Original Article

# In-silico Analysis and Anti-inflammatory Evaluation of Synthesized Amide Derivatives of Long-chain Fatty Acids

**Samuel J. Bunu[1, 2], Haruna Baba[3], Deghinmotei Alfred-Ugbenbo[4]**

*1. Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Nigeria.*
*2. Drug Analysis and Research Center, Ebisamdex Global Ventures Ltd, Yenagoa, Nigeria.*
*3. Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Calabar, University of Calabar, Nigeria.*
*4. Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Bayelsa Medical University, Yenagoa, Nigeria.*

*** Corresponding Author:**
**Samuel J. Bunu, PhD.**
**Address:** Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Nigeria.
**Phone:** +234 8069703966
**E-mail:** samuelbunu2@gmail.com



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## ABSTRACT

**Background:** The search for more active and less toxic anti-inflammatory drugs is the desire of every medicinal chemist. Amide derivatives of fatty acids (FAs) have diverse biological functions.

**Objectives:** The search for more active and less toxic anti-inflammatory drugs is the desire of every medicinal chemist. Amide derivatives of FAs have diverse biological functions.

**Methods:** The current study conducted an in-silico molecular docking analysis using PDB ID: 6DII on synthesized amide derivatives of long-chain FAs (LCFAs) and evaluated and correlated their anti-inflammatory and anti-nociceptive biological mechanisms with those of acetylsalicylic acid as a standard. The synthesis was achieved using glycine, β-alanine, γ-aminobutyric acid (GABA), and palmitoyl chloride. The raw paw edema model was used to assess the anti-inflammatory and analgesic properties.

**Results:** The anti-inflammatory assessment revealed a dose-dependent bioactivity from 20 mg/kg to 50 mg/kg; further increments in the dose led to decreased activity. For the analgesic activity, at 100 mg/kg, N-palmitoyl glycine exhibited 83.2% inhibition of writhing compared to 74.3% inhibition of the standard drug, aspirin (100 mg/kg). The molecular docking studies showed that N-palmitoyl alanine had the highest protein binding affinity, followed by N-palmitoyl, GABA, and N-palmitoyl glycine, higher than acetylsalicylic acid. The compounds interacted with the protein via specific functional groups and protein amino acid residues.

**Conclusion:** The ability of these amide derivatives of LCFAs to biologically inhibit the inflammatory and nociceptive pathways could be attributed to the presence of N-H, C=O, and OH groups, which bind to the GLY-255, THR-300, GLY-302, and ASP-207 residues.

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## Introduction

Fatty acids (FAs) are essential nutrients that regulate an organism's health and growth in mammals [1]. Long-chain FAs (LCFAs) are FAs formed by the hydrolysis of neutral lipids and have aliphatic tails containing 13-21 carbon atoms. Three of the most prevalent LCFAs in anaerobic digesters are palmitate, oleate, and stearate. LCFAs have significant functions in cellular energy metabolism, acting as both a vital energy source and signaling molecules [2, 3]. LCFAs can be classified as saturated or unsaturated based on the presence of at least one double bond in their carbon chains. LCFAs enter cells via passive diffusion and protein-mediated translocation across the plasma membrane, in which FA translocase (FAT/CD36), plasma membrane FA-binding protein (FABPpm), FA transport protein (FATP), and caveolin-1 are thought to play critical roles. Cells absorb LCFAs, which bind to FA-binding proteins (FABPs) and transport them to certain organelles, where they are activated into acyl-CoA to target specific metabolic pathways [4]. LCFA-CoA esters boost their oxidation by acting as allosteric inhibitors of acetyl-CoA carboxylase. This decreases malonyl-CoA synthesis and relieves the inhibition of carnitine palmitoyl-transferase-1, promoting LCFA-CoA transport into mitochondria for β-oxidation [2, 5]. LCFAs are not only important metabolites but also contribute to various physiological processes, including the activation of protein kinase C (PKC) isoforms and nuclear transcription factors, such as peroxisome proliferator-activated receptors (PPARs) [6].

FAs are digested and produced as energy sources throughout biological processes. The metabolic network's primary sources of free FAs (FFAs) include long- and medium-chain FAs generated mostly from dietary triglycerides, as well as short-chain FAs (SCFAs) produced by gut microbial fermentation of otherwise indigestible food fiber [7]. FFAs not only serve as energy sources but also as natural ligands for a group of orphan G protein-coupled receptors (GPCRs) known as free FAs receptors (FFARs), essentially intertwining metabolism and immunity in multiple ways, such as through inflammation regulation and secretion of peptide hormones [7]. Several factors can induce inflammation, including a blood clot, an immune system issue, cancer, an infection, chemical exposure, a physical injury, or a neurological condition, like Alzheimer's disease or depression. Many infections, particularly those caused by viral, bacterial, fungal, or protozoan pathogens, can produce inflammation. Inflammations can have far-reaching medical repercussions since persistent inflammation can aid cancer and trigger autoimmune illnesses [8].

Amide derivatives of FAs are a type of lipid that consists of two chemical moieties, a FAs, and a biogenic amine, joined together by an amide bond, structurally related to the endocannabinoid anandamide (N-arachidonoylethanolamine) [9]. Palmitoyl-ethanolamide belongs to the anandamide class as a possible anti-inflammatory and anti-nociceptive agent. Anandamide is a known endogenous ligand for cannabinoid receptors [10]. Research and analysis of anti-inflammatory agents are common because these drug compounds are employed frequently in current medical practice globally, as all known human disease pathophysiology passes through inflammatory stages [11-15]. The lipid signal is becoming more congested as more FAs amide derivatives are discovered and considered potential therapeutic targets. The identification of N-arachidonoyl-ethanolamine as an endogenous ligand of cannabinoid type-1 and type-2 receptors, as well as the development of various-omics technologies, can lead to the discovery of a large number of naturally occurring N-acyl-amines [16]. Aside from being used as anti-inflammatory agents, reprogramming of lipid metabolism is emerging as a hallmark of cancer, although the role of specific FA species and associated enzymes in carcinogenesis is unclear. While prior research has focused on the participation of LCFAs, such as palmitate in cancer, less attention has been paid to the impact of very LCFAs (VLCFAs) [16].

Studies on palmitoyl ethanolamide (palmitoylamino acids) have shown good anti-inflammatory and anti-nociceptive effects in vitro, but the exact mechanism of action is yet to be elucidated and confirmed, and it was suspected to be related to the inhibition of FAs amide hydrolase (FAAH), the enzyme that metabolizes anandamide and palmitoyl ethanolamide in vivo [10]. Hence, we conducted an in-silico molecular docking analysis using the *Arabidopsis thaliana* FAAH proteins (PDB ID: 6DII) on the synthesized amide derivatives of LCFAs and tested their biological activities to correlate and possibly validate the biological mechanism behind their anti-inflammatory and anti-nociceptive properties. FAAH is an amidase signature (AS) enzyme in most multicellular organisms. FAAH hydrolyzes lipid signaling molecules, specifically N-acyl ethanolamines (NAEs), terminating their activity. The crystal structure of *A. thaliana* FAAH was determined, and critical residues were discovered for substrate-specific interactions [17]. In vertebrates, the endocannabinoid signaling pathway is a key lipid regulatory route that influences various physiological and behavioral functions. NAEs are a class of FAs derivatives that function in this pathway. Their signaling activity is ended by FAAH, which hydrolyzes NAEs to ethanolamine and their corresponding FFAs [18].

## Materials and Methods

### Synthesis and characterization

Several medicines have been developed through the synthetic route, with some in clinical use and others in the pre-clinical phase [19, 20]. The synthesis of the amide derivatives was accomplished using commercially available starting materials (glycine, β-alanine, γ-aminobutyric acid (GABA), and palmitoyl chloride) that met analytical standards and required no further purification. To obtain the amide derivatives of the LCFAs, for N-palmitoyl glycine, glycine (0.546 g, 7.28 mmol) was dissolved in 10 mL of dichloromethane (DCM) and added to 1 mL of triethylamine and palmitoyl chloride (2.2 mL, 7.28 mmol) with constant stirring for 4 hours. The mixture was filtered and washed with HCl (10 mL), and the combined organic filtrate was dried over anhydrous $Na_2SO_4$, evaporated in a vacuum, and recrystallized from a 1:1 methanol and water solution. For N-palmitoyl GABA, (0.34 g, 3.3 mmol) was dissolved in 15 mL 1,4-dioxane and stirred in a solution of 1N NaOH (3.3 mL, 3.3 mmol) added under ice and stirred continuously for 15 minutes. The addition of palmitoyl chloride (3.3 mmol) was followed by 1N NaOH (3.3 mL, 3.3 mmol), and the mixture was stirred at room temperature for 4 hours. The mixture was acidified with 1N HCl to a pH of 3, the solid was collected, and purification was performed (pH 5-6). The final product was recrystallized following the previous procedure. Finally, 1 mL of triethylamine (TEA) was added to N-palmitoyl alanine, β-alanine (0.590 g, 6.6 mmol) in dry dichloromethane (10 mL) while stirring in an ice-cold chamber (0-5 ˚C), followed by the dropwise addition of palmitoyl chloride and a final wash with DCM (10 mL). The ice was removed, and the resulting syrupy mixture was stirred for 2 hours at room temperature, diluted with DCM (20 mL), and washed with 10 mL of 1N HCl and water. The combined organic portion was dried over anhydrous $Na_2SO_4$, and the solvent was removed under vacuum, resulting in a whitish crude solid that was recrystallized as described above.

$$CH_3(CH_2)_{14}COCl + H_2N(CH_2)nCOOH \xrightarrow{CH_2C_{l2}} CH_3(CH_2)_{14}CONH(CH_2)nCOOH$$

Scheme 1. Synthetic route (n=1–3).

The synthesized compounds were characterized using an IR spectrum obtained from a Buck Scientific IR M500 instrument (Buck Scientific Inc., USA), and $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini 200 (250 MHz) (Varian Inc., USA).

### Anti-inflammatory and antinociceptive studies

The raw paw edema model was used to assess the anti-inflammatory and antinociceptive properties of the synthesized amide derivatives of LCFAs. Three doses were tested, including 20, 50, and 100 mg/kg. One of the test compounds was injected into the subplantar area of the right hind paw after an hour of carrageenan suspension (0.1 mL, 1%) in 0.9% NaCl. Paw thickness was determined for 5 hours using a veneer caliper. The anti-inflammatory activity was evaluated using the following formula [21]: Activity =100-[100×(average drug treated/average for control)]. The analgesic activity was evaluated using the following formula [22, 23]: Percentage inhibition (%) =100-[100×(average drug response/average control response)]. The analgesic properties were assessed in a group of five mice administered oral doses of 20, 50, and 100 mg/kg of the test compounds. After 1 hour, the mice were injected intraperitoneally (i.p.) with 0.2 mL of a 0.6% acetic acid solution. Acetylsalicylic acid, also known as aspirin (100 mg/kg), was administered orally as a reference drug, while Tween 80(10%), used to solubilize the synthesized drugs, was used as a negative control. The mean abdominal constrictions per group were used as an indicator of analgesic activity. The percentage inhibitions of abdominal constrictions by the test compounds were compared to the control group. All results were statistically analyzed by one-way analysis of variance (ANOVA), with a P of $<0.005$ considered significant.

### Molecular docking

Arabidopsis FAAH in complex with methyl linolenyl fluorophosphonate (PDB ID: 6DII), obtained from the Protein Data Bank (PDB) was used for the molecular docking studies from the determined FAAH crystal structure of *A. thaliana*, and critical substrate-specific residues for protein-ligand interactions [17]. Hence, inhibiting these proteins may provide insight into the ability of these compounds to act as anti-inflammatory or anti-nociceptive agents. Acetylsalicylic acid and linolenyl fluorophosphonate were used as standard controls in the in-silico molecular docking studies. The test compounds included N-palmitoyl glycine, N-palmitoyl alanine, and N-palmitoyl GABA, respectively. Molecular modeling and docking of the binding protein with ketamine and its analogs (ligands) were conducted using the Maestro software with the OPLS3 2018 force field [24, 25].

## Results

The results are presented in tables and charts following analysis on Microsoft Excel spreadsheet, and Microsoft word version 2019. Figures were prepare using PowerPoint and Python software.

## Discussion

The amide derivatives of LCFAs were obtained in high yield and purity, as shown by their elemental characterization and physicochemical parameter evaluation [10]. We subjected the compounds to in silico molecular docking, which showed promising results compared with the standards, with comparable affinity levels to a known inhibitor of the *A. thaliana* FAs amide hydrolase enzyme, linolenyl fluorophosphonate (-6.85 kcal/mol), and higher affinity than the well-known anti-inflammatory and analgesic agent, acetylsalicylic acid (-5.61 kcal/mol). Among the amide derivatives, N-palmitoyl alanine exhibited the highest protein binding affinity (-6.67 kcal/mol), followed by N-palmitoyl GABA (-6.48 kcal/mol) and N-palmitoyl glycine (-6.38 kcal/mol), respectively (Table 1). This depicts that the synthesized amide derivatives of LCFAs are promising lead compounds in the inhibition of biological inflammatory and nociceptive pathways.

The in vivo anti-inflammatory activity of the synthesized amide derivatives of LCFAs was evaluated using a carrageenan-induced paw edema assay [26, 27]. The anti-inflammatory assessment revealed a dose-dependent bioactivity from 20 mg/kg to 50 mg/kg; further increments in the dose led to decreased activity. The compounds also demonstrated significant anti-nociceptive activity compared with the ASA control. N-palmitoyl glycine exhibited the highest dose-dependent edema inhibition (among the three compounds) ranging from 47 to 49% as the dose increased from 20 to 50 mg/kg, while aspirin, the standard drug (100 mg/kg), produced a 51% inhibition of edema. For the analgesic activity, at 100 mg/kg, N-palmitoyl glycine exhibited an 83.2 % inhibition of writhing compared to a 74.3% inhibition by the standard drug, aspirin (100 mg/kg). N-palmitoyl glycine produced the most pronounced anti-nociceptive effect (Table 2). This is similar to the in silico studies, where N-palmitoyl glycine showed a better protein-binding affinity compared to the aspirin standard (-6.38 kcal/mol vs. -5.61 kcal/mol).

The protein-ligand binding of all the synthesized amide derivatives of the LCFAs was conducted via in silico molecular docking studies using the *A. thaliana* FAAH protein (PDB ID: 6DII). The interaction between 6DII and N-palmitoyl glycine showed that N-palmitoyl glycine had hydrophobic, polar, positive, and negatively charged interactions with different residues of the protein (Figure 1A). Additionally, N-palmitoyl glycine formed hydrogen pi-pi bonding interactions with the carboxylic acid (OH), the amide carbonyl functional group (C=O), and the residues ASP-207, GLY-302, and THR-300 of the protein (Figure 1B). This depicts that the amide C=O and OH groups might be required for the bioactivity of N-palmitoyl glycine.

The interaction of 6DII with N-palmitoyl alanine showed hydrophobic, polar, positive, and negatively charged interactions with different residues of the protein (Figure 2A). N-palmitoyl alanine also formed hydrogen pi-pi bonding interactions between the amide nitrogen functional group (N-H), the carboxylic acid (OH), and the residues GLY-255, THR-300, and GLY-302 of the protein, respectively (Figure 2B). This depicts that the N-H and OH groups of N-palmitoyl alanine may be required for its bioactivity.

The interaction of N-palmitoyl GABA with the protein (6DII) showed hydrophobic, polar, positive, and nega-

**Table 1.** Percentage yield and molecular docking

| Compound ID | % Yield | Melting Point (°C) | Molecular Weight (mg) | PDB ID: 6DII | |
|---|---|---|---|---|---|
| | | | | Docking Score (kcal/mol) | Glide Emodel |
| N-palmitoyl glycine | 1.03(90) | 100-108 | 313.5 | -6.38 | -61.57 |
| N-palmitoyl alanine | 1.14(92) | 110-112 | 327.5 | -6.67 | -61.25 |
| N-palmitoyl GABA | 1.10(92) | 80-82 | 341.5 | -6.48 | -66.31 |
| Acetylsalicylic acid | std | std | 180.16 | -5.61 | -38.66 |
| Linolenyl fluorophosphonate | std | std | 344.4 | -6.85 | -55.18 |

Std: Standard.

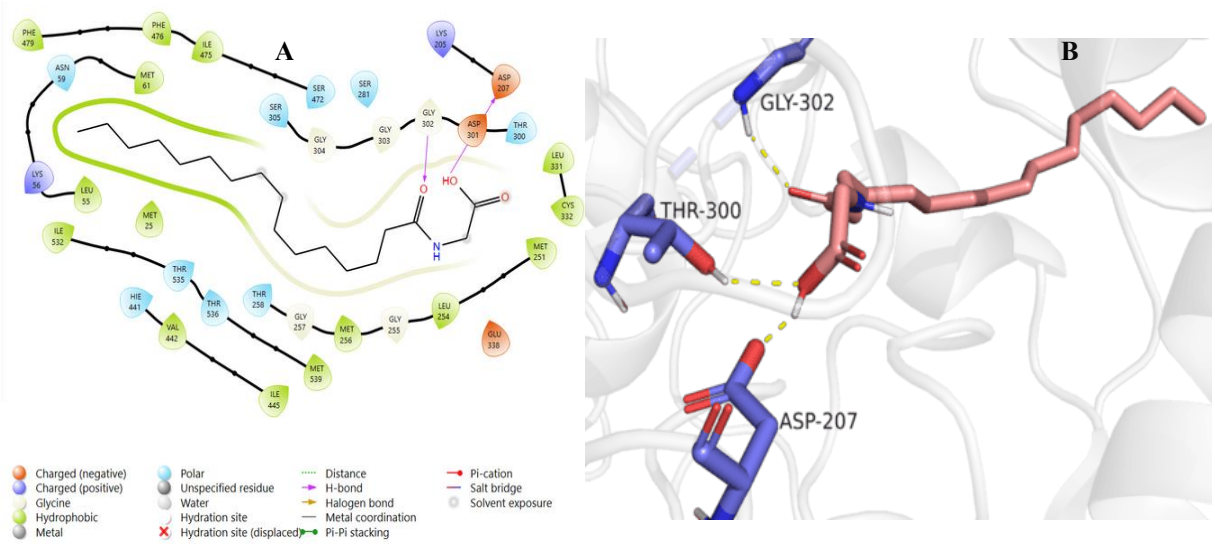


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**Figure 1.** Protein-ligand interaction

A) 6DII-N-palmitoyl glycine 2D interaction, B) 6DII-N-palmitoyl glycine 3D interaction

tively charged interactions with different residues of the protein (Figure 3A). N-palmitoyl alanine also formed hydrogen pi-pi bonding interactions between the amide N-H and OH with ASP-207 and GLY-302, respectively, of the protein (Figure 3B). This suggests that the C=O and OH groups of N-palmitoyl GABA might be required for its bioactivity.

For the standard drugs, acetylsalicylic acid formed hydrogen interactions between the carboxylic acid hydrogen (OH) and the THR-536 residue of the protein (Figures 4A and 4B), while linolenyl fluorophosphonate showed hydrogen interactions between the oxygen of the phosphonate group (P=O) and GLY-302, GLY-303, and SER-305 residues of the protein (Figures 5A and 5B).

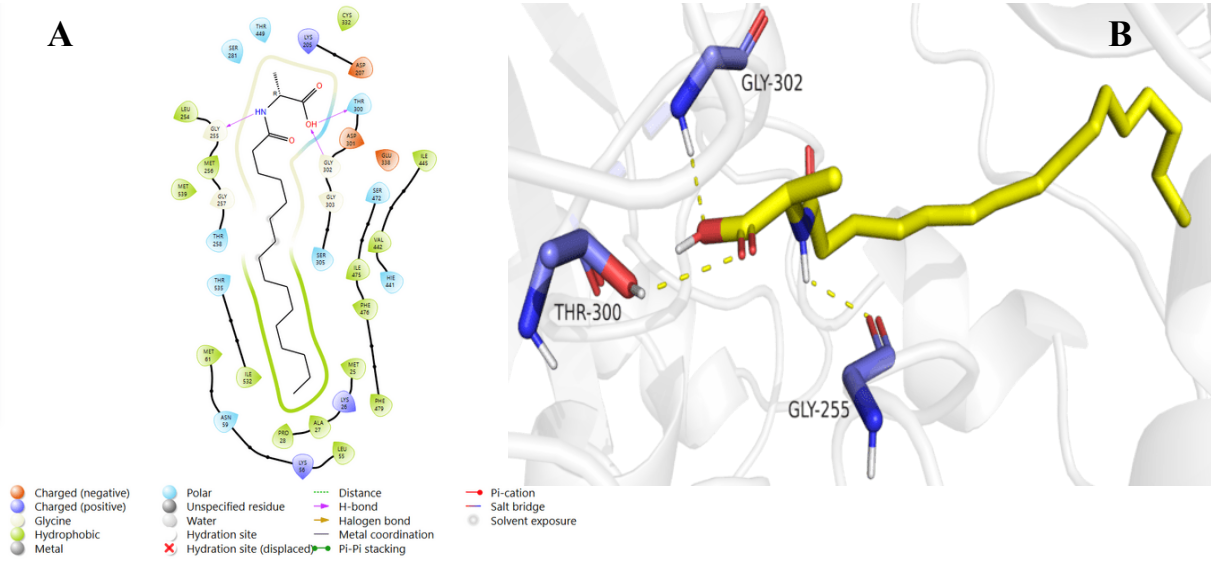


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**Figure 2.** Protein-ligand interaction

A) 6DII-N-palmitoyl alanine 2D interactions, B) 6DII- N-palmitoyl alanine 3D interactions

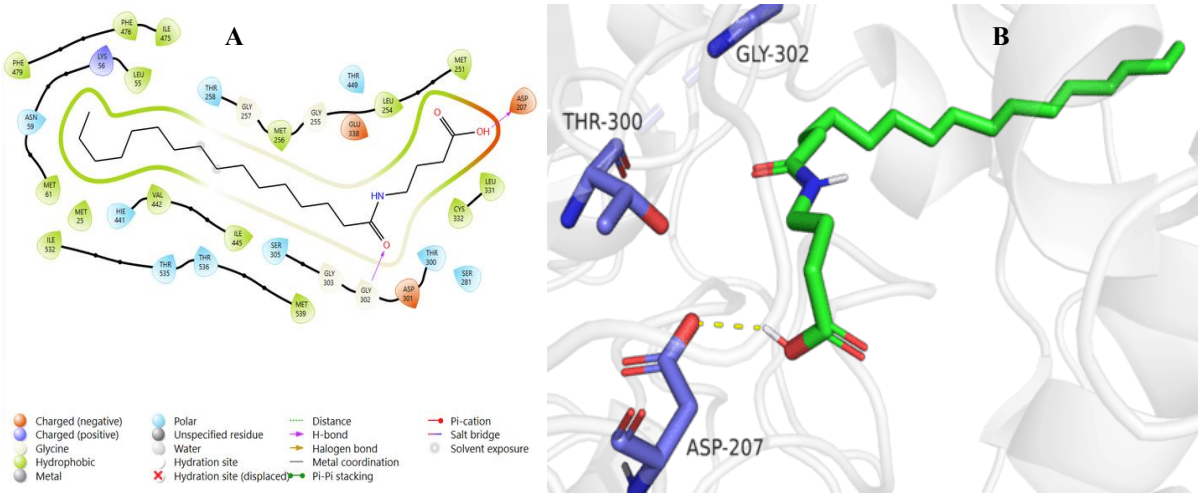


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**Figure 3.** Protein-ligand interaction

A) 6DII-N-palmitoyl GABA 2D interactions, B) 6DII-N-palmitoyl GABA 3D interactions

FAs and vitamins have been reported to protect chemotherapy-induced intestinal mucositis in cancer [28-30]. Hence, the role of FAs is very significant in the current medical practice. The current study was an attempt to suggest a possible biological mechanism for the synthesized amide derivatives of LCFAs. Based on the obtained results, the protein binding mode of the compounds was similar to that of the identified inhibitor (linolenyl fluorophosphonate) of *A. thaliana* FAAH proteins (PDB ID: 6DII), which bound to the GLY-302, GLY-303, SER-305 residues of the protein via the oxygen atom of the phosphonate group. This is very similar to the protein binding mechanism of our novel amide derivatives of long-chain FAs, as revealed by our molecular docking studies. N-palmitoyl alanine showed the highest protein binding (inhibitory) affinity, binding to GLY-255, THR-300, and GLY-302 through the amide N-H and OH functional groups. Additionally, N-palmitoyl glycine, which demonstrated the highest bioactivity, also showed significant protein binding affinity (inhibition), binding to ASP-207, GLY-302, and THR-300 via the carboxylic acid (OH) and amide carbonyl functional group (C=O). This is also comparable to N-palmitoyl GABA, which binds to ASP-207 and GLY-302 through the N-H and OH functional group.

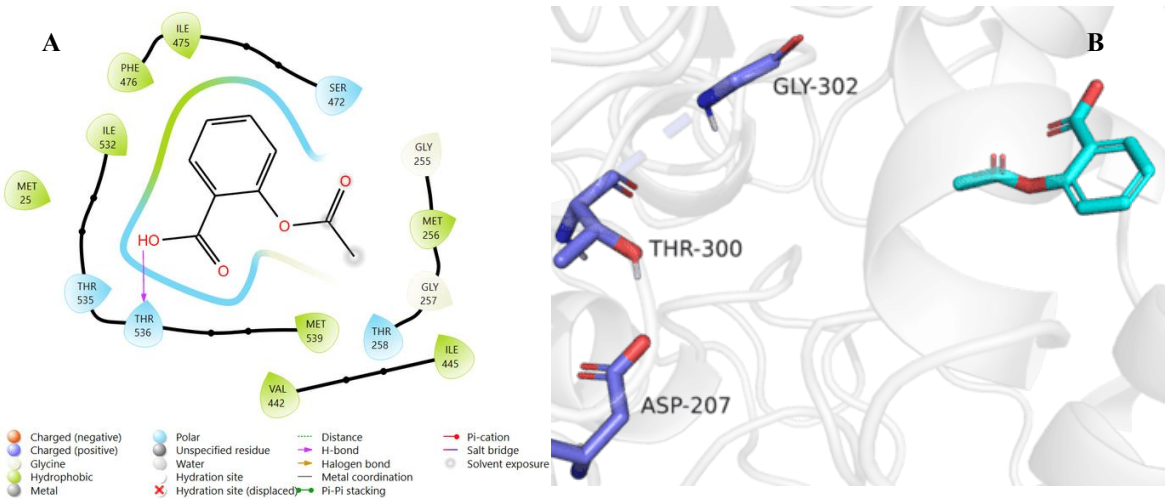


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**Figure 4.** Protein-ligand interaction

A) 6DII-Acetylsalicylic acid 2D interaction, B) 6DII-Acetylsalicylic acid 3D interactions

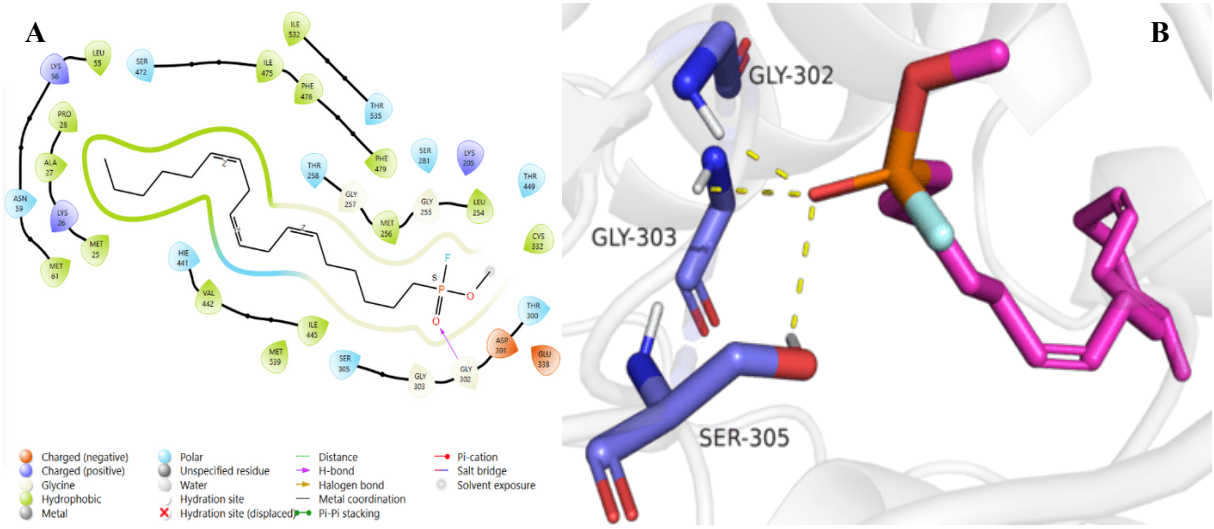


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**Figure 5.** Protein-ligand interaction

A) 6DII-Linolenyl fluorophosphonate 2D interactions, B) 6DII-Linolenyl fluorophosphonate 3D interactions

The stronger effect at 50 mg/kg compared to 100 mg/kg in Table 2 may result from a biphasic or hormetic response, where higher doses saturate target pathways or trigger counteracting mechanisms. Also, pharmacokinetic factors at increased dosage could reduce efficacy [31]. While this finding requires further validation, it aligns with reports of non-linear dose responses for some bioactive compounds.

**Table 2.** Bioassay results

| Compound ID | Anti-Inflammatory Analysis | | | Analgesic/Nociceptive Analysis | | |
|---|---|---|---|---|---|---|
| | Dose (mg/kg) (p.o.) | Mean±SEM Change in Paw Diameter (cm) | % Inhibition (Edema) Relative to the Control (3 hr) | Dose (mg/kg) (p.o.) | Number of Writhings (per 20 mins) | % Inhibition |
| Control (10% tween 80) mL | 0.5 | 1.05±0.03 | - | 0.2 | 100.4±14.71 | - |
| N-palmitoyl glycine | 20 | 0.55±0.02 | 47.2 | 20 | 25±2.71 | 75.2* |
| | 50 | 0.54±0.04 | 49.0* | 50 | 18.6±3.49 | 81.6* |
| | 100 | 0.75±0.04 | 29.0 | 100 | 17.2±1.62 | 83.2* |
| N-palmitoyl alanine | 20 | 0.81±0.01 | 22.4* | 20 | 58.6±7.85 | 41.6 |
| | 50 | 0.63±0.02 | 40.1* | 50 | 53.6±2.79 | 46.5* |
| | 100 | 0.72±0.03 | 31.6* | 100 | 49.8±5.66 | 50.5* |
| N-palmitoyl GABA | 20 | 0.67±0.03 | 36.0 | 20 | 62.6±6.07 | 37.6* |
| | 50 | 0.68±0.04 | 35.4* | 50 | 40.6±7.16 | 59.4* |
| | 100 | 0.99±0.03 | 5.6 | 100 | 42.4±5.24 | 57.4* |
| Acetylsalicylic acid | 100 | 0.51±0.03 | 51.3* | 100 | 25.8±1.16 | 74.3 |

P.o: Per oral (orally), SEM: Standard error of the mean, *P<0.05.

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## Conclusion

There was a common protein binding mode for the synthesized compounds and the identified inhibitor of *A. thaliana* FAs amide hydrolase (PDB ID: 6DII), which involved binding to specific residues of the protein via unique functional groups. Therefore, it can be suggested that the ability of these amide derivatives of LCFAs to biochemically inhibit the inflammatory and nociceptive pathways may be due to the presence of the amide nitrogen and carbonyl oxygen (N-H, C=O) and carboxylic acid (OH) functional groups that bind to the GLY-255, THR-300, GLY-302, and ASP-207 residues of the protein. Thus, these compounds could serve as novel lead molecules in the discovery and design of effective anti-inflammatory and analgesic drugs.

## Ethical Considerations

### Compliance with ethical guidelines

The study was approved by the Research and Ethics Committee of the Faculty of Pharmacy, Niger Delta University, Amassoma, Nigeria (Code: BH-0014).

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### Authors' contributions

All authors contributed equally to this work.

### Conflict of interest

The authors declared no conflict of interest.

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