Synthesis, Structure and Antiparasitic Evaluation of Endoperoxide–Pyrazole Hybrids

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ORIGINAL ARTICLE

ABSTRACT

Introduction: Leishmaniases are neglected tropical diseases with an annual incidence of 1.5 million cases worldwide, mainly affecting low-income populations. The available antileishmanial drugs present serious liabilities, namely high cost, need for extensive treatments, inadequate mode of administration, side effects and loss of efficacy due to parasites' development of resistance. To circumvent these constraints, repurposing available antiparasitic drugs emerges as a promising strategy to control leishmaniases[1,2].

Methodology: Artemisinins and related endoperoxides are used as first-line chemotherapy to combat malaria. Endoperoxide frameworks can be coupled to other heterocyclic moieties of biological or pharmaceutical relevance, potentially leading to novel multi-target drugs with enhanced properties and lower predisposition for loss of efficacy through resistance. Like endoperoxides, pyrazoles also have known applications in medicinal chemistry, namely as antiparasitic agents. Following the hybrid drug concept, we proposed combining antimalarial 1,2,4-trioxanes or 1,2,4,5-tetraoxanes, and pyrazole-containing chemotypes with known antileishmanial activity, in a unique structure, aiming to develop novel antileishmanial agents.

Results: This study reports the synthesis and structure of trioxolane–pyrazole (OZ1, OZ2) and tetraoxane–pyrazole (T1, T2) hybrids, obtained from coupling of 3(5)-aminopyrazole with endoperoxide-containing building blocks, and their respective salt forms. Noteworthy, the pyrazole moiety exhibits prototropic tautomerism, allowing for the formation of distinctive pyrazole-based structures, with diverse reactivities, unravelled in this work[3]. The compounds were evaluated *in vitro* for their antileishmanial activity against promastigotes of *L. tropica* and *L. infantum*, and for cytotoxicity against THP-1 cells. Evaluations against promastigotes revealed compound OZ1•HCl as the most active against both strains, as well as against *L. infantum* amastigotes (IC_{50} of 87 μM). Interestingly, the hydrochloride salts were also evaluated against strains 3D7-GFP and IPC5202 of *P. falciparum,* showing nanomolar activities.

Discussion: Compound OZ1•HCl emerged as the most potent against both strains (IC_{50} of 2.19 nM and 12.30 nM, respectively).

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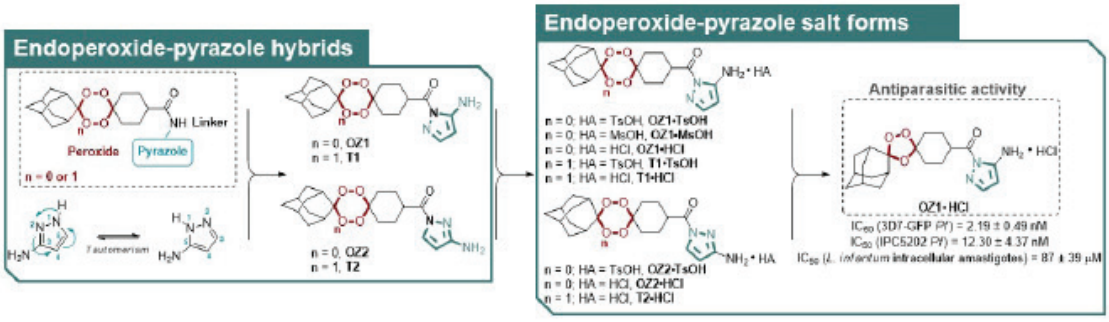

Figure 1. Representative structures of endoperoxide-pyrazole hybrids and their respective salts, reported in this study.

Keywords: antiparasitic chemotherapy, endoperoxide–pyrazole hybrids, tautomerism.

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Bibliographic References:

1. Cabral, LIL, et al. Synthesis and Antileishmanial Activity of 1,2,4,5-Tetraoxanes against Leishmania Donovani. Mol. 2020;25:465.

2. Cortes S, *et al*. *In Vitro* Susceptibility of Leishmania Infantum to Artemisinin Derivatives and Selected Trioxolanes. Antimicrob. Agents Chemother. 2015;59:5032–5035.

3. Amado PSM, *et al.* Synthesis, Structure and Antileishmanial Evaluation of Endoperoxide-Pyrazole Hybrids. Mol. 2022;27:5401.

Targeting the Energy Metabolism of Mycobacterium Tuberculosis: a New Approach to Control Tuberculosis

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ORIGINAL ARTICLE

ABSTRACT

Introduction: Tuberculosis (TB) remains one of the most deadly infectious disease. The development and spread of multidrug resistant TB, along with a latent form of the bacteria, represent the most serious limitations to the elimination of this pathogen[1]. The energy metabolism has received attention as a target for TB therapy after the discovery of the ATP synthase inhibitor bedaquiline[2]. Mycobacterium tuberculosis (Mtb) relies on oxidative phosphorylation to produce ATP, crucial for growth and survival. In both aerobic and anaerobic conditions, the flow of electrons across the respiratory electron transport chain (ETC), to the terminal cytochrome oxidases cyt bc1-aa3 and cyt bd, generates a proton motive force necessary for ATP synthesis by ATP synthase.

Objectives: To develop hybrid compounds with the potential of dual targeting mycobacterial ETC, as the next generation tools to prevent the emergence of resistance and target the latent infection.

Metodology: The design of the hybrid compounds involved the combination of a cytochrome c oxidase (cyt bc1-aa3) inhibitor with a nitroheteroaryl structural motif cable of releasing nitric oxide, a well-known active site ligand of respiratory terminal oxidases. The compounds were screened against Mtb H37Rv wild and Mtb cyt-bd knockout strains. This mutant is hypersusceptible to compounds that target the QcrB subunit of cyt bc1-aa3, enabling a rapid identification of cyt bc1-aa3 inhibitors[3]. Cytotoxicity was assessed against HEK293 cells.

Results: A small library of the hybrid compounds was prepared. Evaluation of the antimycobacterial activity revealed two anti-Mtb agents that share a 5-nitrofuran scaffold and display activity (MIC_{90} < 1 μM) against H37Rv and cytochrome bd knockout cydKO Mtb strains. As the Mtb cydKO strain does not express cyt bd, the inhibition of cyt bc1-aa3 in this mutant strain results in an effective disruption of the ETC. In addition, these compounds showed to be non-cytotoxic at 100 μM.

Conclusions: These results strongly suggest that these hybrid compounds target both terminal oxidases cyt bc1-aa3 and cyt bd. The novelty of this chemotype in the toolbox of antimycobacterial agents, show it is possible to expand the nitrofurano-based hybrids into drug-like compounds that disrupt the mycobacterial energy metabolism.

Keywords: mycobacterium tuberculosis, respiratory chain, bioctive compounds, latency.

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Bibliographic References:

1. A. Campaniço A., Harjivan, S.G., Warner D.F., Moreira R., Lopes F. (2020). Addressing Latent Tuberculosis: New Advances in Mimicking the Disease, Discovering Key Targets and Designing Hit Compounds. Int. J. Mol. Sci, 21. 8854 https://doi.org/10.3390/IJMS21228854.

2. Guo H., Courbon G.M., Bueler S.A., Mai J., Liu J., Rubinstein J.L. (2021) Structure of mycobacterial ATP synthase with the TB drug bedaquiline. Nature, 7840. 143 https://doi.org/10.1038/s41586-020-3004-3.

3. Moosa, A.; Lamprecht, D. A.; Arora, K.; Barry, C. E.; Boshoff, H. L. M.; Ioerger, T. R.; Steyn, A. J. C.; Mizrahi, V.; Warner, D. F. (2017) Susceptibility of Mycobacterium tuberculosis Cytochrome bd Oxidase Mutants to Compounds Targeting the Terminal Respiratory Oxidase, Cytochrome c. Antimicrob. Agents Ch., 61 (10): e01338-17 https://doi: 10.1128/AAC.01338-17.

Solvatocromismo de Miconazol: Estudio Teórico-Experimental

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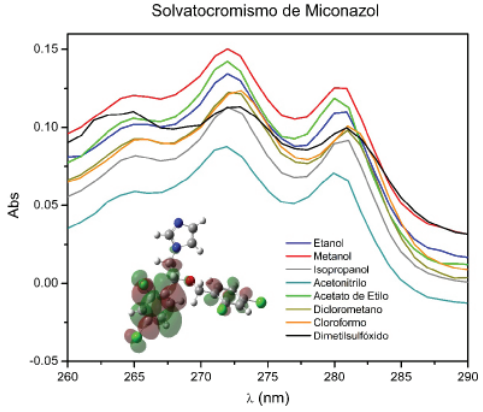
ORIGINAL ARTICLE

RESUMEN

Introducción: El antimicótico miconazol (MNZ) presenta en su estructura un grupo imidazol que ha sido ampliamente estudiado por su importancia en el reposicionamiento de fármacos. Los estudios de solvatocromismo aportan información sobre las interacciones soluto-solvente, aplicable a las diversas etapas farmacéuticas del Ingrediente Farmacéutico Activo (IFA). Esta investigación tiene como objetivo estudiar interacciones soluto-solvente en solventes puros, mediante solvatocromismo teórico y experimental con análisis estadístico multiparamétrico.

Metodología: El estudio teórico se realizó mediante simulación computacional por el método TD-DFT en el nivel de teoría B3LYP/6-31+G(d) y CAMB3LYP/6-31+G(d) con el modelo de solvatación CPCM. Las determinaciones espectrofotométricas al UV (200-400 nm) se realizaron utilizando 5 solventes polares apróticos y 3 polares próticos, mientras que para el estudio teórico se usaron 3 solventes apolares, 5 polares apróticos y 3 polares próticos. El análisis estadístico se realizó aplicando las ecuaciones multiparamétricas de Kamlet-Taft, Catalán y Laurence, en ambos casos.

Resultados: El estudio teórico y experimental mostró un cambio batocrómico del espectro UV a medida que aumenta la polaridad del solvente, indicando que en medios solvatados el estado excitado de MNZ es de mayor polaridad y energía que el estado fundamental. Las ecuaciones de Catalán a $\bar{\nu}$272 nm en B3LYP destacaron una contribución relativa de la polarizabilidad - C_{SP} del 87 %, mientras que en CAM B3LYP - C_{SP} representa un 29 % y la dipolaridad - C_{SP} un 57 %. Las ecuaciones de Laurence evidenciaron una contribución relativa de *-di* (dispersión e inducción) de un 84 % y un 57 % de es (interacciones electrostáticas) a $\bar{\nu}$272 nm en B3LYP; y un 63 % en *-di* y un 26 % en es en CAM B3LYP. Los descriptores moleculares globales demostraron aumento de la polaridad, del $GAP_{HOMO\text{-}LUMO}$ y de la dureza de MNZ con el aumento de la polaridad del solvente, siendo opuesto el efecto en la superficie de energía potencial, el potencial electroquímico, la electronegatividad y la electrofilicidad neta.



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Discusión: Experimental y analíticamente se evidencia un corrimiento batocrómico de los espectros UV del IFA ante el aumento de la polaridad del solvente, siendo equivalentes los resultados computacionales en B3LYP y CAM B3LYP. Es significativo notar que MNZ presenta un $GAP_{HOMO\text{-}LUMO}$ pequeño y una blandura, electronegatividad y electrofilicidad neta elevadas. En conclusión, se destaca una alta contribución en las fuerzas de dispersión e inducción y relativa dipolaridad atribuidas a la interacción de los anillos fenílicos dihalogenados de MNZ con el solvente, siendo despreciables las contribuciones de las uniones por puentes de hidrógeno. Asimismo, los elevados valores de los descriptores moleculares mencionados le confieren al IFA una gran reactividad química.

Palabras clave: miconazol, solvatocromismo, TD-DFT CAM B3LYP.

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Referencias Bibliográficas:

1. Al-Wahaibi, LH, Abdalla, M, Sheena MY. Shyma MY, Costa, RA, Rana, M, et al. Spectroscopic, Solvation Effects and MD Simulation of an Adamantane-Carbohydrazide Derivative, a Potential Antiviral Agent. Polycyclic Aromat. Compd [Internet]. 2022 Feb,43(3):2056-2070.

2. Airinei, A, Isac, DL, Homocianu, M, Cojocaru, C, Hulubei, C. Solvatochromic analysis and DFT computational study of an azomaleimide derivative. J. Mol. Liq. 2017 Aug, 240:476-485.

3. Silva WVD, Silva WVD, Holanda VN. Estudio in silico del potencial de los fármacos azólicos sobre el SARS-CoV-2: un enfoque químico-medicinal. Rev. Interfaces [Internet]. 31 de octubre de 2020;8(3):636-48.

Arylidene-Δ4-3,6-Dione Steroids Potentially useful in the Treatment of Prostatic Diseases

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ORIGINAL ARTICLE

ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) and prostatic cancer (PCa) are the most prevalent prostatic diseases and have high prevalence and impact in society nowadays. Androgens are produced in steroidogenic tissues and bind to the androgen receptor (AR), initiating transcription which in turn results in the synthesis of prostate-specific proteins, as well as in cell proliferation, which is the pathophysiological basis for BPH and PC. Several therapeutic approaches are being used for these conditions, however, these have lower efficacy than the desired and have debilitating side effects. These facts are motivating researchers and industries to the development of improved therapies. Steroids and their oxidation products are widely distributed in living organisms, have relevant bioactivities and are important intermediates for the synthesis of many biologically active molecules. In this context it is important to mention that several steroids are being used in the treatment of the most common prostatic diseases, such as finasteride and abiraterone acetate[1]. This presentation will focus on our recent findings on oxidized steroidal derivatives with potential interest in the treatment of the most prevalent prostatic diseases.

Methods: After the design, chemical synthesis and structural characterization of different oxidized steroidal derivatives, their antiproliferative effect was evaluated in tumoral and non-tumoral prostatic cell lines and in other types of cells by the MTT assay and by microscopy fluorescence. In addition, their 5α-reductase inhibitory effects were also determined by a HPLC-DAD method. Computational docking studies were also performed to explain the observed results.

Results: Interestingly, among other modified steroidal derivatives[2], arylidene-Δ4-3,6-dione steroids have relevant 5α-reductase inhibitory activity and antiproliferative effects in tumoral prostatic cell lines. In addition, of these compounds, 16*E*-(2',4'-dichlorobenzylidene)-androst-4-ene-3,6,17-trione led to apoptosis of androgen-dependent LNCaP cells. Docking studies supported the relevant 5α-reductase inhibitory results and suggested other potential targets of steroid action to be studied for these compounds.

Discussion: Oxidized steroidal derivatives, principally arylidene-Δ4-3,6-diones have high potential in the treatment of the main prostatic diseases, due to their potent and selective effects against prostatic cancer cells as well as to their 5α-reductase inhibitory activity, even superior to the observed with the positive control, finasteride.

Keywords: oxidized arylidenesteroids, prostatic diseases, 5α-Reductase inhibitory activity.

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Bibliographic References:

1. Salvador J.A.R., Pinto R.M.A., Silvestre S.M., J. Steroid Biochem. Mol. Biol. 2013, 137, 199-222.
2. Brito V., Marques M., Esteves M., Serra-Almeida C., Alves G., Almeida P., Bernardino L., Silvestre S., Biomedicines 2023, 11, 812.

Synthesis and Cytotoxic Evaluation of Novel Madecassic Acid Derivatives

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ORIGINAL ARTICLE

ASTRACT

Introduction: Madecassic acid[1] is a naturally occurring pentacyclic triterpenoid found in the traditional medicinal plant *Centella asiatica* (L.) Urban[1].This compound has been shown to possess several pharmacological activities, such as wound healing, antioxidant, and antidiabetic activities. Furthermore, a recent study reported evidence for an apoptotic effect of 1 in an *in vivo* model using mice bearing CT26 cancer cells[2]. Compared to some other triterpenoid scaffolds, only a limited number of 1 derivatives are known, and few of these have been investigated with respect to their anticancer activity[3].

Methodology: Thus, a series of novel 1 derivatives was synthesized and screened for anticancer activity against the NCI-60 panel of cancer cell lines.

Results: All the tested semisynthetic derivatives showed better antiproliferative activities than 1 itself. Among them, compound 29 showed GI_{50} (50% growth inhibition) values ranging from 0.3 to 0.9 μM against 26 different tumour cell lines and revealed selectivity for one colon (COLO 205) and two melanoma (SK-MEL-5 and UACC-257) cell lines at the TGI (total growth inhibition) level. The mode of action of 29 was predicted using the tool CellMiner and confirmed by a series of cell-based and biochemical assays, showing that treatment with 29 results in cell cycle arrest at the G1/S transition and disruption of the mitochondrial membrane potential in tumour cells.

Discussion: Considering the present results, derivative 29 represents a potential lead for the development of new anticancer agents and merits further investigation (figure 1).

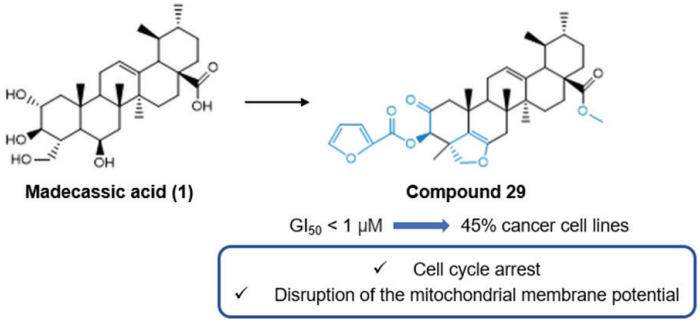

Figure 1. Structure of madecassic acid[1] and its derivative 29 with potential anticancer activity.

Keywords: madecassic acid, anticancer activity, drug discovery.

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Bibliographic References:

1. Wong JH, Barron AM, Abdullah JM. Mitoprotective Effects of *Centella asiatica* (L.) Urb.: Anti-Inflammatory and Neuroprotective Opportunities in Neurodegenerative Disease. Front Pharmacol. 2021 Jun 29;12:687935. doi: 10.3389/fphar.2021.687935.
2. Zhang H, Zhang M, Tao Y, Wang G, Xia B. Madecassic acid inhibits the mouse colon cancer growth by inducing apoptosis and immunomodulation. J BUON. 2014 Apr-Jun;19(2):372-6. PMID: 24965394.
3. Valdeira ASC, Ritt DA, Morrison DK, McMahon JB, Gustafson KR and Salvador JAR. Synthesis and Biological Evaluation of New Madecassic Acid Derivatives Targeting ERK Cascade Signaling. Front. Chem. 2018 6:434. doi: 10.3389/fchem.2018.00434.

Novel Semisynthetic A-ring-cleaved Glycyrrhetinic Acid Derivatives as Potential Anticancer Agents

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ORIGINAL ARTICLE

ABSTRACT

Introduction: Glycyrrhetinic acid[1] is a hydrolyzed metabolite of glycyrrhizin, a major pentacyclic triterpenoid saponin sourced from the roots of Glycyrrhiza species, commonly known as licorice[1,2]. Notably[1], has demonstrated considerable antiproliferative properties against various types of cancers. However, its effectiveness and selectivity as an antitumor agent have limitations.

Methodology: To explore novel potential antitumor agents, a series of innovative glycyrrhetinic acid[1] derivatives was synthesized through the cleavage of its A-ring and coupling with amino acids[3]. The antiproliferative activities of these novel semisynthetic derivatives were evaluated against a panel of nine human cancer cell lines.

Results: Compound 17 was the most active compound, displaying a remarkable IC50 value of 6.1 μM against Jurkat cells, a type of acute T-cell leukemia (figure 1). This derivative was 17-fold more potent than the parent compound[1] against this cancer cell line. Additional studies showed that the anticancer activity of compound 17 was due to cell cycle arrest at the S phase and induction of apoptosis in Jurkat cells.

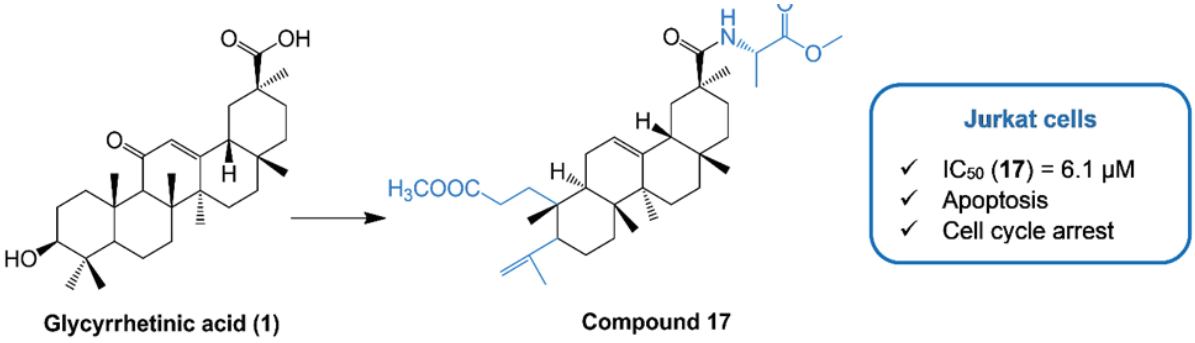

Figure 1. Structure of glycyrrhetinic acid (1) and its derivative 17 with potential anticancer activity.

Discussion: Considering the promising results obtained with derivative 17, further biological studies were performed to gain a deeper understanding of the mechanisms underlying its anticancer activity.

Keywords: pentacyclic triterpenoids, glycyrrhetinic acid, cancer.

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Bibliographic References:

1. Roohbakhsh A, Iranshahy M, Iranshahi M. Glycyrrhetinic Acid and Its Derivatives: Anti-Cancer and Cancer Chemopreventive Properties, Mechanisms of Action and Structure-Cytotoxic Activity Relationship. Curr Med Chem. 2016;23(5):498-517.

2. Hussain H, Ali I, Wang D, Hakkim FL, Westermann B, Ahmed I, et al. Glycyrrhetinic acid: a promising scaffold for the discovery of anticancer agents. Expert Opin Drug Discov. 2021;16(12):1497-516.

3. Alho DPS, Salvador JAR, Cascante M, Marin S. Synthesis and Antiproliferative Activity of Novel A-Ring Cleaved Glycyrrhetinic Acid Derivatives. Molecules. 2019;24(16).