (WLOGP)	2.94	Veber	Yes
Log Po/w (MLOGP)	1.44	Egan	Yes
Log Po/w (SILICOS-IT)	4.73	Muegge	Yes
Log Po/w[b)]	3.03	Bioavailability Score	0.55
Water Solubility		**Medicinal Chemistry**	
Log S (ESOL)	-3.85	PAINS	0 alert
Solubility	4.92e-02 mg/mL ; 1.43e-04 mol/L	Brenk	2alerts: imine, 1 thiocarbonyl group
Class	**Soluble**	Leadlikeness	Yes
Log S (Ali)	-5.11	Synthetic accessibility	2.87
Solubility	2.70e-03 mg/mL ; 7.85e-06 mol/L		
Class	**Moderately soluble**		
Log S (SILICOS-IT)	-4.32		
Solubility	1.64e-02 mg/mL ; 4.75e-05 mol/L		
Class	**Moderately soluble**		

Table 2. Predicted Drug-Likeness, Pharmacokinetic and other ADME properties calculated by SwissADME web tool for compound 2

Compound 3			
Physicochemical Properties		**Pharmacokinetics**	
Formula	$C_{17}H_{16}N_2O_4Se$	GI absorption	High
Molecular weight	391.28 g/mol	BBB permeant	No
Fraction Csp3	0.12	P-gp substrate	No
Num. rotatable bonds	6	CYP1A2 inhibitor	No
Num. H-bond acceptors	6	CYP2C19 inhibitor	No
Num. H-bond donors	2	CYP2C9 inhibitor	No
Molar Refractivity	95.86	CYP2D6 inhibitor	No
		CYP3A4 inhibitor	Yes
		Log Kp (skin permeation)	-7.43 cm/s
Lipophilicity		**Druglikeness**	
Log Po/w (iLOGP)	0	Lipinski	Yes; 0 violation
Log Po/w (XLOGP3)	1.77	Ghose	Yes
Log Po/w (WLOGP)	1.91	Veber	Yes
Log Po/w (MLOGP)	1.44	Egan	Yes
Log Po/w (SILICOS-IT)	2.58	Muegge	Yes
Log Po/w[b)]	1.54	Bioavailability Score	0.55
Water Solubility		**Medicinal Chemistry**	
Log S (ESOL)	-3.36	PAINS	0 alert
Solubility	1.73e-01 mg/ml ; 4.42e-04 mol/l	Brenk	2 alerta heavy metal: imine
Class	**Soluble**	Leadlikeness	No; 1 violation
Log S (Ali)	-3.14	Synthetic accessibility	3.2
Solubility	2.81e-01 mg/ml ; 7.17e-04 mol/l		
Class	**Soluble**		
Log S (SILICOS-IT)	-4.45		
Solubility	1.38e-02 mg/ml ; 3.53e-05 mol/l		
Class	**Moderately soluble**		

Table 3. Predicted Drug-Likeness, Pharmacokinetic and other ADME properties calculated by SwissADME web tool for compound 3



a) b) c)

Figure 2. Target prediction of compounds: a)1, b)2 and c)3

Conclusions

According to the obtained results, all three compounds have demonstrated optimal lipophilicity and moderate solubility necessary for the achievement of good bioavailability when administrated orally. It was also observed that all compounds have potential to be well absorbed into systematic circulation in GIT (gastrointestinal tract), without possibility of crossing blood-brain barrier. Taking into consideration the fact that the candidate drugs should have limited inhibitory activity against CYP enzyme isoforms, the urea-based compound 1 shown no potential to inhibit any of the five P450 isoforms. The target screening has indicated that the family of cytosolic proteins and enzymes were the most probable physiological targets for the screened compounds.

Acknowledgments

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