

Área: OGR

Novel Pyrazole-Thiazolidine Hybrids with Potent Activity Against *Leishmania amazonensis*

Caroline Fortuna (PG),¹ Maria G. F. Franco (IC),¹ Valéria A. Barbosa (PG),¹ Susana M. M. Lopes (PQ),² Rodolfo Bento Balbinot (PG),³ Teresa M. V. D. Pinho e Melo (PQ),² Celso Vataru Nakamura (PQ)³ Fernanda A. Rosa (PQ).^{1*}

carolinefortunacf@gmail.com; farosa@uem.br

¹Department of Chemistry, University Estadual of Maringá (UEM); ²Department of Chemistry, University of Coimbra, (UC); ³Laboratory of Technological Innovation in Drug and Cosmetic Development, (UEM)

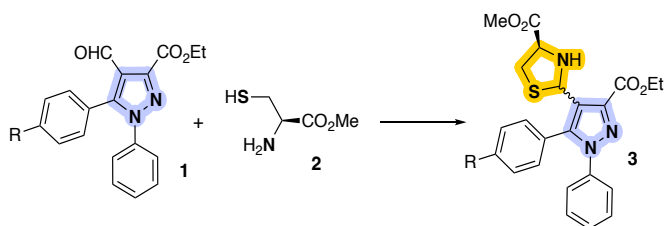
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Highlights

Pyrazoles and thiazolidines are biologically important heterocycles. Condensation of 4-formylpyrazoles with L-cysteine and affords pyrazole-thiazolidine hybrids. The obtained compounds displayed potent antileishmanial activity against *L. amazonensis* with low cytotoxicity.

Resumo/Abstract

Leishmaniasis is a neglected tropical disease caused by protozoa of the genus *Leishmania*, affecting thousands of people worldwide. Despite advances, current treatments still exhibit high toxicity, significant adverse effects, and elevated costs, reinforcing the need for safer and more effective drugs.¹ In this context, heterocyclic compounds such as pyrazoles and thiazolidines have attracted increasing attention due to their broad biological profiles, particularly antiparasitic properties. One synthetic route to thiazolidine rings involves the condensation of sulfur-containing amino acids (e.g., L-cysteine) with aldehydes. Our research group, SINTHET, have focused on the synthesis of aza-heterocycles such as 4-formyl-*N*-arylpyrazoles (**1**).² In this work, these pyrazoles were condensed with L-cysteine methyl ester (**2**)³ (Scheme 1), yielding novel pyrazole-thiazolidine hybrids subsequently evaluated against *L. amazonensis*.



R = NO₂-C₆H₅ (**3a**); F-C₆H₅ (**3b**); Cl-C₆H₅ (**3c**); Br-C₆H₅ (**3d**); Me-C₆H₅ (**3e**); OMe-C₆H₅ (**3f**); C₆H₅ (**3g**);

R:	Yield (%)	J774A.1		<i>L. amazonensis</i> Promastigotes	
		CC ₅₀ ± DP (μM)	CI ₅₀ ± DP (μM)	IS	
NO ₂	82	792,60 ± 55,73	19,92 ± 1,32	39,79	
F	78	613,53 ± 58,48	>200	ND	
Cl	87	760,67 ± 29,70	>200	ND	
Br-P-T	85	676,85 ± 14,17	19,30 ± 0,66	35,07	
Me	60	638,70 ± 55,05	22,56 ± 2,67	28,31	
OMe	66	693,36 ± 74,78	48,43 ± 6,67	14,32	
Ph	60	615,55 ± 35,69	43,43 ± 2,35	14,17	
Miltefosine	ND	54,19 ± 5,23	22,71 ± 1,24	2,39	

Scheme 1: Optimized pyrazole-thiazolidine synthesis and evaluation of antiproliferative activity against *L. amazonensis* and cytotoxicity in J774A.1 macrophages. IC₅₀ = concentration inhibiting 50% of protozoa; CC₅₀ = cytotoxic concentration for 50% of cells; SD = standard deviation; SI = selectivity index (CC₅₀/IC₅₀); ND = not determined.

Different solvents and reaction times were investigated, with dichloromethane providing the best results - complete conversion after 3 h and an isolated yield of 82% (*dr* 76:23). The optimized conditions were applied to a series of substituted pyrazole derivatives, giving yields of 60–85% and diastomeric ratios of 70:30. The pyrazole-thiazolidine hybrids exhibited significant activity against *L. amazonensis* promastigotes, particularly **3a**, **3d** and **3f** (IC₅₀ 19.92–22.56 μM), with low toxicity toward mammalian cells (SI 28.31–39.79), outperforming miltefosine (IC₅₀ 22.71 μM; SI 2.39). Biological assays against amastigote form are currently in progress.

Agradecimentos/Acknowledgments

¹ <https://www.who.int/news-room/fact-sheets/detail/leishmaniasis> (accessed on 14th October 2025), ² *J. Org. Chem.* 2017, 82, 12590–12602. ³ *J. Org. Chem.* 2002, 67, 4045–4054; **Acknowledgments:** State University of Maringá, University of Coimbra, SINTHET e a CAPES