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Chemical modulation of microtubule structure in neurodegenerative diseases

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Microtubules (MTs) are dynamic filaments involved in many essential cellular functions including those needed for cancer cell growth. Taxanes are MT stabilizing agents and the most successful antitumoral drugs targeting MTs. However, despite their mode of action is the stabilization (i.e., do not destroy the filament structure), they produce a paradoxical neurotoxic effect by inducing axon degeneration. This has been related to MT structural modifications upon drug binding. Alternatively, the laulimalide/peloruside binding site also promotes stabilization, but have not been exploited in clinics. We have found that differently to the taxane site, the stabilization mechanism involves exclusively lateral interactions and entails changes on the inter-PF angle. Importantly, some compounds do not modify MT upon binding when compare to native ones. This feature, together with the low cytotoxic effect found, open the possibility of exploiting these compounds in neurodegenerative diseases, where MT structure and function are compromised due to other primary cellular alterations.

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