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Synthesis of a bisindole enyne with anticancer properties

Ganesh Chandra Midya [a,b], Samir Mandal [b], Rakesh Paul [b], Jyotirmayee Dash [b,*]

[a] Department of Chemistry, Jogesh Chandra Chaudhuri College, 30, Anwar Shah Road, Kolkata, 700033, India
[b] School of Chemical Sciences, Indian Association for the Cultivation of Science, 2A & 2B Raja S. C. Mullick Road, Jadavpur, Kolkata, 700032, India

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ABSTRACT

We herein synthesize a bisindole enyne using the iron-catalyzed environmentally benign dimerization method. The enyne kills cancer cells by arresting the cell cycle at the G2/M phase via the necroptosis pathway, a non-apoptotic form of cell death that is also considered a promising and attractive pathway to induce cancer cell death. The inherent fluorescent property has been used to study its localization in cells and its binding interactions with genomic DNA. This work demonstrates bisindole enyne motifs could be a new pharmacophore for developing anticancer agents.

1. Introduction

Cancer remains a critical health problem, and its treatment holds great promise. Depending on the type and stage of cancer, patients are treated with various therapies such as chemotherapy, radiation therapy or sometimes both. Drugs used during chemotherapy have serious side effects on the patients. Therefore, new pharmacophores must be developed to overcome such effects. The indole motif is a privileged and prominent structural motif having a heterocyclic ring system widely distributed in numerous natural and biologically active compounds [1–3]. Indole is readily available and its derivatives are well-known scaffolds in medicinal chemistry exhibiting promising biological properties. Owing to the diverse structural features of indole alkaloids, they exhibit a range of biological profiles, including anti-inflammatory, anticancer, antimicrobial, analgesic, and antihypertensive activities [4–7]. Thus, indoles are building blocks in various biologically active compounds featuring interesting pharmaceutical properties [8–10]. On the other hand, enynes are also a valuable scaffold in Organic Chemistry and are present in many bioactive molecules and drug intermediates [11–13]. These encouraged us to design a class of molecules with an indole ring and an enyne unit. The death of cancer cells, either in a programmed way via apoptosis or by accidental type via necrosis, is a natural barrier to cancer cell development [14–16]. However, a combination of apoptosis and necrosis process commonly known as necroptosis has emerged as a promising therapeutic pathway for cancer treatment [17,18]. We herein report the synthesis of an enyne containing two indole motifs using a direct iron-catalyzed dimerization reaction. The enyne stains the nucleus and induces cell cycle arrest at the G2/M phase. We have further shown that the enyne can cause cell death via the necroptosis pathway and interact with the genomic DNA.

2. Experimental section

2.1. General information

All experiments were carried out under an inert argon atmosphere in flame-dried flasks. Solvents were dried using standard procedures. All starting materials were obtained from commercial suppliers and used as received. Products were purified by flash chromatography on silica gel (100–200 mesh, Merck). ^{1}H NMR spectra were recorded at 500 MHz using Brü ker AVANCE 500 MHz and JEOL 400 MHz instruments at 298 K. Signals are quoted as δ values in ppm using residual protonated solvent signals as internal standard ($CDCl_3$: δ = 7.26 ppm, s). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on either a JEOL-400 (100 MHz) or a Brüker AVANCE 500 MHz (125 MHz) with complete proton decoupling. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane with the solvent as the internal reference (CDCl3: δ 77.16 ppm). HRMS analyses were performed with Q-TOF YA263 high-resolution (Water Corporation) instruments by + ve mode electrospray ionization.

2.2. Synthesis of the enyne

Preparation of 5-iodo-1-methyl-1H-indole 2. To a solution of 5-

* Corresponding author.
E-mail address: ocjd@iacs.res.in (J. Dash).

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