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SYNTHESIS, CHARACTERIZATION, AND IN SILICO STUDIES OF TRICARBONYL[H⁴-5-(N-(4-HYDROXYPHENYL) CINNAMAMIDE) CYCLOHEXA-1,3-DIENE] IRON AND ITS DEMETALLATED DERIVATIVE AS POTENTIAL ANTILEISHMANIAL AGENTS

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ABSTRACT

Leishmaniasis is a neglected tropical disease caused by a protozoan species of the genus Leishmania. The treatment of leishmaniasis has remained insufficient due the limitations of existing drugs. This has necessitated the need to search for new drugs. Acetaminophen-based chalcone N-(4-hydroxylphenylcinnamamide (ACCH) of tricarbonyl (η5-cyclohexadienyl) Iron hexafluorophosphate have been synthesized according to a published procedure to give tricarbonyl [η4-5(N-(4-hydroxylphenyl) cinnamamide) cyclohexa-1,3-diene) Iron (ADDUCT) which on removal of the tricarbonyl moiety through demetallation gave (E)-3-(1′,2′-dihydro-[1′,1′-biphenyl]-3-yl)-N-(4-hydroxyphenyl)acrylamide) (DEM). The synthesized compounds were characterized using Infra-red measurement. The In-silico studies of ACCH, ADDUCT and DEM were conducted against leishmanolysin (ID PDB: 1LML) using PyRx and visualized using Biovia Discovery 2024 with Miltefosine used as standard drug. The ADMET analysis of the synthesized compounds and the standard drugs was carried out using SwissADME and Protox 3.0. The Infra-red data showed the presence of ν(CO) band due to coordinated diene organometallic moiety at 2100 cm-1 and 1910 cm-1 in the ADDUCT, absent in DEM and the emergence of new Fe-C band at 495 cm-1 . The docking results showed that ACCH, ADDUCT and DEM with docking scores values of -6.4, -7.4, and -8.1 kcal/mol interact more with amino acids in the active sites of receptor protein via H-bond, pi-pi interaction than the standard drugs miltefosine (docking score -5.0 kcal/mol). ADMET analysis showed good oral bioavailability, less toxicity and high gastrointestinal absorption compared to Miltefosine. This can serve as a lead to potential antileishmanial drugs.

Keywords: Leishmaniasis, Acetaminophen-based Chalcone, Tricarbonyl (η5-cyclohexadienyl) Iron hexafluorophosphate, Demetallation; Silico Studies

INTRODUCTION

Leishmaniasis is one of the twenty neglected tropical diseases (NTDs) (WHO, 2023), which affect more than one billion people worldwide (WHO, 2024); thus, contributing to high morbidity and mortality rate among affected populations (Azubuike *et al*., 2025). Hence, identified as a major public health problem (Monzote, 2009). Leishmaniasis is a disease caused by protozoan parasites of the genus *Leishmania*,spread through the bite of an infected female phlebotomine sand fly (Akbaria *et al.*, 2017; Cosma *et al*., 2024; Oryan, 2015). The conventional treatment involves the use of Pentavalent antimonial (Sbv) as first-line treatment for the previous decades followed by Amphotericin B, Miltefosine(only oral drug approved) and Paromomycin (Roatt *et al*., 2020; Mohapatra, 2014). Despite their effectiveness the use of these drugs has been limited due to severe toxicity and side effects, treatment failures and reported emerging resistance which necessitate the need for an alternative drug with less toxic severe side effects (Dorlo *et al*. 2014; Sundar *et al*. 2007a, b; Srivastava *et al*. 2017). One approach in addressing this need is through drug repurposing, which involves prediction of second uses for "old" clinically used drugs through screening them against relevant disease targets ((Ashburn and Thor 2004). Focusing on leishmaniasis drug repurposing, computational approaches are the main strategies that have been applied with relative success among the diseases (Roatt *et al*., 2020). In this regard, molecular docking is a computational strategy to predict binding sites between the ligands (drugs) and the target (receptor) (Bustamante *et al*. 2019).

Acetaminophen (N-acetyl-P-aminophenol), generally known in the USA (also brand-named in Europe as paracetamol), is one of the frequently used drugs both over-the-counter and on prescription for pain (analgesic) and fever (antipyretic) in adults and children. (Graham *et al*., 2013). Acetaminophen was listed by WHO as essential medicines which is safe, economical with versatile mechanism of action and therapeutical use for various diseases. (Kouznetsov, 2024). This has made acetaminophen our target drug for the preparation of chalcone. Chalcones, or 1,3-diphenyl-2-propen-1-ones, are one of the most significant classes of flavonoids in the whole plant kingdom. (Sahu *et al*., 2012). The chemistry of chalcones still received great attention in the 21st century due to the large number of replaceable hydrogens that allows a large number of derivatives and a variety of promising biological activities to be generated, including including anticancer (Gao *et al*., 2020), anti-inflammatory (Mahapatra *et al*., 2017) antidiabetic (Rocha *et al*., 2020)], cancer chemopreventive (Xu *et al*., 2015) , antioxidant (Lin *et al*., 2019), antimicrobial (Henry *et al*., 2020), antileishmanial (de Mello *et al*., 2018) and antimalarial activities (Cheng *et al*., 2020). Thus, we prepared N-(4-hydroxylphenyl)cinnamamide a chalcone based on acetaminophen scaffold. The prepared chalcone was now modify enroute organometallic complexes.

Organometallic complexes have shown potential in overcoming drug resistance, permitting enhanced specificity and drug targeting and decreasing the side effects associated with chemotherapy (Allardyce and Dyson., 2006). The incorporation of organometallic functionalities modifies the physicochemical properties of bioactive compounds, (Soba *et al*., 2023), and adjusts the compound's hydrolysis rate (Rivsas *et al*., 2024) as well as its redox activity. Dienyl-Fe$(CO)_3$ cations have gained importance as useful intermediates in modern organic synthesis. The availability, low cost, and nucleophilic reactivity of the dienyl organometallics made

them valued building blocks for the synthesis of structurally varied materials (Eugene-Osoikhia *et al*., 2025).

One way of restoring the activity of organic drugs for which resistance has arose is to modify the structure to contain a metal, such as in organometallic compounds. (Allardyce and Dyson, 2006). There were many instances of modification using organoiron compounds reported, for instance, aromatic groups in penicillin and cephalosporine were modified by substituting with ferrocenyl moieties to give ferrocenyl derivatives of the antibiotics with enhanced activity (Chellan and Sandler, 2020). Odiaka *et al*., 2014 also reported the modification of some alkaloids (Gedunin, khivorin and polyavolensinol) by incorporation of the dienyliron fragment resulting the modified alkaloids with improved activity (Adebesin *et al*., 2016; Adebesin *et al*., 2019; Odiaka *et al*., 2014). Recently, mentronidazole and sulphamethoxazole antibiotics were modified to give better optical properties (Eugene-Osoikhia *et al*., 2025).

Herein, we report the preparation of N-(4-hydroxylphenyl)cinnamamide chalcone based on acetaminophen scaffold, subsequent modification using organometallic complexes and inslico studies against *Leishmaniasis.*

MATERIALS AND METHODS

General Procedure

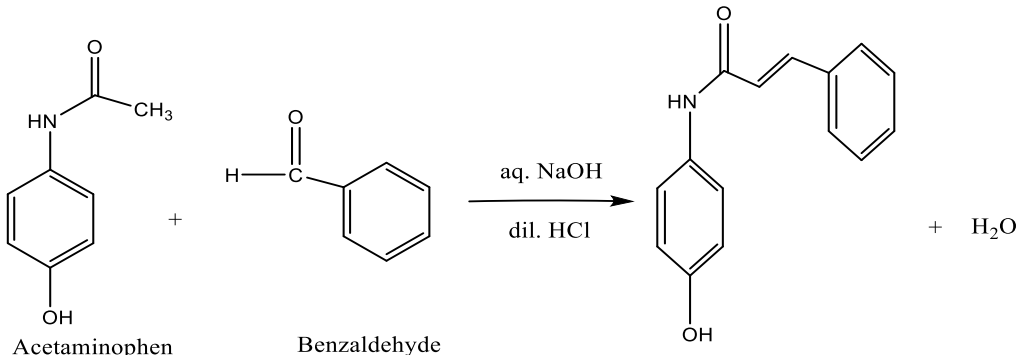
Infrared spectra were recorded as KBr disc on a Perkin-Elmer BX II FT-IR spectrometer 4000–400 cm^{-1}. Melting points were determined with Stuart SMP10 melting point apparatus and reactions monitored on TLC aluminium sheets impregnated with silica gel 60 F_{254}.

Chemicals and Reagents

The complex $[(\eta^5\text{-}C_6H_7)Fe(CO)_3]PF_6$ was obtained in pure form from Sigma Aldrich and was used without further purification. Other reagents used were acquired in their purest grades available (BDH) and used without further purification. Acetaminophen was obtained as a gift from Bond Pharmaceutical Awe, Oyo State, Nigeria.

Synthesis of Acetaminophen Based Chalcone (N-(4-Hydroxylphenyl) Cinnamamide (ACCH))

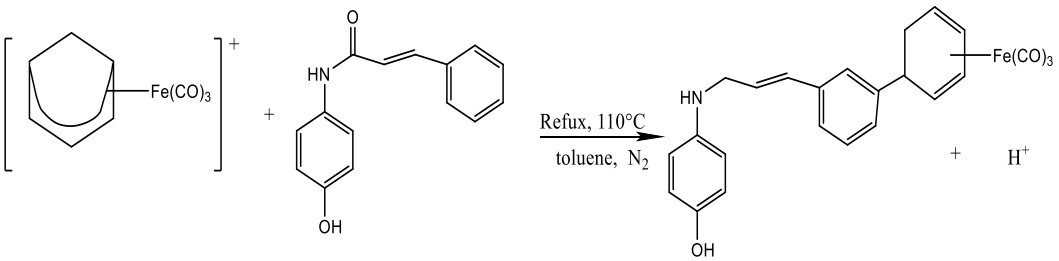
This was carried out as shown in scheme 1 below according to Campos-Buzz *et al*., 2007. To a stirring solution of acetaminophen (0.257 g; 1.7 mmol) and benzaldehyde (0.182 g; 1.7 mmol) in 50 ml ethanol was added 50% w/v aq. NaOH solution (1.5 mL) . The reaction mixture was stirred overnight at room temperature. It was then neutralized with 1N HCl. The product obtained was filtered to give a yellow precipitate. The percentage yield obtained was 93.3%.



Scheme 1: Synthesis of Acetaminophen Based Chalcone (N-(4-hydroxylphenyl)cinnamamide (ACCH))

Formation of an Adduct

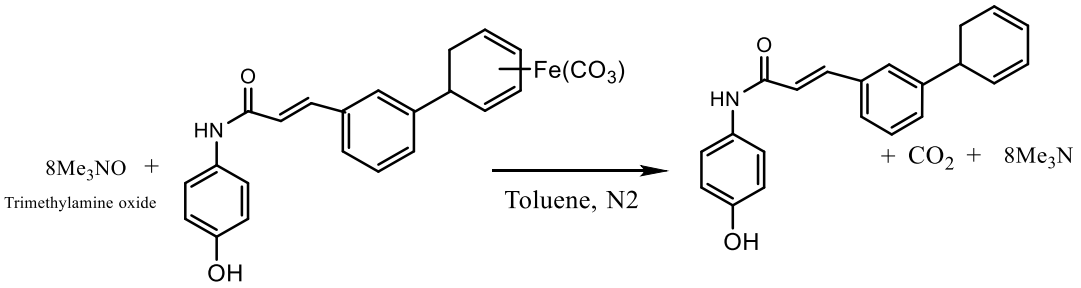
Tricarbonyl[η^4-5(N-(4-hydroxylphenyl) cinnamamide) cyclohexa-1,3-diene) Iron was synthesized as shown in scheme 2 according to a published procedure by Odiaka *et al*., 2014. (0.05 g, 0.1634 mmol) $[(\eta^5\text{-}C_6H_7)Fe(CO_3)]$ $[PF_6]$ and a two-fold molar excess of the synthesized N-(4-hydroxylphenyl) cinnamamide (0.078 g, 0.3268 mmol) was refluxed in a two-necked round-bottom flask (50 cm^3) under nitrogen gas in 30 ml toluene at 110 °C for 48 h. The mixture was allowed to cool to room temperature and was allowed to concentrate to give a light-yellow solution. This solution was shaken with (20/20, v/v) diethyl ether/water. The aqueous layer was set aside while the organic layer was concentrated to give brown precipitate, which was allowed to dry. The percentage yield obtained was 27.4 %.



Scheme 2: Synthesis of [η^4-5(N-(4-hydroxylphenyl) Cinnamamide) Cyclohexa-1,3-diene) Iron

Demetallation Reaction: Formation of (E)-3-(1′,2′-dihydro-[1′,1′-biphenyl]-3-yl)-N-(4-hydroxyphenyl) acrylamide) (DEM)

The demetallation process was achieved using Odiaka *et al.,* 2014 method. The adduct (0.0172 g, 0.038 mmol) was weighed into a two-necked round-bottom flask (50 cm^3) and an eight-fold molar excess of Me_3NO (0.138 g, 0.301mmol) was added under nitrogen in 25 ml toluene. The solution was refluxed for 4 hrs. The solution was allowed to cool to room temperature to obtain a light-yellow oil. The percentage yield obtained was 32 %.



Scheme 3: Formation of (E)-3-(1′,2′-dihydro-[1′,1′-biphenyl]-3-yl)-N-(4-hydroxyphenyl) Acrylamide) (DEM)

Computational Approach

Molecular docking was carried out using PyRx. ADMET analysis was done using SwissADME and Protox 3.0.

Ligand sample Preparation

ChemDraw Pro v16.0 was used to make a two-dimensional model of the chemical structure while the ligand compound samples were being prepared. To minimize and change the structures, the molecular mechanics force field (MMFF2) was used. This field was also present in the 3D display of ChemDraw. The file was finally saved in PDB format (Ambarwati *et al*., 2022).

Preparation Control Drug for Docking

The three-dimensional (3D) structure of the control medication. Miltefosine was used as standard drug.

Retrieval and Preparation of Target Proteins

The three-dimensional (3D) structures of the target protein or receptor, leishmanolysin (ID PDB: 1LML) , were obtained from the Protein Data Bank (PDB) (http://rcsb.org) (Desai and Joshi, 2019). The drug targets or ligands underwent processing to ensure they were formatted correctly for upload into the PyRx window, thereby facilitating a more efficient docking process The refinement process was conducted using the Biovia Discovery Studio Visualizer.

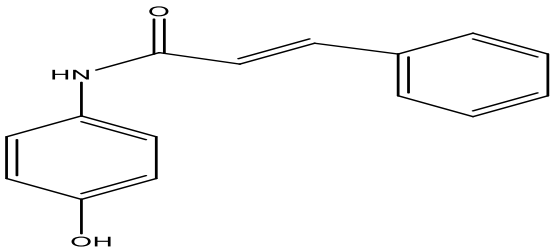
Molecular Docking

Molecular docking was carried out using PyRx to convert the obtained protein structures into macromolecules using the AutoDock Vina docking program to carry out the execution of the docking procedure against the target protein's leishmanolysin (ID PDB: 1LML) active site to define the grid box. The binding energy of the docked complex were included in the results, available for download in a .csv file. The Biovia Discovery Studio application 2024 was employed to visualize the docked complexes fig. X (Trott *et al*., 2010). Miltefosine was used as standard drug. The standard drug, ACCH, Adduct, and DEM were docked into the active pocket of leishmanolysin (ID PDB: 1LML) and were visualized using Biovia Discovery 2024.

In the drug design context, pharmacokinetic and toxicological properties are crucial aspects of achieving good oral bioavailability and safe drugs (Garcia *et al*., 2021). ADMET analysis was carried out using Swiss ADME and Protox 3.0. Swiss ADME was used to determine the pharmacokinetic properties of the drugs while Protox 3.0 was used for the toxicological properties of the drugs. ADMET analysis of ACCH, Adduct, DEM and standard drugs were all analysed.

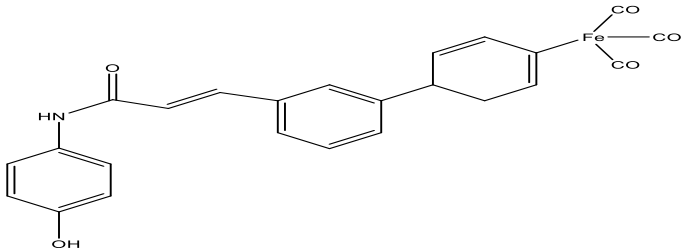
RESULTS AND DISCUSSION

The reaction of $[(\eta^5\text{-}C_6H_7)Fe(CO)_3]PF_6$ with N-(4-hydroxylphenyl) cinnamamide (ACCH) (Fig.1) gave brown solid organometallic adduct (Fig. 2)**,** which on demetallation gave light-yellow oil DEM (Fig.3). The melting points were 90°C, 168°C and 315°C respectively. Their structures are shown in Fig1-3 below.



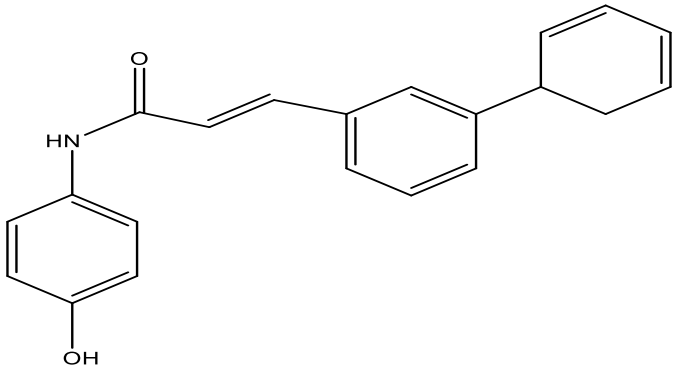
Molecular Formula: $C_{15}H_{13}NO_2$

Figure 1: Structure of N-(4-hydroxylphenyl) Cinnamamide (ACCH)



Molecular Formula: $C_{24}H_{19}FeNO_5$

Figure 2: Tricarbonyl [η⁴-5(N-(4-hydroxylphenyl) Cinnamamide) cyclohexa-1,3-diene) Iron (adduct)



Molecular Formula: $C_{21}H_{17}NO_2$

Figure 3: (E)-3-(1', 2'-dihydro-[1',1'-biphenyl]-3-yl)-N-(4-hydroxyphenyl) Acrylamide (DEM)

Infra-red Studies

Given below are the Infra-red spectra data of the synthesized compounds:

Acetaminophen

$C_8H_9NO_2$. White solid IR (film) V_{max} cm^{-1}: 3322 (broad) (O-H str. of phenol); 3163 (assymetric) and 3107(symmetric) (N-H str. of amide); 2795 (C-H str. of alkane); 1561 (N-H bend of amide II); 1505 (C=C str. of aromatic); 1651 (C=O str. of amide I); and 1225 (C-O str. of phenol).

N-(4-hydroxylphenyl) Cinnamamide (ACCH)

$C_{15}H_{13}NO_2$. Yellow solid IR (film) V_{max} cm^{-1}: 3439 (broad) (O-H str. of phenol); 3062 (assymetric) and 3029 (symmetric) (N-H str. of amide); 2927 (C-H str. of alkene); 1602 (C=C str. of alkene), 1692 (C=O str. of amide I), 1495 (N-H bend of amide II), 1451 (C=C str. of aromatic) and 1334 (C-O str. of phenol).

Tricarbonyl[η⁴-5(N-(4-hydroxylphenyl)Cinnamamide) Cyclohexa-1,3-diene) Iron (ADDUCTS)

$C_{24}H_{19}FeNO_5$. Yellow solid IR (film) V_{max} cm^{-1}: 3429 (broad) (O-H str. of phenol); 3067 (assymetric) and 3025 (symmetric) (N-H str. of amide); 2917 (C-H str. of alkene), 2042 and 1971 (vCO of coordinated diene organometallic moiety), 1702 (C=O str. of amide I), 1597 (C=C of alkene), 1493 (C-C str. of C_6H_7), 1454 (C=C of aromatic), and 495 (Fe-C band).

(E)-3-(1',2'-dihydro-[1',1'-biphenyl]-3-yl)-N-(4-hydroxyphenyl) Acrylamide (DEM)

$C_{21}H_{17}NO_2$. Light-yellow oil IR (film) V_{max} cm^{-1}: 3256 (broad) (O-H str. of phenol); 2960 (C-H str. of alkene); 2200 (broad) (v(CO) coordinated diene organometallic moiety); 1642 (C=O str. of amide I), 1481 (N-H of amide II), 1462 (C=C str. of aromatic), and 1240 (C-O str. of phenol).

The FT-IR assignment of acetaminophen was consistent with the report of Zapata *et al*., 2021. ACCH exhibited carbonyl stretching vibrations for the enones (=C-C=O) between 1650 cm^{-1} and 1685 cm^{-1} (Bruan *et al*. 2006). The amide C=O stretching vibration observed at 1651 cm^{-1} was shifted to 1692 cm^{-1} in ACCH (Kudo and Nakashinma, 2020). The formation of the ADDUCT were confirmed by the presence of v(CO) bands at 2042 cm^{-1} and 1971 cm^{-1} characteristics of cationic tricarbonyl (1,3-diene-substituted)iron derivatives as reported by Adebisin *et al*., 2016 which was absent in ACCH and the emergence of Fe-C bands at 495 cm^{-1}. The demetallation reaction to give DEM was ascertained by the disappearance of the Fe-C bands at 495 cm^{-1} (Adebisin *et al*., 2016; Odiaka *et al*., 2014).

Computational Report

Molecular Docking

Results of the binding energies of the compounds and the standard drug are presented in Table1 and Fig. 4 below. The binding energy of ACCH, ADDUCT and DEM ranged from -6.4 kcal/mol to -8.1 kcal/mol compared to Miltefosine with -5.0 kcal/mol. The lower binding energy of the synthesized compounds indicated that the compounds exhibit good stability and interacted well with the active site of the enzyme 1LML receptor compared to Miltefosine (Khaldan *et al*., 2023).

Table 1: Binding Energy of the Synthesized Compounds and the Standard Drugs

Compounds	Binding Affinity (kcal/mol)
ACCH	-6.4
ADDUCT	-7.4
DEM	-8.1
Miltefosine	-5.0

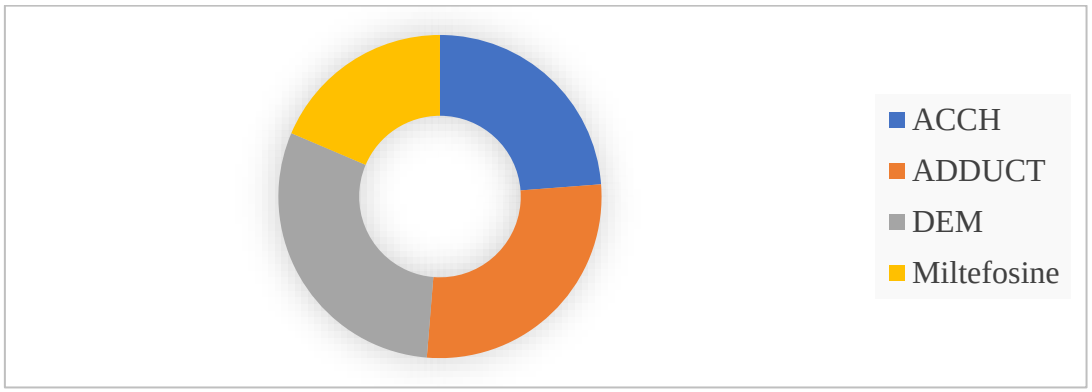


Figure 4: Pie Chart Representing Binding Affinity of the Synthesized Compounds and the Standard Drug

Molecular Docking Interaction

Inspection of the interaction of the docked structures reveal the most favorable interactions within the active site. The molecular docking interaction result of ACCH, ADDUCT, DEM and Miltefosine are shown in Fig. 5 (a-d).

The OH group of ACCH afforded three conventional hydrogen bonding interactions with HIS268 and THR229 residues. HIS268 and THR229 afforded conventional hydrogen bonding with H of the OH group at distances of 4.89 Å and 3.98 Å respectively, while HIS268 afforded one conventional hydrogen bonding with O of the OH group at 3.98 Å. The benzene ring without OH group provide a pi-pi stacked interaction with TRP226 at a distance of 5.64 Å as shown in Fig 5(a).

The H of the OH group of the ADDUCT showed one conventional hydrogen bonding interaction with LYS158 at a distance of 6.65 Å while the O of the OH group give a carbon hydrogen bonding interaction with HIS159 at a distance of 3.74 Å. The benzene ring without an OH group undergo two pi-alkyl interactions with VAL569 and LEU167 with distances of 4.84 Å and 6.22 Å respectively as shown in Fig. 5(b).

The OH group of the DEM afforded two conventional hydrogen bonding interaction with ALA225 and LEU224, the H end of the OH group showed one conventional hydrogen bonding interaction with ALA225 at a distance of 2.90 Å while the O end of the OH group showed one conventional hydrogen bonding interaction with the LEU224 at a distance of 4.2 Å. The carbonyl group also show one conventional hydrogen bonding interaction with HIS334 at a distance of 5.89 Å. Five pi-alkyl interactions with ALA349, VAL261, VAL223, ALA136, and TRP226 was also observed. The benzene ring with an OH group afforded two pi-alkyl interactions with ALA349 and VAL261 at distances of 6.29 Å and 5.68 Å respectively, the benzene ring without OH group afforded one pi-alkyl interaction with VAL223 at a distance of 5.84 Å, and the cyclohexadiene group showed two alkyl interactions with ALA136 and TRY226 at distances of 7.02 Å and 4.8 Å respectively. The benzene ring without an OH group afforded one pi-pi stacked interaction with TRY226 at a distance of 6.05 Å as seen in Fig. 5(c).

Miltefosine showed 8 alkyl interactions with LEU420, LEU257, PRO460, ALA349, and LEU224 at distances of 4.27 Å, 4.67 Å and 5.23 Å, 4.82 Å and 6.28 Å, 4.29 Å and 4.78 Å, 9.82 Å respectively. LEU257, PRO460, and ALA349 provided two alkyl interactions each. Two pi-anion interaction with HIS264 and GLU265 at distances of 4.28 Å and 7.66 Å respectively and three carbon hydrogen bonding with PRO347 at a distance of 6.36 Å, GLU265 at distances of 6.30 Å and 6.37 Å as observed in Fig. 5(d).

Conventional hydrogen bond is considered the most favorable (or rewarded contact) with the highest level of complementarities between binding site and ligand (Korb *et al*., 2009). Availability of more favaourable interactions than unfavourable interactions suggest that the product formed will be more stable (Okeke and Okeke, 2022).These showed ACCH, DEM and ADDUCT to be more stable compared to miltefosine which had no conventional hydrogen bond. Carbon-hydrogen bond was a form of covalent interaction where a carbon shared its outer valence electron with up to four hydrogen atoms. This bond confered more strength to the complex formed than van der Waals forces (Okeke and Okeke, 2022). Pi-pi stacked interaction was formed in the DEM due to high polarizability of aromatic rings leading to dispersive interactions of nucleobases such as in DNA (Tanuj, 2017). The important number of hydrogen bonding interaction gave ACCH, ADDUCT and DEM great pharmacological importance as hydrogen bonds heavily affect the pharmacological action of ligands (Khaldan *et al*., 2023). On the other hand, Miltefosine show less hydrogen bond.

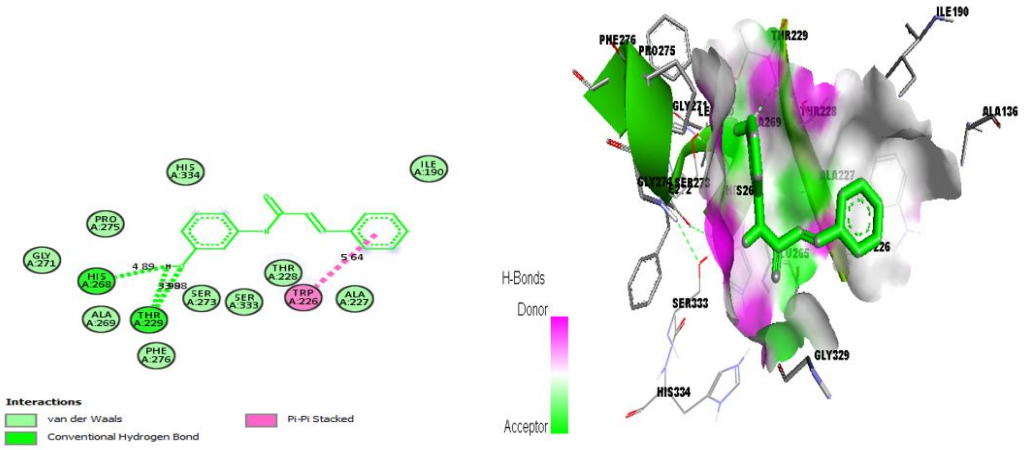


Figure 5: (a) 2D and 3D Interaction ACCH with Leishmanolysin (ID PDB: 1LML)

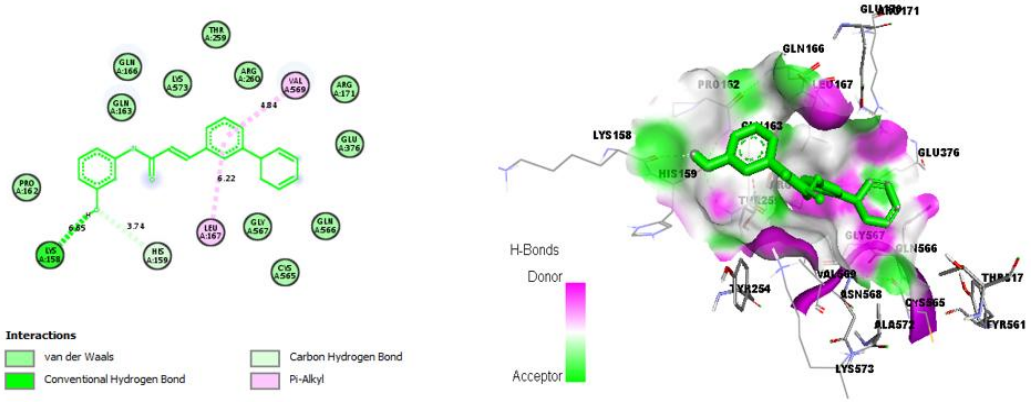


Figure 5(b): 2D and 3D Interaction of ADDUCT with leishmanolysin (ID PDB: 1LML)

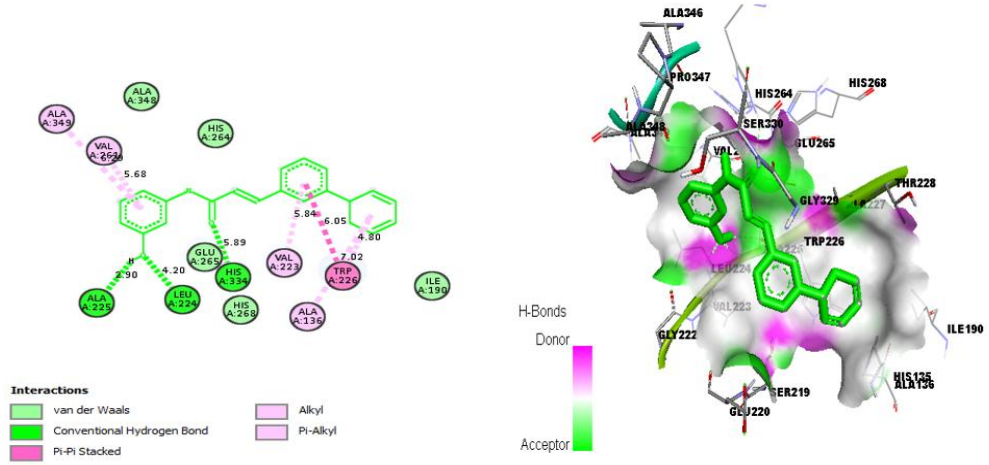


Figure 5(c): 2D and 3D Interaction of DEM with Leishmanolysin (ID PDB: 1LML)

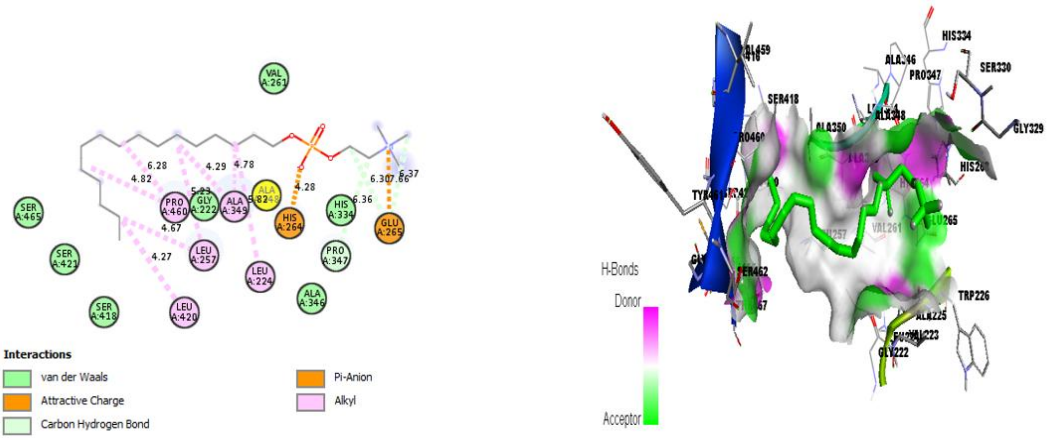


Figure 5(d): 2D and 3D Interaction of Miltefosine Leishmanolysin (ID PDB: 1LML)

ADMET Report

Pharmacokinetic and toxicological properties are important aspects to achieve good oral bioavailability and safe drugs in the drug design context. (Garcia *et al*., 2021). As a result, ADMET computational assessments of ACCH, ADDUCT, DEM and Miltefosine were performed to evaluate the highest inhibitory efficacy against leishmanolysin (ID PDB: 1LML) as presented in Table 2 and Table 3.

Table 2: ADME Prediction of ACCH, ADDUCT, DEM and Miltefosine

Compounds (Chemical formular)	GIA	BBB Perma-nent	p-gp substrate	CYP Inhibitor	LIPINSKI Rule of Five	Consensus $LogP_{O/W}$	Water Solubility
ACCH ($C_{15}H_{13}NO_2$)	High	Yes	No	1A2, 2C9	Yes	2.66	Soluble
ADDUCT ($C_{24}H_{19}FeNO_5$)	High	No	No	1A2, 2C9	Yes	2.70	Moderately Soluble
DEM ($C_{21}H_{17}NO_2$)	High	Yes	No	1A2,2C9, 2C19, 3A4	Yes	3.78	Moderately Soluble
Miltefosine ($C_{21}H_{46}NO_4P$)	Low	No	Yes	2C9, 3A4	Yes	3.35	Moderately Soluble

KEY: GIA: Gastrointestinal Absorption, BBB Permeant: Blood-brain Barrier Permeability, P-gp Substrate: Permeability Glycoprotein Substrate

Table 3: Toxicity Prediction of ACCH, ADDUCT, DEM and Miltefosine

Compounds (Chemical formular)	Mutagenicity	Cardio-toxicity	Immuno-toxicity	Respiratory toxicity	Carcino-genicity	Neuro-toxicity
ACCH ($C_{15}H_{13}NO_2$)	Yes	No	No	No	Yes	Yes
ADDUCT ($C_{24}H_{19}FeNO_5$)	No	No	Yes	No	No	No
DEM ($C_{21}H_{17}NO_2$)	Yes	No	Yes	No	Yes	Yes
Miltefosine ($C_{21}H_{46}NO_4P$)	No	Yes	Yes	Yes	No	No

Absorption

The absorption properties such as water solubility, intestinal absorption (human), P-glycoprotein properties and Lipinski's rule of five were calculated. Solubility plays a vital role both in the theoretical and practical applications of chemical compounds (Martnez *et al*., 2017). The capacity to of a drug to dissolve in a specific solvent has substantial effects on the reactivity, stability, and bioavailability of a compound. In pharmaceuticals field, solubility held significant importance in drug design and formulation (Tran *et al*., 2019). ACCH showed good solubility while others including the standard drug are moderately soluble in water as shown in Table 2. Low water solubility does not disqualify consideration of compounds as potential drugs; however, it indicates some challenges associated with the development of a form of the drug that enables its absorption and ensures adequate bioavailability (Czeleń *et al*., 2023). Human intestinal absorption was used to predict the proportion of drugs absorbed in the human intestine (Sinha *et al*., 2020). All the synthesized compounds (ACCH, ADDUCT and DEM) showed high gastrointestinal absorption which guarantee good absorption by the human intestine while Miltefosine shows poor absorption in the human intestine. P-glycoprotein (P-gp) functions as a pump and an efflux transporter that help transport xenobiotics out of the cell, playing a significant role in the pharmacokinetic and pharmacodynamic properties of drugs, such as reducing bioavailability (Vilar *et al*.,2019). P-glycoprotein properties help to determine the probability of interaction between the tested drugs and the receptor of the protein as an inhibitor or substrate, which may contribute to a significant reduction in the permeability of drugs through membranes (Sinha *et al*., 2020). The synthesized compounds show no p-gp substrate while Miltefosine show pg-substrate which implied they may contribute to a significant reduction in the permeability of drugs through membranes. Currently, many theoretical approaches such as the Lipinski's rule of five assess the physical-chemical theoretical parameters related to the oral bioavailability (Lipinski, 2004). Log Po/w is used as

a standard descriptor to assess lipophilicity. Compounds' lipophilicity affects how easily they pass through biological membranes. It may be reduced when lipophilicity is too low, but excessively hydrophilic substances often cannot diffuse passively through them (Duran-iturbide *et al*., 2020). Consensus LogPo/w is the mathematical average of the values anticipated by the five proposed techniques. Its distribution implies that it is influenced by the MW and thus contributes to the drug-like ness (Ojuka *et al*., 2023). According to most filters (rule of 5) for drug-likeness, a lipophilicity range of 0 to 5 is usually considered optimal for drug design (Waring *et al*., 2010; Ononamadu *et al.*, 2021) . The consensus LogP o/w suggested that ACCH, ADDUCT, DEM and Miltefosine were lipophilic. The obtained results suggested that synthesized compounds ACCH, ADDUCT, DEM and Miltefosine did not violate Lipinski's rule and thus demonstrated good bioavailability on oral admnistration.

The distribution study of the compounds and the controls were carried out. The brain is protected from much of the potential chemical interference by the BBB, an evolutionarily conserved barrier that selectively separates the brain from the circulatory system. The Blood Brain Barrier (BBB) controls the transport of ions, proteins, hormones, and immune cells between the brain and the blood, necessary for adequate brain function (Cornelissen *et al*., 2023). A compound's capacity to reach into the brain is a significant parameter that may help decrease adverse effects and toxicities or enhance the compounds' efficiency whose pharmacological activity is within the brain (Sinha *et al*., 2020). The result of this study as shown in Table 2, shows that ACCH, DEM with the exception of the ADDUCT and Miltefosine will cross the blood brain barrier which implied the potential of ACCH and DEM in treatment of brain disease.

Metabolism and Excretion

Drugs metabolism and the potential activity of their metabolite's interaction within the patient's body is an important factor in the evaluation of new drugs (Czeleń *et al*., 2023). Cytochrome P450 facilitates the metabolism of drugs (Sinha *et al*., 2020). Inhibitors of this enzyme may affect the metabolism of the drugs, and the drugs may have a reverse effect (Domínguez-Villa *et al*., 2021). Although only CYP1, CYP2, CYP3 and CYP4 are responsible in the metabolism of drugs, 17 categories of CYPs have been identified in humans till present, thus, only the types (1A2, 2C9, 2C19, 2D6 and 3A4) are responsible for biotransformation of drugs for more than 90 %, pass the first step of metabolism (Zanger and Schwab, 2013). Therefore, it is indispensable to evaluate the ability of compounds to inhibit cytochromes (CYP). As shown in Table 2, ACCH inhibited 1A2, and 2C9; ADDUCT inhibited 1A2, and 2C9; and DEM inhibited 1A2,2C9, 2C19, and 3A4. CYP2C19 responsible for the metabolism of drugs such as proton pump inhibitors and antidepressants, so it is unlikely that important drug interactions will occur in patients with leishmaniasis, 2C9 is responsible for approximately 15% of drug metabolism, including nonsteroidal anti-inflammatory used in the treatment of cutaneous leishmaniasis (deSantiago-Silva *et al*., 2022). The two isoforms 2D6 and 3A4 are mainly responsible for drug metabolism (Rodrigues-Junior *et al*., 2020). CYP1A2 is an important metabolizing enzyme in the liver, which comprise approximately 13 % of all CYP protein (Thorn *et al*., 2012). Miltefosine inhibits 2C9 and 3A4. The DEM and miltefosine, may cause dug-drug interaction (Tirona and Kim, 2017).

Toxicity

An important aspect of the study of chemical substances as potential drugs is the analysis of their toxicity in terms of interaction with the human body. The pharmacological action of a given drug may be accompanied by a set of undesirable side effects (Czeleń *et al*., 2023). National Cancer Institute defined cardiotoxicity as the 'toxicity that affects the heart'. This definition includes a direct effect of the drug on the heart but also an indirect effect due to the enhancement of hemodynamic flow alterations or due to thrombotic events (Albini *et al*., 2010). The synthesized compounds ACCH, ADDUCT and DEM were not toxic to the heart compared to miltefosine which is cardiotoxic. ADDUCT was also seen to be non-mutagenic, non-cardiotoxic, non-carcinogenic, non-neurotoxic and non-respiratory toxic which implied it was less toxic to a patient with leishmaniasis compared to ACCH, DEM and Miltefosine the standard drug.

CONCLUSION

ACCH, ADDUCT and DEM, have been synthesized and in-inslico studies against Leshimaniasis obtained by molecular docking. From the result of docking,ACCH, ADDUCT and DEM showed good binding energy and interacted well within the active pocket of leishmanolysin compared to Miltefosine. Their ADMET analysis also showed good absorption, distribution and metabolism compared to Miltefosine except DEM which may cause drug-drug interaction. ACCH, ADDUCT and DEM did not exhibit p-gp substrate while Miltefosine showed pg-substrate which implied they may contribute to a significant reduction in their permeability through cell membranes. ADDUCT displayed lesser toxicity compared to ACCH, DEM, and Miltefosine which showed the potential of this study as a lead for new antileishmanial drugs.

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