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Short Communication

The Anticancer Drug Ellipticine: Insights of Pharmacological Activity and Mechanism of Action

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INTRODUCTION

The tetracyclic natural product Ellipticine (5,11-dimethyl-6H-pyrido[4,3-b]carbazole) is an alkaloid found in Apocynaceae plants whose derivatives exhibit anti-cancer properties [1]. Ellipticine possesses a fused benzimidazole ring, and the substitution at the C-9 position substantially increases the cytotoxic activity. Notably, 9-hydroxy-N-methylellipticinium acetate, an Ellipticine derivative, has emerged as a clinically successful drug for treating metastatic breast cancer, myeloblastic leukemia, and certain solid tumors. Most recent studies revealed that Ellipticine and its derivatives show high efficacy against HIV due to its effectiveness, minimal toxic side effects, and absence of hematological toxicity [2]. It is also noted that like many anti-cancer agents Ellipticine exhibits a multi-modal mechanism of action with DNA intercalation and topoisomerase-II inhibition. Ellipticine also uncouple mitochondrial oxidative phosphorylation and thereby disrupt the energy balance of cells. Over the last two decades, the synthesis of Ellipticine and its derivatives for clinical purposes to treat several types of cancer has become a hot topic in organic chemistry.

DESCRIPTION

Discovery and synthesis

Ellipticine was first identified by Goodwin et al., from the leaves of the Australian evergreen tree Ochrosia Ellipticine 1959. In the same year, Woodward and co-workers reported the first synthesis of Ellipticine. Over the past few decades, the syntheses of these natural product analogs have attracted many research groups to improve anticancer activities. Because of their excellent pharmacological importance, and the potent and selective inhibition of cell growth and proliferation, this group of alkaloids has provoked us towards its synthesis [3]. Recently, we described the gram-scale total synthesis of Ellipticine using Pd-catalyzed decarboxylative cross-coupling as a key step [4]. This study not only demonstrates the scalability and robustness of the synthetic approach but also highlights the adaptability and effectiveness of this method in obtaining a wide range of structurally diverse molecules, especially in medicinal chemistry.

Mechanism of action

In the last decade, Ellipticine and its derivatives have been extensively studied due to their antitumor and anti-HIV activities. Ohashi, et al. reported that Ellipticine also causes the selective inhibition of p53 protein phosphorylation in various human cancer lines which agrees with its cytotoxic activity [5]. However, various mechanisms of action of Ellipticine have been proposed to demonstrate these effects. The first mechanism of action of Ellipticine was reported including DNA intercalation and topoisomerase II inhibition. Subsequently, bio-oxidation and adduct formation, kinase inhibition, and interaction with p53 tumor suppressor have been surveyed. The scope of this short communication covers salient features of the biological activity of Ellipticine, and its mechanism of action.

DNA intercalation and topoisomerase II inhibition

Ellipticine causes damage to the structural integrity of DNA through covalent binding by forming covalent DNA adducts after its enzymatic activation with Cytochrome P450 (CYP) or peroxidases [6]. However, the metabolites responsible for such binding have not yet been characterized. The formation of a ternary complex between topoisomerase II, DNA, and drug is critical for nucleic acid breakage and subsequent cell death.

Bio-oxidation and adduct formation

Auclair and Paoletti demonstrated that Ellipticine also serve as asubstrate for peroxidises *in vivo* by employing a Horse Radishperoxidise (HRP)-hydrogen peroxide oxidizing system as a model of bio-oxidation [7]. Later, Stiborova, et al. identified the formation DNA adducts after activation of bycytochrome P450

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(CYP) and have isolated several metabolites formed by human cytochrome P450 enzymes [8].

Kinase inhibition

c-Kit kinase is a type III Receptor Tyrosine Kinase (RTK), which plays a key role in mast cellsurvival, differentiation, maturation and function. The most common enzymatic pocket mutation in c-Kit kinase is the D816V point mutation, which is associated with germ cell tumours, adult mastocytosis and a small proportion of a typical pediatric mastocytosi [9]. It was reported that several Ellipticine derivatives exhibited c-Kit kinase inhibition. Among them, 9-Hydroxyellipticine and 9-hydroxy-N-methylellipticinium was the most active of the series, with equal inhibition of wild type and D816V mutated c-Kit.

Interaction with p53 tumor suppressor

It is evident that Ellipticine and several derivatives can activate the transcription function of p53, increasing the function of some mutant p53 types by 5–6 fold. Moreover, Immuno precipitation experiments demonstrated that treatment with Ellipticine induced a shift of mutant p53 conformation towards that of wild type p53, thus restoring function.3-(9-methoxy-5,11-dimethyl-6H-pyrido[4,3-b]carbazol-6-yl)propan-1-aminium chloride identified as a potential lead compound for p53 activation and studied its effects on three cancer cell lines [10].

CONCLUSION

In summary, we have discussed the mechanisms of actions of Ellipticine's anticancer activity, which associated include DNA intercalation and topoisomerase II inhibition, bio-oxidation and adduct formation, kinase inhibition, Interaction with p53 tumor suppressor. We believe that this study would be useful further elicit widespread attention in the quest for more research towards the bioactivity of Ellipticine and their derivatives.

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