Molecular Classification of 5-Amino-2-Aroylquinolines and 4-Aroyl-6,7,8-Trimethoxyquinolines as Highly Potent Tubulin Polymerization Inhibitors

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ABSTRACT

Algorithms for classification and taxonomy are proposed based on criteria as information entropy and its production. It is classified a series of 5-amino-2-aroylquinolines (AAQs) and 4-aroyl-6,7,8-trimethoxyquinolines (TMQs) combretastatin analogues for anti-cancer activity. 5-Amino-6-methoxy-2-aroylquinoline AAQ showed anti-proliferative activity more potent as compared to combretastatin A-4 (CA4), against various human cancer cell lines and a multidrug resistance (MDR) cancer cell line. On the basis of AAQ/TMQ structure–activity relationship new derivatives are designed. The AAQs/TMQs are classified using nine characteristic chemical properties in molecules. Many classification algorithms are based on information entropy. When applying the procedures to sets of moderate size, an excessive number of results appear compatible with data and suffer a combinatorial explosion. However, after equipartition conjecture, one has a selection criterion between different variants resulting from classification between hierarchical trees. A classification of anti-cancer agents is obtained. The features denote positions $R_{2-8}$ on the quinoline bicycle.

Keywords: 4-aroyl-6,7,8-trimethoxyquinolines (TMQs), 5-amino-2-aroylquinolines (AAQs), anti-cancer agents, multidrug resistance (MDR), quinoline bicycle,

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INTRODUCTION

Microtubules are dynamic structures, which play a crucial role in cellular division and are recognized as an important target for anti-cancer therapy (Jordan & Wilson, 2004). A number of naturally occurring compounds, e.g., paclitaxel, epithilone A, vinblastine, dolastatin 10, combretastatin A-4 (CA4) and colchicine (COL, cf. Figure 1), exhibit anti-cancer properties by interfering with tubulin de/polymerization dynamics, resulting in mitotic arrest.

Reports showed that drugs binding to COL domain underwent research as vascular-disrupting agents for cancer therapy; e.g., clinical candidates of microtubule inhibitor, CA4 phosphate (CA4P, Zybrestat) and AVE-8062 (Ombrabulin), act as vascular disrupting agent (VDA), which rapidly depolymerize microtubules of newly formed vasculatures and subsequently shut down the blood supply to tumours (Dark et al., 1997; Gaya & Rustin, 2005; Hinnen & Eskens, 2007; Lippert, 2007; Patterson & Rustin, 2007; Siemann, 2006; Siemann et al., 2005, 2009; Tozer et al., 2005, 2008). Sulphonamide-containing small-molecule compound, ABT-751, showed efficacious anti-mitotic activity, by tubulin polymerization inhibition, and underwent clinical trials (Fox et al., 2008; Mauer et al., 2008). Current available clinically used chemotherapeutic microtubule inhibitors present high toxicity, and potential is limited by multidrug resistance (MDR) development. There was great interest in identifying novel microtubule inhibitors, which overcame various resistance models and exhibited improved pharmacology profiles (Chaplin et al., 2006; Hsieh et al., 2005; Li & Sham, 2002; Liou et al., 2007, 2008; Mahindroo et al., 2006; Prinz et al., 2009; Reddy et al., 2008; Romagnoli et al., 2008; Simoni et al., 2008; Tron et al., 2006). Quinolines are a pharmaceutically active class of heterocyclic compounds (Joule et al., 1995). Microtubule-inhibitors analysis indicated that 3,4,5-trimethoxyphenyl/3,4,5-trimethoxybenzoyl and p-methoxyphenyl groups play an important role in bioactivity. Nien et al. (2010) explored core quinoline, coupled with group 3,4,5-trimethoxybenzoyl, as tubulin polymerization inhibitors (cf. Figure 2a–c).

Natural products contributed to discovery of 50% of modern drugs (Newman & Cragg, 2007). Because of natural products’ structural diversity and potent bioactivity, scaffolds provide opportunities for scientists in development of numerous bioactive products (Fishbach & Walsh, 2009). Mitotic process of division step of cell cycle involves microtubule assembly. Since microtubule dynamic structures play role in cellular division, they are important target for anti-cancer therapy. Natural products were identified as potent anti-proliferative agents, e.g., COL, podophyllotoxin (Kelleher, 1976) and CA4 (Hamel, 1996). Mechanism involved interaction with microtubules at COL binding site leading to M-phase arrest; e.g., CA4 attract-

Figure 1. Natural tubulin polymerization inhibitor colchicine
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