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Evaluation of cytotoxicity and antiviral effect of new oseltamivir analogues against influenza A virus

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The emergence of mutations on influenza A virus such as the H274Y, confers high resistance against neuraminidase inhibitors. Due to the above, we design new derivates of oseltamivir which increase the affinity on mutant variants and on many subtypes. The new arylic-oseltamivir derivates are targeted to a conserved amino acids group in the active site of neuraminidase (Arg118, Arg292, Arg371). According to bioinformatics tools, there are several interactions (pi-cation, pi-pi) between the arylic compounds and the aromatic or positively charged residues, which improve properties as stability and recognition of the oseltamivir. In order to confirm this, we evaluated the antiviral activity of these compounds on influenza AH1N1 virus. Based on virtual screening (molecular dynamics, docking studies) six compounds with the best scoring on Kd and ΔG, the best properties both physicochemical (Lipinski rules) and toxicological, were selected; these compounds were synthesized and then one of these was evaluated for inhibitory activity in vitro against influenza AH1N1 virus by the Enzychrom neuraminidase assay kit. The cytotoxicity of each compound was determined at different concentrations (250 μM to 5000 μM) in Vero, HeLa and MDCK cells by trypan blue and MTT assays at 24 and 48h. Furthermore, the antiviral activity of the compound (with p-hidroxylaniline group) was evaluated at minimal cytotoxic concentration by the titration of supernantant of infected MDCK cells (5 MOI). Finally, we analyzed the roughness surface of infected, treated and non-infected cells by Atomic Force Microscopy. We found that only two compounds were cytotoxic at 250 μM and the IC50 of the arylic compound tested was lower (75 μM) than the oseltamivir carboxylate (200 μM). Moreover, this compound (p-hidroxylaniline group) had the best antiviral activity (47% plaques reduction), compared with oseltamivir carboxylate (35% plaques reduction) (ANOVA one way, α 0.05). We conclude that a new oseltamivir derivate had better antiviral activity than oseltamivir carboxylate, as virtual screening predicted. The compounds showed no cytotoxicity at high concentrations and the best compound has better inhibitory effect than the oseltamivir at lower concentrations. However, it is necessary to verify the activity of these compounds in another influenza virus strains including H274Y mutant.

Biography

She is doctorate student in the area of Conservation Medicine at High School of Medicine of the National Polytechnic Institute in Mexico City. She is biochemical engineer and she has a master degree on health sciences. Currently she is in the 6th semestre of doctorate at the program on medicine research.

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