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Exploring the Therapeutic Potential of Amino-Substituted Anthraquinones and 1,4,5-Trihydroxyanthraquinone: A Novel Approach in the Battle Against Trypanosomiasis

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Abstract

Substituted anthraquinones with hydroxyl groups are vital in organic synthesis due to their promising biological properties relevant to clinical applications. In this study, we synthesized amino-substituted anthraquinones and 1,4,5-trihydroxyanthraquinone from 1,4-dihydroxyanthraquinone and anacardic acid, respectively. In vitro testing against Trypanosoma brucei parasites showed notable activity and selectivity against human cell lines. Molecular docking analysis indicated favourable binding affinity of the compounds with the active site of trypanothione reductase. Overall, our study suggests that derivatives of substituted 1,4-dihydroxyanthraquinone hold promise in developing active drugs against trypanosomiasis.

Introduction

Trypanosomatids, digenetic protozoan parasites prevalent in tropical and subtropical regions, cause debilitating diseases, with African trypanosomes posing significant threats to human, livestock, and wildlife health, leading to severe economic consequences. Human African trypanosomiasis (HAT or sleeping sickness) and Chagas disease are classified as "Neglected Tropical Diseases" by the World Health Organization [1].

Existing clinically approved drugs for HAT, such as Pentamidine, suramin, eflornithine, and melarsoprol, have limitations, including high toxicity, complex administration routes, and resistance issues. The urgency for new chemotherapies to combat HAT is evident, prompting the development of Fexinidazole, a promising oral treatment for both acute and chronic stages. However, the search for new drug candidates remains crucial, necessitating target-based and phenotypic screening approaches.

Target-based drug discovery, challenging for neglected tropical diseases, benefits from Trypanothione reductase as a genetically validated enzyme in Trypanosomatidae's unique thiol metabolism. TR, essential for the parasite's antioxidant defense, serves as a viable drug target due to its absence in mammalian hosts [2].

Natural products, such as anthraquinones, offer valuable chemical libraries for drug development, with anthraquinones exhibiting diverse biological activities. Notably, 1,4-dihydroxyanthraquinone, found in anthracycline antibiotics used in cancer treatment, serves as a building block for various antiparasitic drugs. Cashew nut shell liquid, a by-product of cashew agribusiness, emerges as a cost-effective source for organic synthesis, containing unique compounds like anacardic acid with potential antimicrobial and antiparasitic properties [3].

In this study, we explore the synthesis of amino-substituted anthraquinones and 1,4,5-trihydroxyanthraquinone, emphasizing their potential against Trypanosoma brucei parasites. Utilizing CNSL, we derive compound 6, leading to the synthesis of hydroxyanthraquinone 9. This research aligns with the ongoing quest for effective drugs against trypanosomiasis.

Results

This study outlines the synthesis of 1,4-dihydroxyanthraquinone derivatives, commencing with anacardic acid 1 extracted from cashew nut shell liquid (CNS). The chemical structure of anacardic 1, featuring carboxylic acid functionality and a pentadecyl side chain in an ortho arrangement, allows structural modification leading to the formation of 3-ethoxy phthalic acid 6 [4].

3-Ethoxy phthalic acid 6 is recognized as a crucial synthon for preparing pharmaceutically significant hydroxyanthraquinones, including anticancer drugs like Adriamycin and daunomycin. Common methods for synthesizing this reagent suffer from multiple steps, low yields, and the use of expensive chemicals. Therefore, this study successfully accomplished the synthesis of 3-ethoxyphthalic acid 6 from locally available CNSL, utilizing readily available and cost-effective chemicals. The process involved ethoxylation of anacardic acid 1 using diethyl sulfate, followed by reduction of the double bond to yield the saturated ester. Subsequent bromination at the benzylic position, dehydrobromination, and oxidation resulted in the formation of 3-ethoxy phthalic acid 6 with a yield of 64% [5].

The chemical structures of the synthesized compounds were confirmed through spectroscopic methods (NMR, IR, and MS). Notably, the Friedel-Crafts acylation technique, using a eutectic mixture of AlCl3 and NaCl, was employed to react 3-ethoxyphthalic acid 6 with 1,4-dihydroxybenzene 8, yielding 1,4,5-trihydroxyanthraquinone 9 and 1,4-dihydroxyanthraquinone 10.

However, challenges arose during purification due to regiochemical control issues in the intermolecular Friedel-Crafts reaction, resulting from a Hayashi rearrangement. To address this, a modified Marschalk reaction was utilized, introducing hydroxyalkyl groups at position 2 of quinizarin 10 using sodium dithionite under basic conditions. This

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led to the formation of alcohol anthraquinones 11-13, using aldehydes such as 2-chlorobenzaldehyde, acetaldehyde, and propionaldehyde [6].

The synthesis pathway was monitored using TLC, requiring specific ratios of aliphatic aldehydes and limited reaction times. Subsequent chlorination and amination of aryl hydroxyanthraquinone 11 produced various Anthraquinone amines 16-23 in yields ranging from 22-80%. Additionally, the study explored the synthesis of Anthraquinone thiosemicarbazone 24 through Dess-Martin oxidation and treatment with thiosemicarbazide.

The confirmation of the newly synthesized compounds was supported by spectroscopic analysis and mass spectrometry, providing a comprehensive overview of the successful synthesis pathway.

The docking process was carried out using Maestro 12.6, a component of the Schrödinger suite software, with Trypanothione reductase as the designated drug target. The protein comprises two chains, A and B, with chain B utilized in the glide grid docking. Seventeen ligands were subjected to docking within the active sites of Trypanothione reductase. Docking results were evaluated through visual inspection to discern the mode of interaction with the receptor protein. Biovia discovery studio was employed for the analysis of docked poses, and Pymol software was utilized to generate 3D representations of protein-ligand interactions [7].

Test compounds 18 and 23, which exhibited notable activity against trypanosomes, demonstrated favourable poses with binding affinities of-7.857 and-7.351 kcal/mol, respectively. Compound 18 exhibited active hydrogen bonding interactions with amino acids LYS 60, ALA 363, and ALA 365, while compound 23 showed two hydrogen bonds with amino acids LYS 60 and THR 335. Similarly, test compounds 12 and 13 actively engaged in hydrogen bonding with amino acids LYS 60 and ASP 327 [8].

Compounds 15 and 24, which displayed slightly higher activity against trypanosomes, exhibited a moderate binding affinity of-5.4 kcal/mol with the target protein. Compounds 15 and 24 appeared to form hydrogen bonds with THR 51, ARG 287, THR 335, SER 14, and Pi-Pi Cation with PHE 198.

Remarkably, nearly all test compounds demonstrating activity against T. b. brucei showcased hydrogen bonding interactions with amino acid residues such as LYS 60, ALA 363, ALA 365, ASP 327, THR 51, and THR 335. Intriguingly, each of these 1,4-dihydroxyanthraquinone derivatives demonstrated interactions, including halogen, pi-anion, and pi-alkyl, with the amino acid CYS 57, a pivotal amino acid involved in hydride transfer. The interaction of these ligands with Cystines disrupts the reduction of trypanothione disulphide to dihydro-trypanothione [9,10].

Conclusion

In this study, we successfully synthesized derivatives of 1,4-dihydroxyanthraquinone and assessed their efficacy against trypanosomes. Additionally, we carried out the derivatization of anacardic acid from cashew nut shell liquid (CNSL) to produce 3-ethoxyphthalic acid, a key synthon in the preparation of hydroxyanthraquinone. The in vitro biological evaluation of the test compounds against Trypanosoma brucei (T.b) revealed the potency of 1,4-dihydroxyanthraquinone derivatives against trypanosomes.

Our findings highlighted that hydroxy-alkyl-1,4-dihydroxyanthraquinone, particularly those with aliphatic substituents, exhibited notable activity against T. brucei when compared to their hydroxyaryl-1,4-dihydroxyanthraquinone counterparts. Molecular docking analysis demonstrated favorable poses for the compounds, with docking scores ranging from good to moderate. Based on our results, we propose 1,4-dihydroxyanthraquinone derivatives as promising initial structures for the development of drug candidates targeting neglected tropical diseases.

Supplementary Materials include 1H NMR and 13C NMR spectra of selected test compounds and the percentage viability of cells against the test compounds.

Acknowledgement

None

Conflict of Interest

None

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