Discovery and development of tylophorine derived dibenzoquinolines-33b compounds into therapeutic agents

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Abstract

We investigated the role of the tylophorine E ring on the biological activities through synthesis of a series of derivatives, bearing modifications at the E ring and N-substitutions. All the derivatives were submitted for a variety of tests, anti-cell growth against a panel of cancer cell lines, suppressing nitric oxide production inLPS/IFNgamma stimulated RAW264.7 cells, and anti-viral replication in TGEV infected ST cells detected by inhibition of TGEV N and S protein expression. The uncyclized derivatives, dibenzoquinolines, do not have the enantimerism issue at C13a position. We have synthesized a series of novel tylophorine-derived dibenzoquinolines and evaluated for their biological activities. The role of tylophorine E ring was explored unprecedentedly for the first time. Unlike other reported tylophorine derivatives, the potent tylophorine-derived dibenzoquinolines appear to retain similar modes of action to those of tylophorine in terms of multi-biological activities for anti-inflammation, anti-cancer cell proliferation, and anti-coronavirus. The most potent compound dibenzoquinolines-33b (DBQ-33b) showed improved solubility, in vivo efficacies in a murine tumor xenograft model administrated orally and a murine paw edema model, good bioavailability, and no significant neurotoxicity tested by a rota-rod test for motor coordination. More orally active leads derived from DBQ-33b have been designed and synthesized and development of DBQ-33b derived lead compounds into therapeutic agents is ongoing.

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Footnotes

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