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Green synthesis of α-amino phosphonates using cassia fistula fruit pulp: Dual α-amylase and α-glucosidase inhibitors

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ABSTRACT

Diabetes is largely developing in the human population due to modern and sedentary lifestyles, leading to serious health complications that affect nerves, eyes, and kidneys. Organophosphorus compounds have diverse pharmacological properties, including antidiabetic properties. In the recent literature, α-aminophosphonates were prepared by green synthesis using orange peel as a biocatalyst. In the current study, we have prepared the same compounds via Pudovik reaction using substituted aromatic aldehydes, aniline, and diethyl phosphite with Cassia fistula fruit pulp (CFFP) as a natural catalyst under reflux. The reaction mechanisms of imine (Schiff's base) formation and Pudovik reaction products (5a-5h) were presented. Their antidiabetic potential was evaluated through molecular docking and in vitro studies against α-amylase and α-glucosidase. Notably, the compounds 5f, 5e, and 5d showed strong dual inhibitory activity with binding energies of -6.7848, -6.7843 and -6.7598 KCal/Mol, respectively, for 1B2Y and, -9792, -6.8492 and -6.808 KCal/Mol, respectively, for 5NN8 at active site residues; similarly, for in vitro studies the compounds exhibited inhibitory activity against IC50 values 0.75, 2.17, 4.51 µg/ml, respectively, for α-amylase and, 0.38, 1.81, 3.76 µg/ml, respectively, for α-glucosidase enzymes. Among these are also compounds 5f, indicating promising antidiabetic lead compounds, warranting further drug development studies for a therapeutic candidate. This study contributes to the existing literature by introducing CFFP as a novel, natural catalyst for the Pudovik synthesis of α-aminophosphonates and providing comprehensive dual inhibitory antidiabetic data against α-amylase and α-glucosidase.

Contribution/Originality: The novelty of this study stems from the synthesis of α-aminophosphonates using Cassia fistula fruit pulp (CFFP) as a sustainable, natural catalyst. Furthermore, we provide a mechanistic insight into the Pudovik synthesis of these derivatives and evaluate their antidiabetic potential through dual-target molecular docking against α-amylase and α-glucosidase.

1. INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder, profoundly impacts the body's ability to regulate blood glucose levels. The two primary forms, type 1 and type 2 diabetes, arise from distinct pathogenic mechanisms. Type-1 diabetes

is characterized by the autoimmune destruction of pancreatic β-cells, leading to an absolute deficiency in insulin production [1]. Conversely, far more prevalent type-2 diabetes involves insulin resistance, where the body's cells fail to respond effectively to the insulin produced by the pancreas, often coupled with a relative insulin deficiency over time, leading to hyperglycemia [2]. Hyperglycemia damaging effects on both the microvasculature (nerves, eyes, kidneys) and macrovasculature (heart, brain, peripheral arteries), contributing to long-term complications and reduced quality of life [3]. The therapeutic strategy of employing α-glucosidase inhibitors to manage blood sugar levels offers a valuable approach by targeting carbohydrate digestion in the small intestine. The need for novel therapeutic agents with improved selectivity for intestinal α-glucosidase over pancreatic α-amylase is therefore compelling. The development of such selective inhibitors would represent a significant advancement in diabetes management, offering comparable or superior glycemic control with enhanced tolerability and improved patient compliance.

Over the last ten years, organophosphorus compounds and their derivatives have garnered significant interest due to their diverse applications in biological, pharmaceutical, agricultural, and medicinal chemistry, along with their value as intermediates in organic synthesis [4-9]. Among these, α-aminophosphonates have emerged as a particularly important subclass. Their prominence stems from their structural resemblance to α-amino acids, where the typical carboxylic acid group is replaced by a phosphonic acid or a related phosphorus-containing moiety [10-12]. This structural analogy contributes to their notable biological relevance [13-17].

Recently, the usage of plant-derived parts and their compounds for the synthesis of chemical reactions has been increasing due to their importance in green synthesis. Green synthesis, including solvent-free, ultrasound, microwave, electrochemical, light-mediated strategies, and water as a solvent [18]. Different classes of α-aminophosphonates have been synthesised by using biocatalysts such as lemon powder [19], orange peel [20], cellulose-SO_3H [21, 22], lipase enzyme [23], and penicillin G acylase [24]. The *Cassia fistula* is one of the medicinal plants that has numerous pharmacological properties [25].

This species also acts as a reducing agent [26]. Chemical analysis of *Cassia fistula* fruit pulp powder demonstrated substantial phenolic (22mg/kg) and flavone (4mg/kg) content [27]. Other identified components include volatile oils, waxy/residue derivatives [28], and various carbohydrates [29]. It has a major anthroquinone derivative of orange-brown coloured crystals called rhein (1,8-dihydroxy-3-anthraquinone) [30] and is 325 mg from 30 g of *C. fistula* fruit pulp [31]. While traditional reducing agents are often acidic and pose an environmental threat by generating poisonous wastes that harm living beings, the field is rapidly moving toward green synthesis. This eco-friendly approach utilizes various non-toxic plant parts and their derivatives as reducing agents, with extracts from green tea, marigold flower, lemon, rose flower, orange peel, bougainvillea flower, copperleaf, and radish root being common examples [26].

In the recent study of the literature, α-aminophosphonates (5a-5h) were synthesised from substituted aromatic aldehydes, aniline, and dimethylphosphite in the presence of natural orange peel powder as a catalyst under reflux conditions [20]. Our study introduces a novel and highly efficient application of *Cassia fistula* fruit pulp (CFFP) extract, a member of the Fabaceae family native to the Indian subcontinent, which acts as a reducing agent. As rhein is the major constituent in the fruit pulp, this chemical structure might be allowing it to donate electrons for reducing other molecules.

This green synthesis method, which utilizes only shed-off fruits, offers three key advantages: it avoids using living parts of the plant, helps with environmental cleaning, and enables effective waste management. In relation to exploring the pharmacological properties of 5a-5h compounds, in our current study, we focused on the synthesis of the same compounds by using the CFFP as a biocatalyst and examined their potency by *in vitro* studies to inhibit α-amylase and α-glucosidase enzymatic reactions. Furthermore, docking experiments were conducted to compare the outcomes with the experimental findings.

2. MATERIALS AND METHODS

2.1. Collection and Preparation of Catalyst

Fresh parts of the naturally available CFFP were collected from different regions of the Chittoor district of Andhra Pradesh, India (Figure 1a). A voucher specimen PARC/2022/4819 has been deposited and confirmed by the Plant Anatomy Research Centre (PARC), Chennai. Fruit pulp (Figure 1b) was separated from fruit (Figure 1a) and made into small pieces, followed by shade-drying for 5 days, and blended into a fine powder. It was stored in a sterile container for further application as a natural biocatalyst.

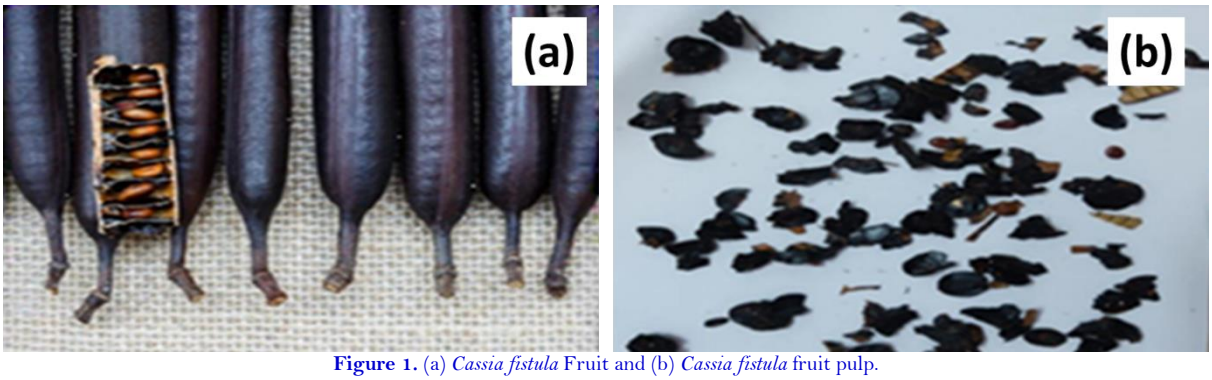


Figure 1. (a) *Cassia fistula* Fruit and (b) *Cassia fistula* fruit pulp.

2.2. Synthesis of α-Aminophosphonates

The methodology of synthesis of α-aminophosphonates was adopted from Ghodke et al. [20] by changing the catalyst to CFFP. In our study, after completion of each reaction, the reaction mixture was cooled, and the solid catalyst CFFP particles, which do not dissolve in the ethanol solvent, were filtered through the Buckner funnel. The collected CFFP catalyst was then washed with a small amount of ethanol to remove any adsorbed organic product. For all the reactions, we used the fresh catalyst of CFFP crushed powder, but not the recycled. All the structures of the compounds were confirmed by comparing the literature values [20].

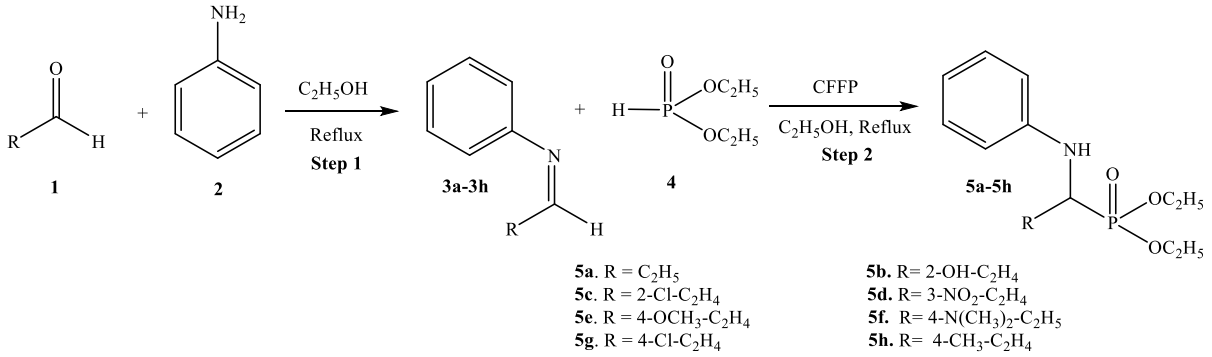


Figure 2. Synthesis of α-aminophosphonates (5a-5h).

The reaction mechanisms of Figure 2 were described in Figure 3 and Figure 4. In the Figure 3 the aromatic primary amine reacts with an aldehyde (carbonyl compound), forming a carbinolamine intermediate, followed by dehydration, which forms an imine (Schiff's base) [32].

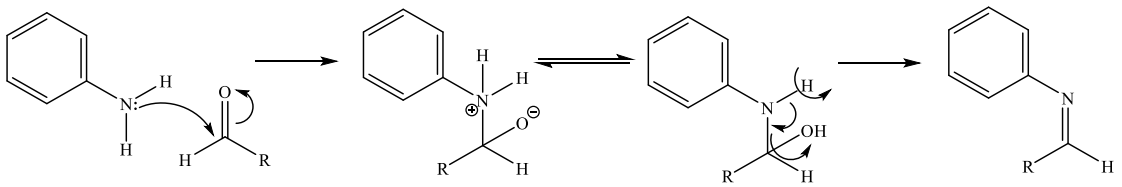


Figure 3. Reaction mechanism for the formation of an imine or Schiff's base from an aromatic amine and an aldehyde.

The most stable form of tetracoordinate phosphine oxide tautomerizes with the less stable form of tricoordinate phosphinous acid (Scheme 3) [33]. In the Pudovik reaction, the tricoordinate phosphinous acid cyclises with an imine in an unstable transition form and converts to α-aminophosphonate [34].

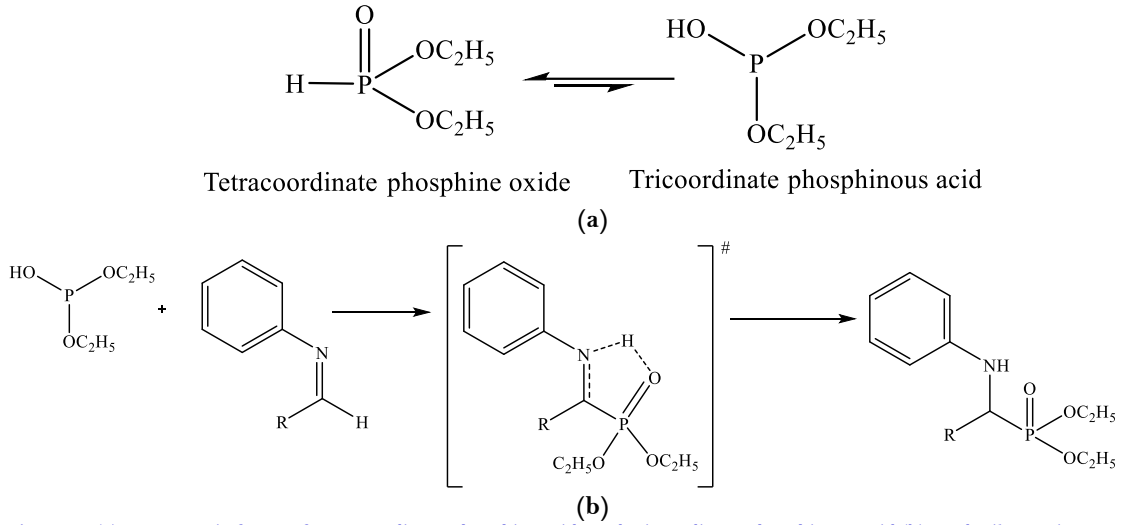


Figure 4. (a). Tautomeric forms of tetracoordinate phosphineoxide and tricoordinate phosphinous acid (b). Pudovik reaction mechanism.

3. RESULTS AND DISCUSSION

The successful application of CFFP as a novel, highly efficient and reusable natural catalyst aligns with the principles of green chemistry and the increasing emphasis on sustainable synthetic methodologies. Our findings strongly support a growing body of work that validates the use of unfunctionalized and modified biomass waste as effective heterogeneous catalysts for C-P bond formation. The current work is a key extension of the methodology pioneered by Ghodke et al. [20], who reported a nearly identical protocol using Orange Peel Powder (OPP) as a catalyst for α-aminophosphonate synthesis [20]. The comparable efficiency and operational simplicity between the CFFP and OPP systems confirm the presence of inherent catalytic sites (likely acidic functional groups from pectin, cellulose, or phenolic compounds) in various forms of agricultural waste, establishing them as cost-effective and environmentally benign alternatives to traditional toxic acid or metal catalysts.

The results of heterogeneous Acid Catalysis are also consistent with the performance of other naturally derived solid acid catalysts. For example, the use of Cellulose-SO_3H as a recyclable, solid-acid catalyst has been reported to efficiently catalyze the solvent-free Kabachnik–Fields reaction, further emphasizing that functionalized cellulose (the major component of CFFP) provides an excellent platform for promoting this transformation [22]. Similarly, the use of Natrolite zeolite, a natural mineral, has shown excellent catalytic activity and recyclability under solvent-free conditions, reinforcing the general utility of natural, heterogeneous acid surfaces in this reaction [35]. These studies collectively validate the catalytic mechanism facilitated by the solid-phase *Cassia fistula* catalyst.

Several studies have demonstrated that the Kabachnik–Fields reaction can be achieved in good to high yields (up to 83%) using a simple catalyst-free protocol under solvent-free conditions at elevated temperatures [36]. The mechanism in these cases is proposed to rely solely on the intrinsic acidity of the dialkyl phosphite or the thermal activation of the reagents to promote imine formation and subsequent nucleophilic addition. This approach fundamentally contrasts with our method, which relies on CFFP (catalyst) and ethanol (solvent). The existence of highly efficient catalyst-free routes suggests that the primary advantage of the CFFP may not be sheer catalytic activity, but rather its role in offering a highly accessible, sustainable, and recyclable platform for heterogeneous catalysis. Future work could focus on investigating if a solvent-free protocol using CFFP could further optimize the sustainability and overall reaction rate, potentially leading to a superior, fully waste-minimizing methodology.

From the reaction Figure -2, the structure of the product is characterized by the variation in the 'R' group of the initial aldehyde. This 'R' group is attached to the carbon bearing both the amine and the phosphonate moiety. To discuss the SAR, the different 'R' groups and their potential impact observed as, in 5a, R = C_2H_5 (Ethyl). It is relatively lipophilic and has minimal electronic effects. It serves as a baseline for comparison with the other substituted derivatives. In 5b, R = 2-OH-C_2H_4 (2-Hydroxyethyl), the introduction of a hydroxyl group makes the molecule more hydrophilic and introduces the possibility of hydrogen bonding. This could enhance water solubility and potentially alter interactions with biological targets that involve hydrogen bonding. In **5c**, R = 2-Cl-C_2H_4 (2-Chloroethyl), the presence of a halogen (chlorine) introduces an electronegative atom and increases the lipophilicity compared to the hydroxyl group, but might be less hydrophilic than the ethyl group. Halogens can participate in halogen bonding and can also be metabolically labile. In 5d**,** R = 3-NO_2-C_2H_4 (3-Nitropropyl), the nitro group (−NO_2) is a strong electron-withdrawing group. Its presence will significantly alter the electronic properties of the molecule, potentially affecting its interactions with biological targets that are sensitive to electron density. The increased polarity due to the nitro group might also influence solubility and membrane permeability. In 5e, R = 4-OCH_3-C_2H_4 (4-Methoxybutyl), the methoxy group (−OCH_3) is an electron-donating group through resonance and electron-withdrawing through induction (due to the electronegativity of oxygen). It introduces a polar ether linkage and increases lipophilicity compared to a hydroxyl group. The longer chain separates the methoxy group from the chiral centre, potentially diminishing its direct influence on interactions around that centre. In 5f**,** R = 4-$N(CH_3)_2C_2H_4$ (4-(Dimethylamino) butyl), the dimethylamino group (−$N(CH_3)_2$) is a basic and electron-donating group. It can be protonated at physiological pH, leading to a positive charge on the molecule. This can significantly impact its solubility, distribution, and interactions with negatively charged biological targets. In 5g, R = 4-Cl-C_2H_4 (4-Chlorobutyl), similar to 5c, this compound contains a halogen. The chlorine atom is further away from the chiral center compared to 5c, which might lead to different steric and electronic effects at the active site of a biological target. In 5h**,** R = 4-CH_3-C_2H_4 (4-Methylbutyl), contains a lipophilic alkyl group. Compared to the ethyl group in 5a, the longer chain and the presence of a methyl substituent might influence hydrophobic interactions and membrane permeability.

3.1. In Silico Docking Studies for the Enzymes α-amylase and α-Glucosidase

The docking studies of the compounds 5a-5h for the enzymes with the pdb 1B2Y for α-amylase and 5NN8 for α-Glucosidase were performed using our previous methodology [37], and the results of binding inhibitions were presented (Table 1).

Table 1. Docking results of 1B2Y and 5NN8 inhibition by 5a-5h.

Compound	1B2Y binding energy (KCal/Mol)	5NN8 Binding Energy (KCal/Mol)
5a	-6.3117	-6.2332
5b	-6.2729	-6.2499
5c	-6.4867	-6.3225
5d	-6.7598	-6.808
5e	-6.7843	-6.8492
5f	-6.7848	-6.9792
5g	-6.2296	-6.366
5h	-6.229	-6.5076
Acarbose	-8.4731	-7.5478

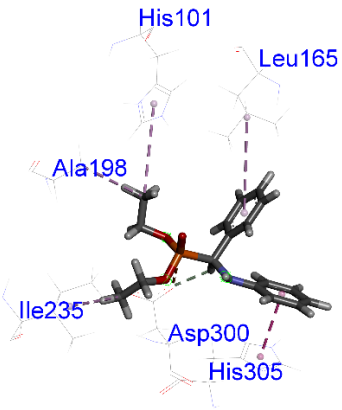
3.2. In-Vitro α-Amylase and α-Glucosidase Inhibitory Assay

The revised methodology of a well-established procedure for *in vitro* analysis of α-amylase inhibitors [38, 39] and α-glucosidase inhibitors [40] was adopted. The screening was conducted for the compounds 5a-5h at various doses ranging from 5 to 25 μg/mL, and the resulting IC_{50} values were presented (Table 2). The compounds 5f, 5e, and 5f showed effective inhibition of the target enzymes.

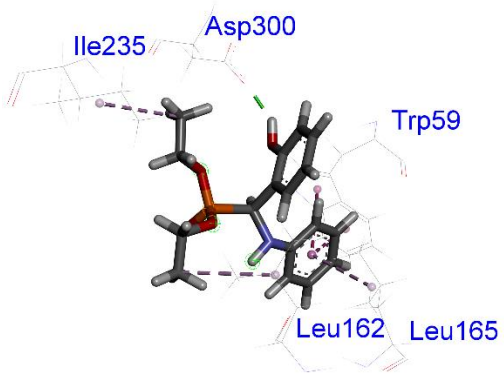
Table 2. *In vitro* analysis of α-amylase and α-glucosidase inhibition by 5a-5h.

Ligand	α-Amylase IC_{50} (µg/mL)	α-Glucosidase IC_{50} (µg/mL)
5a	13.24	13.24
5b	10.41	10.41
5c	9.13	9.13
5d	4.51	3.76
5e	2.17	1.81
5f	0.75	0.38
5g	5.48	5.48
5h	6.9	6.9
Acarbose	16.14	6.46

The current study evaluated the binding affinities and inhibitory activities of a series of novel compounds (5a-5h) against two key digestive enzymes, viz., α-amylase and α-glucosidase, with the PDB database IDs 1B2Y and 5NN8, respectively, which are crucial therapeutic targets in the management of type-2 diabetes. The docking results for both proteins (Table 1) revealed that all tested compounds exhibited appreciable binding affinities toward both enzymes, with binding energies ranging from approximately -6.0 to -7.0 kcal/mol. In comparison, Acarbose, a clinically used standard, displayed the strongest binding energies at -8.4731 KCal/mol for α-amylase and -7.5478 KCal/mol for α-glucosidase. Among the tested compounds, with a slight variation, 5d has -6.7598 and -6.608 KCal/Mol for α-amylase and α-glucosidase, respectively, and was relatively better in binding affinities. The binding interactions of the ligands with 1B2Y at active site were shown as 5a: Asp300, Leu165, His101, Ala198, Ile235, His305; 5b: Asp300, Leu165, Trp59, Leu162, Ile235; 5c: Asp300, Leu165, Ala198, Leu162, Trp59, His305; 5d: Asp300, Leu165, His305, Leu162, His101, Tyr62, Trp59, Asp356; 5e: Asp300, Leu165, His201, Tyr151, Glu233, Ile235, Phe256, His101; 5f: Asp300, Leu165, His305, His299, Asp356, Trp59, Tyr62, Ala198, Asp197, His101; 5g: Asp300, Ile235, Ala198, Trp59, His305, Asp356; 5h: Asp300, Leu165, Tyr62, His305, Asp356 and the positive control Acarbose were shown as Asp300, Gly306, Tyr62, Glu233, Tyr151, Lys200, Leu162 (Figure 5). Similarly, the binding interactions of 5NN8 for all the ligands at active site were shown as 5a: Ala93, Ala97, Val321, Trp273, Asp91; 5b: Ala93, Ala97, Tyr543, Pro94, Pro125, Asp91, Val321; 5c: Ala93, Arg275, Asp91, Pro125, Gly123, Gln124; 5d: Ala93, Trp126, Tro125, Gly123, Trp273, Asp91, Val321, Lys96; 5e: Ala93, Arg275, Val321, Asp91, Gly123, Pro125, Trp126; 5f: Ala93, Arg275, Val321, Trp273, Gly123, Asp91, Pro125, Cys127, Trp126, Ile98; 5g: Ala93, Trp126, Gly123, Pro125, Trp273, Asp91, Arg275, Val321; 5h: Ala93, Ala97, Trp126, Pro125, Asp91, Val321, Pro94, Tyr543; and Acarbose: Trp126, Ile98, Ala97, Lys96, Pro94, Arg275, Val544 (Figure 6).



5a



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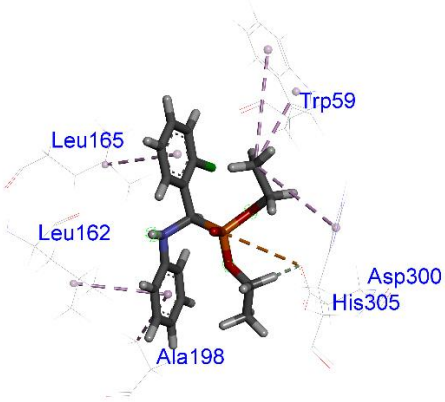
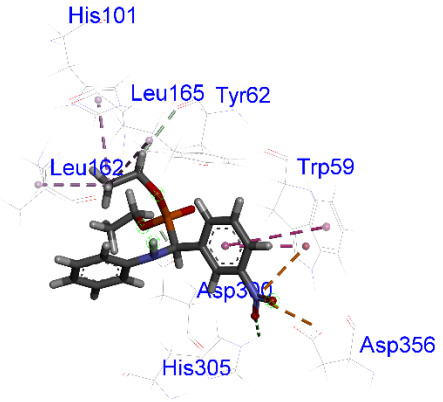
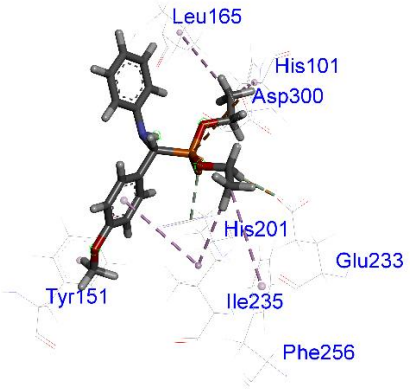


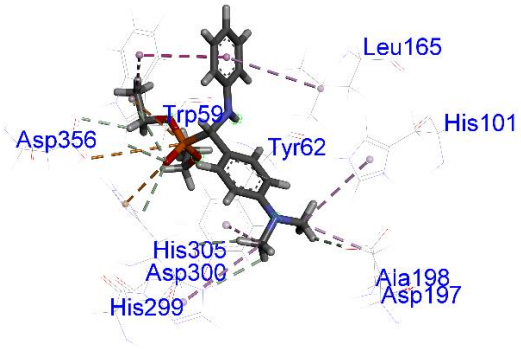
5c



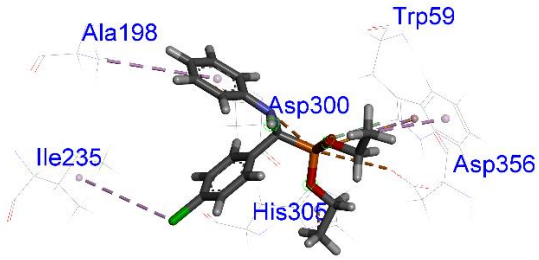
5d



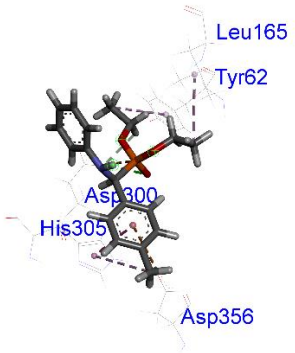
5e



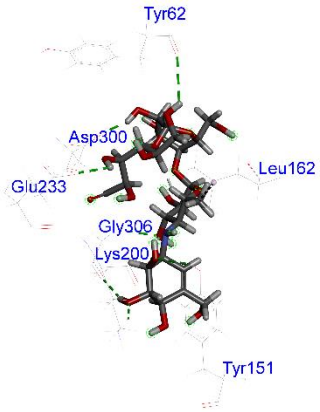
5f



5g

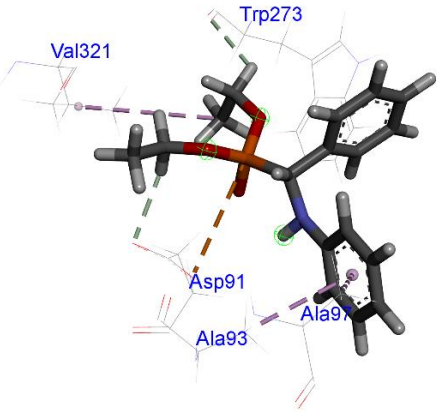


5h

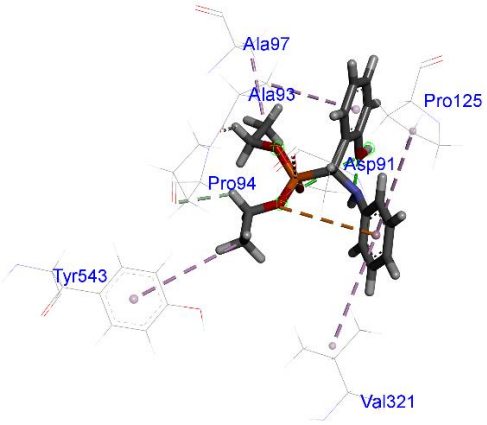


Acarbose

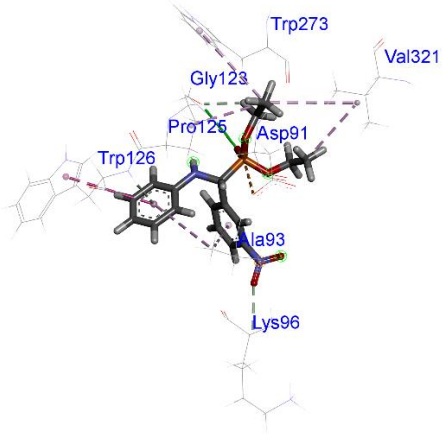
Figure 5. Binding interactions of the synthetic compounds **5a-5h** and standard, acarbose with the protein 1B2Y.



5a



5b



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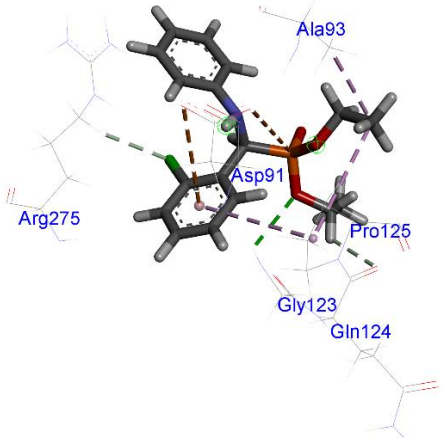
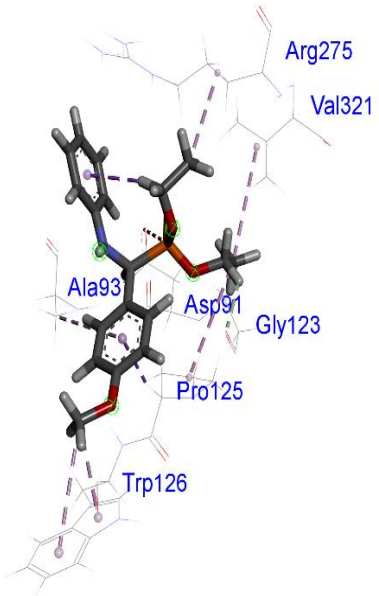
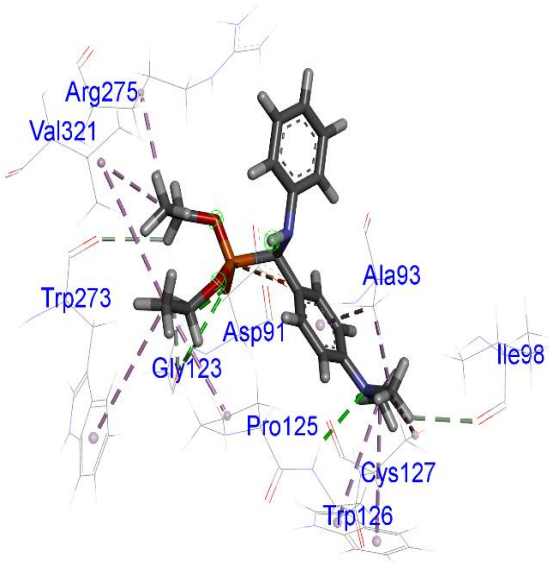


5d



5e



5f

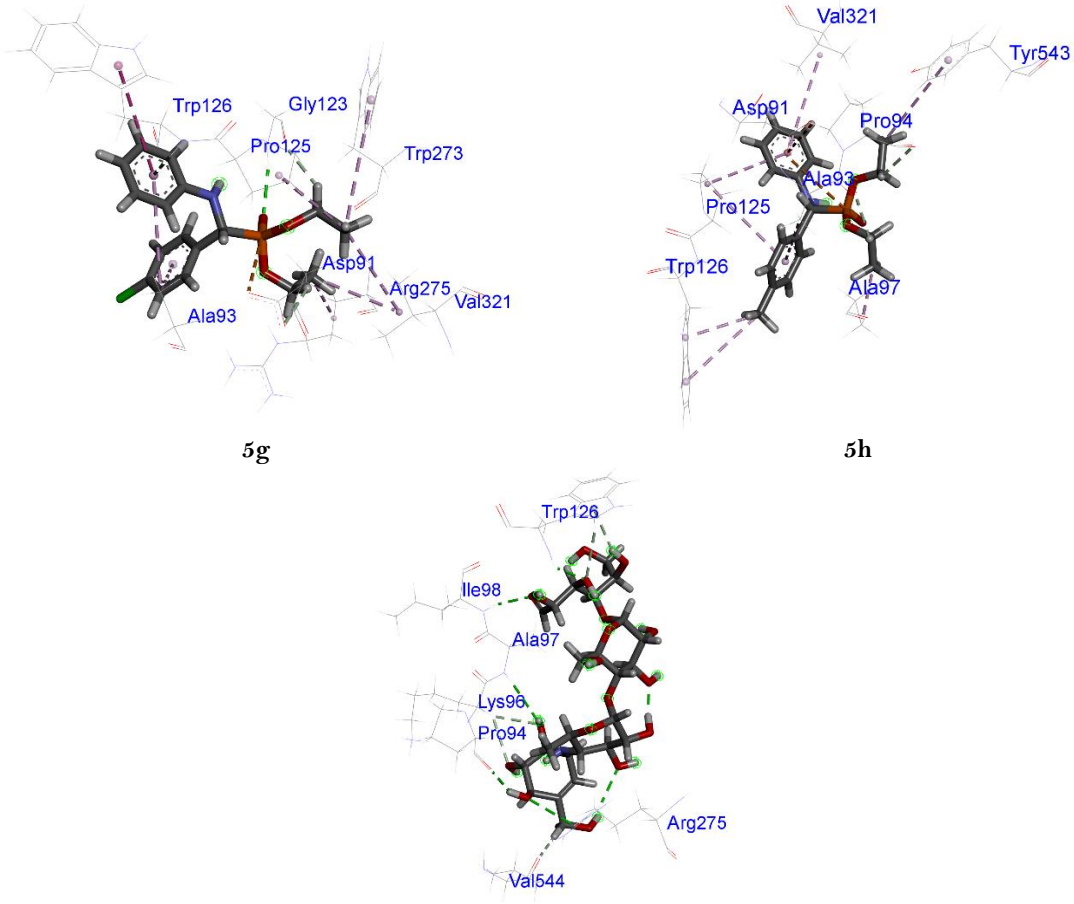


Figure 6. Binding interactions of the synthetic compounds 5a-5h and standard, acarbose with the protein 5NN8.

The interaction analysis of ligands with the 1B2Y protein reveals that certain residues consistently play a crucial role in ligand binding. Asp300 is the most frequently involved residue, appearing in all ligand interactions, including the reference compound Acarbose, indicating its critical role in the catalytic activity of the enzyme. Other residues, such as Leu165, Trp59, His305, Ala198, and His101, are also commonly involved, suggesting they contribute to the stabilization of ligands within the binding pocket. Notably, ligand 5f exhibits the most extensive interactions (10 residues) with the binding energy of -6.7548 KCal/Mol, indicating strong and diverse binding potential. It overlaps significantly with Acarbose in terms of key interacting residues, making it a promising candidate for further investigation. The other ligands, viz., 5e and 5d, also have shown strong binding affinities with -6.7843 and -6.7598 KCal/Mol, respectively (Table 1). For the 5NN8 protein, residues such as Ala93, Asp91, Val321, Pro125, and Trp126 appear most frequently across the ligand set, suggesting they are central to ligand recognition and binding. Similar to the trend observed in 1B2Y, ligand 5f again shows the highest number of interactions, including both hydrophobic and polar residues, indicating strong binding affinity (Table 1). The reference compound Acarbose interacts with a slightly different set of residues, such as Ile98, Lys96, and Val544, suggesting a distinct orientation or binding mode. Nevertheless, ligands like 5e, 5f, and 5g share multiple common residues with Acarbose, implying they may mimic its inhibitory action. Overall, ligand 5f demonstrates the most consistent and robust interaction profile across both targets.

The IC_{50} values of the ligand series (5a–5h) for α-glucosidase and α-amylase enzymes suggest varying degrees of antidiabetic potential. Among them, ligand 5f exhibited the strongest dual inhibition, with an IC_{50} of 0.38µg/mL for α-glucosidase and 0.75 µg/mL for α-amylase. This is consistent with its extensive hydrogen bonding and hydrophobic interactions with critical active site residues, including Asp300, His305, His101, and Trp59. Ligands 5e and 5d also demonstrated relatively potent activity, with IC_{50} of 1.81 and 3.76 µg/mL, respectively, for α-glucosidase,

attributed to favourable interactions with residues such as Tyr151, Glu233, and Asp356. The trend in activity correlates well with binding site affinity and the presence of electron-donating groups such as *o*-OCH_3 (5e) and *o*-$N(CH_3)_2$ (5f) or withdrawing substituents (*m*-NO_2) (5d) on the phenyl ring, affecting their interaction strength and binding orientation. In comparison, Acarbose, the positive control, showed IC_{50} values of 6.46 µg/mL against α-glucosidase and 16.14 µg/mL against α-amylase, indicating a stronger inhibitory effect on the former enzyme. Several ligands, notably 5f, 5e, and 5d, displayed better potency than Acarbose, particularly against α-glucosidase (Table 4). These findings highlight the potential of the synthesized ligands, especially 5f, as promising antidiabetic candidates. Their superior activity compared to Acarbose suggests that further *in vitro* and *in vivo* evaluations are warranted to validate their therapeutic potential and pharmacokinetic profiles.

4. CONCLUSION

The study successfully established a simple, green, and highly efficient protocol for the one-pot, three-component synthesis of α-aminophosphonates using CFFP as a novel, natural, and heterogeneous catalyst. The synthesized compounds (5a-5h) demonstrated significant and dual inhibitory activity against both α-amylase and α-glucosidase, positioning them as promising lead molecules for antidiabetic drug development. The heterogeneity of the CFFP catalyst is a major advantage for sustainable separation and potential reusability. The molecular docking and in vitro analysis of ligands 5a–5h against α-amylase and α-glucosidase enzymes demonstrated promising antidiabetic potential. Docking studies revealed that ligands such as 5f, 5e, and 5d showed strong binding affinities, forming multiple interactions with key catalytic residues, including Ala93, Asp91, Trp126, and Val321 in α-amylase and Asp300, His305, Trp59, and Tyr62 in α-glucosidase. These interactions were correlated with high binding stability and optimal positioning within the enzyme's active sites, suggesting a high likelihood of inhibitory activity. The in vitro IC_{50} values supported the docking results, with ligand 5f exhibiting the lowest IC_{50} values for both enzymes, outperforming the standard drug Acarbose. Several other ligands also showed comparable or superior activity, especially against α-glucosidase. The combined findings from docking and IC_{50} estimation suggest that these ligands, particularly 5f, could serve as effective dual inhibitors of key carbohydrate-digesting enzymes and warrant further biological evaluation and lead optimization for antidiabetic drug development.

4.1. Implications

This work carries significant implications for both synthetic organic chemistry and medicinal chemistry. First, the successful use of an abundant agro-waste like CFFP eliminates the need for expensive, toxic, or rare metal-based catalysts, strongly promoting the principles of green and sustainable chemistry in the synthesis of high-value compounds. This simultaneously provides a compelling strategy for the valuation of agricultural by-products, converting environmental waste into a valuable chemical resource. Second, the demonstrated dual inhibitory activity against α-amylase and α-glucosidase provides a clear, high-potential pathway for developing new-generation antidiabetic agents that target both key carbohydrate-hydrolyzing enzymes, offering a more comprehensive therapeutic approach.

4.2. Limitations

Despite the successful methodology, the study has several limitations. The current study was primarily restricted to substituted aromatic aldehydes and aniline, meaning the efficacy of the CFFP catalyst for substrates involving less reactive ketones or different classes of amines (e.g., secondary or aliphatic) was not fully explored. Furthermore, while the catalyst is easily separated, a detailed study on its long-term stability and reusability over multiple reaction cycles was not provided. This is a crucial factor for evaluating its viability for large-scale industrial applications. Finally, the precise nature of the active catalytic sites on the CFFP surface has been inferred, but not conclusively determined via advanced spectroscopic analysis.

4.3. Future Research Suggestions

To overcome the noted limitations and build upon these findings, future research should focus on three key areas. First, investigate the effect of chemical pre-treatment, such as sulfonation or acid functionalization, on the CFFP to potentially enhance its catalytic activity, stability, and recyclability. Second, validate the most potent derivatives from the study for *in vivo* antidiabetic evaluation using relevant animal models to establish the acute and chronic toxicity profile.

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