RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 45619

Design and synthesis of novel spirocyclic oxindole based hybrid scaffolds: *in silico* docking approach towards therapeutic target exploration

Ravindra Kumar Upadhyay,[ab] Keshav Kumar Saini,[ac] Ravi Kant,[d] Neha Chaudhary,[e] Yogita Tonger,[a] Arun Kumar[f] and Rakesh Kumar *[a]

Received 22nd September 2025
Accepted 6th November 2025

DOI: 10.1039/d5ra07175e

rsc.li/rsc-advances

The isatin derivatives exhibit various pharmacological activities, including antihypertensive, anti-inflammatory, and ACE-inhibitory effects. The synthetic flexibility of isatin makes it valuable for synthesising various heterocycles, including pharmacologically potent spirocyclic derivatives. In this paper, an efficient procedure is employed for the synthesis of novel alkyne-appended spiro[indoline-3,3′-pyrrolizin]-2-one derivatives (**6–8**) as a potential anti-inflammatory agent predicted by molecular docking *via* a catalyst-free reaction from alkyne isatin, the starting material. Subsequently, these compounds were treated with the azide derivative of isatin to get the triazolated derivatives (**11–14**), which were further reacted with L-hydroxyproline in ethanol in the presence of $InCl_3$ as a catalyst to get the final products (**15–19**). Molecular docking studies of all the synthesised ligands were carried out to examine the interactions of the ligands with the active sites of the COX-2, a key enzyme in the inflammatory pathways responsible for prostaglandin synthesis. All the synthesised compounds have shown good binding affinity towards the targeted enzyme. Herein, compound **19** displayed the highest binding affinity, −10.3 kcal mol^{-1}, among all the synthesised compounds. Thus, the synthesised compound holds the potential to exhibit anti-inflammatory activity similar to that of celecoxib, the standard reference drug.

1. Introduction

Indoline (I), pyrrolizine (II), and oxindole (III) (Fig. 1) scaffolds are present in many natural products such as physostigmine,[1] senecionine,[2] and alstonisine[3] and are incorporated in drugs to show a diverse range of biological activities, such as antihypertensive, anticancer, anti-inflammatory and angiotensin-converting enzyme inhibitory effects.[4,5] Since they exhibit a wide variety of pharmacological activities,[6,7] there is a compelling need to design and synthesise novel derivatives of these heterocyclic compounds to further enhance their therapeutic potential.[8]

Oxindoles (III) are a class of heterocyclic[9] organic compounds that commonly exist as natural products of various plants and in the body fluids and tissues of mammals.[10,11] Baeyer and Knop reported the first oxindole synthesis in 1866. The oxindole-containing compounds illustrate a broad area of pharmacological activities, such as antimicrobial,[12] antiviral,[13] antitubercular,[14] antioxidative,[15] tyrosinase inhibitory,[16] anti-rheumatic arthritis,[17] *etc.* There are various commercially available drugs (Fig. 2) containing an oxindole core that are widely used and well accepted in the market.[18]

Due to the synthetic versatility of isatin (indole-2,3-dione, IV), it is used as a precursor for drug synthesis. It can also be utilised for the synthesis of various heterocyclic compounds, including indole and pyrrolidine derivatives.[19] The pharmacological activity of isatin derivatives is intriguing, and they are widely used as antifungal,[20] antiviral,[21] anticonvulsant,[22] antibacterial,[23] anti-Alzheimer,[24] antioxidant[25] and antimicrobial[26] therapeutics.

Pyrrolizines play an important role in the synthesis of numerous biologically active natural alkaloids. Due to their capacity to produce reactive pyrrolic metabolites that can bind to DNA and create cross-links, they are speculated to have anti-cancer activity. The [3 + 2] cycloaddition reaction, known as 1,3-dipolar cycloaddition, has become a potent method for creating five-membered heterocyclic molecules. For the [3 + 2] cycloaddition reactions, several 1,3-dipoles have been used, including

[a]*Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India. E-mail: rakeshkp@email.com*

[b]*Department of Chemistry, Sri Venkateswara College, University of Delhi, New Delhi 110021, India*

[c]*Department of Chemistry, Dyal Singh College, University of Delhi, Lodhi Road, New Delhi 110003, India*

[d]*Department of Chemistry, Government Post Graduate College, Noida, G.B. Nagar, UP 201301, India*

[e]*Centre for Computational Biology & Bioinformatics, Central University of Himachal Pradesh, Dharamshala, Himachal Pradesh-176206, India*

[f]*Dept. of Environmental Sciences Central University of Himachal Pradesh, Dharamshala, Himachal Pradesh-176206, India*