II SIMPÓSIO INTERNACIONAL EM INVESTIGAÇÕES QUÍMICO-FARMACÊUTICAS

Itajaí-2019

Área: FAR 09

CARBAZOLES DERIVATIVES TO OVERCOME MULTIDRUG RESISTANCE: A BRAND-NEW CLASS OF SAFE AND EFFECTIVE ABCG2 INHIBITORS

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INTRODUCTION

The ABCG2 transporter is considered the most promising target to overcome multidrug resistance (MDR) in cancer. Nevertheless there are still no prosperous inhibitors of ABCG2 to be forwarded to clinical steps of drug development. Carbazol, an aromatic compound obtained from coal-tar distillation with many pharmacological activities, was reported as an inhibitor of CK2 protein, which is highly comprehended in numerous pathologies, including cancer. The circumstances presented above reveal the relevance of testing carbazoles derivatives (CDs) as ABCG2 inhibitors, aim of this study.

MATERIAL AND METHODS

Stably transfected cells to overexpress ABC transporters were used. Inhibition assays: cells were treated with mitoxantrone/CDs and the intracellular fluorescence was quantified by flow cytometry. Cell viability: according to MTT method; CDs cytotoxicity was evaluated in a range of 0.09-100 µM and the reversion assay was performed using 0.49 and 10 µM of CDs in co-treatment with SN-38 (0.1 nm-20 µM). ATPase assay: commercial kit. Confocal microscopy: cells treated with Hoescht 33342/CDs. Antibody 5D3 binding assay: flow cytometry.

RESULTS

All compounds showed great inhibition results (IC_{50} values: 0.49-3.39 µM), a selective profile for ABCG2 and a remarkable non-cytotoxicity (IG_{50} values higher than 100 µM). The most auspicious compound was established as a noncompetitive and substrate independent inhibitor with no allosteric effects. Its capacity to reverse the ABCG2-mediated resistance phenotype was verified after long-term assays, which are closer to clinical reality. Finally, molecular docking analysis demonstrated that the bonds between ABCG2 amino acid residues and the fused rings of the compound are mainly responsible for their interaction, emphasizing the importance of its hydrophobic core.

CONCLUSIONS

We identified the first carbazoles derivatives capable of inhibiting the ABCG2-mediated substrates transport with a potent, selective and non-cytotoxic behavior. Their ability to reverse the resistance mediated by ABCG2 enables future preclinical trials. Also, docking studies listed the prior chemical attributes that must be considered in future design of new compounds for this purpose.

ACKNOWLEGMENTS

CNPq (400953/2016-1), Fundação Araucária (Code 006-09/2016), CAPES (Finance Code 001), PPGCF-UFPR and LCDR team.

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