Aryl Substitution on the Triazine Platform Wheels the Microtubule Dynamics and Enforce Contrasting Cell Signalling Pathways

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Abstract:
Identification of key pharmacophore features is crucial in drug design and discovery. Microtubule dynamics is essential for maintaining various key intracellular regulatory functions, including the bipolar spindle structure and axonal transport of neurons. It makes microtubules one of the most attractive molecular targets for development of both anticancer as well as neuroprotective agents. Recently, triazine scaffold has evolved as a potential anti-tubulin molecular core. Here, we showcased how an amino acid substitution on triazine scaffold can influence the regulation of microtubule dynamics. We adopted an elegant approach to design a small library containing eight C-3 symmetric triazine-amino acid conjugates, among them three aromatic amino acid substituted triazine molecules named CW, CF and CY displayed contrasting behaviour in tubulin polymerization, whereas others remained silent. Results suggest that CW inhibits whereas CF and CY promote tubulin polymerization through their interactions at the DCVJ and the taxol binding site respectively. Further, in vitro and in vivo studies confirmed significant antimitotic activity of CW and neuroprotective potential of CY indicating pivotal roles of indole and phenol moiety respectively. Finally, we established the fact that aryl groups of both CW and CY are in close proximity of their respective binding pockets in tubulin and the plausible conformation of their tubulin bound state was inferred by performing STD NMR and TR-NOESY studies. This study demonstrates the first comprehensive account of fundamental insight about the power of aryl group in controlling microtubule dynamics, and how it emerges as the key molecular entity in the development of two novel "molecular wheels" that enforce contrasting cellular fates.

References and Notes:

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Bio-Sketch of Speaker

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