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Prediction of pharmacokinetics profile of new cytotoxic compounds from *trunk bark and root bark* of *Citrus x paradisi (*Rutaceae*)*

Prédiction du profil pharmacocinétique des nouveaux composés cytotoxiques isolés des écorces du tronc et des racines *de Citrus x paradisi (Rutaceae)*

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Article original

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RESUME

Introduction: According to the WHO, cancer is the second leading cause of death worldwide. In fact, the International Agency for Research on Cancer has estimated that there will be 20 million and 9.7 million new cases of cancer and deaths in 2022, respectively. Although chemotherapy is effective, the drugs used not only attack cancer cells, but also healthy cells. It is in this context that this study is being conducted with the aim to search new drug candidates with fewer side effects.
Material and method: 24 Pharmacokinetic and toxicity parameters of these molecules have been predicted using chemical computational methods.
Results: According to the Lipinski rules, the 1-Formyl-5-Hydroxy-N-Methylindolin-1-ium is the best drug candidate for all pharmaceutical forms and a good lead compound. For oral form, the 23 (s) -isolimonexin and the decyloxycleomiscosin D are not good drugs candidates. However, due to their hydrophilic character, the IV formulations would be appropriate. The 23 (s) -isolimonexin is also a good leader. All those molecules would be highly toxic with a low therapeutic index and eliminated from kidney as metabolites with a short half-life time.
Conclusion: Only 1-Formyl-5-Hydroxy-N-Methylindolin-1-ium would be a good drug candidate and a good lead compound for all pharmaceutical forms. On the other hand, 23(s)-isolimonexine and decyloxycleomiscosin D would not be good drug candidates for oral forms.

ABSTRACT

Introduction: Selon l'OMS, le cancer est la deuxième cause de décès dans le monde entier. En effet, l'agence internationale de recherche sur le cancer a estimé à 20 millions et 9,7 millions, les nombres respectifs de nouveaux cas de cancer et de décès enregistrés en 2022. Bien que la chimiothérapie soit efficace, les médicaments utilisés s'attaquent non seulement aux cellules cancéreuses, mais également aux cellules saines. C'est dans ce contexte que la présente étude s'inscrit dans le but de rechercher de nouveaux candidats médicaments possédant moins d'effets secondaires.
Matériel et méthode: 24 paramètres de pharmacocinétique et de toxicité des molécules étudiées ont été prédits en utilisant les méthodes de chimie computationnelle.
Résultats: Selon les règles de Lipinski, le 1-Formyl-5-Hydroxy-N-Méthylindolin-1-ium est le meilleur candidat médicament pour toutes les formes pharmaceutiques et un bon composé de tête. Pour la forme orale, la 23(s)-isolimonexine et la décyloxycléomiscosine D ne sont pas de bons candidats médicaments. Cependant, en raison de leur caractère hydrophile, les formulations IV seraient appropriées. La 23(s)-isolimonexine est également un bon leader. Toutes ces molécules seraient hautement toxiques avec un faible index thérapeutique et éliminées du rein sous forme de métabolites avec une courte demi-vie. Par conséquent, il serait recommandé d'utiliser des formulations hydrophobes ou de substituer les groupements moins hydrophiles par des groupements plus hydrophobes (pour la 23(s)-isolimonexine et la décyloxycléomiscosine D) ou des formulations d'enrobage (23(s)-isolimonexine) ; ou de privilégier les formes à libération prolongée pour limiter le risque toxique qui pourrait être induit par plusieurs administrations rapprochées et garder une concentration efficace.
Conclusion: Seul le 1-Formyl-5-Hydroxy-N-Méthylindolin-1-ium serait un bon candidat médicament et un bon chef de fil pour toutes les formes pharmaceutiques. En revanche, la 23(s)-isolimonexine et la décyloxycléomiscosine D ne seraient pas de bons candidats médicaments pour les formes orales.

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Introduction

Citrus X Paradisi is a hybrid species of the Rutaceae family issue from the crossing of the grapefruit (*Citrus Maxima*) and orange (*Citrus sinensis*) in which many compounds with cytotoxic properties have been isolated [1,2]. Indeed, recent studies permitted to highlight the cytotoxic properties of 3 new compounds isolated from trunk bark. and root bark of *Citrus x Paradisi* and belonging to the Alkaloid family (1-formyl-5-hydroxy-n-methylindolin-1st -Ium), coumarins (decyloxycleomiscosin d) and limonoïd (23-*s*-isolimonexin) [3-5]. However, approximately 90% of drug screening failures were due to poor pharmacokinetic profiles [6,7] resulting in lack of clinical efficacy (40–50%), trusting toxicity (30%) and inadequate drug-like properties (10 to 15%).[8] Unfortunately, the problem is noticed at a late stage of drug development[9]. In order to transcends such drug failure, the specification of pharmacokinetic profile of these new molecules by the means of *in silico* techniques becomes imperative in the early internships of Drug Development for an adequate guidance during the choice of administration and galenic forms for the following animals pre-clinical trials and humans clinical trials.

Materials and Methods

The prediction of the parameters ADMET of the 3 compounds was carried out using the reference software in SwissADME prediction, ADMETLABS version 2.0, PKCSM and ACDLABs version V.0.0.184 [10-12]. The prediction is based on a combination of 2D and 3D similarities with a known product library [13,14].

a. Selection of ADMET parameters

The selected parameters are those which describe the kinetic properties and the toxicity of the molecules. 24 Parameters ADMET selected were listed in table 5.

b. Identification of the compounds

The molecules were identified by their 3 - dimensional chemical formula [13,14].

c. Selection of compounds and drugs with similar chemical formula

Software has a known product database including drugs [15]. These compounds selected according to their similarity to each of the 3 molecules studied, will define the geometric spaces in which they will be compared each to other [16-18].

d. Experimental procedure

The structures of the compounds have been drawn in software to generate the smiles from which the parameters will be calculated according to the instructions described in the manuals of use [12,19-21].Then the data was extracted and analyzed.

e. Data analysis

The values of the 24 parameters calculated by software are compared to that of the drugs tested *in vivo* [12], using the rules defined by scores. These rules establish the similarities and dissimilarities between the molecules. Thus, two molecules with a similar structure have similar properties[13].The 2 rules used for the interpretation of our data are the rule of 5 [23-24] and the rule of 3 [25]. The rule of 5 stipulates that: if for a molecule, at least two of the conditions: mol_mw <500, qplogpo/w <5, HBD ≤ 5, and HBA ≤ 10 are not verified, the molecule may have a low absorption or a low permeability. And, according to the rule of 3, if beyond his good biological activity, the number of violation of 3 rule is at most 3 times, the molecule is a good lead-compound.

Results

The **figure 1** below present the molecular structures of 1-Formyl-5-hydroxy-N-methylindolin-1-ium (**1**), Decyloxycleomiscosin D (**2**) and 23-*S*-Isolimonexine (**3**) isolated from trunkbark and roobark of *Citrus X Paradisi Macfad.*

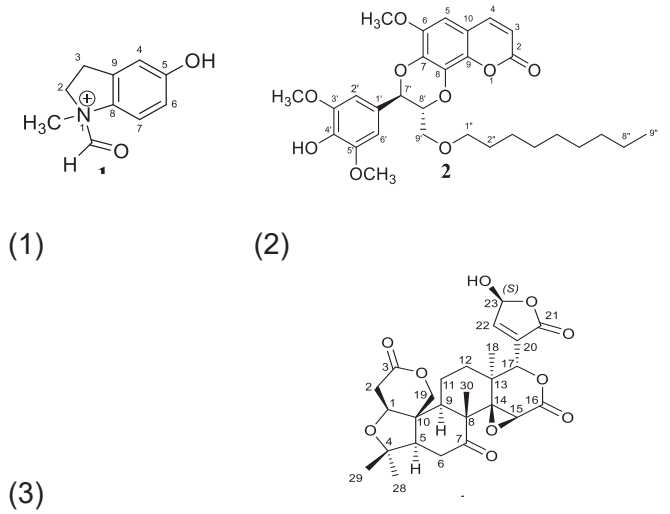

Figure 1. *molecular structures of compounds 1 to 3.*.

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The tables 1, 2, 3, 4, 5 and 6 present values of physico chemical and pharmacokinetics parameters of the compounds 1, 2 and 3 predicted by ACDlabs (**A**), SwissADME (**S**), ADMETlab (**L**) and pkCSM (**P**) software

Table 1. *key parameters that describe the pharmacokinetic profile of studied compounds.*

ADMET	Description	Parameters
Physico chemical properties	Intrinsic physical and chemical characteristics of a substance	MW, HBD, HBA, TPSA, Log P, Log S, S, pKa, Log D
Absorption	Transportation of the unmetabolized drug from the site of administration to the body circulation system	Caco-2, Pgp, Bioavailability
Distribution	Reversible transfer of an unmetabolized drug through the body's blood and tissues	Log BB, PPB, Vd, Fu
Physico chemical properties	Intrinsic physical and chemical characteristics of a substance	MW, HBD, HBA, TPSA, Log P, Log S, S, pKa, Log D

Physicochemical properties:
MW – Molecular weight,
HBA – Hydrogen Binding Acceptor,
HBD – Hydrogen Binding Donor,
TPSA – Typological Polar surface Area,
log Po/w—log of octanol/water partition coefficient;
log S—log of the solubility in mol/L;
pKa—negative log of the acid dissociation constant (Ka),
Log D - log of Dissociation constant.

Absorption:
Log P Caco-2—log human intestinal membran partition coefficient;
Bioavailability; PgP—Permeability glycoprotein.
Distribution: Vd: Volume of distribution,
BB–Brain Barrier penetration;
PPB—Plasma Protein Binding,
Fu: Fraction unbound.

Metabolism:
CYP450—Cytochrome P450 inhibition;
HLM Sites—Points susceptible to initiating metabolic **transformation in Human Liver Microsomal.**

Elimination:
Cl—Clearance;
$T_{1/2}$—Half-life time.

Toxicity: Oral acute toxicity;
hERG—Cardiac toxicity;
AMES—Mutagenicity.

a. Physico-chemical properties

The interpretation of the physico-chemical descriptors MW, HBA, HBD, NRB and TPSA (**Table 2**) was done by Lipinsky's rule. The values of the physico-chemical parameters of compounds 1, 2 and 3 predicted by ACDlabs, SwissADME and pkCSM software show that conditions MW <500, QPLOGD <5, HBD ≤ 5, and HBA ≤ 10 of the rule of Lipinski 5 are only violated for compounds 2 and 3 (twice at most). The physico-chemical properties of these compounds predicted by the 3 software (A), (S) and (L) are concordant to their predictions on absorption and distribution.

b. Absorption and Distribution profile

Polar compounds (2) and (3) cannot cross the Blood Brain Barrier which is strongly lipophilic (**Tables 3&4**). The absorption predicted at the intestinal level would correspond to a passive dissemination mode for the compound 1 (Log P Caco-2 <5 and PPB <30%). This would explain good oral bioavailability predicted by ACDlabs software (97.73%). On the other hand, compounds (2) and (3) would have low bioavailability (1.63 and <30% respectively for ACDlabs software) due to their hydrophilic character. This low bioavailability would also be explained by a strong affinity of these protein compounds (92.5% for compound 2) and a low concentration of the Fraction unbound (Fu: 10% and 40% respectively for compounds 2 and 3). In addition, at the level of Caco-2 cells, there would be a phenomenon of efflux induced by the P-Glycoprotein which would tend to reduce the absorption of its substrate molecules (P-GP probability: 0.46 for the compound 3).

c. Metabolism profile

The predictions on metabolism of these products by the ACDlabs and ADMETlab software in Table 5 reveal that although compound (1) is 2 times less likely (HLM: 7) to be metabolized than the 2 others (HLMS: 14), it appears that it is not a good substrate for CYP isoforms and may not be able to inhibit CYP drug metabolism (**Table 5**). The products would be eliminated on metabolites forms but there would also be a high probability that compound (1) also be eliminated on unchanged form. Compound (1) would not have any enzymatic inhibitory effects. On the other hand, the probabilities that compounds (2) and

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(3) are substrates for CYP3A4 are high (0.9 and 1 respectively) and those of inhibiting it are low (0.22 and 0.16 respectively). Only compound (3) would have a low probability to inhibit CYP 2C19 and 2C9 (0.32 and 0.2 respectively). In addition, it would be unstable with respect to metabolism due to the effect of the first liver passage.

Table 2: *physico-chemical descriptors MW, HBA, HBD, NRB and TPSA.*

N°	MW			HBA			HBD			NRB	TPSA (A^2)		
	A	S	P	A	S	P	A	S	P	S	A	S	P
1	178.21	178.21	178.21	3	3	2	1	1	1	1	37.3	40.54	76.81
2	542.62	542.63	542.62	9	9	9	1	1	1	14	102	105.82	228.08
3	502.43	520.53	520.53	10	11	10	1	2	1	1	147.19	147.19	212.62

Table 3: *solubility descriptors Log P(o/w), Log Sw, S, pKa, LogD.*

N°	Log P(o/w)			Log Sw (pH=7)		S (pH=7, mg/ml)		S (pH=7, mg/ml)		pKa	LogD
	A	S	P	A	S	A	S	A	S	A	A
1	2.12	0.47	1.04	-	-1.76	-	-1.76	-	3.08	8.1	-3.61
2	7.26	5.33	6.17	- 8.8	- 8.61	- 8.8	- 8.61	1.38	1.33	9.61	6.38
3	- 0.8	1.21	0.14	- 1.08	2.63	- 1.08	2.63	1.6	1.22	11.2	-0,87

Table 4. *key parameters which describe the absorption and Distribution.*

Parameters	Absorption					Distribution			
	BB penetration		Log P caco-2 (pH=7)	Bioavailability (%) (D=10mg)		Vd (L/kg)	P-Gp substrate probability	PPB (%)	Fu (%)
Software Compounds	**A (Log)**	**S**	**A**	**A**	**S**	**L**	**A**	**L**	**L**
1	- 0.88	Yes	1.51	97.73	55	1.52	0.6	28.79	78.89
2	- 0.22	No	12.1	1.63	55	0.43	0.16	92.50	10.0
3	- 0.37	No	9.98	<30%	17	0.36	0.46	29.19	47.23

Table 5: *metabolism parameters values of compounds predicted by ACDlabs (A), ADMETlabs (L) software.*

Parameters	First liver passage		HLMS	Metabolism (CYP value IC_{50} < 10 µM) probability																	
				Substrate										Inhibitor							
				CYP2C9		CYP2C19		CYP2D6		CYP3A4		CYP1A2		CYP2C19		CYP2C9		CYP2D6		CYP3A4		CYP1A2	
Software Compounds	**A**	**L**	**A**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**	**A**	**L**
1	0.11	-	7	0.03	No	0.02	No	0.06	No	0.01	No	0.04	No	0.02	No	0.02	No	0.01	No	0.01	No	0.04	No
2	0.12	-	14	0.02	Yes	0	No	0.06	No	0.9	Yes	0.07	No	0.32	Yes	0.2	Yes	0.01	No	0.22	Yes	0.07	No
3	0	High	14	0	No	0	No	0	No	1	No	0	No	0.03	No	0	No	0	No	0.16	No	0	No

Very low (green); high (red)

d. Elimination profile

Metabolism predictions indicate that compounds (2) and (3) would be eliminated as metabolites. The elimination parameters (Clearance, Half-live time) and acute toxicity (probability to block hERG channels, LD_{50}, Ames Test) of compounds (1), (2), and (3) were predicted by the ACDlabs and ADMETlabs software (**Table 6**). The 3 compounds would be eliminated by kidney with a very low flow rate (< 15ml/min) and have a very short elimination half-time life ($T_{1/2}$<1 hour).

e. Toxicity profile

Concerning their toxicity (**Table 6**), only compound 2 has a high probability of blocking hERG potassium channels in the heart and the predicted LD_{50}

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(mg/kg) vary from 1.6 to 3.44 for the 3 compounds in oral, intraperitoneal administration in rats and mouse.

Compounds	Cl (ml/min/Kg)	$T_{1/2}$ (H)	hERG Inhibitor probability	LD_{50} (mg/kg)						Ames test probability
	L	L	A	Rat IP	Mouse IP	Rat Oral	Mouse Oral	Rat IV	Mouse IV	Mouse IV
1	13.66	0.93	0.01	2.29	2.19	3.02	2.91	2.04	-	-
2	3.89	0.34	0.75	3.27	2.8	3.44	3.31	2.08	-	-
3	4.43	0.84	0.01	2.16	1.96	1.66	2.15	0.35	1.6	1.6

Discussion

The ADMET parameters predicted by ACDlabs were similar to those of SwissADME (S) and ADMETlab (L) software considered as online reference software[10].

For the 3 software used, only compound (1) would be able to cross the biological membranes and have good permeability while the compound (3) would have poor absorption [23,26]. According to the SwissADME reference software, the 2 compounds (1 and 3) also would not have good absorption compared to Lipinski data. The value of the pKa predicted > 7 indicates that the 3 compounds are acidic. This suggests that part of the molecules would be absorbed in the stomach, but the most important would be absorbed in the intestinal level[28]. However, compounds (2) and (3) would be very soluble because the solubilities in predicted water (1.38 mg/ml and 1.6mg/ml respectively) are less than 1g/ml [28]. They therefore have a hydrophilic character. Furthermore, the number of times that the 3 compounds violate the rule of 3 (MW≤300, Clogp ≤ 3, rotating links ≤ 3 HBD ≤ 3, HBA ≤ 3 (PSA) ≤ 60A°^{2}) is 0 (for compound 1), 3 (for compound 3) and> 3 (for compound 2). This means that compounds 1 and 3 would have lead-likeness properties.

The predicted data of absorption and distribution suggest that the 23 (*s*)-isolimonexin and the decyloxycicuscosin D are not good candidates drugs for the oral galenic forms. Nevertheless, it is possible to improve their bioavailability by using

hydrophobic galenic formulations to be administered intramuscularly or intra rectal allowing the first hepatic passage, coating formulations (for compound 3) or by modifying the properties physico-chemicals of the molecule as is the case with the pro-drugs [28]. On the other hand, the Formyl-5-Hydroxy-N-Methylindolin-1-Ium (1) would be a good drug candidate for oral forms (oral Availability: 97.73%). This oral absorption percentage close to 100% as well as the probability that this molecule has to cross the Blood Brain Barrier complies with the data reported on the Indole alkaloids [23,29]. Concerning the apparent Volume of distribution (Vd), the predicted values for the 3 molecules are included in the range values of the known drugs (between 0.06 l/kg and 20 l/kg) [28]. Decyloxycleomiscosin D would have a strong plasma proteins binding (92.5%). This PPB value is comparable to those of Digitalin (cardiotonic), Aspirin (NSAIDs) and Oxacillin (antibiotic) [28]. and suggests that the concomitant consumption of Decyloxycleomiscosin D and these drugs or any other P-Gp substrates drugs like antiarrhythmic (Quinidin, Propafenon), statins (Atorvastatin, Simvastatin), calcium channel blockers (Diltiazem, Verapamil, Nicardipine, β-blockers (Celiprolol, Tanilolol), Quinolones (Levofloxacine, Sparfloxacine) [19] would induce an exacerbation of their toxic effects by competition in P-Gp receptors.

23(s)-isolimonexine and Decyloxycleomiscosin D would have enzymatic inhibitory effects on CYP3A4. Which suggests that the administration of one or the other molecule concomitantly with other substrates of this isoform (Benzodiazepines, Tricyclic antidepressants, Opioid analgesics, Dihydropyridines, Protease inhibitors, Statins, Immunosuppressants) would reduce the metabolism of these substrates [30]. As a result, they could be found in abnormal concentrations in the blood and cause toxic effects. Similarly, 23(*s*)-isolimonexine could increase the concentrations of Cytochrome P450 CYP 2C9 isoenzyme substrates

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like Non-steroidal Anti-flammatories (Ibuprofen, Diclofenac), Sartans (Valsartan), oral hypoglycemics (Glibenclamide, Glicazide, Glimeripide) and 2C19 isoenzyme substrates like benzodiazepines, H-pump inhibitors, imipramine antidepressants (Imipramine).

1-Formyl-5-hydroxy-N- methylindolin-1-ium and 23(*s*)-isolimonexine, may not induce arrhythmias and cardiac arrest by lengthening the repolarization interval between cardiac QT waves by acting on hERG potassium channels like observed in most drugs [31]. On the other hand, it is possible that Decyloxycleomiscosin D induce the blockage of these channels. Therefore, concomitant administration of Decyloxycleomiscosin D with other hERG potassium channel drugs blockers (such as artemisinin-based combinations used in the treatment of malaria) could exacerbate the risk of inducing arrhythmias. The LD_{50} (mg/kg) varying from 0.35 (IV) to 3.44 (oral route) in rats, suggest that the toxic doses of these compounds are almost the same when administered orally or intraperitoneally. On the other hand, by the IV route, the toxic doses are lower (generally 1 mg compared to the oral route for compounds (1) and (2) or almost 2 mg for compound 3). Therefore, the Maximum Daily Doses Recommended (MDDR) which define the toxicity threshold should be < 2 mg/kg when the products are administered by IP, oral or IV route (compounds 2 and 3) and < 0.35 for the compound (3) administered by IV route. This MDDR therefore being between 1 and 50 mg/kg would classify these 3 molecules in category 2 on the Hodge and Sterner scale corresponding to highly toxic molecules. However, predicted oral LD_{50} < 500 mg/kg would reduce oral toxicity by classifying the molecules as moderately toxic [312]. However, this very low toxic threshold would tend to reduce the therapeutic index in particular for the compound (2) which has a very strong Plasma Proteins Binding and all these compounds which appear very fleeting ($T_{1/2}$ < 1H) would require several daily doses or forms with prolonged release in order to maintain the plasma concentration within the therapeutic range. Furthermore, these compounds also have a low probability to induce gene mutations (Ames test probability ≤ 0.25).

Conclusion

The pharmacokinetic profile of tree new compounds with cytotoxicities effects (1-Formyl-5-hydroxy-N-methylindolin-1-ium, 23(s)-isolimonexine and Decyloxycleomiscosin D) defined by the software revealed that 1-Formyl-5-hydroxy-N-methylindolin-1-ium have good drug-like and lead-like properties. It would therefore be a good drug candidate for all galenic forms. On the other hand, 23(*s*)-isolimonexine and Decyloxycleomiscosin D are not good drug candidates for oral forms but it is possible to improve their pharmacokinetic properties by structural modifications such as the introduction of hydrophobic groups, or hydrophobic formulations, or coating formulations (23(*s*)-isolimonexin). However, due to their hydrophilic nature, 23(*s*)-isolimonexine and Decyloxycleomiscosin D would be good drug candidates for the IV route. 23(*s*)-isolimonexin has also a good lead-like properties. The three molecules would be highly toxic with a low therapeutic margin and 23(*s*)-isolimonexine and Decyloxycleomiscosin D would have enzymatic inhibitory effects on CYP3A4. Consequently, it would also be preferable to use sustained release forms not only to limit the toxic risk which could be induced by several administrations close together due to the short half-lives of these molecules, but also to maintain an effective concentration.

Author Contributions

Conceptualization: F.A.E.M., **methodology:** F.A.E.M., **validation:** D.B.M., J.D.W., and J.C.N., **formal analysis:** F.A.E.M., D.B.M., J.D.W., and J.C.N.; investigation: F.A.E.M., M.H.J.N and L.N., **writing - original draft preparation:** F.A.E.M., **writing - review and editing**: D.B.M., J.D.W., E.M.M, and J.C.N., **supervision**: D.B.M., **funding acquisition**: F.A.E.M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: None

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