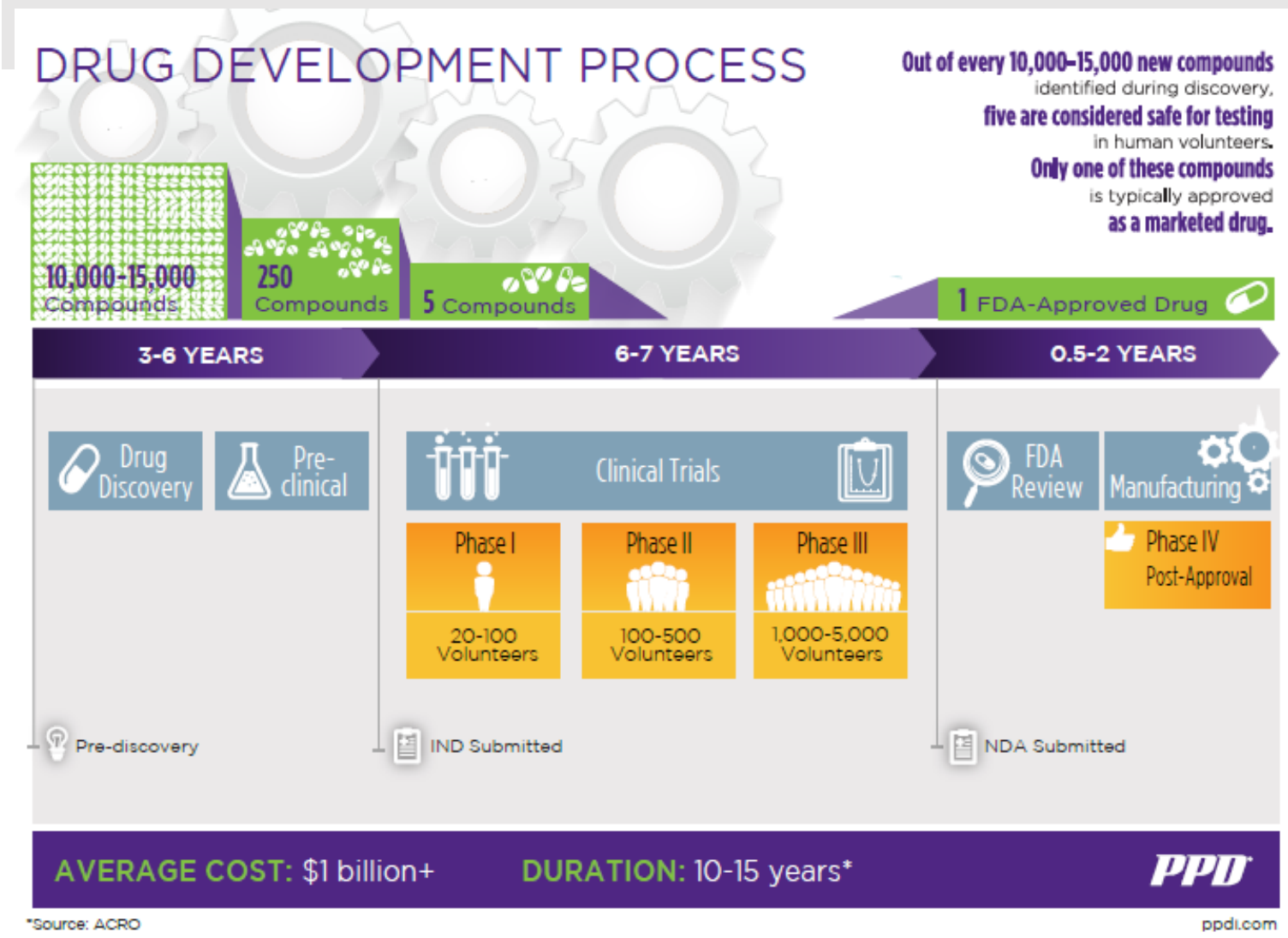


Computational investigation of the hERG channel blocking profile of iboga-indole alkaloids

Smith B. Babiaka^{1,2}, Conrad V. Simoben³, Kennedy O. Abuga⁴

¹Department of Chemistry, University of Buea, Buea, Cameroon, ²Department of Microbial Bioactive Compounds, Interfaculty Institute of Microbiology and Infection Medicine, University of Tübingen, Tübingen, Germany, ³Structural Genomics Consortium, University of Toronto Toronto, Ontario M5G 1L7, Canada, ⁴Department of Pharmaceutical Chemistry, Pharmaceutics and Pharmacognosy, Faculty of Health Sciences, University of Nairobi, Nairobi, Kenya.

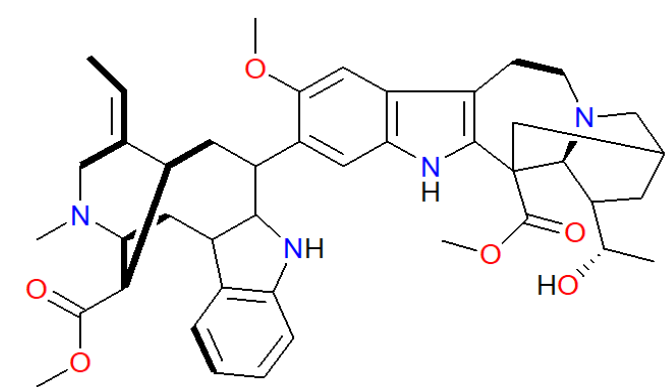
BACKGROUND



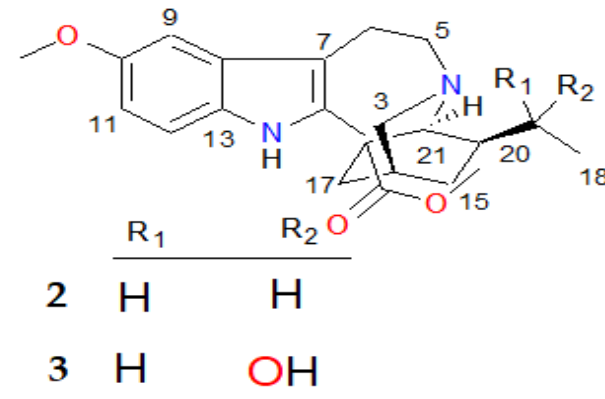
- ❑ The hERG channel is a voltage-gated K⁺ channel playing an essential role in the normal electrical activity in the heart.
- ❑ This ion channel has emerged as an important antitarget in early drug discovery and development.
- ❑ Blockage of hERG K⁺ channel has then become a severe limitation for the introduction of new drugs in the market (Kratz *et al.*, 2017)
- ❑ Terfenadine, sertindole, cisapride and astemizole have been withdrawn from the market because of hERG channel blocking profile (Kamiya *et al.*, 2008; Killeen *et al.*, 2009; Siramshetty *et al.*, 2016)

RATIONALE

- ❑ Recently, voacangine has been identified as a potent blocker of the hERG cahnnel, IC₅₀ of 0.30 µM in HEK293 cells (Mair *et al.*, 2016).



Voacarine



Voacangine (2)
Voacristine (3)

- ❑The hERG channel blocking profile of NPs is often

neglected.

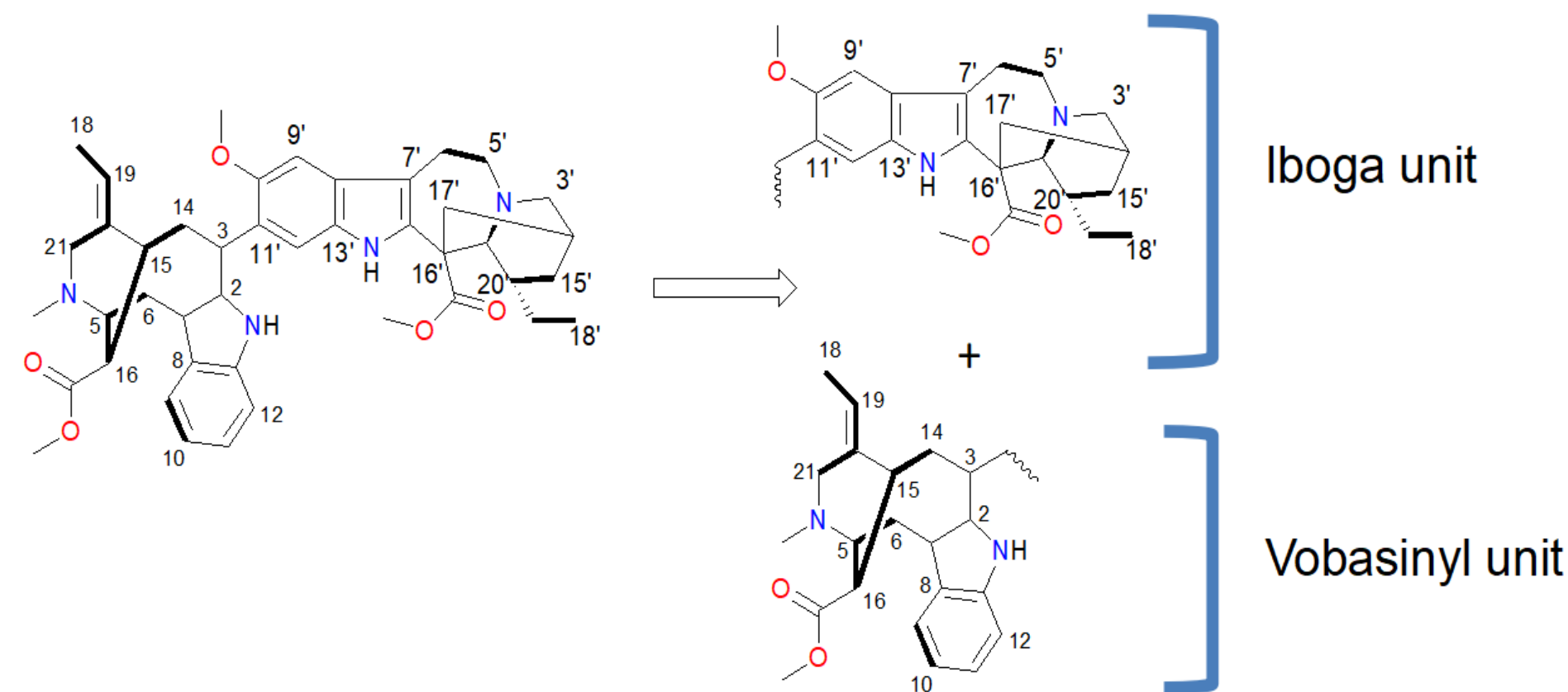
- ❑This has prompted us to assess the hERG channel related toxicity of iboga alkaloids in order to identify safety liabilities of botanicals.

- ❑ Perform an assessment of log (hERG) of 70 iboga alkaloids using Deep Learning and Qikprop software.

RESULTS/CONCLUSIONS

Compound	a#stars	clogHERG
New isomer	12	-8.74
Voacangine	0	-6.12
Coronaridine	0	-6.24
Voacamine	12	-8.75
Voacarine	12	-8.76
Conoduramine	12	-8.56

PERSPECTIVES



- ❑ All the bisindole alkaloids are hERG channel blockers, aromatic rings and hydrophobic interactions are the hERG channel blocker pharmacophore. Further in vivo studies are warrantable to assess the cardiotoxicity of the iboga indole alkaloids.
- ❑ Predicted IC₅₀ value for blockage hERG K⁺ channels (concerns < -5 (Duffy *et al.* 2000; Jorgensen *et al.* 2002).

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