Title

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Abstract

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Objectives Cyclooxygenases (COXs) play a vital role in the inflammatory cascade. The over-expression of COX-2 is a predictive biomarker for progression of pre-malignant lesions towards invasive cancer. This makes early detection of COX-2 expressing lesions of high clinical relevance. Current fluorescent probes for COX-2 mostly employ a ligand-linker-fluorophore design. This has proved successful but retains limitations, including a high background signal. Self-immolating triggers for COX-2 would facilitate the generation of activatable probes, reducing background signal, as well as COX-2 targeted pro-drugs. Our objective is to develop such a trigger.

Methods Our approach is based upon aspirin, which acetylates a serine in the COX active site. We installed a self-immolating linker and latent fluorophore *para* to aspirin's phenolic acetyl and sought to introduce selectivity for COX-2 over COX-1 by replacing the carboxyl moiety with either an ester or an alkyl thioether ('R'). When deacetylated the revealed phenol participates in a 1,6-quinone-methide elimination, releasing the fluorophore. We synthesized two probes with different R groups and tested their activation by purified COX enzymes via fluorimetry. Finally we

attempted to image differential COX expression in cellulo.

Results Activation of both probes was measured in vitro. In comparison, three control proteins showed no activation indicating that the probes were specific for COXs. No significant difference in probe activation was observed between COX-1 and COX-2. When tested in cellulo, no evidence of COX-specific activation was measured.

Conclusions The encouraging COX-specific activation observed in vitro represents the first step towards COX-targeted self-immolating probes. Improvements in the selectivity between COX isoforms and the probe functionality in cellulo are required if they are to fulfil their promise.

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