Naphtho[1,2-*b*]furan-4,5-dione inhibits MDA-MB-231 cell migration and invasion by suppressing Src-mediated signaling pathways

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Abstract Naphtho[1,2-b]furan-4,5-dione (NFD), a bioactive component of Avicennia marina, has been demonstrated to display anti-cancer activity. Breast cancer is a highly malignant carcinoma and most deaths of breast cancer are caused by metastasis. In this study, we showed that NFD blocked migration and invasion of MDA-MB-231 breast cancer cells without affecting apoptosis or growth arrest. NFD caused significant block of Src kinase activity in MDA-MB-231 cells. Moreover, NFD treatment was correlated with reduced phosphorylation of FAK at Tyr 576/577, 861 and 925 sites, p130^{Cas} at Tyr 410, and paxillin at Tyr 118. NFD also suppressed the activation of phosphatidylinositol 3-kinase/ Akt. Consistent with inhibition of these signaling pathways and invasion, NFD reduced the expression of matrix metalloproteinase-9. Furthermore, Src antagonist PP2 caused a significant decrease in the phosphorylation of FAK, p130^{Cas}, paxillin, and PI3K/Akt. Our findings provide evidences that NFD inhibits Src-mediated signaling pathways involved in controlling breast cancer migration and invasion, suggesting that it has a therapeutic potential in breast cancer treatment.

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Introduction

Breast cancer is one of the most common malignant disease and the most aggressive cancer type of woman in the world [1]. Metastasis is a hallmark of cancer and the principal cause of cancer-related mortality [2]. However, because of poor diagnosis accuracy and limited therapeutics, the remedy of breast cancer is still far from satisfactory. Thus, the screening of compounds which suppress tumor metastasis is specifically necessary and will bring a novel maneuver for treatment of breast cancer.

An abundance of evidence suggests that a primary role of Src family kinases (SFKs), in particular c-Src, is to regulate cell adhesion, motility, and invasion [3]. Src is elevated in many human tumors, including breast cancer, and is often associated with aggressive disease [4–7]. Notably, increased Src activity is believed to correlate strongly with metastatic potential and poor prognosis in breast cancer [5, 6]. A recent study using Src^{-/-} mice demonstrated that abolishing Src expression/activity decreases tumor cell extravasation and subsequently decreases experimental metastasis [8]. Src regulates important intracellular signaling pathways, including the focal adhesion kinase (FAK), Crk-associated substrate (p130^{Cas}), paxillin, and the phosphatidylinositol 3-kinase (PI3K) pathways [9, 10]. Thus, Src kinase has been recognized as an attractive molecular target for cancer therapy and development of Src inhibitors for cancer treatment is increasing interest.

Previous studies show that 1,2- and 1,4-naphthoquinones fused with furan or pyran ring are important groups for cytotoxicity to cancer cell lines, with 1,2-naphthoquinones having better activity [11, 12]. Naphtho[1,2-*b*]furan-