

Area: ORG **Heterocyclic Aminochalcones as Anticancer Prototypes: *In Silico* Analysis of Structural and Pharmacokinetic Properties****Manuela Cosmo de Oliveira (IC),¹ Fátima de Campos Buzzi (PQ)².****manuelacosmo@edu.univali.br**¹Pharmacy Course, UNIVALI; ²PPGCF, UNIVALI.Key Words: *In silico*; aminochalcones; heterocycles.**Highlights**

Two aminochalcones containing furan and thiophene rings showed cytotoxic activity superior to doxorubicin and were identified as lead prototypes. Ten new chalcones were evaluated *in silico*, displaying suitable physicochemical and pharmacokinetic profiles for orally active drug development.

Abstract

Cancer remains one of the leading causes of death worldwide, and traditional treatments such as chemotherapy and radiotherapy have become progressively less effective due to multidrug resistance (MDR). This scenario reinforces the need for new chemotherapeutic agents, such as chalcone-derived compounds, which exhibit broad anticancer properties and the ability to act on multiple molecular pathways. These compounds emerge as promising alternatives to improve therapeutic outcomes compared with currently available therapies. Previous results obtained by our research group with two aminochalcones containing furan and thiophene rings demonstrated significant cytotoxic activity against different human neoplastic cell lines, MCF-7 (breast adenocarcinoma), MDROv (NCI-ADR/RES, multidrug-resistant ovarian cancer), and H460 (large cell lung carcinoma), showing superior results compared with doxorubicin, the reference drug. Based on these results, the study was expanded to include ten additional chalcones, evaluated *in silico*, which exhibited highly favorable pharmacokinetic and physicochemical profiles for drug development. The molecular weights ranged from 213 to 229 g/mol, and the topological polar surface areas (TPSA) ranged from 56 to 71 Å², indicating good membrane permeability. Meanwhile, LogP (XLOGP3) values between 2.0 and 3.3 revealed a suitable balance between lipophilicity and solubility, favoring passive diffusion. All compounds showed high gastrointestinal absorption, reinforcing their potential for oral bioavailability, and the metabolic profile indicated no inhibition of CYP3A4, reducing the risk of relevant drug interactions. The most promising chalcones were those containing a furan ring and variation of the amino group position between the meta and ortho positions, which exhibited parameters nearly identical to the active prototype molecule. This prototype displayed *in silico* data that stood out for its superior predicted solubility and narrower spectrum of CYP inhibition. The two new molecules showed similar molecular weight, TPSA, LogP, compliance with Lipinski's rules, and metabolic profile (inhibiting only CYP1A2 and CYP2C19), resulting in a safe and balanced profile. These molecules demonstrated high solubility (ESOL/AlI = Soluble), bioavailability of 0.55, and are considered ideal functional analogs for expanding structure–activity relationship (SAR) studies. Furthermore, the chalcone containing an amino group at the ortho position and a furan ring at position 3 showed physicochemical parameters within the ideal range for permeability, adequate solubility, and high gastrointestinal absorption. Although its synthesis is slightly more complex, it remains highly feasible and stands out as a promising candidate for future drug development. Thus, the results indicate that these three aminochalcones exhibit the most favorable balance of physicochemical and pharmacokinetic properties, underscoring their potential as lead structures for the synthesis of novel anticancer agents.

References:¹Chowdhary, S. et al. (2024). *Expert Opinion on Drug Discovery*, 19 (12), 1417–1437.**Acknowledgments**

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