Structure-Activity Relationship Studies of 3-Aroylindoles as Potent Antimitotic Agents

劉景平

Liou JP;Mahindroo N;Chang CW;Guo FM;Lee SW;Yeh TK;Tan UK;Kuo CC;Chang YW;Lu PH;Tung YS

Abstract

The concise synthesis and structure-activity relationship (SAR) studies of 3-aroylindoles were carried out in an effort to improve the potency and solubility of anticancer drug candidate BPR0L075 (8) by exploring structure modifications through three regimens: substitution of the B ring, at the N1 position, and of the 3-carbonyl linker. The SAR information revealed that the methoxy group of the B ring could be replaced with an electron-donating group such as methyl (in compound 9) or N,N-dimethylamino (in compound 13) while retaining both strong cytotoxic and antitubulin activities. The introduction of amide (compounds 30-33) and carbamate (compounds 34-37) functionalities at the N1 position of 8 gave analogues with potent antiproliferative activities. The cytotoxic potency of 8 was improved by replacing the carbonyl group with sulfide (compound 41) or oxygen (compound 43), indicating that the carbonyl moiety is important but not essential. The N,N-dimethylamino derivative 13 not only displayed potent cytotoxicity and antitubulin activity, but also showed a markedly improved physicochemical profile relative to the parent compound.