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Short communication

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Bioinformatics-Guided *In Vitro* Method to Demonstrate the Inhibition of Cardiovascular Drug (R)-Rivaroxaban towards Cytochrome P450 (CYP) 3A4

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***SUMMARY*. The present study aims to investigate the inhibition behavior of (R)-rivaroxaban towards of cytochrome P450 (CYP) 3A4 using bioinformatics-guided *in vitro* method. Supposed that (R)-rivaroxaban has similar structure with ketoconazole, the structure of (R)-rivaroxaban was docked into the activity site of CYP3A4 from which ketoconazole was extracted. From multiple confirmations of (R)-rivaroxaban, the best orientation exerts close distance (1.85 Å) with the catalytic center of CYP3A4. The amino acids forming the interaction with (R)-rivaroxaban are consisted of Ser119, Thr309, and Phe304, and several hydrogen bonds formed between amino acids and the structures of (R)-rivaroxaban. The co-docking of (R)-rivaroxaban and ketoconazole was carried out, and the results showed that (R)-rivaroxaban has closer distance (1.85 Å) than ketoconazole (2.1Å), indicating that (R)-rivaroxaban is a strong inhibitor. *In vitro* experiment showed that (R)-rivaroxaban inhibited CYP3A4-catalyzed midazolam metabolism. In conclusion, much attention should be given to the drug-drug interaction between (R)-rivaroxaban and the good substrates of CYP3A4.**

RESUMEN. El presente estudio tiene como objetivo investigar el comportamiento de inhibición de (R)-rivaroxaban hacia el citocromo P450 (CYP) 3A4 utilizando un método *in vitro* de bioinformática guiada. Dado que (R)-rivaroxaban tiene una estructura similar al ketoconazol, (R) -rivaroxaban se ancló en el sitio activode CYP3A4 cuando se extrajo el ketoconazol. De múltiples confirmaciones con (R) -rivaroxaban, la mejor orientación se ejerce a corta distancia (1,85 Å) con el centro catalítico de CYP3A4. Los aminoácidos que interaccionan con (R)-rivaroxaban son Ser119, Thr309 y Phe304, con varios enlaces de hidrógeno formados entre los aminoácidos y las estructuras de (R)-rivaroxaban. También se llevó a cabo el co-acoplamiento de (R)-rivaroxaban y ketoconazol y los resultados mostraron que (R)-rivaroxaban tiene una distancia más cercana (1,85 Å) que el ketoconazol (2.1 Å), lo que indica que (R)-rivaroxaban es un fuerte inhibidor. Los experimentos *in vitro* mostraron que el metabolismo de midazolam catalizado por CYP3A4 resulta inhibido por (R)-rivaroxaban. En conclusión, se debe prestar mucha atención a la interacción fármaco-fármaco entre (R)-rivaroxaban y los buenos sustratos del CYP3A4.

KEY WORDS: rivaroxaban, enantiomers, cytochrome P450 3A4, docking

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