

Prediction of structure-Pharmacokinetic-toxicity relationship of a new indol alkaloid isolated from stembark of *Strychnos johnsonii* (Loganiaceae)

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INTRODUCTION

Drug development is an expensive, difficult and sometimes inefficient process. However, the constraints related to this process tend to be reduced in the early stages of drug development. Indeed, computational approaches have been developed and guide researchers towards the most active and best tolerated molecules as well as the most suitable dosage forms and drug uses.

In this work, we isolated a new indol alkaloid from the stembark of *Strychnos johnsonii* (Loganiaceae) harvested in Cameroon and used computational approaches to predict his structure-pharmacokinetic-galenic pharmacy relationships.

AIM

Study structure-Pharmacokinetic-toxicity relationship of a new indol alkaloid in order to research the drug like and lead like properties.

METHODOLOGY



Fig.1: Chromatographic column

A phytochemical study was carried out on the stem barks of *Strychnos johnsonii* using chromatographic methods (Column and TLC). And the structure of the isolated compound were determined by a complete 1D and 2D NMR spectroscopic analysis and by a comparison with published data.

Then, the descriptors of ADMET parameters of the isolated new compound were predicted by QikProp software.

ADMET	Descriptors/parameters
Physico chemical properties	MW, HBD, HBA, TPSA, Log P, Log S, S, pKa, Log D
Absorption	Caco-2, Pgp binding, Bio availability
Distribution	Log BB, PPB, Vd, Fu
Metabolism	CYP P450 inhibition, HLM sites
Elimination	T 1/2, Cl
Toxicity	hErg, AMES Test

1 Selection of ADMET parameters

2 Identification of the compounds
Drawing the structure

3 Selection of compounds and drugs with similar chemical formula

4 Experimental procedure
Smile decoded → instructions software

5 Data analysis
Lipinski Rules of 3 & 5, medicinal chemistry properties

Fig.2: Schema of ADMET parameters prediction

RESULTS

Structure elucidation

Yellow powder obtained in a mixture of *n*-Hexan/EtOAc (8.5 :1.5).

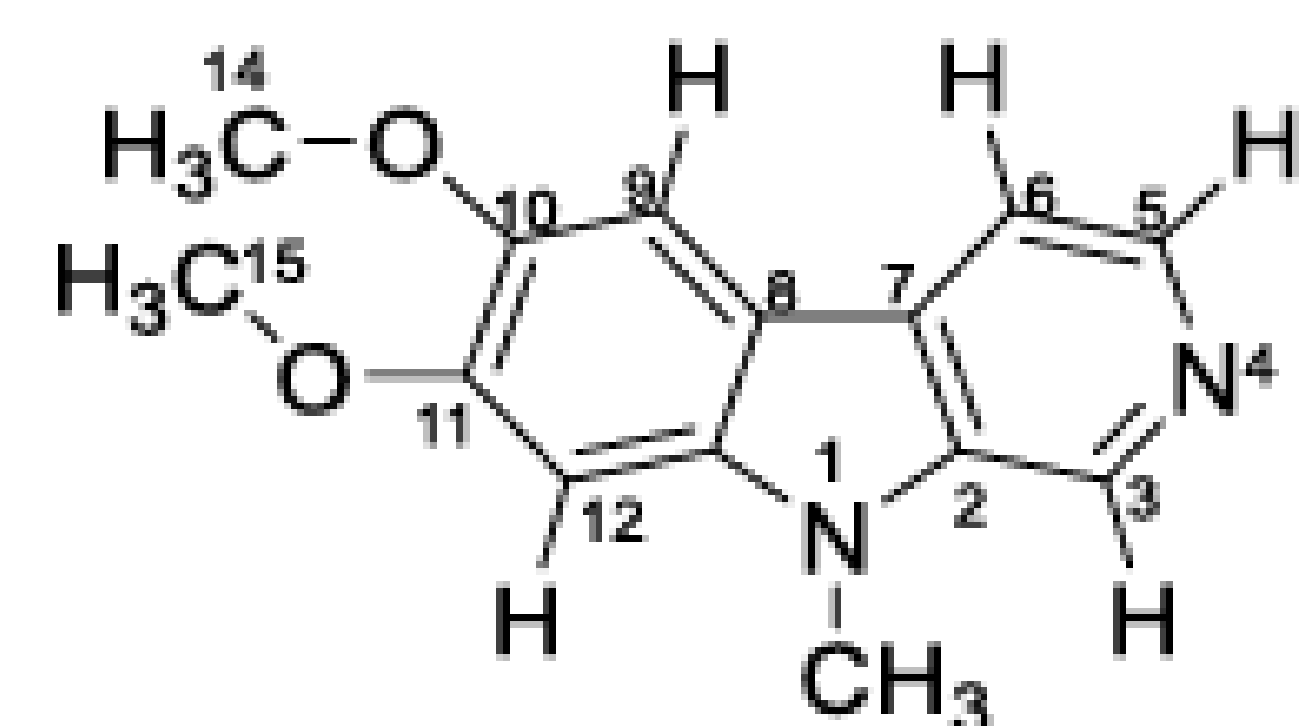


Fig.3: Structure of the isolated compound 10,11-dimethoxy-N₁-β-methylcarbolin

Structure-ADMET relationship Prediction

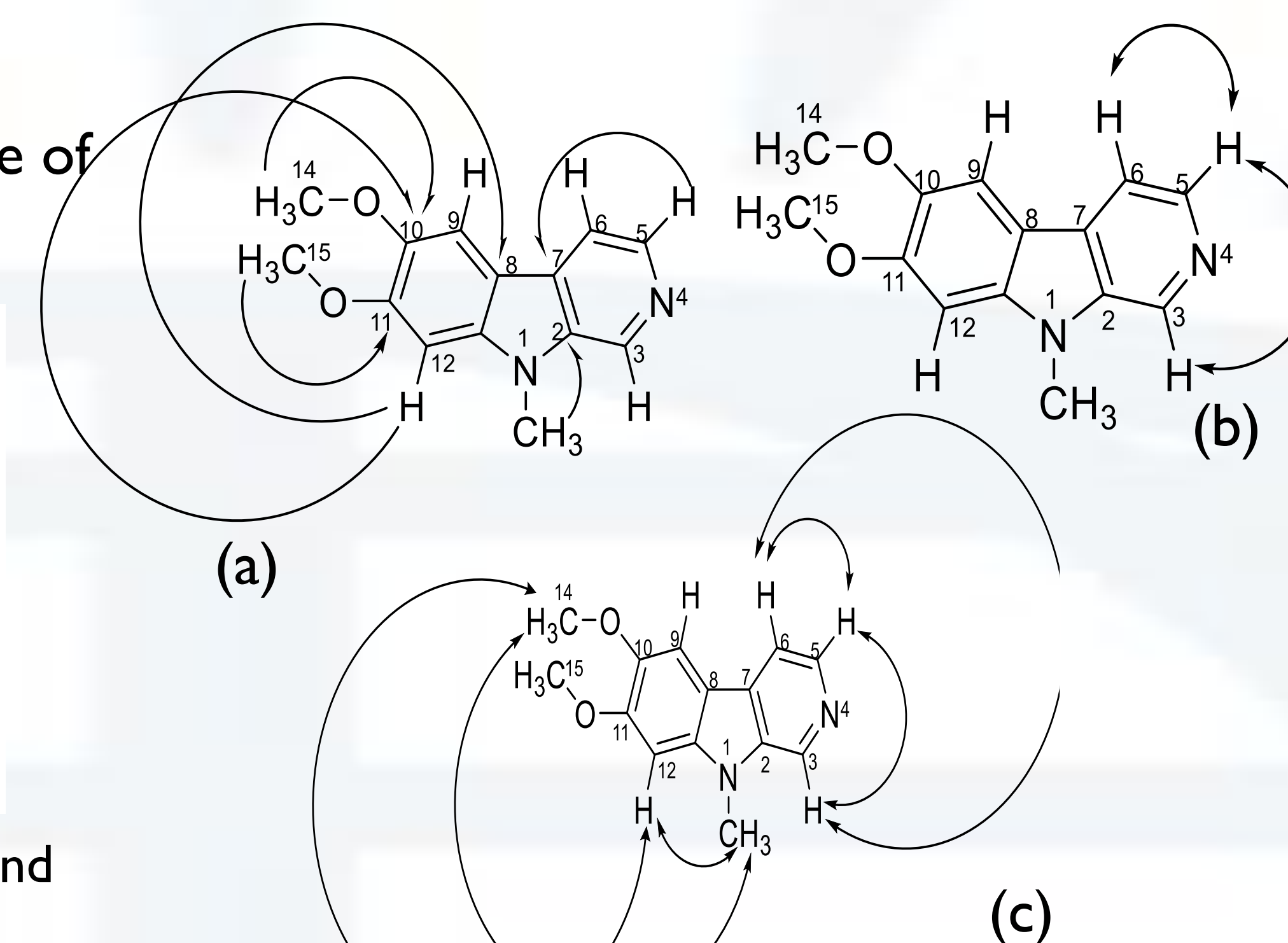


Fig.4: HMBC (a), COSY (b) et NOESY (c) correlations of the 10,11-dimethoxy-N₁-β-methylcarbolin

Table 2: Physicochemical, Absorption and Bio availability descriptors predicted by QikProp software.

Physicochemical & Distribution					Metabolism	Elimination	Toxicity
HBD	HBA	PSA (Å ²)	logKhsa	logKp	Métabolites	MDCK	Log IC ₅₀ hERG
0	3	28,8	0,09	-1,15	3	2991,5	-4,95

Table 3: Physicochemical, Distribution, Metabolism, Elimination and Toxicity descriptors predicted by QikProp software

#stars	MW (Da)	SASA (Å ²)	FOSA (Å ²)	FISA (Å ²)	Volum e (Å ³)	logP	logS	CNS	logBB	Caco-2	PHOA
0	242,2	481,7	252,2	28,7	813,1	3,2	-3,44	1	0,19	5285,1	100

#Stars: Number of properties or values described out of the range of known similar drugs

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DISCUSSION

1. Structure elucidation

Spectra analysis given the chemical formula C₁₄H₁₄N₂O₂ with signals of

5 aromatic protons (H-3, H-5, H-6, H-9 and H-12), N-méthyl proton and 2 methoxyl protons (Fig. 3)

These protons characterize an indol structure[1] confirmed in DEPT et NMR¹³C with

One N-méthyl carbon (C-1), 2 Oxyméthyl carbones (C-13 and C-14) and 11 aromatic carbons : (C-2), (C-3), (C-5), (C-6), (C-7), (C-8), (C-9), (C-10), (C-11). (C-12), and (C-13), (Fig. 3)

The position of carbons in the final structure (Fig. 4) based on the COSY, HSQC, HMBC, and NOESY correlations spectra

2. Structure – pharmacokinetic & toxicity predictions

10,11-diméthoxy-Na-méthyl-β- Carbolin would be able to cross biological membrane and have a good bio availability [2, 3]. Results similar to those observed to the *Areca catechu* and tropanic alkaloids [4,5]

The oral and IV bio availability of the new compound are both comparable.

The molecule does not violate Lipinski's rule of 3, thus predicting that it would be a good leader [6].

Based on toxicity predictions, unlike most drugs that cause arrhythmias and cardiac arrest by prolonging the repolarization interval between cardiac QT waves through action on hERG potassium channels [7] the new compound isolated may not have these adverse effects.

Activity at the level of the Central Nervous System may induce the Antiparkinsonian and Anticonvulsant effects already observed in the indole alkaloid family [5]. On the other hand, the prediction of high renal elimination (about 6 times normal compared to that of known drugs) suggests that the molecule could be harmful to the kidney, or even lead to renal failure.

CONCLUSION

The phytochemical study of the stembark of *Strychnos johnsonii* led to the isolation of a new indol alkaloid (10,11-dimethoxy-N1-methyl-β-carboline)

This indol alkaloid showed properties of good lead like and drug like candidate.

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