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Research paper

Discovery of novel mifepristone derivatives via suppressing KLF5 expression for the treatment of triple-negative breast cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is one of the most malignant breast cancers currently with a lack of targeted therapeutic drugs. Accumulating evidence supports that KLF5 represents a novel therapeutic target for the treatment of basal TNBC. Our previous studies revealed that mifepristone is capable of suppressing TNBC cell proliferation and promoting cancer cell apoptosis by inhibiting KLF5 expression. Nevertheless, its anticancer efficacy is only modest with high dose. Moreover, its main metabolite *N*-desmethyl mifepristone with the removal of one methyl moiety results in a significant loss of anti-proliferative activity, indicating an important pharmacophore domain around this methyl moiety. To improve the pharmacokinetic properties including metabolic stability and enhance the anticancer activities, a focused compound library by altering this sensitive metabolic region of mifepristone has been designed and synthesized for scaffold repurposing and structural optimization. Compound **17** (**FZU-00,004**) has been identified with an attractive anticancer profile against TNBC via suppressing KLF5 expression.

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1. Introduction

Triple-negative breast cancer (TNBC), as one of the most aggressive diseases with a low overall survival rate, is characterized by the absence of expression of estrogen receptor α (ER α), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) [1]. Due to lack of the expression of these most commonly targeted receptors in human breast cancer, conventional hormonal or HER2 therapies are not effective for TNBC patients [2]. Accordingly, standard adjuvant cytotoxic chemotherapy is the only

choice, while drug resistance, and cancer metastasis as well as poor prognosis might eventually result in higher mortality rate [3–5]. Therefore, discovery of new targets and development of mechanism-based targeted therapies for the treatment of TNBC is urgently needed [6].

To effectively tackle this disease, tremendous investigations have been explored, especially on large-scale genomic analyses and molecular-profiling focusing on the development of targeted agents against TNBC [7]. Distinct oncogenic signaling cascades including the EGFR family members and downstream nodes have been identified as potential targeted pathways in the pathogenesis of TNBC [8,9]. Among these achievements, several classes of compounds such as mTOR inhibitors [10], selective CB₂ agonists [11], and bromodomain inhibitors [12] (Fig. 1) have been reported to display anticancer efficacy in the TNBC xenografts. However, only a few of them are advanced into clinical trials for the treatment of TNBC patients [13].

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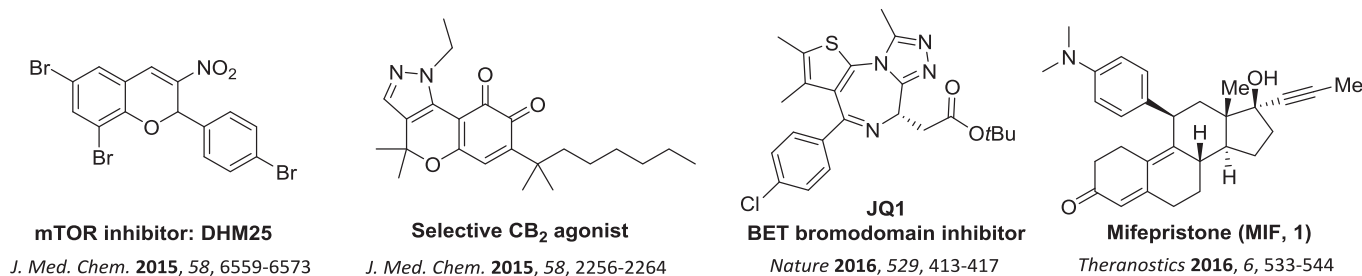


Fig. 1. Selected anticancer agents against triple-negative breast cancer (TNBC).

Krüppel-like factor 5 (KLF5), one important member of zinc-finger-containing transcription factors, regulates a wide range of genes expression [14–17]. In clinical settings, positive KLF5 expression is an unfavorable prognostic marker associated with shorter survival for breast cancer patients [18]. In addition, our previous studies demonstrated that KLF5 is frequently overexpressed in basal-type breast cancer, especially in basal TNBC cell lines [19–22]. As a key regulator, our recent work revealed that depletion of KLF5 significantly suppresses basal TNBC cell proliferation, survival and tumor growth *in vivo* [23,24]. Furthermore, accumulating evidence suggests that KLF5 represents a novel therapeutic target for basal TNBC [25–31].

Recently, we found that mifepristone (MIF, **1**, Fig. 1), one of the essential medicines widely used for medical abortion and emergency contraception, suppresses the tumor growth of TNBC cells and patient-derived xenografts through inhibiting KLF5 expression [32]. Due to the absence of expression of PR in TNBC cell lines, our further mechanism investigations suggest that mifepristone as a potent PR antagonist inhibits basal TNBC in a non-canonical pathway through inducing the expression of miR-153 to suppress the expression of KLF5. Despite mifepristone displays *in vivo* antitumor efficacy in two xenograft models, its relatively moderate potency has limited its further clinical application for TNBC [32]. One potential reason is that mifepristone undergoes rapid metabolism resulting in one major metabolite *N*-monodemethyl mifepristone (RU42633) [33–35]. Pharmacokinetic studies have shown that this major metabolite displays the AUC (area under the curve) level higher than mifepristone [36–39]. Our further biological studies revealed that this main metabolite *N*-desmethyl mifepristone with the removal of one methyl group results in a significant loss of antiproliferative activity, indicating an important pharmacophore region around this methyl moiety.

Recently, scaffold repurposing of old drugs emerges as an attractive drug discovery strategy through rational structural

alteration and optimization [40]. The known pharmacokinetics parameters of mifepristone provided detailed information. Its sensitive metabolic site offers a potential structural optimization approach to the improvement of the anticancer activity [40]. As a continuation of our previous studies [32], we plan to design a focused compound library by altering this sensitive metabolic region of mifepristone with the aim to improve the drug properties and anticancer activity (Fig. 2). Herein, we report our structural optimization findings and the discovery of a novel promising lead compound with an attractive *in vitro* and *in vivo* anticancer profile against TNBC via regulating KLF5 expression. To the best of our knowledge, this is the first paper to develop new anti-TNBC drugs based on the scaffold of mifepristone.

2. Results and discussion

2.1. Chemistry

Generally, amides including sulfonamides and carboxamides are considered as metabolic stable fragments [41]. It was structural rotational envisioned that chemical alterations on this metabolic instable site via simple amide modifications might lead to novel mifepristone derivatives with improved metabolic stability and anticancer efficacy. The synthesis of mifepristone derivatives **3–34** is depicted in Scheme 1. Our previous effort on the practical *N*-demethylation of mifepristone resulted in development of a suitable condition for the large-scale preparation [42]. By using LiOAc as a superior base and I₂ as the *N*-demethylation agent, this major metabolite *N*-monodemethyl mifepristone was obtained in an excellent yield (>90%). This key intermediate was treated with various substituted acid or acyl chloride or sulfonyl chlorides to readily afford the corresponding amides or sulfonamides in moderate to excellent yields. This simple chemistry with ease of synthesis allowed for the rapid generation of a focused compound

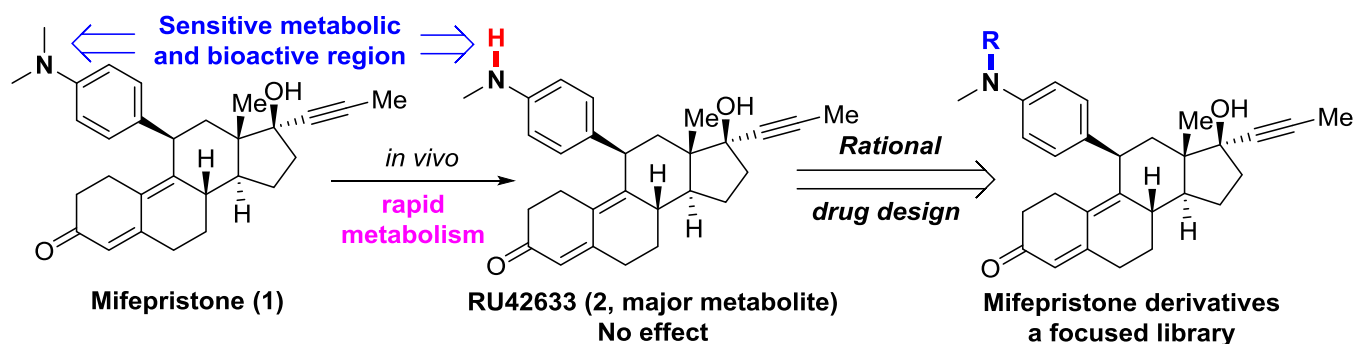


Fig. 2. Rational drug design of a focused compound library based on the sensitive metabolic region of mifepristone.

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