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Synthesis, biological evaluation and molecular docking studies of a new series of chalcones containing naphthalene moiety as anticancer agents

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ABSTRACT

A series of chalcones containing naphthalene moiety **4a**–**4p** have been synthesized, characterized by ^{1}H NMR and ^{13}C NMR and evaluated for their *in vitro* anticancer activity. The majority of the screened compounds displayed potent anticancer activity against both HCT116 and HepG2 human cancer cell lines. Among the series, compound **4h** with a diethylamino group at the para position of the phenyl ring exhibited the most potent anticancer activity against HCT116 and HepG2 cell lines with IC_{50} values of 1.20 ± 0.07 and 1.02 ± 0.04 μM, respectively. The preliminary structure–activity relationship has been summarized. Tubulin polymerization experiments indicated that **4h** effectively inhibited tubulin polymerization and flow cytometric assay revealed that **4h** arrests HepG2 cells at the G2/M phase in a dose-dependent manner. Furthermore, molecular docking studies suggested that **4h** binds to the colchicine binding site of tubulin.

1. Introduction

Microtubules are a key cytoskeletal constituent of the eukaryotic cell and play important roles in various cellular processes including mitosis, cell division, cell shape, intracellular transport and motility [1,2]. Antimicrotubule agents disrupt microtubule dynamics resulting in disruption of cell cycle progression and subsequently induction of cell death. The essential role of microtubules in mitotic spindle formation makes them one of the most attractive targets for the design and development of anticancer agents [3–5]. Antimitotic agents such as taxanes (e.g. paclitaxel and docetaxel) and vinca alkaloids (e.g. vinblastine and vincristine) have been widely used in the clinical treatment of different human cancers over the past decade [6]. However, the clinical use of these compounds was always limited by the high toxicity, the development of drug resistance, side effects, poor solubility, low oral bioavailability and complex synthesis [7]. Therefore, discovery and development of novel anticancer agents targeting tubulin are urgently needed.

On the other hand, the naphthalene ring system is a prominent structural motif found in a wide range of biologically active natural products, pharmaceuticals, and materials [8,9]. Previous literature reports indicated that naphthalene and its derivatives have diverse types of biological activity, including anticancer [10], antibacterial [11], anti-inflammatory [12], antioxidant [13], and antifungal activity [14]. It is important to point that naphthalene ring could be used as a useful moiety in the design of new anticancer agents [9]. Over the last few years, numerous naphthalene derivatives have been reported to show anticancer activity by inhibiting tubulin polymerization (Fig. 1, **I–III**) [15–17].

Natural products and their derivatives have historically been incomparable as a source of therapeutic agents now playing a crucial role in modern drug discovery and development, especially in the area of cancer therapy [18–22]. Millepachine (Fig. 2), one of naturally occurring pyranochalcones, is isolated from *Millettia pachycarpa* for the first time in our group, displayed potent cytotoxicity against a variety of human cancer cells with an IC_{50} range of 0.76–4.66 μM [23,24]. Our previous studies revealed that millepachine and its derivatives could strongly inhibit the growth of cancer cell lines and tubulin polymerization by binding to the colchicine site of tubulin and caused cells to arrest in the G2/M phase of the cell cycle [24–26]. Hence, millepachine can be used as a lead compound for the development of novel anticancer agents that target tubulin.

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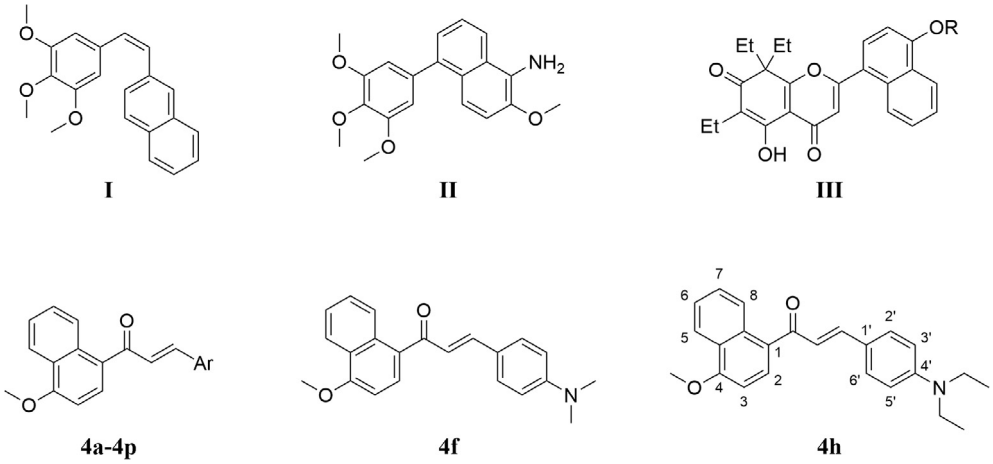

Fig. 1. The chemical structures of some tubulin inhibitors containing naphthalene moiety.

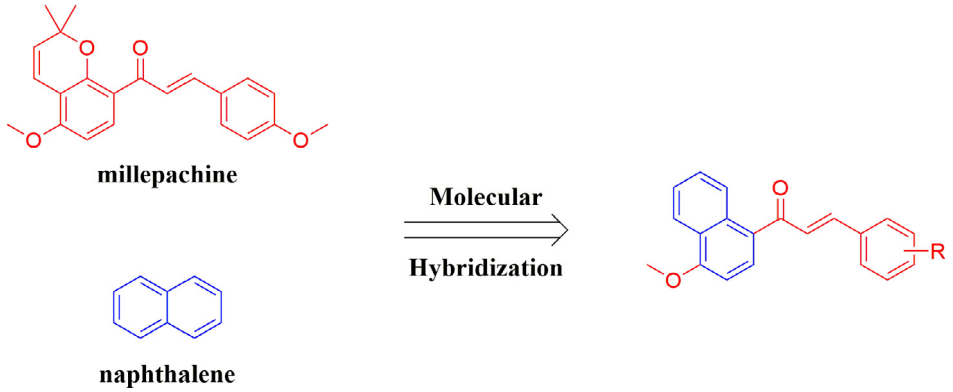

Fig. 2. A design for the synthesis of chalcones containing naphthalene moiety.

Molecular hybridization is a useful strategy for structural modification of lead compound in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy [27,28]. As a part of our search for novel tubulin polymerization inhibitors [24–26], we report herein the design and synthesis of a hybrid scaffold by incorporating millepachine with naphthalene moiety in a single molecule (Fig. 2). The synthesized compounds were tested for their *in vitro* anticancer activity against several human cancer cell lines. Furthermore, molecular docking was also performed to investigate the interaction of inhibitors with the colchicine binding site of tubulin.

2. Chemistry

A new series of chalcones containing naphthalene moiety **4a**–**4p** were synthesized as showed in Scheme 1. 1-(4-methoxynaphthalen-1-yl)ethan-1-one **2** was prepared by Friedel-Crafts acylation of 1-methoxynaphthalene **1** with acyl chloride. 1-Methoxynaphthalene **1** was added to a solution of $AlCl_3$ and acyl chloride in dry CH_2Cl_2 and the mixture was stirred at 0 °C for 30 min and then stirred at room temperature for overnight. After standard workup, the residue was purified by chromatography to give 1-(4-methoxynaphthalen-1-yl)ethan-1-one **2**. Condensation of **2** with different substituted aldehydes **3** under Claisen-Schmidt conditions using 50% KOH in methanol provided the desired compounds **4a**–**4p** in moderate to high yields.

The structures of all the title compounds (**4a**–**4p**) were elucidated by ^1H and ^{13}C NMR spectra. For instance, the ^1H NMR spectrum of **4h** (Supplementary Materials) showed a triplet at δ 1.21 ppm (6H, J = 7.2 Hz) and a quartet centered at δ 3.39 ppm (4H, J = 7.2 Hz) due to ethyl group. The methoxy protons appeared as a three protons singlet at δ 4.08 ppm. Two doublet signals at δ 6.64 ppm and δ 7 0.46 ppm with coupling constant of 8.8 Hz were attributed to the aromatic protons of C3′,5′-H and C2′,6′-H of the 4-(diethylamino)phenyl group, respectively (Fig. 1). The olefinic protons of —CO—CH═CH— appeared as two doublets at 7.11 and 7.58 ppm with coupling constant of 15.6 Hz. Moreover, the coupling constant J = 15.6 Hz demonstrated that the double bond was in an (*E*)-configuration. Two doublets signals at δ 6.83 ppm (J = 8.0 Hz) and δ 7.79 ppm (J = 8.0 Hz) corresponding to the protons of C3-H and C2-H of naphthalene, respectively. C5-H and C8-H of naphthalene gave corresponding doublets at δ 8.33 ppm and δ 8.47 ppm, respectively, with coupling constant of 8.0 Hz. The other two protons of naphthalene (C6-H and C7-H) appeared as multiplet in the region of 7.50–7.60 ppm. All these data are in agreement with the structure of compound **4h**. Moreover, in its ^{13}C NMR spectra, the number of signals equals the number of different carbons in the molecule.

3. *In vitro* anticancer activity screening

All the synthetic compounds **4a**–**4p** were screened for their *in vitro* anticancer activities against HCT116 human colon carci-