European Journal of Pharmaceutical Sciences 188 (2023) 106529

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Design, synthesis and biological evaluation of a novel bioactive indane scaffold 2-(diphenylmethylene)c-2,3-dihydro-1H-inden-1-one with potential anticancer activity

Tao Zhang [a,b,c,*,1], Vilmar Bandero [c,1], Claire Corcoran [c], Ismael Obaidi [b,d], Manuel Ruether [e], John O'Brien [e], Lorraine O'Driscoll [c], Neil Frankish [c], Helen Sheridan [b,c,*]

[a] School of Food Science and Environmental Health, Technological University Dublin, Grangegorman, Dublin 7, D07 ADY7, Ireland
[b] The Trinity Centre for Natural Products Research (NatPro), School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, D02 PN40, Ireland
[c] Drug Discovery Group, School of Pharmacy and Pharmaceutical Sciences and Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, D02 PN40, Ireland
[d] College of Pharmacy, University of Babylon, Babylon, Iraq
[e] School of Chemistry, Trinity College Dublin, Dublin 2, Ireland

ARTICLE INFO

Keywords:
Indanone
Benzophenones
Anticancer
In vitro cytotoxicity
Cell cycle analysis

ABSTRACT

Over the past decades, designing of privileged structures has emerged as a useful approach to the discovery and optimisation of novel biologically active molecules, and many have been successfully exploited across and within different target families. Examples include indole, quinoline, isoquinoline, benzofuran and chromone, etc. In the current study, we focus on synthesising a novel hybrid scaffold constituting naturally occurring benzophenone (**14**) and indanone (**22**) ring systems, leading to a general structure of 2-(diphenylmethylene)-2,3-dihydro-1H-inden-1-one (**23**). It was hypothesised this new hybrid system would provide enhanced anti-cancer activity owing to the presence of the common features associated with the tubulin binding small molecule indanocine (**10**) and the estrogen receptor (ER) antagonist tamoxifen (**24**). Key hybrid molecules were successfully synthesised and characterised, and the *in vitro* cytotoxicity assays were performed against cancer cell lines: MCF7 (breast) and SKBR3 (breast), DU145 (prostate) and A549 (lung). The methyl-, chloro- and methoxy-, *para*-substituted benzophenone hybrids displayed the greatest degree of cytotoxicity and the *E*-configuration derivatives **45**, **47** and **49** being significantly most potent. We further verified that the second benzyl moiety of this novel hybrid scaffold is fundamental to enhance the cytotoxicity, especially in the SKBR3 ($HER2^+$) by the *E*-methyl lead molecule **47**, MCF7 (ER^+) by **45** and **49**, and A549 (NSCLC) cell lines by **49**. These hybrid molecules also showed a significant accumulation of SKBR3 cells at S-phase of the cell cycle after 72 hrs, which demonstrates besides of being cytotoxic *in vitro* against SKBR3 cells, **47** disturbs the replication and development of this type of cancer causing a dose-dependent cell cycle arrest at S-phase. Our results suggest that DNA damage might be involved in the induction of SKBR3 cell death caused by the hybrid molecules, and therefore, this novel system may be an effective suppressor of HER2+/Neu-driven cancer growth and progression. The present study points to potential structural optimisation of the series and encourages further focussed investigation of analogues of this scaffold series toward their applications in cancer chemoprevention or chemotherapy.

1. Introduction

The indane scaffold (**1**) is of key importance in medicinal chemistry. It occurs in a range of natural products that have been isolated from organisms that occur at different evolutionary levels in the plant kingdom. Indane metabolites have been isolated from natural resources include simple indanone (**2**) from the cyanobacterium *Nostoc* (Jaki et al., 1999), tripartin (**3**) from the culture broth of the *Streptomyces* sp. associated with a larva of the dung beetle *Copris tripartitus* (Kim et al., 2013), the illudalane sesquiterpenes granulolinden A (**4**) and

* Corresponding authors.
E-mail addresses: tao.zhang@TUDublin.ie (T. Zhang), banderv@tcd.ie (V. Bandero), corcorcl@tcd.ie (C. Corcoran), obaidii@tcd.ie (I. Obaidi), ruethern@tcd.ie (M. Ruether), jeobrien@tcd.ie (J. O'Brien), lodrisc@tcd.ie (L. O'Driscoll), nfrnkish@tcd.ie (N. Frankish), hsheridn@tcd.ie (H. Sheridan).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ejps.2023.106529
Received 8 February 2023; Received in revised form 23 June 2023; Accepted 14 July 2023
Available online 17 July 2023