Bioorganic Chemistry 75 (2017) 86–98

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

New indole-based chalconoids as tubulin-targeting antiproliferative agents

Hassan Mirzaei [a], Mohammad Shokrzadeh [b], Mona Modanloo [a], Ali Ziar [b], Gholam Hossein Riazi [c], Saeed Emami [d,*]

[a] Student Research Committee, Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[b] Department of Toxicology and Pharmacology, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[c] Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran
[d] Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

ARTICLE INFO

Article history:
Received 4 July 2017
Revised 5 September 2017
Accepted 6 September 2017
Available online 7 September 2017

Keywords:
Chalcones
1,3-Diaryl-2-propen-1-ones
Indole
Anticancer
Cytotoxic activity
Tubulin polymerization

ABSTRACT

Tubulin-targeting compounds have a broad anticancer spectrum and are an important class of chemotherapeutic agents. Due to the importance of 3-bromo-3,5-dimethoxyphenyl scaffold in the anticancer activity of microtubule inhibitors such as crolibulin (EPC2407), we introduced this functionality into the indole-derived chalcones. Thus, we describe here the synthesis and biological evaluation of new indole-based chalconoids as tubulin-targeting antiproliferative agents. The best result was obtained by compound **9b** against A549 cell with IC_{50} of 4.3 μg/mL, being more potent than the reference drug etoposide. Further biological evaluations revealed that compound **9b** can inhibit tubulin polymerization and decrease the mitochondrial thiol content, resulting the induction of apoptosis in cancer cells. Docking studies with tubulin indicated that compound **9b** could bind to the colchicine binding site.

1. Introduction

Microtubules, one of the essential components in cells cytoskeleton, participate in the cellular processes such as mitosis, cell division, cell signaling, and intracellular transport [1–3]. Thus, microtubule dynamics has considered as a therapeutic target for cancer chemotherapy by tubulin-targeting agents. The tubulin protein is an α,β-heterodimer that forms the core of the microtubules. Since cancer cells undergo mitosis more rapidly, this means that they are more susceptible to tubulin-targeting agents than normal cells [3,4]. The antimitotic drugs interfering with microtubule dynamics are categorized into two classes: one type of drugs such as colchicine inhibits establishment of the mitosis spindle and another type of them such as paclitaxel inhibits the dissociation of the mitotic spindle. Colchicine (**1**, Fig. 1) which contains trimethoxybenzene scaffold binds to the β-tubulin subunit and co-polymerized into microtubules [5]. Indeed, the incorporation of the ligand into the colchicine-binding site makes conformational changes which allow the inclusion of colchicine-tubulin complex inside the microtubule filament [6,7].

Besides colchicines, other colchicine-domain binders such as podophyllotoxin (**2**) [8], combretastatin A-4 (**3**) [9] and chalcones (**4**, Fig. 1) which contain trimethoxybenzene scaffold have been considered as potential antimitotic agents [10]. Among these compounds, the combretastatin A-4 and chalcone derivatives have been gained extensive interest due to their simple structure and synthetic accessibility [11,12]. Chalcones (1,3-diaryl-2-propen-1-ones) exhibit broadly biological activities [13] including anticancer properties [14–18]. Chalcones consist of α,β-unsaturated carbonyl structure with two attached aromatic rings. Numerous structure-activity studies have been conducted in order to improve the cytotoxic potency and antitubulin activity of chalcones. Particularly, the replacement of aromatic rings with various heteroaryl moieties was utilized by medicinal chemists to find new chalcone-like compounds with potent antitubulin activity [10].

Recently, a great number of indole-based small molecules have been identified as tubulin polymerization inhibitors with potential of interacting with colchicine domain [19]. Accordingly, replacement of the aromatic rings with the indole nucleus in the chalcone structure would be a great modification to attain potent tubulin polymerization inhibitors and effective anticancer agents [20–22]. In this context, two methoxylated indole-based chalcones IPP51 (**5**) and JAI-51 (**6**) have been reported as microtubule inhibitors (Fig. 2). The biological assessments revealed that IPP51 selectively

* Corresponding author.
E-mail address: sd_emami@yahoo.com (S. Emami).

http://dx.doi.org/10.1016/j.bioorg.2017.09.005
0045-2068/

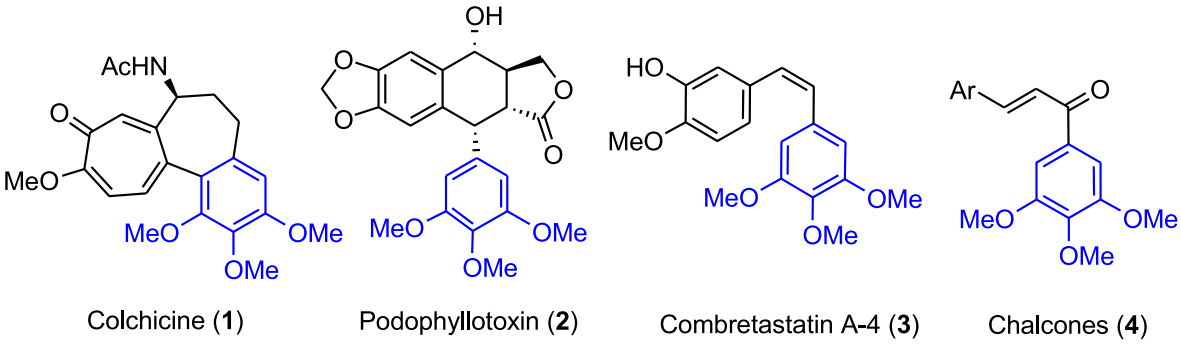

Fig. 1. Structures of tubilin polymerization inhibitors as colchicine-domain binders with a trimethoxybenzene scaffold.

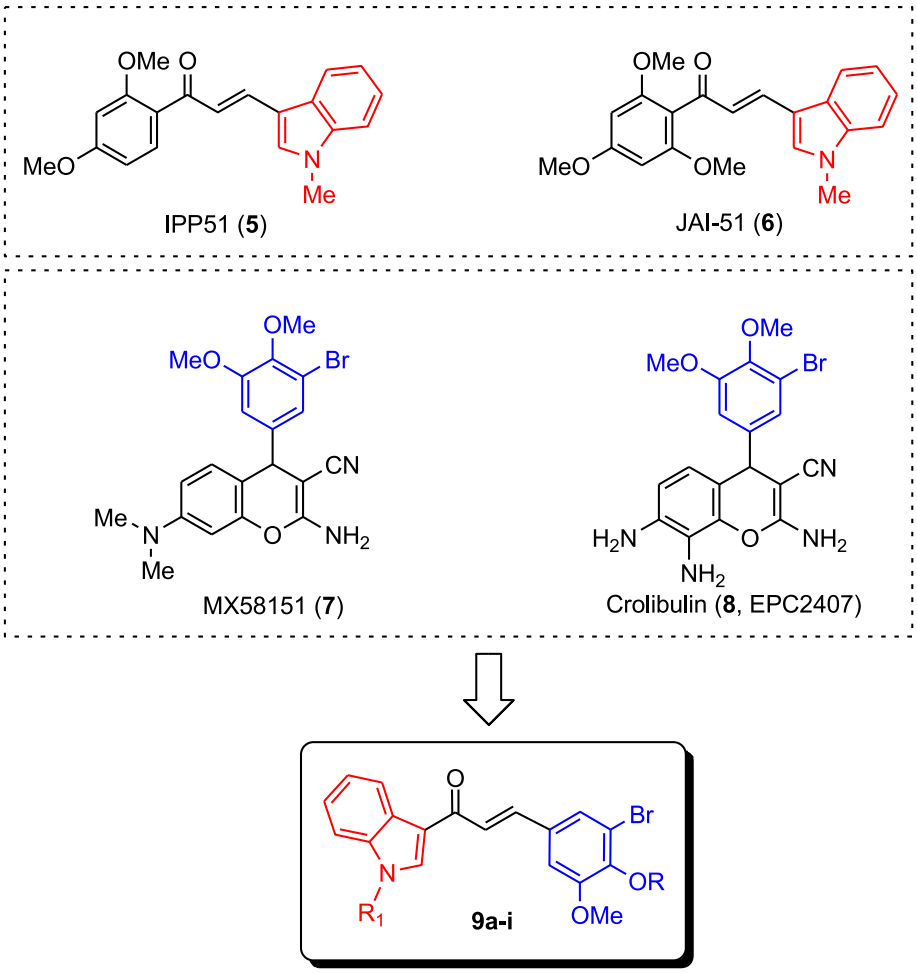

Fig. 2. Design of new indole-based chalconoids **9** from the structures of known methoxylated indole-based chalcones [IPP51 (**5**) and JAI-51 (**6**)], and chromene derivatives [MX58151 (**7**) and crolibulin (**8**, EPC2407)], bearing 3-bromo-4,5-dimethoxy-phenyl moiety, have been reported as microtubule inhibitors.

inhibits proliferation of bladder carcinoma cells and competes with colchicines for binding to the soluble tubulin [23–25]. The trimethoxy analog JAI-51 (**6**) showed antiproliferative activity against four human and a murine glioblastoma cell lines. The in vitro assays demonstrated that the latter compound can bind to tubulin and can occupy the colchicine binding site [25].

On the other hand, two chromene derivatives MX58151 (**7**, Fig. 2) and crolibulin (**8**, EPC2407), bearing a 3-bromo-4,5-dimethoxy-phenyl moiety, are new microtubule inhibitors [26,27]. Crolibulin has attained to clinical trials [27]. Due to the importance of 3-bromo-4,5-dimethoxy- functionally and indole moiety in the antiproliferative and tubulin polymerization inhibitory activities, we introduced both features in the chalcone structure to design new indole-based chalconoids **9** (Fig. 2). Thus, we report here the synthesis, antiproliferative activity, in vitro biological assessments and docking study of new (*E*)-1-(1*H*-indol-3-yl)-3-phenylprop-2-en-1-ones **9** as tubulin-targeting anticancer agents.

2. Results and discussion

2.1. Chemistry

The synthetic routes to indole-derived chalcones **9a-k** are illustrated in Scheme 1. Initially, 3-acetyl-1*H*-indole (**10**) was