The cytotoxic potential of cationic triangulenes against tumour cells

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TOTA (Trioxatriangulenium ion) is a close-shelled cabocation known to intercalate strongly with the DNA double helix.[1] The cytotoxicity of **TOTA** and its four close structural analogues, **ADOTA**, **Pr-ADOTA**, **Pr-DAOTA** and ***n*-Butyl-TATA** were tested against the breast cancer cell line MDA-MB-231 and colon cancer cell line HCT116.[2] The most potent derivatives **Pr-ADOTA** and **Pr-DAOTA** had IC_{50} values of ~80 nM for MDA-MB-231 but slightly higher for HCT116 in the low hundreds nM range. A 3D model assay of HCT116 spheroids was also used, mimicking a tumour environment; again both **Pr-ADOTA** and **Pr-DAOTA** were very active with IC_{50} values of 38 nM and 21 nM, respectively. Molecular modelling suggest that the planar derivatives intercalate between the base pairs of the DNA double helix. However, only modest DNA double stranded DNA cleavage was observed using the γH2AX assay as compared to camptothecin, a topoisomerase I poison suggesting a different mechanism. Finally, a robust density functional theory (DFT) model was built to predict the pK_{R+} stability values, *i.e.*, to design derivatives, which predominantly have a non-intercalating buckled form

in healthy tissues followed by a nucleophilic attach of water on the central carbon, but a planar form at relatively low pH values rendering them *only* cytotoxic in the interior of tumours.

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2. E. Leung, L. I. Pilkington, M. M. Naiya, D. Barker, A. Zafar, C. Eurtivong, J. Reynisson, *Med. Chem. Commun.*, 2019, **10**, 1881.