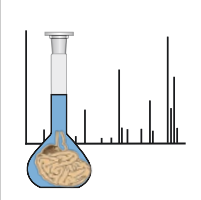
doi:10.2533/chimia.2019.206 Chimia 73 (2019) 206



Highlights of Analytical Sciences in Switzerland

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Piperine Analogs as Modulators of the Central Nervous System

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Keywords: $GABA_A$ · *In vitro* metabolism · Piperine analogs · Silensomes · UHPLC-MS/MS · UHPLC-QTOF-MS

Central nervous system-active drugs such as benzodiazepines or the so-called Z-drugs act *via* an allosteric modulation of $GABA_A$ receptors. However, these drugs have well-known side-effects which largely result from their lack of $GABA_A$ receptor subtype selectivity. Therefore, drug discovery efforts in this field are directed towards identifying subtype-selective $GABA_A$ receptor modulators to overcome the limitations of existing drugs. In a library screening for $GABA_A$ modulatory natural products, we identified some years ago piperine as a positive allosteric modulator which interacted with a benzodiazepine-independent binding site, which was compliant with Lipinski's rule of five, and which showed *in vivo* activity in rodents. Given that piperine is also an activator of TRPV1 (transient receptor potential vanilloid type 1) receptors involved in pain signaling and thermoregulation, systematic structural modifications of the parent structure were carried out in several cycles of optimization, aiming at separating $GABA_A$ modulatory from TRPV1 activity.

To guide further structural modifications, biopharmaceutical properties of selected compounds from three cycles of optimization were assessed. Using fit-for-purpose bioanalytical UHPLC-MS/MS methods and UHPLC-QTOF-MS, we evaluated i) metabolic stability and metabolite formation in microsomal incubations, ii) performed CYP450 (cytochrome P450) reaction phenotyping in Silensomes, and iii) determined unbound fraction in whole blood using rapid equilibrium dialysis.

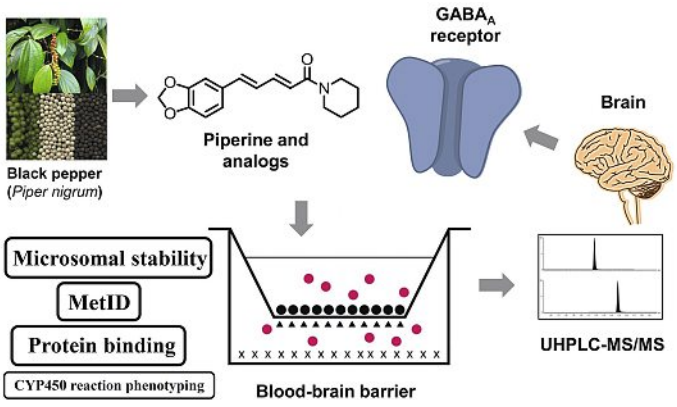
Piperine analogs (SCT-29, LAU 397, and LAU 399) were rapidly metabolized, with a significant contribution of the highly polymorphic CYP2C9 (which would lead to a highly varying drug response between individuals) and showed strong binding to blood constituents (which in turn would result in a low hepatic extraction ratio).

Therefore, the next cycle of medicinal chemistry optimization focuses on lowering lipophilicity, in order to decrease metabolic liabilities and extensive protein binding.

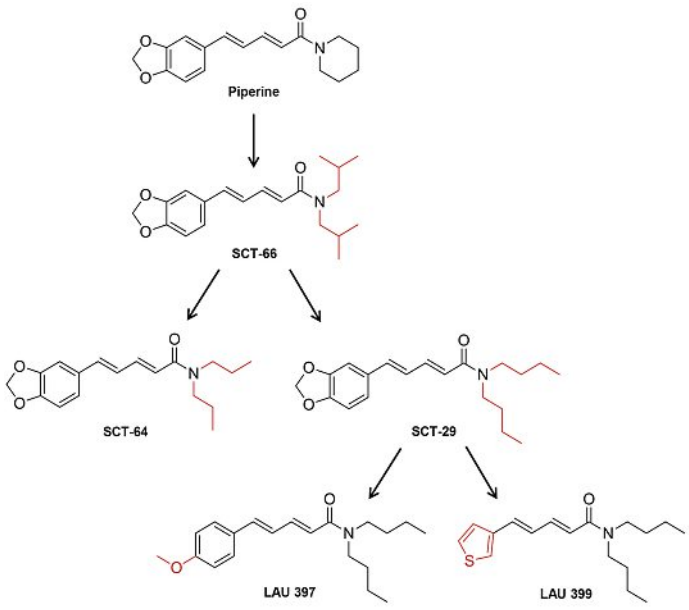
Received: January 4, 2019

Reference

V. Zabela, T. Hettich, G. Schlotterbeck, L. Wimmer, M. O. Mihovilovic, F. Guillet, B. Bouaita, B. Shevchenko, M. Hamburger, M. Oufir, *J. Chromatogr. B* **2018**, *1072*, 379.



Drug-like properties optimization of piperine (from *Piper nigrum*) and analogs as $GABA_A$ receptor modulators using various drug metabolism and pharmacokinetics assays.



Chemical structures of piperine and selected analogs from three cycles of optimization.

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