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Computational approach for predictions of site of metabolism of colchicine and new indole–quinoline derivative as anticancer agent

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ABSTRACT The optimization of pharmacokinetic properties is vital in drug development, necessitating comprehensive metabolism studies to predict effective therapeutic doses. In contemporary research, *in silico* and mechanistic approaches are increasingly employed to design molecules and anticipate their metabolic pathways. This study focuses on the investigation of potential sites of metabolism (SOMs) of new indole–quinoline derivatives and colchicine. *In silico* methodologies were used to identify the potential **SOMs** for both compounds, corroborating our findings through docking studies against various cytochrome P450 (**CYP**) isoforms. The results were further validated through molecular docking studies using AutoDock, followed by molecular simulations conducted with Internal coordinates normal mode analysis server (**iMOD**). Biotransformer 3.0, suggested 13 possible metabolites for colchicine mainly due to *O*-dealkylation mediated by **CYP1A2** and **CYP2C9** while 12 metabolites resulted from the indole-quinoline derivative mainly by hydroxylation and *O*-dealkylation reactions facilitated by **CYP1A2, CYP2C9** and **CYP3A4** enzymes. Docking studies concluded that both compounds have better affinity towards **CYP1A2** and **CYP2C9** than standard. The results suggest how colchicine and indole-quinoline derivatives are metabolized and stress the need of **CYP** enzyme interactions for these pathways. The results of our biotransformation computation study pointing toward understanding the metabolic pattern of colchicine and indole-quinoline derivative and future directions include experimental validation of predicted metabolites using *in vitro* or *in vivo* systems. These insights can be integrated into absorption, distribution, metabolism, excretion, and toxicity profiling to optimize drug-like properties and minimize potential toxicity.

KEY WORDS Biotransformation, Cytochrome P450, Molecular docking, Sites of Metabolism.

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