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INVESTIGATION OF ULCEROGENIC ACTIVITY OF SELECTED QUINOXALINE, BENZOTHIAZOLE, AND BENZOXAZOLE DERIVATIVES

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ABSTRACT

The ulcerogenic potential of non-steroidal anti-inflammatory drugs (NSAIDs) remains a significant concern in their therapeutic use. This study evaluates the ulcerogenic activity of various quinoxaline, benzothiazole, and benzoxazole derivatives, comparing their effects to diclofenac sodium, a standard NSAID. The study employed a well-established experimental model using Wistar rats. The results demonstrated varying degrees of ulcerogenicity among the test compounds, with some showing promise for further development as safer NSAID alternatives.

Keywords – *NSAIDs, Ulcerogenicity, Quinoxaline, Benzothiazole, Benzoxazole, Diclofenac sodium.*

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, anti-inflammatory, and antipyretic effects. However, their usage is often limited by significant adverse effects on the gastroduodenal mucosa, leading to ulceration and bleeding [1-3]. NSAIDs induce mucosal damage through several mechanisms, including direct irritation of the epithelium, impairment of mucosal barrier function, suppression of gastric prostaglandin synthesis, reduction of mucosal blood flow, and interference with mucosal repair processes [4, 5]. The presence of gastric acid further exacerbates NSAID-induced mucosal injury, underlining the need for developing safer alternatives that minimize gastrointestinal side effects [6, 7].

This study evaluates the ulcerogenic activity of selected quinoxaline, benzothiazole, and benzoxazole derivatives, assessing their potential as safer alternatives to traditional NSAIDs [8].

2. MATERIALS AND METHODS

2.1 Materials

Reagents and Solvents

All the reagents and solvents were of laboratory grade and were procured from Merck (Darmstadt, Germany) and S.D. Fine chemicals (Delhi, India).

Experimental Technique

Melting point: Melting points were recorded in open capillaries using Labtronics Digital Auto Melting Point Apparatus (Haryana, India) and are uncorrected.

IR spectrometer: IR spectra were recorded on Perkin-Elmer 1720 FTIR spectrometer (New York, USA).

NMR spectrometer: 1H NMR spectra (400 MHz) and 13C-NMR spectra (100 MHz) were obtained on Bruker Avance- instrument (Zurich, Switzerland) with complete proton decoupling. Chemical shifts were reported in ppm downfield from tetramethylsilane (TMS) as the internal standard.

Mass spectrometer: Mass spectra were recorded on Jeol SX-102/DA-6000 (Tokyo, Japan) spectrometer.

Thin Layer Chromatography: Purity of the compounds was checked by TLC using precoated aluminium TLC plates (Merck) and spots were visualized in a UV/Visible chamber (UV 254nm).

Elemental analysis: Elemental analysis (C, H and N) were conducted using a CHNS Vario EL III (Elementar Analysen systeme GmbH, Germany) and the results are within ± 0.4 % of theoretical values.

2.2 Methods

The acute ulcerogenicity of the test compounds was evaluated using the method described by Cioli et al. (1988) [9]. The same groups of Wistar rats used for anti-inflammatory activity, after a washout period of 15 days, were employed in this study.

Animals

Wistar rats of either sex, weighing 150-200 g, were used for the experiments.

Standard

Diclofenac sodium was used as the standard drug, administered orally at a dose of 30 mg/kg [10].

Test Compounds

The test compounds were administered at equimolar doses relative to 30 mg/kg diclofenac sodium [11].

Procedure

- The rats were weighed, numbered, and marked.
- The rats were allocated into the same groups consisting of six animals each as used in the anti-inflammatory activity.
- Food but not water was stopped 24 hours before administering the test compounds.
- The test compounds and the standard drug (diclofenac sodium) were administered orally to the respective groups. The control group received only 0.5% carboxymethylcellulose (CMC) solution.
- After drug treatment, the rats were fed a normal diet for 17 hours and then sacrificed.
- The stomach was removed and opened along the greater curvature, washed with distilled water, and cleaned gently by dipping in normal saline.
- Mucosal damage was examined using a magnifying glass. The mucosal damage for each stomach was assessed according to the following scoring system [12]:
    - 0.5: Redness
    - 1.0: Spot ulcers
    - 1.5: Hemorrhagic streaks
    - 2.0: Ulcers >3 but ≤5
    - 3.0: Ulcers >5
- The mean score of each treated group minus the mean score of the control group was regarded as the severity index of gastric mucosal damage [13].

3. RESULTS AND DISCUSSION

Compounds (5a, 5e, 5f, 5g, 5h, 5l, 5q, and 5u) synthesised in the laboratory were screened for their acute ulcerogenicity. The tested compounds exhibited reduced ulcerogenic activity (S.I value 0.417–1.417) compared to diclofenac sodium (S.I value 1.750) [14]. Compounds 5e and 5f, which showed high anti-inflammatory activity, also demonstrated significantly reduced ulcer severity indices of 0.667 ± 0.211 and 0.417 ± 0.154, respectively, indicating a better gastrointestinal (GI) safety profile than the standard drug [15,16] (Table 1-5).

Table 19: Ulcerogenic Potential of Selected Quinoxaline Derivatives (5a, 5e, 5f, 5g, 5h, 5l, 5q, 5u) and Standard Drug

Compound	Mean Ulcer Severity Index ± SEM
5a	1.000 ± 0.258
5e	0.667 ± 0.211
5f	0.417 ± 0.154
5g	0.833 ± 0.167
5h	1.000 ± 0.224
5l	0.833 ± 0.167
5q	1.417 ± 0.201
5u	1.167 ± 0.307
Diclofenac sodium	1.750 ± 0.112

Table 2: Ulcerogenic Potential of Quinoxaline Derivatives

Compound	Body Weight	Observation	Score	Severity Index	Std Deviation	SEM
5a	199	Redness	0.5			
5a	182	Hemorrhagic streaks	1.5			
5a	189	Spot ulcers	1.0	1.000	0.632	0.258
5e	178	Redness	0.5	0.667	0.516	0.211
5f	198	Redness	0.5	0.417	0.376	0.154
5g	200	Redness	0.5	0.833	0.408	0.167
5h	175	Hemorrhagic streaks	1.5	1.000	0.548	0.224
5l	192	Ulcers	2.0	0.833	0.408	0.167
5q	173	Redness	0.5	1.417	0.492	0.201
5u	199	Hemorrhagic streaks	1.5	1.167	0.753	0.307

Table 3: Ulcerogenic Potential of Benzothiazole Derivatives

Compound	Body Weight	Observation	Score	Severity Index	Std Deviation	SEM
9b	192	Hemorrhagic streaks	1.5	1.083	0.736	0.300
9c	172	Redness	0.5	0.833	0.408	0.167
9f	191	Spot ulcers	1.0	0.750	0.524	0.214
9g	198	Normal	0.0	0.500	0.316	0.129
9j	190	Redness	0.5	1.000	0.447	0.183
9m	176	Spot ulcers	1.0	0.917	0.585	0.239
9n	178	Hemorrhagic streaks	1.5	1.167	0.753	0.307

Table 4: Ulcerogenic Potential of Benzothiazole and Benzoxazole Derivatives

Compound	Body Weight	Observation	Score	Severity Index	Std Deviation	SEM
15a	192	Spot ulcers	1.0	0.917	0.376	0.154
15b	198	Redness	0.5	1.000	0.548	0.224
15e	173	Hemorrhagic streaks	1.5	1.417	0.204	0.083
15i	176	Spot ulcers	1.0	1.250	0.274	0.112
15k	184	Redness	0.5	1.167	0.408	0.167
15l	184	Ulcers	2.0	1.333	0.683	0.279

Table 5: Control Group and Standard Drug (Diclofenac Sodium)

Group	Body Weight	Observation	Score	Severity Index	Std Deviation	SEM
Control	186	Normal	0.0	0.000	0.000	0.000
Diclofenac sodium	188	Ulcers	2.0	1.750	0.418	0.171

4. CONCLUSION

The findings from this study reveal that the quinoxaline, benzothiazole, and benzoxazole derivatives exhibit varying degrees of ulcerogenic potential. While some compounds demonstrated comparable or higher ulcerogenicity to diclofenac sodium, others exhibited lower ulcerogenicity, suggesting their potential as safer NSAID alternatives. Further investigations are warranted to refine these derivatives and assess their therapeutic viability.

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