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THE USE OF LIPINSKI'S RULE OF FIVE AND CHEMGPS-NP TO ESTIMATE THE LEADLIKENESS OF CYTOTOXIC TRICYCLIC COMPOUNDS

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Introduction: Cancer pharmacotherapy is improving each year. However, severe side effects are still quite evident. In addition, antineoplastic agents are usually administered intravenously. This can be very uncomfortable, since an IV line usually must be placed each administration. In this sense, the search for new oral anticancer drugs, less toxic to normal cells, is relevant. Natural products (NPs) arise as a promising source of cytotoxic compounds, mainly due to their unique heterocyclic rings and aromaticity. Fused tricyclic backbones, such as the xanthones and anthraquinones, call the attention for their pharmacological potential, considered preferred platform for the development of new drugs. Therefore, in this study, the Lipinski's rule of five (R5) and chemical global positioning system-natural products (ChemGPS-NP), a Principal Component Analysis-based technique used to predict bioactivity and pharmacokinetic properties of NPs, were used to estimate the leadlikeness of tricyclic NPs and derivatives. This allowed to indicate the most promising class of tricyclic NPs to develop oral anticancer agents. **Methods:** 706 cytotoxic tricyclic compounds were retrieved from the literature, selected based on their potency (IC_{50} < 20 µM) and on evaluation method (MTT 48h), mainly belonging to abietane, acridine, anthraquinone, carboline, phenanthrene, and xanthone classes. Compounds were drawn using ChemDraw Ultra 12.0 software (CambridgeSoft, Cambridge, MA, United States) and physicochemical properties were calculated. SMILES codes were generated and used to estimate compounds' distribution in chemical space, by ChemGPS-NP (http://chemgps.bmc.uu.se). Twenty seven oral chemotherapeutic agents approved by the FDA were used as references. **Results:** Eighty three percent of tricyclic NPs and derivatives complied with R5 (9% higher than the drugs). Histograms demonstrated that most non-complying NPs violated both molecular weight and logP. Based on ChemGPS-NP, it was possible to observe that the acridines, carbolines and phenanthrenes seemed to not cluster properly with drugs' chemical space. On the other hand, abietanes anthraquinones and xanthones seemed to be the most promising classes, falling into drug-like space. Histogram analysis of these classes highlighted that 30% of anthraquinones and more than 50% of abietanes did not follow R5. Instead, only 7% of xanthones did not comply for R5. **Conclusion:** Considering both ChemGPS-NP positioning, as well as physicochemical histograms and R5 compliance, xanthones were highlighted as a promising source of novel anticancer compounds with oral bioavailability.

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