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IN VITRO CARDIOVASCULAR TOXICITY RISK ASSESSMENT OF NOVEL H₂S-DONATING ANTHRACYCLINE

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Background: Conjugation of doxorubicin (DOX) with H₂S-donors gave rise to novel anthracyclines, such as CC2790A, which failed to inhibit topoisomerase II and displayed more potent cytotoxic effect and higher intracellular retention than the parent compound in DOX-resistant U-2OS osteosarcoma cells (Chegaev et al., 2016).

The well known anthracyclines cardiovascular toxicity, however, might limit their use.

Methods: Therefore, the aim of this study was to investigate CC2790A-induced effects on the mechanical activity of fresh and cultured rat aorta rings, on Cav1.2 channel current (ICa_{1.2}) of aortic A7r5 cells as well its cytotoxicity on A7r5, endothelial EA.hy926 cells, and H9c2 cardiomyocytes (Chegaev et al., 2016; Fusi et al., 2016, a, b). DOX was used as reference compounds.

Results: At concentrations $\geq 1 \mu\text{M}$, DOX partially increased phenylephrine-induced contraction in fresh endothelium-intact rings, while CC2790A was ineffective. Conversely, in endothelium-denuded rings both drugs were ineffective. CC2790A and DOX did not affect the concentration-response curve to high KCl.

In arteries cultured with both drugs for 7 days, CC2790A blocked both phenylephrine- and high KCl-induced contractions at a concentration 10-fold higher than that of DOX.

CC2790A, at the maximum concentration tested of $10 \mu\text{M}$, exhibited a weak Ca²⁺ antagonist property in single A7r5 cells.

CC2790A and DOX exerted cytotoxic effects at concentrations $>1 \mu\text{M}$ or $>0.1 \mu\text{M}$, respectively in both EA.hy926 and A7r5 cells. DOX ($0.01\text{-}1 \mu\text{M}$), at variance with CC2790A ($0.1\text{-}1 \mu\text{M}$), induced cell cycle arrest in G₀/G₁ phase and significantly increased the proportion of cells in the sub-G₀/G₁ phase. Furthermore, it caused apoptosis, as confirmed by contrast phase microscopy (cell shrinkage, membrane blebbing, presence of apoptotic bodies and attachment loss), by phosphatidylserine externalization (Annexin-V/propidium iodide labelling) as well as DNA fragmentation (DAPI staining).

CC2790A, retained within H9c2 cells like DOX, was significantly less toxic and produced lower amounts of intracellular reactive oxygen species than the lead.

Discussion: In conclusion, CC2790A is a novel H₂S-donating anthracycline characterize by a more favourable toxicological profile and a better efficacy towards drug-resistant cells. In the context of earlier attempts to use H₂S-donating drugs in cancer therapy, CC2790A is worthy of further investigations in preclinical and clinical settings.

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Chegaev et al. (2016). *J Med Chem.* 59(10):4881-9.

Fusi et al. (2016). *Naunyn Schmiedebergs Arch Pharmacol.* 389(9):1033-43.

Fusi et al. (2016). *Basic Clin Pharmacol Toxicol.* 120(5):434-41.