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Research paper

Design and discovery of silybin analogues as antiproliferative compounds using a ring disjunctive – Based, natural product lead optimization approach

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ABSTRACT

The present study reports the synthesis and anticancer activity evaluation of twelve novel silybin analogues designed using a ring disjunctive-based natural product lead (RDNPL) optimization approach. All twelve compounds were tested against a panel of cancer cells (i.e. breast, prostate, pancreatic, and ovarian) and compared with normal cells. While all of the compounds had significantly greater efficacy than silybin, derivative **15k** was found to be highly potent (IC_{50} < 1 μM) and selective against ovarian cancer cell lines, as well as other cancer cell lines, compared to normal cells. Preliminary mechanistic studies indicated that the antiproliferative efficacy of **15k** was mediated by its induction of apoptosis, loss of mitochondrial membrane potential and cell cycle arrest at the sub-G1 phase. Furthermore, **15k** inhibited cellular microtubules dynamic and assembly by binding to tubulin and inhibiting its expression and function. Overall, the results of the study establish **15k** as a novel tubulin inhibitor with significant activity against ovarian cancer cells.

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1. Introduction

Natural products research has help elucidate previously unknown biochemical mechanisms, while identifying several clinically effective anticancer drugs, such as paclitaxel, doxorubicin, vinblastine, and vincristine [1]. Silymarin is a polyphenolic flavonoid complex found in the dried fruits of the milk thistle plant (*Silybum marianum*) [2–4]. Over the last few decades, the pharmacological properties of different components of silymarin i.e. silybin A **(1)**, silybin B **(2)**, isosilybin A **(3)**, isosilybin B **(4)**, silychristin **(5)**, isosilychristin **(6)**, silydianin **(7)** and (+)-taxifoline **(8)** as shown in (Fig. 1) have been extensively investigated [5–13]. Of these aforementioned compounds, silybin was found to be the most potent antiproliferative component of silymarin and it has been reported to inhibit numerous cancers, including breast [14,15], colon [16], liver [17,18], lung [19], ovary [20], prostate [21–23], and skin cancer [24,25]. Silybin's cytotoxic and chemopreventive efficacy results from concomitantly targeting multiple important cancer targets [17]. For example, silybin 1) produces cell cycle arrest at both the G1/and G2 phase s 2) activates Erb1 signalling; 3) induces cyclin-dependent kinase (CDK) inhibition; 4) down-regulates specific anti-apoptotic proteins; 5) inhibits kinases required for cell survival; and 6) inhibits inflammatory transcription factors [21,24,26–31]. Furthermore, silybin produces antimetastatic activity by targeting dysregulated stemness pathways, such as the Wnt/beta-catenin/epithelial to mesenchymal transition (EMT). Both *in vitro* and *in vivo* studies indicate that silybin has an excellent safety profile, with no significant induction of toxicity or

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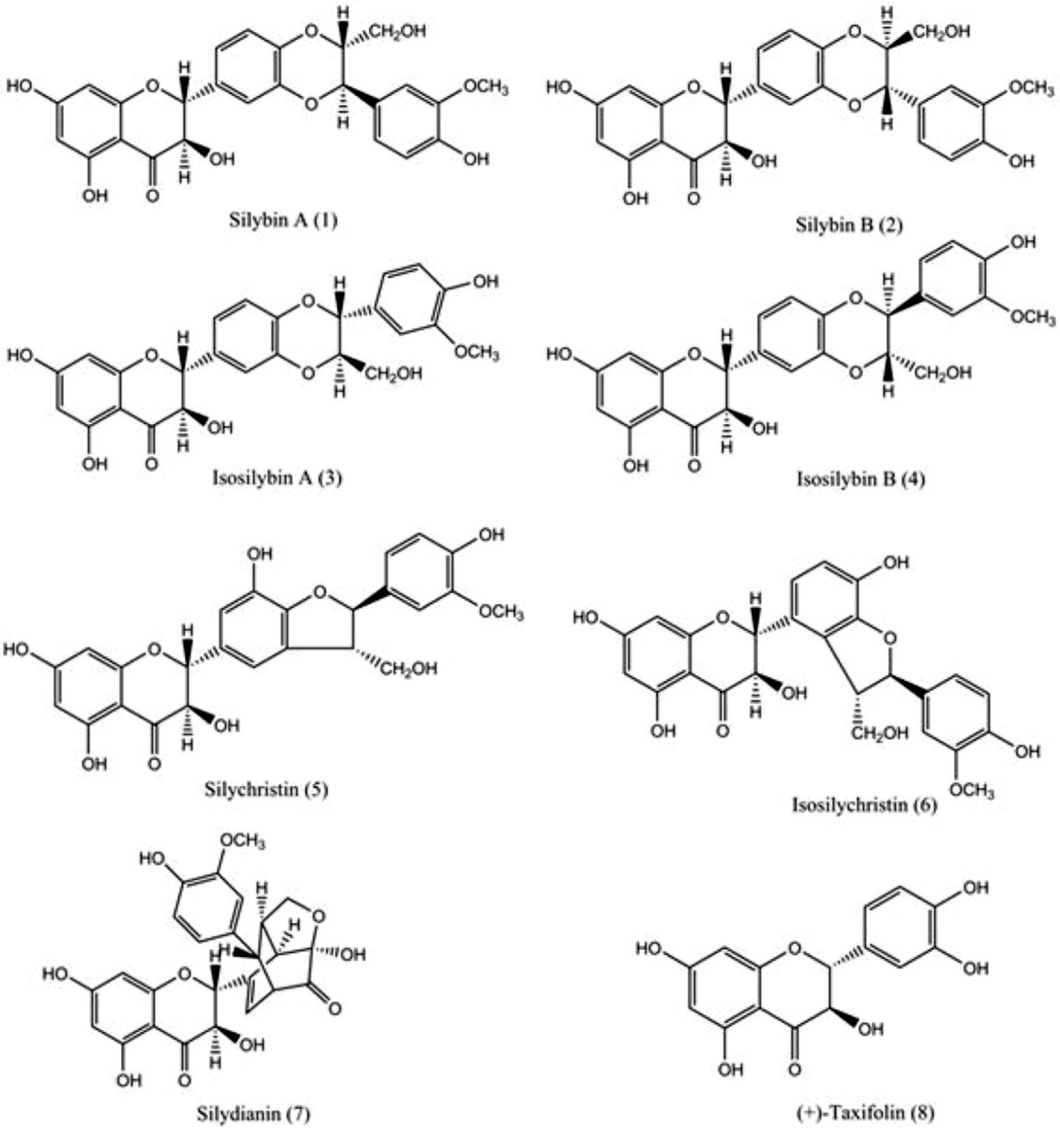

Fig. 1. The chemical structures of the active constituents of Silymarin, the main polyphenolic flavonoid found in the milk thistle plant extract: (silybin A (1), silybin B (2), isosilybin A (3), isosilybin B (4), silychristin (5), isosilychristin (6), silydianin (7) and (+)-taxifoline (8).

carcinogenesis at doses up to 1200 mg daily [32]. Although silybin, a polyphenolic natural product, has anticancer efficacy in preclinical models, its pharmacokinetic (PK) limitations such as poor absorption, rapid metabolism, and poor bioavailability have hampered its clinical use [33]. Attempts to overcome these issues with structural modifications of the phenol and alcohol functions of silybin [5,34] through esterification [35], phosphorylation [36], glycosidation [33], and oxidation of the C-23 alcohol [37] have had limited success.

Structural modification of a natural product lead (NPL) is a frequently used approach in NPL based drug discovery. NPL optimization can be used to attain novel bioactive molecules with improved pharmacological and PK properties, along with target selectivity [38,39]. The strategy of splitting fused ring structures of NPL by following a 'disjunctive approach', more often results in new bioactive molecules with a similar mechanism of action and improved PD/PK [40,41]. Herein, we report a NPL optimization strategy consisting of sequential exclusion of functional groups, and a ring disjunctive approach coupled with exploration of different functional groups on the silybin core structure. Simplification of the silybin core structure by removing functionality, chirality and ring opening, allowed us to identify the minimum pharmacophore required for efficacy to inhibit cancer cell proliferation (Fig. 2). This strategy also resulted in the identification of an anticancer lead, (E)-3-(3-(benzyloxy) phenyl)-1-phenylprop-2-en-1-one (**15a**). We further optimized **15a** by substituting advantageous functional groups to obtain more potent derivatives. The design, synthesis, identification, SAR, and antiproliferative profile of these derivatives are reported herein. In addition, additional pharmacodynamic mechanisms (cytotoxicity, anti-apoptosis and tubulin inhibition) of the optimized molecule **15k** are identified and reported herein.

2. Results & discussion

2.1. Chemistry of new silybin analogues

General methods for the preparation of chalcones involve the Claisen–Schmidt condensation of appropriate aryl methyl ketones and aldehydes in the presence of either an acid or base [42]. The compounds, **15a** – **15k**, were prepared by reacting 3-(benzyloxy)

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