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Synthesis and Anti-Cancer Activity of New Spiro[5.5]undecane Compound by Efficient Microwave Reaction

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Abstract

Microwave-assisted organic synthesis has gained significant attention for speeding up reactions, improving yields, and reducing reaction times. In this study, we investigated the microwave-induced reaction between dimedone and (1E,4E)-1,5-bis(4-fluorophenyl)penta-1,4-dien-3-one to synthesize 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione. The reaction was conducted using a microwave irradiation system, which allowed for a more environmentally friendly and energy-efficient process. Key parameters such as reaction time, temperature, and power settings were optimized for maximum yield. The synthesized compound was characterized using spectroscopic methods, including IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. The same reaction was also performed using a conventional method at room temperature which took 2-3 hours. The microwave approach was preferred due to its efficiency. Our findings indicate that microwave irradiation significantly enhances reaction efficiency, offering a fast method for synthesizing complex organic molecules. This technique has potential applications in various fields, including pharmaceutical chemistry and materials science, with a growing demand for sustainable and efficient chemical processes. Additionally, we conducted an in vitro anti-cancer activity experiment to evaluate the synthesized compound's biological activity.

Keywords

Anti-cancer, dimedone, microwave, synthesis.

Article History

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INTRODUCTION

The Spiro[5.5] undecane structure is known to occur in phytochemicals, as well as in alkaloids, terpenoids, and other natural products (Ahmed et al., 2012). Numerous spiro-oxindole derivatives have been found to have a wide range of biological applications, including antimicrobial and antitumor activities, as well as acting as inhibitors of the human NK-1 receptor (Okita and Isobe, 1994; Puri S et al., 2023) Spiro heterocycles and their derivatives were synthesized using dimedone, and the resulting compounds were tested in vitro for their antibacterial activity against Gram negative bacteria including *Escherichia coli* and Gram positive bacteria such as *Staphylococcus aureus* (Majumdar et al., 2018)

Microwave irradiation has various advantages over classical reactions, including greater yields, faster reaction times, and fewer byproducts (Soni et al., 2020). This study focused on developing microwave-assisted synthesis methods for 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione **(2a)** through a cascade cyclization process involving a [5+1] double Michael addition reaction.

A literature review reveals limited research on the reactivity of α,β-unsaturated carbonyl compounds with dimedone (**1a**) and there was limited information on the biological activities of the products of the combination of dimedone (**1a)** with the (1E,4E)-1,5-Bis(4-fluorophenyl)penta-1,4-dien-3-one (Ahmed et al., 2011) . Accordingly, we herein report the synthesis of 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione (**2a**) from dimedone and (1E,4E)-1,5-Bis(4-fluorophenyl)penta-1,4-dien-3-one (**1b**), along with an investigation of its anticancer activity (Figure 1).

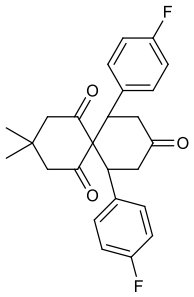

Figure 1: Structural formula of 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione (**2a**).

MATERIALS AND METHODS

Chemical and Reagents

Dimedone **(1a)**, p-fluoroaldehyde, dichloromethane, and triethylamine were obtained from Sigma-Aldrich and Merck. Analytical grade chemicals were utilized unless otherwise specified. (1E,4E)-1,5-bis(4-fluorophenyl)penta-1,4-dien-3-one **(1b)** was synthesized through an aldol condensation reaction involving substituted benzaldehydes and acetone in a 2:1 ratio, using an ethanolic NaOH solution as the catalyst as described in our previous research (Burgaz et al., 2024) (Figure 2).

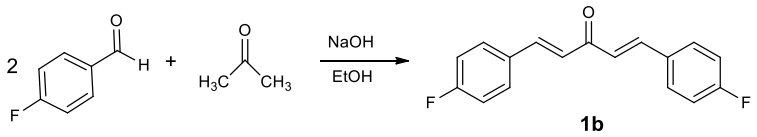

Figure 2: The general synthesis reaction of penta-1,4-diene-3-one derivatives.

^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as the solvent and TMS as the internal reference on a Bruker Avance 400 MHz Spectrometer, as shown in the supplementary information. MS spectra were collected with an Agilent 19091 N-136 GC–MS instrument. A CEM-Focused Microwave™ Synthesis System, which has programmable settings, infrared temperature monitoring, and a continuous microwave power supply system with a tunable output from 0 to 300 W (±30 W), was utilized to conduct microwave-irradiated processes.

Our study aimed to develop microwave-assisted synthesis procedures for 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione **(2a)** via a cascade cyclization process involving the [5+1] double Michael addition reaction. The MW-process not only produces high-quality results, but also shortens reaction times from 2-3 hours to about 15-20 minutes. This reaction requires the coupling of dimedone **(1a)** and (1E,4E)-1,5-Bis(4-fluorophenyl)penta-1,4-dien-3-one (**1b)** catalyzed by triethylamine at microwave. This method developed demonstrates exceptional efficiency in producing spiro[5.5]undecane derivative **2a**, achieving yields of up to 98 % (Figure 3).

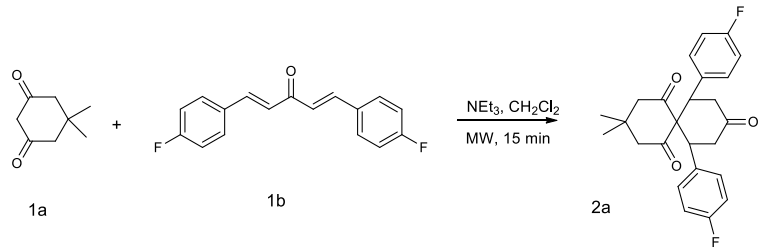

Figure 3: Synthesis reaction of 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione (**2a**) from starting materials.

General microwave technique for the synthesis of 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione (2a): A mixture of dimedone **(1a)** (1 mmol) and (1E,4E)-1,5-Bis(4-fluorophenyl)penta-1,4-dien-3-one (**1b)** (1 mmol) were weighed into a microwave flask 5 mL CH_2Cl_2 and triethylamine (1.25 mmol, 0.128 g) were added. The reaction mixture was heated under microwave irradiation (200 W, 40 °C) for 15 minutes. The reaction steps are followed by TLC testing. The reaction mixture was put into 10 mL of cold water and extracted using chloroform (3x20 mL). The organic extracts were dried with $MgSO_4$. Column chromatography (gradient, from Hexane: Ethyl Acetate (4/1) was used after solvent evaporation.

Cell culture and cytotoxicity assay

The anti-cancer activity of compound 2a was evaluated against the SK-HEP-1 adenocarcinoma cell line. The cells were kept in DMEM supplemented with 10% FBS, 100 U/mL penicillin, 2 mM L-glutamine, 100 mg/mL streptomycin, and NEAA at 37 °C in humidified CO2 (5%) (ESCO CelCulture® CO_2 incubator) SK-HEP-1 cancer cell lines were subjected to a 48-hour. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay to evaluate the anti-cancer activity of the newly synthesized compound. At a density of $5x10^3$ cells/ml, cells were seeded into 48-well plates and subjected to varying doses of the chemicals dissolved in the maintenance medium. DMSO was used as the solvent-control group. The effect of DMSO at peak chemical concentrations was determined to be nonsignificant, the final concentration of DMSO was consistently kept below 1%. Following the 48-hour treatment, the MTT assay proceeded as previously described (Kunter et al., 2023). MTT assays have been carried out three times independently.

RESULTS AND DISCUSSION

The synthesis of new substituted Spiro[5.5]undecane-1,5,9-trione (or 1,3,5,9-tetraone) derivatives has garnered significant interest in recent years because of their possible uses in medicinal chemistry and materials science. In this study, we successfully synthesized 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione and characterized it using ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectrometry (MS). Despite numerous proposals in the literature, no consensus has been reached regarding the optimal treatment strategy for hepatocellular carcinoma (HCC), which remains a significant clinical challenge. Although cytotoxic chemotherapeutics are available for clinical use, their efficacy has been limited. Currently, liver transplantation or surgical resection remains the most effective treatment option for HCC. Therefore, there is a pressing need for novel insights to enhance our understanding of HCC and to develop more effective therapeutic strategies. Each newly synthesized compound represents a potential opportunity for advancing therapeutic applications in this context. This study evaluates the anticancer properties of a newly synthesized compound. MTT assay results revealed a statistically significant, concentration-dependent reduction in the viability of the adenocarcinoma cell line SK-HEP-1 (Figure 4). Notably, compound 2a exhibited potent anticancer activity against SK-HEP-1 cells, with an IC_{50} value of 23.67 ± 4 µM.

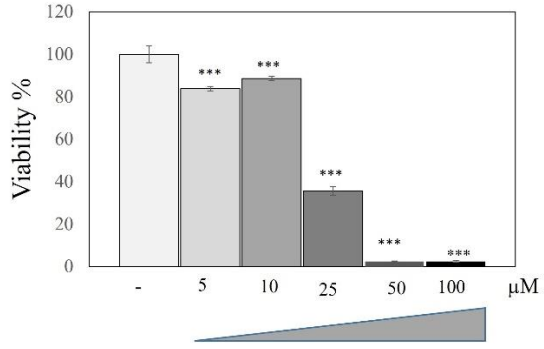

Figure 4: Effect of 2a on the viability of SK-Hep1 cells (MTT). (***p< 0,001).

This synthesized compound exhibits interesting pharmacological activity regarding anti-cancer effect on liver tissue and has shown promise as a building block for designing novel drug candidates.

7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione (2a)

White solid, (422 mg, 92%). Mp 182-192 ^{0}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06-7.02 (m, 4H, Ar-H), 6.98-6.94 (m, 4H, Ar-H); 3.80-3.75 (dd, 2H, *J*= 14.4, 4.0 Hz, H_{8e} and H_{10e}); 3.60-3.53 (t, 2H, *J*= 14.4 Hz, H_7); 2.51-2.47 (dd, 2H, *J*= 14.8, 4.0 Hz, H_{8a} and H_{10a}); 2.01 (s, 2H, H_{2a} and H_{4a}), 1.64 (s, 2H, H_{2e} and H_{4e}), 0.14 (s, 6H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.28 (C=O), 203.15, 158.78, 156.32, 129.90, 126.10, 111.16, 110.94, 65.02, 51.62, 49.62, 45.34, 39.26, 24.31. MS: 410.17 (411 [M+1]. Anal. calc. for $C_{25}H_{24}F_2O_3$ (410.17): C 73.16, H 5.89, F 9.26; found: C 73.22, H 5.92, F 9.17.

CONCLUSION

In summary, synthesizing the 7,11-bis(4-fluorophenyl)-3,3-dimethylspiro[5.5]undecane-1,5,9-trione (2a) marks a valuable step forward in the quest for new bioactive compounds, particularly within anticancer drug research. Through a microwave-assisted method, we effectively condensed dimedone and (1E,4E)-1,5-Bis(4-fluorophenyl)penta-1,4-dien-3-one, producing a novel compound with notable biological potential. The compound's in vitro anticancer assessments indicate its promising therapeutic prospects, suggesting that further structural modifications in this compound could enhance efficacy and selectivity against cancer cells. This research expands the current synthesis knowledge of spiro[5.5]undecane-1,5,9-trione derivatives and underscores their emerging utility as frameworks for anticancer agents. By positioning our findings within the broader literature, we underscore the critical need for ongoing studies on these derivatives. We aim to inspire new approaches for designing anticancer compounds with enhanced biological properties.

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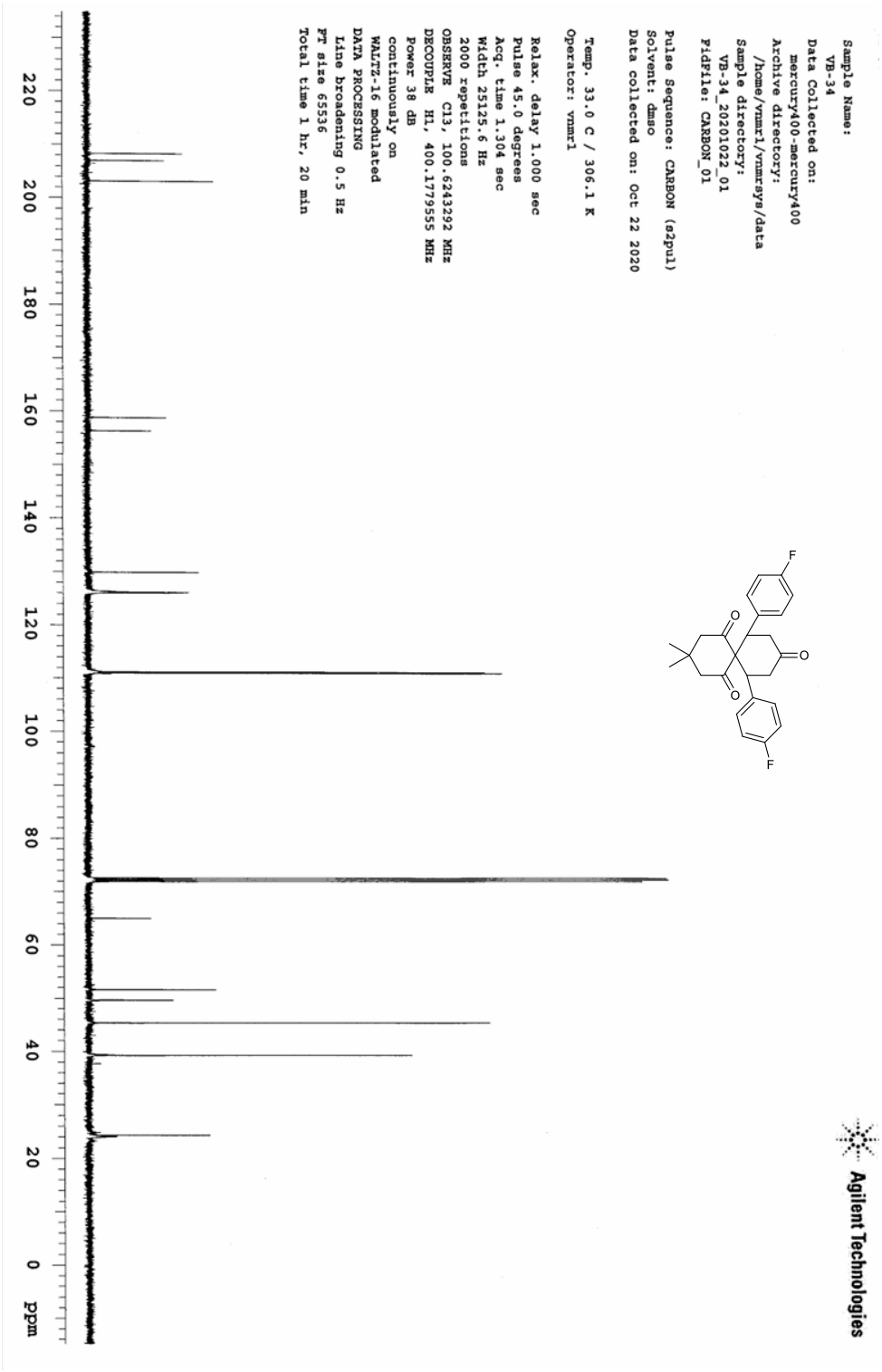
SUPPLEMENTARY INFORMATION

1. ^{1}H-NMR spectrum of **2a** compound.

2. ^{13}C-NMR spectrum of **2a** compound.



3. MS spectrum of **2a** compound.