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Synthesis and biological evaluation of 4,6-diaryl-2-pyrimidinamine derivatives as anti-breast cancer agents

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ABSTRACT

Breast cancer is the most frequently diagnosed cancers and the leading causes of cancer death among females worldwide. Estrogen receptor positive has been identified as the predominant internal reasons, involving in more than 70% breast cancer patients and SERMs which competes with estradiol for the binding to ERα in breast tissue are widely used in the treatment of ER+ breast cancer, such as tamoxifen, raloxifene. However, many SERMs may cause negative side effects due to their estrogenic activity in other tissues and approximate 50% of patients with ER-positive tumors either initially do not respond or become resistant to these drugs. Here, a series of designed 4,6-diaryl-2-pyrimidinamine derivatives had been synthesized to treat estrogen receptor positive breast cancer by simultaneously antagonizing ER and inhibiting VEGFR-2. Bioactivity evaluation showed that these compounds could significantly inhibit the proliferation of MCF-7, HUVEC and Ishikawa cells. Further studies identified compound **III-3A** could antagonize against estrogen action and inhibit the phosphorylation of VEGFR-2 as well as inhibit angiogenesis in vivo. The results indicated designed 4,6-diaryl-2-pyrimidinamine derivatives can be used to further study as anti-breast cancer drugs.

Breast cancer is the most frequently diagnosed cancers and the leading causes of cancer death among females worldwide according to GLOBOCAN 2012.[1] Susceptible population of breast cancer have common characteristics, including advanced age, low parity, delayed age at first delivery, short duration of breastfeeding, overeating, limited exercise and so on. Breast cancer is a heterogeneous disease and multiple subtypes have been defined. The overexpressed of estrogen receptor α (ERα) which is a member of the large superfamily of nuclear receptors has been identified as the predominant internal reasons, involving in more than 70% breast cancer patients, and this type of patients are tagged as ER positive (ER+).[2] In this case, the continuous activation of ERα by estrogens induce the proliferation of tumor cell, so the blocking-up of ER signaling by competitively binding to ER with anti-estrogens or estrogen deprivation is an effective therapeutic strategy.[3] Selective estrogen receptor modulators (SERMs) which compete with estradiol for the binding to ERα in breast tissue are widely used in the treatment of ER+ breast cancer, such as tamoxifen, raloxifene.[4] However, many SERMs may cause negative side effects due to their estrogenic activity in other tissues, such as endometrial cancer.[5] Moreover, up to approximate 50% of patients with ER-positive tumors either initially do not respond or become resistant to these drugs within 5 years of treatment.[6] Thus contribute to a significant obstacle towards ER+ breast cancer treatment. Hence, there is a great need for the development of new drugs to improve therapeutical effect in the breast cancer treatment.

The significance of the 2-pyrimidinamine scaffold in medicinal chemistry is widely known. Many of these compounds are serving as anticancer agent (Fig. 1). Here, we noticed that 4,6-diaryl-2-pyrimidinamine derivatives shows good activity in pharmacological studies.[7–10] These compounds have similar toluylene likely to tamoxifen (Fig. 2), and the distance of two 4-C in phenyl is approximate equal to tamoxifen (9.8 Å vs 9.3 Å, simulation by Chem3D). Moreover, 2-pyrimidinamine scaffold is the key skeleton of pazopanib and JNJ-17029259[11] which are the vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors. It's known that VEGFR-2 plays key role in the angiogenesis pathway which participates in the proliferation, metastasis, and invasion of breast

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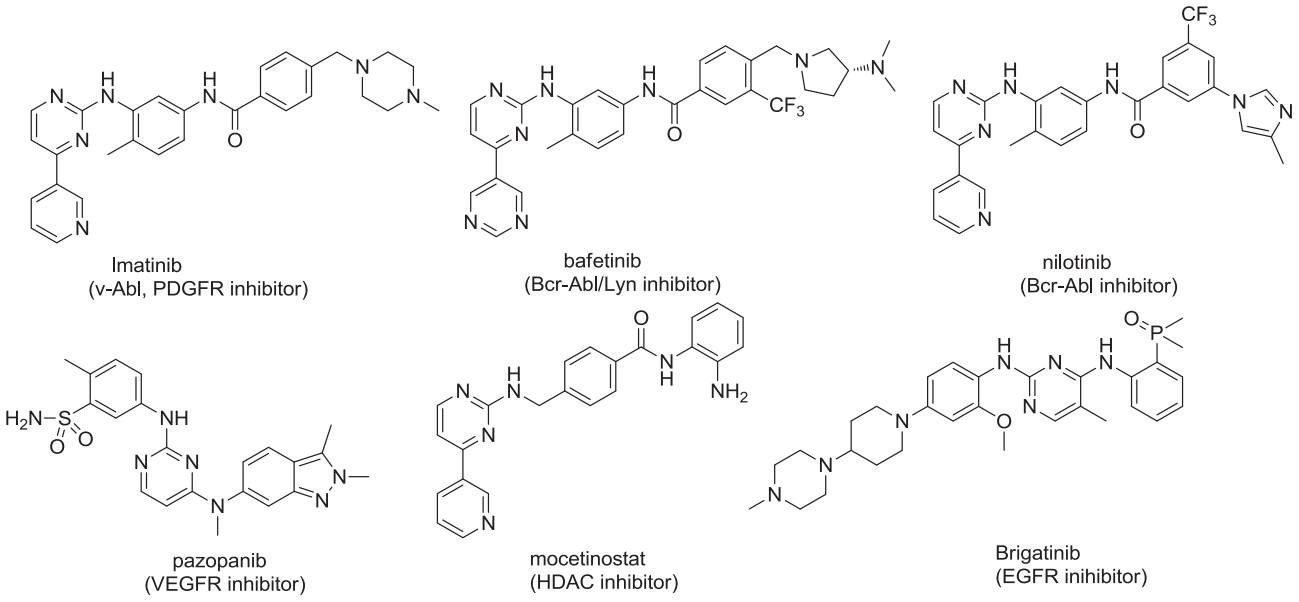

Fig. 1. Anti-cancer drugs with the 2-pyrimidinamine scaffold.

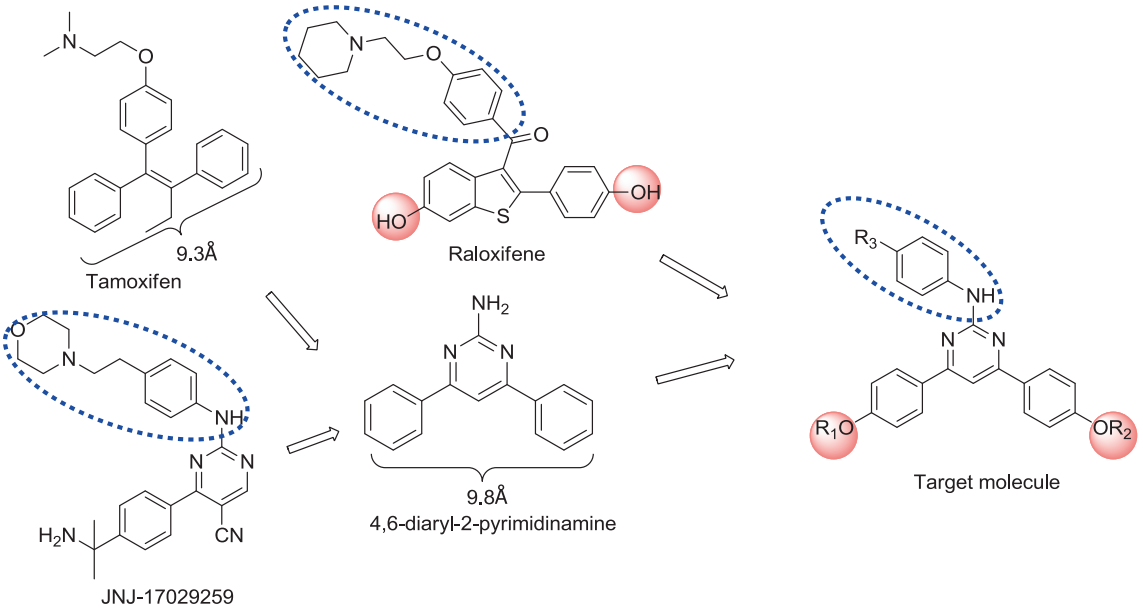

Fig. 2. The design of target molecules based on 4,6-diaryl-2-pyrimidinamine scaffold.

cancer cells.[12] And studies identified that VEGFR-2 involve in tamoxifen resistance via the Ras/MAPK pathway.[13,14] The combination of tamoxifen and a low dose of brivanib alaninate, a VEGFR-2 inhibitor, was reported not only to maximize therapeutic efficacy but also to retard SERM resistant tumour growth.[15] Thus urge us to design new molecules which have potential to anti-breast cancer via the inhibition of ER and VEGFR-2 based on 4,6-diaryl-2-pyrimidinamine scaffold (Fig. 2). Studies found that the phenolic groups which exist in 4-hydroxytamoxifen and raloxifene, interact to the binding domain of ERα, mimicking to estradiol A-ring.[4] Meanwhile, the side chains, 4-[2-(dimethylamino)ethoxy]phenyl of tamoxifen or 4-[2-(1-piperidinyl)ethoxy]phenyl of raloxifene are critical for anti-estrogenic activity, and this side chain also exist in JNJ-17029259 (the Blue Oval, Fig. 2). So according to the combination principle of medicinal chemistry, it's easy to design new structure based on the 4,6-diaryl-2-pyrimidinamine scaffold (Fig. 2).

The synthetic route of target 4,6-diaryl-2-pyrimidinamine derivatives is shown in Scheme 1. The key intermediate, 4,6-bis (4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**4**), was prepared from the commercially available urea, 1-(4-methoxyphenyl)-ethanone, and 4-methoxybenzaldehyde according to Biginelli reaction in high yields. Then, intermediate **4** was dehydrogenize and the hydroxy was replaced by chloro under the reflux of phosphorus oxychloride to give 2-chloro-4,6-diaryl-2-pyrimidine (**5**). This pyrimidine reacted a nucleophilic replacement with substitutional aniline to give new compounds **III-1A**–**III-12A**. At last, under the catalysis of BBr_3, the takeoff of one or two methoxy group of compounds **III-1A**–**III-12A** obtained the end-products **III-1B**–**III-12B** and **III-1C**–**III-12C**. Finally, we got three series of