Vinflunine inhibits CaM-STOP interaction

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Vinca alkaloids vinblastine and vincristine are widely used in therapy of leukemia and solid tumors. Their action is associated with alterations of the mitotic spindle functions. A number of studies show that some Vinca alkaloids inhibit CaM target interaction. The newest microtubule inhibitor, vinflunine (Javlor), is remarkably more active and less toxic than vinblastine against a number of tumors. The high antitumor activity of this molecule is not well understood since it binds to tubulin with affinity several-fold lower than that of vinblastine. We characterized the influence of Vinca alkaloids on CaM STOP (stable tubule only polypeptide) complex formation by using a combination of thermodynamic and mass spectrometric approaches. Our results revealed different binding modes to CaM for vinflunine and vinblastine. We demonstrate that vinflunine is a better inhibitor for STOP binding to calmodulin than vinblastine. We suggest that vinflunine action on calmodulin can have an effect on microtubule dynamics. These data may contribute to a better understanding of the superior antitumor efficiency and lower toxicity of vinflunine.