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Research Article

# $Cp_2ZrCl_2$: AN EFFICIENT CATALYST FOR MULTICOMPONENT SYNTHESIS OF CAROTENOID DEHYDROSQUALENE SYNTHASE INHIBITING PYRANO[2,3-d]PYRIMIDINEDIONES

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**ABSTRACT**

**Objectives:** The present protocol deals with zirconocene dichloride ($Cp_2ZrCl_2$) catalyzed synthesis of pyrano[2,3-d]pyrimidinediones through one-pot multicomponent reactions of aromatic aldehydes with malononitrile and barbituric acid at ambient temperature. All the synthesized compounds were characterized and evaluated for antibacterial, antifungal, and antioxidant activities. Furthermore, a molecular docking was carried out to reveal the atomic insights between synthesized compounds and carotenoid dehydrosqualene synthase (PDB ID: 3ACX).

**Methods:** All the synthesized compounds were evaluated for their *in vitro* antimicrobial activity by diffusion method. Antioxidant activities such as 1,1-diphenyl-2-picrylhydrazyl and radical scavenging activity. A mixture of barbituric acid 1 (1 mmol), malononitrile 2 (1 mmol), benzaldehyde 3a (1 mmol), ethanol (5 mL), and $Cp_2ZrCl_2$ (5 mol %) was stirred at ambient temperature for specified time. After completion of reaction as indicated by thin-layer chromatography, the obtained crude product was filtered and purified by column chromatography on silica gel (Merck, 60–120 mesh) using ethyl acetate:pet. ether to afford pure product which was then characterized by spectroscopic methods such by FTIR, nuclear magnetic resonance ($^1H$ NMR), $^{13}C$ NMR, and mass spectroscopy.

**Results:** All the synthesized pyrano[2,3-d]pyrimidinediones were characterized by spectroscopic analysis. The results revealed that pyrano[2,3-d] pyrimidinediones (4 a-k) displayed the zone of inhibition in the range of 3–13 mm. The most active compound 4b displayed largest zone of inhibition of 13 mm for *Escherichia coli* (NCIM-2832) and 9 mm for *Bacillus subtilis* (NCIM-2635). The antifungal and antioxidant activity of all synthesized pyrano[2,3-d]pyrimidinediones (4a-k) showed moderate to good activity. Molecular docking studies suggest that pyrano[2,3-d]pyrimidinediones might inhibit the carotenoid dehydrosqualene synthase activity.

**Conclusion:** All the synthesized pyrano[2,3-d]pyrimidinediones display moderate to good antibacterial, antifungal, and antioxidant activity. This molecular docking studies supported that pyrano[2,3-d]pyrimidinediones might inhibit the carotenoid dehydrosqualene synthase (PDB ID: 3ACX).

**Keywords:** Zirconocene dichloride, Pyrano[2,3-d]pyrimidinediones, Antimicrobial, Antioxidant, Carotenoid dehydrosqualene synthase, Molecular docking.

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## INTRODUCTION

Zirconocene represents an important class of organometallic compounds in which zirconium is sandwiched between two cyclopentadienyl rings. Due to high reactivity and feeble acidity, zirconocenes have attracted substantial applications in the area of catalysis [1]. Initially, the zirconocene catalyst was limited to the olefin polymerization. However, recent reports concerning to successful applications of zirconocene in synthetic chemistry have been demonstrated their versatility in organic synthesis which has spurred a resurgence of interest in this class of compounds [2]. Zirconocene dichloride ($Cp_2ZrCl_2$) is an air and moisture stable and non-hazardous, $d^0$ zirconocene that has been subject of immense interest in catalytic technology due to its Lewis acidic character. It is one of the most efficient and widely employed catalysts in Ziegler–Natta polymerization [3]. Organometallic Lewis acids play an important role in green chemistry and sustainable development [4]. Recently, $Cp_2ZrCl_2$ has been explored for the synthesis of carbonyl group transformation reactions [5], bis(indole)methanes [6], intramolecular coupling of alkyne, EtMgBr (ethylene or CO) [7], quinozolin-4(3H)-ones [8], 1-amidoalkyl-2-naphthols [9], and benzimidazoles [10]. In addition, $Cp_2ZrCl_2$ has also been employed for acetylation of phenols/alcohols/amines [11], coupling of terminal alkynes, and intramolecular coupling of amines and alkynes. Significant application of zirconium in organic synthesis mainly includes $Cp_2Zr(II)$ species, the so-called zirconocene [12] and Reformatsky and Barbier reactions [13].

Pyrano[2,3-d]pyrimidinediones are heterocyclic scaffolds with multifarious biological applications. They are typical annelated uracils used in the treatment of B16 melanoma and P388 leukemia [14]. In addition, they possess antibronchitic [15], cardiotonic [16], antifungals [17], antimalarial [18], antihypertensive [19], analgesics [20], and antiviral [21]. Moreover, many of its derivatives are used in natural products, carbohydrates, alkaloids, polyether antibiotics, pheromones, antihypertensives, cardiotonic, bronchodilator, antibronchitic and antitumor activity, anti-inflammatory activity, antiallergic, and antibronchitic [22-25]. Due to intriguing structure and diverse biological properties, considerable efforts have been devoted for the development of efficient methods for the synthesis of pyrano[2,3-d]pyrimidinediones [26]. Among several approaches developed for this purpose, one-pot multicomponent reaction of aromatic aldehydes with active methylene compounds and barbituric acid represents the most efficient and powerful process for synthesis of pyrano[2,3-d]pyrimidinediones [27]. Several techniques such as ultrasound, microwave irradiation, as well as ionic liquids have been reported to carry out this reaction [28,29]. However, despite impressive progress, there is a still scope to develop new protocol for synthesis of