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http://www.aphinfo.com/ijmpbs

July-September 2023

INTERNATIONAL JOURNAL OF MEDICAL, PHARMACEUTICAL AND BIOLOGICAL SCIENCES

eISSN : 2832-787X, pISSN : 2832-7888

Aarya Publishing House

Research Article | Volume-3 | Issue-2 | Article ID: 0054

TOXICOLOGICAL EVALUATION OF TARGETED HYBRID COMPOUNDS: IMIDAZOPYRIDINE DERIVATIVES LINKED TO HETEROCYCLIC RING SYSTEMS FOR CANCER TREATMENT

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Received: 3 September 2023 / Revised: 22 September 2023 / Accepted: 23 September 2023 / Available online: 30 September 2023

ABSTRACT

The present study investigates the synthesis and toxicological profile of novel imidazopyridine-based hybrid compounds, linked to thiazolidinone, methyl thiazolidinone, and triazolothiadiazole. These compounds, known for their potent anticancer and antioxidant properties, were subjected to acute toxicity and cardiotoxicity studies in female Wistar rats. A dose of 500 mg/kg of compounds 5h, 6h, and 9d was administered, with no observed mortality, indicating an oral LD50 between 500-2000 mg/kg. Pathological examination, biochemical tests, and histological analysis of the heart and liver were conducted. The results show minimal hepatotoxicity and cardiotoxicity compared to doxorubicin, making these compounds promising candidates for further therapeutic development.

Keywords *– Imidazopyridine, Thiazolidinone, Triazolothiadiazole, Targeted Hybrid Compounds, Acute Toxicity, Cardiomyopathy.*

1. INTRODUCTION

Cancer treatment often involves the use of chemotherapeutic agents that target rapidly dividing cells. However, many of these agents, including tyrosine kinase inhibitors like doxorubicin, are associated with significant side effects such as cardiotoxicity and hepatotoxicity [1]. The development of safer and more effective anticancer agents is critical in minimizing these adverse effects.

Hybrid compounds, particularly those incorporating heterocyclic structures, have gained significant attention for their ability to enhance the therapeutic efficacy of anticancer drugs while reducing toxicity. Imidazopyridine, a nitrogen-containing heterocycle, is well-documented for its anticancer activity, particularly when combined with other bioactive heterocycles such as thiazolidinone and triazolothiadiazole [2-4]. The aim of this study was to synthesize novel hybrid compounds containing imidazopyridine and evaluate their toxicological profiles, particularly focusing on acute toxicity, hepatotoxicity, and cardiotoxicity.

Previous studies have reported that imidazopyridine derivatives exhibit potent anticancer activity against a variety of cancer cell lines [5-7]. In addition, the incorporation of other heterocyclic systems, such as thiazolidinone, has been shown to enhance the antioxidant and anticancer properties of these compounds [8]. However, the toxicological evaluation of such compounds remains a critical step in the development of these agents for therapeutic use. Acute toxicity studies are one of the fundamental tools in drug development, determining the lethal dose (LD50) and guiding the safe dose levels for further testing [9]. The current study

focused on evaluating the safety profile of three potent compounds (5h, 6h, and 9d) by assessing their acute toxicity, and the impact on liver and heart function in a rat model.

2. MATERIALS AND METHODS

2.1 Reagents and Solvents

All chemicals, including solvents and reagents, were obtained from commercial suppliers such as S.G. Enterprises (India), S.D. Fine Chemicals (India), and CDH (India). Silica gel G (160-120 mesh) was used for thin-layer chromatography (TLC), and Whattman no.1 filter paper was used for vacuum filtration. The solvents used for TLC were Toluene:Ethylacetate:Formic acid (T:E:F-5:4:1), Chloroform:Methanol (C:M; 9:1), and Benzene:Acetone (B:A; 9:1).

2.2 Animals

Female Wistar rats, weighing 110-115g, were used for the study, maintained under standard conditions (25±2°C, light/dark cycle) as per OECD guidelines. Animals were acclimatized for one week before the experiments.

2.3 Acute Toxicity Study

The rats were randomly divided into five groups (n=5 per group). Compounds 5h, 6h, and 9d were administered orally at a dose of 500 mg/kg body weight. The control group received 0.5 ml of 1% carboxymethylcellulose (CMC). Mortality was recorded 24 hours post-treatment, and the oral LD50 was determined.

2.4 Biochemical and Histological Analysis

Blood samples were collected after 14 days for serum analysis, including SGOT, SGPT, total protein, and alkaline phosphatase levels. The animals were sacrificed, and heart and liver tissues were preserved in 40% formalin for histopathological examination. The tissues were stained with haematoxylin and eosin and examined under a light microscope at 100x and 400x magnification.

2.5 Statistical Analysis

Data were analyzed using ANOVA followed by the Student's t-test, with a significance level set at $p<0.01$.

3. RESULTS AND DISCUSSION

3.1 Acute Toxicity

Compounds 5h, 6h, and 9d were administered at a dose of 500 mg/kg, with no mortality observed in any of the groups. Based on OECD guidelines, the compounds exhibited an oral LD50 greater than 500 mg/kg but less than 2000 mg/kg, suggesting a moderate toxicity profile.

3.2 Biochemical Parameters

The levels of SGOT and SGPT, indicative of liver function, were analyzed for each group (Table 18). Compound 6h showed values close to the control group, suggesting minimal liver toxicity. In contrast, compound 5h showed significantly higher levels of SGOT and SGPT, indicating some liver damage. Both 5h and 9d showed biochemical parameter levels lower than the doxorubicin-treated group, which exhibited severe hepatotoxicity.

3.3 Histopathological Findings

Microscopic examination of heart tissues revealed normal texture in the cardiac fibers of the test groups, with no significant alterations observed. In contrast, the doxorubicin group exhibited signs of cardiotoxicity, including vacuolation and inflammation, further highlighting the safety of compounds 5h, 6h, and 9d compared to the standard chemotherapeutic agent.

3.4 Toxicity Comparison with Doxorubicin

The results from both biochemical and histological examinations indicate that compounds 5h, 6h, and 9d have a lower risk of causing hepatotoxicity and cardiotoxicity compared to doxorubicin, which is known to cause severe side effects in cancer patients [10-14].

Table 1. Effects of potent compounds on the liver enzyme (transaminases) in liver function test.

Compound[a]	SGOT ± SEM	SGPT ± SEM
6h	39.63 ± 1.47	25.21 ± 1.78
5h	47.36 ± 2.19	51.85 ± 2.27
9d	37.83 ± 1.94**	28.46 ± 2.89**
Control[b]	36.74 ± 1.67	32.41 ± 1.62
Doxorubicin	53.29 ± 1.56	58.35 ± 2.13

Data were analyzed by ANOVA followed by Student's t-test for n = 6 at **p < 0.01.

[b] Control group-treated for 15 days with 0.5% carboxymethylcellulose.

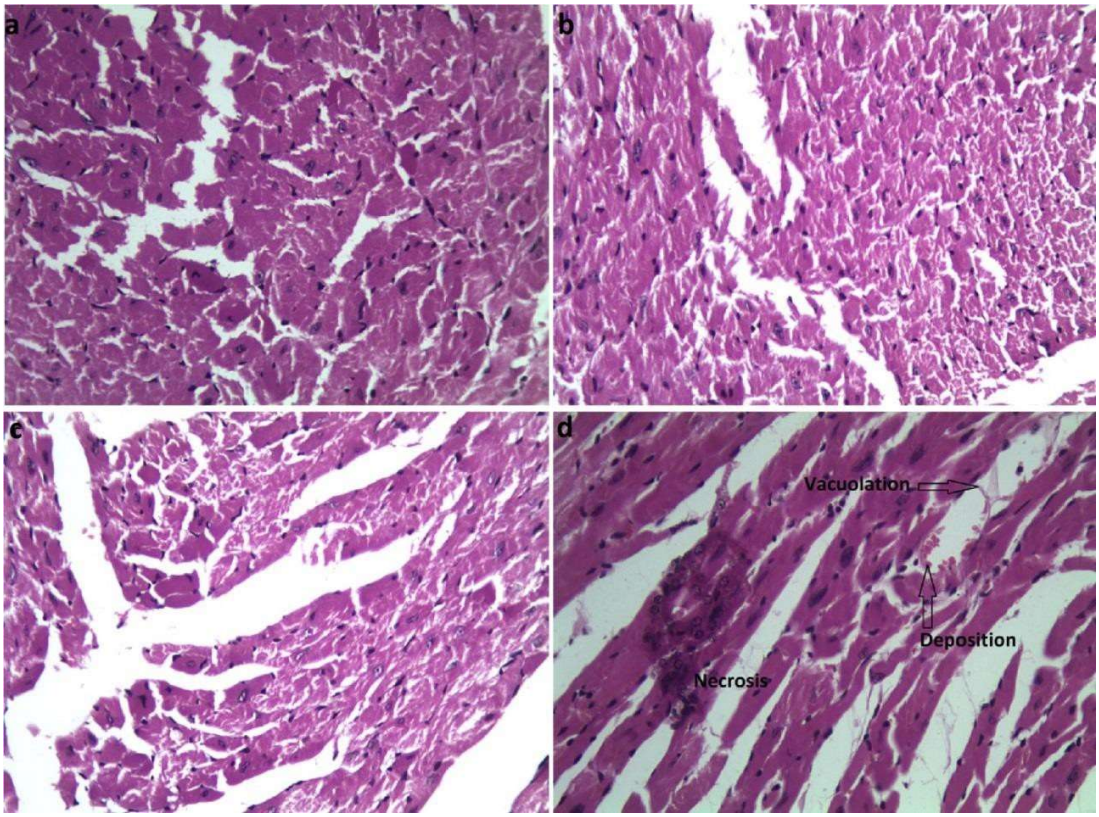

Figure 1. Microphotographs represent the response of compounds (a) 5h, (b) 6h (c) 9d and (d) doxorubicin; all three compounds represents the normal texture of cardiac fibre Microphotographs represent the response of Doxorubicin displaying cardiac muscle toxicity like necrosis, vacoulation, and deposition in left ventricle tissue.

4. CONCLUSION

The synthesized imidazopyridine-based hybrid compounds 5h, 6h, and 9d exhibit promising anticancer activity while showing a relatively safe toxicity profile in acute toxicity and cardiotoxicity studies. These compounds did not cause significant liver or heart

damage in Wistar rats, making them potential candidates for further development in cancer therapy with minimal side effects. Further studies are required to assess their long-term safety and efficacy.

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