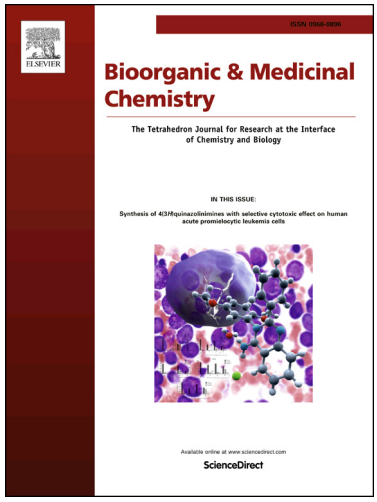

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PII: S0968-0896(17)30346-2
DOI: http://dx.doi.org/10.1016/j.bmc.2017.05.002
Reference: BMC 13718

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 20 February 2017
Revised Date: 21 April 2017
Accepted Date: 2 May 2017

Please cite this article as: Yang, L., Hu, Z., Luo, J., Tang, C., Zhang, S., Ning, W., Dong, C., Huang, J., Liu, X., Zhou, H-B., Dual functional small molecule fluorescent probes for image-guided estrogen receptor-specific targeting coupled potent antiproliferative potency for breast cancer therapy, *Bioorganic & Medicinal Chemistry* (2017), doi: http://dx.doi.org/10.1016/j.bmc.2017.05.002

Dual functional small molecule fluorescent probes for image-guided estrogen receptor-specific targeting coupled potent antiproliferative potency for breast cancer therapy

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ARTCLE INFO

Article history:

Received
Received in revised from
Accepted
Available online

Keywords:

Estrogen receptor
Fluorescent probes
Coumarin derivatives
Breast cancer
Antiproliferative activity

ABSTRACT

A strategy by integrating biological imaging into early stages of the drug discovery process can improve our understanding of drug activity during preclinical and clinical study. In this article, we designed and synthesized coumarin-based nonsteroidal type fluorescence ligands for drug-target binding imaging. Among these synthesized compounds, **3e**, **3f** and **3h** showed potent ER binding affinity and **3e** (IC_{50} = 0.012 μM) exhibited excellent ERα antagonistic activity, its antiproliferative potency in breast cancer MCF-7 cells is equipotent to the approved drug tamoxifen. The fluorescence of compounds **3e** and **3f** depended on the solvent properties and showed significant changes when mixed with ERα and ERβ *in vitro*. Furthermore, target molecule **3e** could cross the cell membrane, localize and image drug-target interaction in real time without cell washing. Thus, the coumarin-based platform represents a promising new ER-targeted delivery vehicle with potential imaging and therapeutic properties.

1. Introduction

Molecular imaging, as a vital detection technique to characterize and quantify biological processes, has profound significance in determining drug targets, exploring drug activity and guiding the synthesis of drugs.[1-3] Furthermore, the action of drug at subcellular level can be more clearly observed using the real-time live cell imaging. The estrogen receptors (ERα and ERβ), members of the superfamily of nuclear receptors, have emerged as attractive pharmaceutical targets for therapeutic intervention in various diseases, including osteoporosis and breast cancer,[4-6] which are regarded as important hormone-regulated modulator of intracellular signalling and gene expression.[7, 8] In most of primary breast cancers, ERα protein could be detected,[9] which is by far one of the most successful drug targets in cancer drug discovery. In the existing literature reports, the ER-status of nearly one-third of breast cancer are still unknown,[10] and it also remains ambiguous to explain the mechanism between drugs and ligands, as well as the distribution and dynamics of drugs at the cellular level.

In the latest study, fluorescence imaging has been widely used to detect and localize drug target because of its low cost, non-invasive operation, and easy data analysis.[11-13] Though the existing fluorescence imaging technology includes green fluorescence protein fused receptor[14] and the conjugated ligands with the fluorophore (**1** and **2**) by the linking group[15-21] could be