[2+2]-Photocycloaddition directed to building blocks for Medicinal Chemistry

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Cyclobutanes are an underrepresented structural motif in Pharma screening libraries and yet offer a well-defined three-dimensional vectorized topology that can readily overcome the molecular 'flatness' (low sp^3 character) which is associated with poor physicochemical properties. Indeed, compounds with a low sp^3 character (low "3D shape") generally have lower aqueous solubility, selectivity and may display higher CYP inhibition, plasma-protein and hERG binding which negatively impact drug likeness.

We have developed rapid access to complex cyclobutane compounds using intramolecular [2+2]-photocycloaddition (PCA) of α, β-unsaturated lactones as novel medicinal chemistry scaffolds.[1]

Our work has been extended to intermolecular [2+2]-photocycloadditions which can be performed in a quite simple and practicable experimental set-up and leading in all cases to the desired cyclobutane derivatives. Various degrees of fluorinations in the precursor molecules were tolerated providing further alterations in the physicochemical properties. The power of photochemistry in producing highly substituted cyclobutanes could be demonstrated for the generation of novel sulfur-containing building blocks of distinct three-dimensional shape as new starting points for medicinal chemistry.

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