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Multi-functionalized biologically active isatin-tagged dihydropyrimidine derivatives: green synthesis by the use of recyclable Fe-dopped Ce-oxide nanoparticles, computational studies and *ex vivo* cytotoxic activity against breast cancer cells

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A new class of compounds was designed and synthesised using a molecular hybridisation technique based on the dihydropyridine, isatin, triazole, thiazole, benzothiazole, and glucose scaffolds. The alkyne derivatives of dihydropyridine were synthesised by using reusable Fe-doped Ce-oxide nanoparticles *via* a three-component Biginelli reaction. The substances were then tested for their cytotoxic effects on two human breast tumour cell lines, MCF-7 and MDA-MB-231, as well as non-cancerous breast epithelial cell lines (*i.e.*, HEK293). The primary objective was to synthesise the more efficient breast cancer cell inhibitory molecules, which contain multiple scaffolds, and to investigate their potential as anti-breast cancer cell inhibitory therapeutic agents. Notably, compound-**6**, **7** and **14a** exhibited remarkable anti-cancer activity against two prominent breast-cancer cell-lines, MCF-7 and MDA-MB-231. The IC_{50} values of the compounds **6**, **7**, and **14a** against MCF-7 and MDA-MB-231breast cancer cell lines were found to be the lowest. The successful synthesis of these dihyropyrimidines using an environmentally friendly approach emphasises the significance of sustainable and eco-friendly methodologies in pharmaceutical research.

Introduction

Today, breast cancer is the most common disease and the second most prevalent cause of cancer death among women.[1] Many commercially available anti-breast cancer medications, such as alpelisib, anastrozole, cyclophosphamide, docetaxel, and tamoxifen citrate, are used to treat breast cancer (Fig. 1). Drug resistance to cancer chemotherapeutic agents is a profound medical issue. Moreover, many breast cancer patients are non-responsive or non-tolerant to most of the commercially available anti-breast cancer drugs.[2] As a result, there is a pressing need to design hybrid chemotherapeutic medication with multiple modes of action in a single molecule, apart from exploiting novel targets. These merged pharmacophores may address the active sites of many targets and provide a way to overcome drug resistance. The design of procedures with the lowest environmental impact is another significant element of modern organic synthetic methodology.[3] The use of one-time catalysts (metallic, acidic, and basic) and organic solvents is the primary source of environmental pollution.[4] The development of a new efficient and environment friendly improved process in organic synthesis is a need of the hour. In the past few years, carrying out organic reactions using new recyclable and waste-derived catalysts in green solvents has gained popularity due to environmental concerns.[5,6] One-pot cascade reactions are preferred over conventional methods since they are simple, quick, efficient, highly selective, give higher yields, maintain good atom economy, involve minimum steps, and eliminate waste production.[7] Biginelli reaction is a three-component reaction and it has received a lot of attention in the last few years because a variety of catalysts have been found that enable the synthesis of the resulting dihydropyrimidines (DHPMs) with exceptional yield, in contrast to the inconsistent performance observed in the early studies.[8] The Biginelli reaction is a one-pot condensation reaction with three components, which produces biologically active dihyropyrimidine by using β-keto esters, aldehydes, and urea/thiourea.[9] Several one-pot strategies for synthesising DHPM derivatives have been documented over the past decade, and several modifications have also been established to enhance the

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