RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2024, **14**, 23785

Design, synthesis, molecular docking and *in vitro* anticancer activities of 1-(4-(benzamido)phenyl)-3-arylurea derivatives†

Prafulla Sabale, *[a] Nusrat Sayyad,[a] Abuzer Ali, [b] Vidya Sabale, [c] Mohammed Kaleem, *[d] Turky Omar Asar,[e] Amena Ali, [f] Md. Ali Mujtaba [g] and Md. Khalid Anwer [h]

In both premenopausal and postmenopausal women, oestrogens play a critical role in the development of breast cancer. Aromatase is an enzyme that catalyses the final step in the biosynthesis of estrogen and has emerged as a promising target for therapeutic intervention. This study aimed to design and evaluate novel 1-(4-(benzamido)phenyl)-3-arylurea derivatives as potential aromatase inhibitors. Through molecular docking, promising leads were identified and synthesized. Spectroscopic techniques confirmed their structural integrity. Cytotoxicity against various cancer cell lines was assessed using MTT assay. Docking investigations against the aromatase enzyme (3s7s) elucidated binding interactions and energies. Compound **6g**, exhibiting a binding energy of −8.6 kcal mol^{-1} and interacting with ALA306 and THR310 residues, showed the most promising activity. It demonstrated GI_{50} values ranging from 14.46 μM, 13.97 μM, 11.35 μM, 11.58 μM, and 15.77 μM against A-498, NCI-H23, MDAMB-231, MCF-7, and A-549 respectively. Lastly, the physicochemical, and ADMET properties of the compound were predicted. These findings highlight the potential of 1-(4-(benzamido)phenyl)-3-arylureas as a new class of antitumor agents targeting aromatase. Their versatility and superior activity compared to standard chemotherapeutic agents, like doxorubicin, warrant further investigation for the development of broader-spectrum anticancer drugs.

Received 18th April 2024
Accepted 13th July 2024

DOI: 10.1039/d4ra02882a

rsc.li/rsc-advances

1. Introduction

Cancer is a complicated disease with some distinct characteristics, one of them is dysregulated cell production.[1–3] It is caused by an imbalance between the expression of oncogenes and proto-oncogenes, which is caused by genetic and epigenetic abnormalities.[4,5] Globally, the number of cancer diagnoses has climbed to 19.3 million, and each year, 10 million deaths related to cancer are reported. The most common type of cancer among women is breast cancer (BC), globally.[6] BC is a highly complex disease with distinct biological subtypes and several targeted prognostic markers of therapeutic significance.[7] Approximately 2.3 million (11.7%) new instances of breast cancer were reported in 2020, and 684 996 (6.9%) fatalities were linked to the disease.[1] Furthermore, It is predicted that by 2040, there will be around 3 million new cases of breast cancer and one million more deaths from the disease.[8] The prognosis and clinical manifestations vary considerably amongst patients. BC develops through multiple pathways, including aromatase enzyme-regulated estrogen synthesis that primarily affects the expression of aromatase enzyme is highest in or near breast tumor sites and is known to catalyze the last step of conversion of androgen to estrogen.[9] Elevated expressions of estrogen and aromatase in breast cancer tissues than non-cancerous have been reported by several studies.[10] Tamoxifen has been used as standard endocrine therapy for a decade, however, the development of third-generation aromatase inhibitors (Anastrozole, Letrozole, Exemestane) has greater efficacy and improved disease-free survival compared to tamoxifen.[11] Although many

[a]*Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Mahatma Jyotiba Fuley Shaikshanik Parisar, Nagpur-440033, India. E-mail: prafullasable@yahoo.com; nusratsayyad11@gmail.com; Tel: +919158537050*

[b]*Department of Pharmacognosy, College of Pharmacy, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia. E-mail: abuali@tu.edu.sa*

[c]*Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, 440037, India. E-mail: vidyasabale@gmail.com*

[d]*Department of Pharmacology, Dadasaheb Balpande College of Pharmacy, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, 440037, India. E-mail: kaleemmubin88@gmail.com*

[e]*Department of Biology, College of Science and Arts at Alkamil, University of Jeddah, Saudi Arabia. E-mail: tasar@uj.edu.sa*

[f]*Department of Pharmaceutical Chemistry, College of Pharmacy, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia. E-mail: amrathore@tu.edu.sa*

[g]*Department of Pharmaceutics, Faculty of Pharmacy, Northern Border University, Arar, Saudi Arabia. E-mail: M.Mujtaba@nbu.edu.sa*

[h]*Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O. Box 173, Al-Kharj 11942, Saudi Arabia. E-mail: m.anwer@psau.edu.sa*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ra02882a