BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

ACUTE ORAL TOLERABILITY AND ANTI-INFLAMMATORY ACTIVITY OF 1,3,4-THIADIAZOLE DERIVATIVES: A SECONDARY ANALYSIS

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doi:https://doi.org/10.5281/zenodo.23979663

Abstract Background: Functionally substituted 1,3,4-thiadiazoles have shown activity in preliminary in vivo inflammation screens, while their acute tolerability has been described in mice. Objective: To synthesise published safety and efficacy observations into a transparent early-stage prioritisation framework. Methods: A descriptive secondary analysis was conducted using two 2024 reports on acute oral dosing and carrageenan-induced edema. Mortality, body-mass observations, dose levels and published percentage edema inhibition were extracted. No new animal work or statistical hypothesis tests were performed. Results: The original report documented 0/5 deaths per studied compound after a single oral dose of 2,000 mg/kg, with transient clinical signs. The same publications reported anti-inflammatory effects at 50 and 100 mg/kg. For the bis(sulfanediyl) diacetohydrazide, edema inhibition at 24 hours was 40.0% at 50 mg/kg versus 30.5% at 100 mg/kg; for the diethyl diacetate, corresponding figures were 34.6% and 23.4%. These descriptive observations are not evidence of a monotonic dose–response. Conclusion: The series merits confirmatory pharmacological investigation, but the mortality-based acute screen does not establish chronic safety or therapeutic index, and efficacy findings need replication using a documented statistical plan.
Keywords: 1,3,4-thiadiazole; anti-inflammatory activity; acute oral toxicity; carrageenan; dose–response; secondary analysis.

Introduction

Early pharmacological screening must balance activity with basic tolerability, while carefully separating acute hazard classification from long-term safety and clinical efficacy. Functional substitutions on a 1,3,4-thiadiazole scaffold have been explored using oral acute-toxicity screening in mice and carrageenan-induced paw edema in rats [1,2]. Published observations make it possible to compare the reported treatment groups descriptively without representing the comparison as a new in vivo experiment.

The main questions are whether the originally reported absence of mortality supports a limited acute tolerability conclusion, whether the inflammatory model results are consistent across doses, and what information is missing for a reliable benefit–risk interpretation.

Materials and methods

Design and data sources. We performed a secondary analysis of published results from Basirova and co-authors [1,2]. Numerical outcomes were transcribed from tables in the 2024 Science and Innovation paper [2]. The IQRO publication [1] supplies further details about the original oral toxicology and edema protocols. No new experiments or statistical calculations requiring individual-level data were conducted.

Acute toxicity: The prior work describes male outbred albino mice of approximately 22 ± 2 g, five animals per treatment group, and a single oral treatment dose of 2,000 mg/kg. Monitoring continued for 14 days. Transient breathing/behavioural or eye-related changes were observed early

after dosing; the original publication reported no deaths [1]. Although the authors refer to OECD TG 420, the present manuscript does not independently certify complete guideline compliance.

Inflammatory model: The previous report describes acclimatised rats, carrageenan injection into the hind paw, and oral test doses of 50 and 100 mg/kg given 1 h before carrageenan [1]. Percentage inhibition was taken from the published 24-h results [2]. As the publication provides no accessible full individual measurements for reanalysis, displayed percentages are descriptive and no new p values, effect-size confidence intervals or corrected comparisons are claimed.

Table 1. Published acute oral mortality observations; compound nomenclature follows the source (*substituent designation requires chemical identity verification).

Derivative as named in source	Dose	Deaths / number tested
Bis(sulfanediyl) diacetohydrazide	2,000 mg/kg	0/5
Diethyl bis(sulfanediyl) diacetate	2,000 mg/kg	0/5
2-Amino-5-ethyl-1,3,4-thiadiazole	2,000 mg/kg	0/5
2-Amino-5-(tert-butyl)-1,3,4-thiadiazole*	2,000 mg/kg	0/5

Source: previously published data, cited in the text. No new experiments were performed.

Results

Acute observations. No fatalities were reported among five mice per test compound at 2,000 mg/kg [1,2]. Mean body masses in the experimental groups were broadly similar to control values over 14 days according to the original publication. The reported transient early reactions prevent an inference of complete absence of toxicity; the observation can support only the more limited conclusion that a lethal effect was not detected in these small groups at the administered single dose.

Anti-inflammatory activity. Four compounds were described in the screening series. The published 24-h inhibition table shows that the diacetohydrazide and diethyl diacetate had the largest inhibition percentages at 50 mg/kg among the doses shown for these two compounds. Specifically, the diacetohydrazide had 40.0% inhibition at 50 mg/kg versus 30.5% at 100 mg/kg, while the diethyl diacetate had 34.6% and 23.4%, respectively [2]. The amino-substituted compounds displayed 0% or lower inhibition under some tested conditions. The original publications also discuss the third-hour response, but only the 24-h percentages are compared in our Table 2.

No new significance testing. The 2024 articles include p value annotations for some observations; their exact statistical models, individual-animal datasets and multiplicity handling are unavailable here. Accordingly we do not extend their statistical inferences.

Table 2. Reported 24-hour inhibition of carrageenan-induced edema by dose; percentages reproduced from the prior publication (not newly measured).

Reported compound	50 mg/kg	100 mg/kg
Bis(sulfanediyl) diacetohydrazide	40.0%	30.5%
Diethyl bis(sulfanediyl) diacetate	34.6%	23.4%
2-Amino-5-ethyl-1,3,4-thiadiazole	0%	21.3%

2-Amino-5-(tert-butyl)-1,3,4-thiadiazole*	30.5%	0%

Source: previously published data, cited in the text. No new experiments were performed.

Discussion

The absence of deaths in five animals following a single administration of 2,000 mg/kg is a preliminary acute oral-tolerability signal, but is not an experimentally measured LD50. OECD Test Guideline 420 uses fixed-dose decision rules for hazard classification [3]; a reported threshold above 2,000 mg/kg should not automatically be described as definitive evidence of GHS Category 5, because the classification depends on decision pathways and toxic signs. Likewise, no information on repeated dosing, histopathology or cardiometabolic toxicity is supplied in the source papers.

The inflammation results are potentially useful for candidate selection but not for firm potency ranking. Higher administered doses did not uniformly increase 24-h inhibition, and such a pattern may reflect exposure differences, variability or experimental details unavailable in the summary; none of these possibilities can be distinguished using aggregate figures alone. The control-group percentage shown at 3 h in the source table cannot be treated as zero without knowing the original outcome definition, another reason to avoid combining the two endpoints mathematically.

Importantly, the acute toxicity study employed mice and the efficacy study employed rats, so a naive ratio of 2,000 mg/kg to 50 mg/kg would not constitute a measured therapeutic index. Future work should report exact treatment allocation, sex and age, formulation, dose randomisation, blinded paw measurements, prespecified sample sizes and adverse effects at effective doses.

Limitations

This analysis is restricted to published tables and descriptions rather than underlying animal records. Experimental groups and sample sizes for all efficacy comparisons, dispersion for all 24-h percentages, precise compound characterisation and complete ethical approval information could not be independently verified. The reports were published in 2024, so any subsequent submission must transparently state the overlapping source data and obtain the journal's approval for secondary publication.

Conclusion

Previously published preclinical findings identify the bis(sulfanediyl) diacetohydrazide and related diethyl diacetate as candidates for follow-up anti-inflammatory assessment, with no reported deaths at a single oral 2,000 mg/kg dose in small mouse groups. The data should be regarded as preliminary: neither long-term safety nor an established therapeutic window can be inferred. Replicated dose–response studies with complete reporting are warranted.

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