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Nano $TiO_2.SiO_2$ catalyzed, microwave assisted synthesis of new α-aminophosphonates as potential anti-diabetic agents: In silico ADMET and molecular docking study

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Abstract: Using microwave irradiation, an effective and greener method for the synthesis of α-aminophosphonates via Kabachinic-Fields reaction in a solvent-free environment is devised. An in silico ADMET and molecular docking analysis was performed on all of the compounds to get insight into their drug likeliness behaviour as well as their capacity to block the enzyme α-amylase (PDB ID: 3IJ8). The compounds with the highest binding affinity and pharmacokinetic properties were developed. The newly created compounds were spectroscopically examined to establish their structure, and all of them were tested for in vitro α-amylase inhibitory action. The compounds **7j** (IC_{50}: 99.9±0.3 µg/mL) and **7e** (IC_{50}: 102.0±0.7 µg/mL) showed stronger inhibitory efficacy than acarbose, the reference medication. The compounds **7g** (IC_{50}, 106.7±0.4 µg/mL), **7d** (IC_{50}, 108.4±0.3 µg/mL), **7h** (IC_{50}, 115.0±0.4 µg/mL), and **7f** (IC_{50}, 119.2±0.4 µg/mL) have shown to inhibit the target enzyme significantly.When compared to the reference drug, Acarbose (IC_{50}, 102.6±0.8 µg/mL), all of the remaining compounds showed modest to good inhibition with IC_{50} values ranging from 125.6±0.6 to 152.7±0.2 µg/mL. The findings revealed that the vast majority of these drugs have strong α-amylase inhibitory action.

Keywords: α-aminophosphonates; ADMET; molecular docking; α-amylase; acarbose;

1. Introduction

Organophosphorus compounds have gained importance in synthetic organic, agricultural, industrial, medicinal chemistry because of their diverse chemical, biological, and physical properties.[1-4] For example, α-aminophosphonates (α-Aps) are a fascinating class of bioactive analogues that resemble active peptide transition states and have properties similar to naturally occurring amino acids.[5] α-Aps possess broad range of applications in the field of industry[6], biology[7], and medicine.[8,9] They are useful compounds as anti-cancer agents[10], antitumor

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reagents[11,12], anti-inflammatory[13,14], antibiotics[15,16], herbicides[17], fungicides[18], bactericides[19], enzyme inhibitors[20], anti-thrombotic agents[21], plant growth regulators[22], anti-oxidants[23], protease inhibitors[24], glutamine synthetase[25], peptide mimetics[26], metal corrosion preventor[27], antiviral agents[28], and anti-diabetic agents.[29]Some α-Aps with heterocycle moieties have been produced in recent years and have exhibited interesting biological activity. The presence of heterocyclic motifs in the structure of α-Aps has been shown to greatly increase their bioactivities.[30-33] Thiazoles are a heterocyclic compound that has been found in a wide range of biological systems. The thiazole moiety is a crucial pharmacophore for the synthesis of a variety of biological substances, including vitamin B1 (thiamine), which plays a role in acetylcholine synthesis and so aids in the regular functioning of the nervous system.[34] Furthermore, thiazole derivatives play an important role in medicinal chemistry and are commonly found in the structure of a variety of natural products and bioactive compounds.[35-45]

The nucleophilic addition of phosphites to imines, i.e. the Kabachnik-Fields (K-F) reaction, was shown to be a convenient approach among the several synthetic processes proposed for the synthesis of α-Aps.[46] Because of their robustness in terms of operational simplicity, nontoxicity, reusability, low cost, and ease of isolating products from the reaction mixture after completion of the reaction, solid acidic catalysts have gained popularity in organic synthesis. Nano-TiO_2 has proven to be an effective catalyst for a variety of chemical transformations.[47-50] Because of their broad reach and advantage of having a big surface area, binary association catalysts have recently sparked a lot of interest in synthetic aspects. The benefits of employing Nano-TiO_2 supported on SiO_2 as a binary heterogeneous association catalyst in synthesis include its ease of use, reusability, and environmental friendliness. Nano TiO_2.SiO_2 has recently been employed for photocatalytic oxidation of trinitrotoluene.[51] Recently, Sravya*et al*., have reported synthesis of α-Apscatalyzed by nano TiO_2.SiO_2.[52]

MW irradiation, on the other hand, provided a novel method of energising the reaction mixture because it involves the direct transfer of energy to the substrate molecules and will increase the rate of the reaction through rapid kinetic excitation of molecules.[23] Microwave aided organic syntheses have received a lot of interest from chemists in recent years due to its benefits such as faster reaction times, cleaner products, operational simplicity, greater yields, and the ability to achieve successful synthesis of heterocyclic bioactive molecules.[14,53] The utilisation of a solvent-free reaction state has been demonstrated to be an efficient method for a wide range of chemical processes.[54] This is an ideal platform for the three components of the K-F reaction, which can be completed in a single pot.

Our recent studies demonstrated that organophosphorus compounds bearing with heterocyclic moiety would be effective as α-amylase inhibitors in the diabetic treatment.[55,56,57]By considering the above facts and in continuation of our studies towards developing new methods for the synthesis of bioactive α-Aps,[14,58,59,60] we decided to explore the possibility of implementing a microwave mediated one-pot three-component reaction for the preparation of α-Aps using nano TiO_2.SiO_2 as catalyst under solvent free condition.

2. Experimental

2.1. Materials and Characterization Techniques

Using Marvin view software, the structures of all the compounds were sketched, optimised, and transferred into the appropriate format. The 1-Click docking software, which is driven by the Auto Dock Vina docking algorithm, was used to conduct the *in silico* molecular docking study. The structures of all the compounds were drawn, optimized, and converted into the required format using Marvin view software. *In silico* molecular docking study was done using 1-Click docking software powered by Auto Dock Vina docking algorithm. To calculate IC_{50} values and to draw the graphs related to biological activity, Graph Pad Prism 9 software was used. The chemicals were purchased from Sd. Fine Chem. Ltd. in India, and only a small percentage of them were refined using normal methods. All of the reactions took place on a magnetic agitator that also served as a hot plate. The purity of the compounds was checked by TLC on an Al sheet of silica gel. NMR spectra of ^{31}P (161.9 MHz), ^{1}H (400 MHz), and ^{13}C (100 MHz) were recorded using a Bruker

AMX spectrometer. On the SHIMADZU 2010A, L.C. MS was recorded and CHN analysis was performed on the T. F. Flash 1112 apparatus. The IR spectra were documented using an FTIR spectrometer (Bruker IFS 55, Equinox) in KBr. Chemical shift, coupling constants, and *J* values are all expressed in Hz and ppm, respectively. Peaks in NMR spectra were represented by the symbols 's' for singlet, 'd' for doublet, 't' for triplet, and 'm' for multiplet.

2.2. Procedures

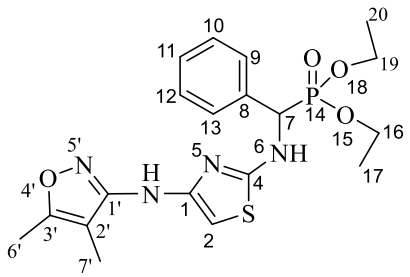
*2.2.1. Synthesis of N^4-(4,5-dimethylisoxazol-3-yl)thiazole-2,4-diamine (**5a**)*[61]

Amine (0.020 mol) (**1a**) was dissolved in dry dioxan and the solution was cooled to 0 ºC. Now chloro acetyl chloride (0.020 mol) (**2**) was added drop wise with stirring. The reaction mixture was then stirred at room temperature for 10-15 minutes, poured into water (20 mL) and extracted with chloroform (3 × 25 mL). Organic layers were collected, combined, washed with 10% HCl (10 mL) followed by water (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by re-crystallization from ethanol to get intermediate compound**.**To this compound in a round bottomed flask; thiourea (0.152g, 0.020 mol) (**3**) and a mixture of 5mL of distilled water and 2mL of acetic acid were added and then refluxed for about 2 hours. Now the mixture was transferred into a separating funnel and extracted first with $CHCl_3$ and then with water. The organic layer was collected and dried over anhydrous Na_2SO_4 and the solvent was evaporated to get N^4-(4,5-dimethylisoxazol-3-yl)thiazole-2,4-diamine **4a**. The T.L.C was used to know the progress of the reaction.

*2.2.2. Microwave Assisted Synthesis of α-aminophosphonates (**7a-j**)*

The mixture of benzaldehyde (**5**) (1.02mL, 0.010 mol), N^4-(4,5-dimethylisoxazol-3-yl)thiazole-2,4-diamine (**4a**) (2.10g, 0.010 mol), diethyl phosphite (**6**) (1.3 mL, 0.020 mol) were placed in a flat bottomed flask. To this mixture, nano $TiO_2.SiO_2$ (5 mol%) was added and the mixture was MW irradiated at 400W under solvent free condition at ambient temperature for about 15 minutes. The progress of the reaction was monitored by TLC (ethylacetate: *n*-hexane, 4:6). After completion of the reaction as checked by TLC, the reaction mixture was cooled to room temperature. Dichloromethane (DCM) (15 mL) was added to the reaction content and stirred for 10 min. The catalyst, nano $TiO_2.SiO_2$ was separated by filtration as residue, washed with DCM (2×10mL) and the residue was dried under vacuum at 100 °C to utilize in further studies. The combined organic layer was washed with water (15 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum at 50 °C to obtain crude product. The pure compound, diethyl (4-(4,5-dimethylisoxazol-3-ylamino)thiazol-2-ylamino)(phenyl)methylphosphonate (**7a**) was obtained by column chromatography using ethyl acetate: *n*-hexane (7:3) as eluent. The same procedure was used for the preparation of the remaining compounds **7b-j.**

*2.3. Characterization of Title Compounds (**7a-j**)*



7a

*Diethyl (4-(4,5-dimethylisoxazol-3-ylamino)thiazol-2-ylamino)(phenyl)methylphosphonate (**7a**):* solid. M.P. 168-170 °C. Yield: 95%. δ_H (DMSO-d_6): 9.42 (s, 1H, -NH), 7.24 (t, *J*=7.6 Hz, 2H, Ar-H), 7.15 (t, *J*=7.6 Hz, 1H, Ar-H), 7.07 (d, *J*=7.2 Hz, 2H, Ar-H), 5.84 (s, 1H, Thiazole-H), 5.53 (s,

1H, -NH), 4.17 (q, *J*=7.2 Hz, 4H, O-$\underline{CH_2}CH_3$), 3.87 (s, 1H, methine-H), 2.27 (s, 6H, -2CH_3), 1.25 (t, *J*= 6.8 Hz, 6H, O-$CH_2\underline{CH_3}$); δ_C (DMSO-d_6): 145.5 (C-1), 112.2 (C-2), 166.5 (C-4), 58.2 (C-7), 135.5 (C-8), 128.4 (C-9 & C-13), 129.4 (C-10, C-12), 127.5 (C-11), 61.3 (C-16 & C-19), 14.2 (C-17 & C-20), 148.8 (C-1'), 109.2 (C-2'), 157.1 (C-3'), 6.8 (C-6'), 1.7 (C-7'); δ_P (DMSO-d_6): 18.5 ppm; IR (KBr) (ν_{max} cm^{-1}): 3282, 3184 (NH), 1222 (P=O), 1019 (P-O-C_{alip}); LCMS (m/z, %): 437 ($M+H^+$,100); For $C_{19}H_{25}N_4O_4PS$; calcd: C, 52.28; H, 5.77; N, 12.84%; found: C, 52.20; H, 5.89; N, 12.95%.

The spectral data of compounds **7b-j** is available in supporting information.

2.4. In Silico Analysis

Using the Swiss ADME tool from the Swiss Institute of Bioinformatics (http://www.sib.swiss), all of the designed molecules were *in silico* predicted for their physicochemical, lipophilicity, water-solubility, pharmacokinetic/ADME, drug-likeness properties, and medicinal chemistry.

2.5. In silico Molecular Docking Studies

The binding mechanism of **7a-j** with the targeted enzyme, pancreatic α-amylase, was investigated using in silico molecular docking. The RCSB, Protein Data Bank, was used to obtain the crystal structure of this enzyme (PDB ID: 3IJ8). Water molecules, heteroatoms, and co-factors were removed from the structure to make it more efficient. Charges, hydrogen bonds, and atoms that were missing were added. The process of docking ligands with proteins and their interactions were investigated using the discovery studio visualizer V16.1.0.15350.[62, 63]

2.6. α-Amylase Inhibitory Activity

All the newly synthesized compounds were screened for their inhibitory activity against α-amylase using standard protocol through minor changes reported by B. Nickavar and G. Amin (2011) which was at first proposed in the literature[64]. (See Supplemental Materials for detailed procedure)

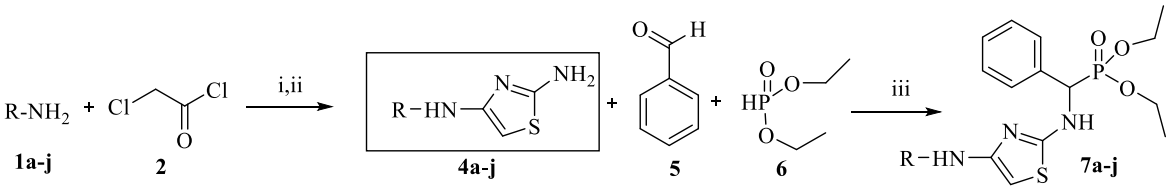
One of the best measures of a drug's efficiency is IC_{50} (half-maximal inhibitory concentration). It reflects the amount of drug required to block a biological process by half, and so serves as a measure of antagonist drug potency in pharmacological research. In the present study, the IC_{50} values were calculated by plotting the concentration (X-axis) verses the percent inhibitory activity (Y-axis). Using the linear (y=mx+c) equation on this graph for y=50 value x point becomes IC_{50} value.

3. Results and Discussion

3.1. Chemistry

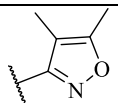
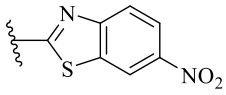
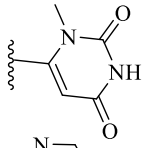
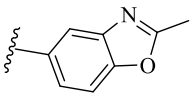
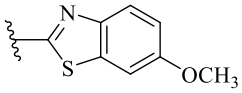
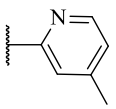
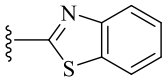
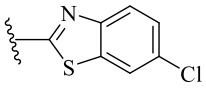
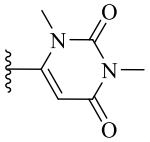
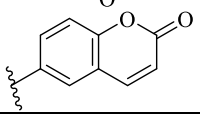
In the present work, we have designed and synthesized a series of α-Aps(**7a-j**) with good yields (90-96%) under solvent free condition using nano $TiO_2.SiO_2$ as catalyst. The synthetic strategy of α-Aps (**7a-j**) was presented in Scheme 1.

Initially, a model reaction containing a combination of 4,5-dimethylisoxazol-3-amine (**4a**), benzaldehyde (**5**), and diethyl phosphite was carried out (**6**). The reaction was carried out at 40 °C using tetrahydrofuran (THF) as the solvent and no catalyst at the start of the research. The product, diethyl (4-(4,5-dimethylisoxazol-3-ylamino)thiazol-2-ylamino)(phenyl)methylphosphonate (**7a**), was generated with a low yield (39%) of the model molecules (Table 1, entry 1). The reaction was then performed in the presence of a catalyst. The model reaction was carried out using catalyst (5 mol%) such as $NiBr_2$, $AlCl_3$, $LaCl_3$, $CuCl_2$, $ZnCl_2$, $BF_3.Et_2O$, and $BF_3.SiO_2$ in quest of an efficient catalyst. Table 1 summarises the findings (entries **2-8**).



1a-j **2** **4a-j** **5** **6** **7a-j**

i) 1,4-Dioxane, 0-5^{0}C; ii)Thiourea (**3**), Acetic acid; iii) Nano TiO_2-SiO_2, MW, Solvent free

Compd.	R	Compd.	R	Compd.	R
7a		**7d**		**7g**	
7b		**7e**		**7h**	
7c		**7f**		**7i**	
				7j	

Scheme 1. Nano TiO_2.SiO_2 catalyzed synthesis of α-Aps

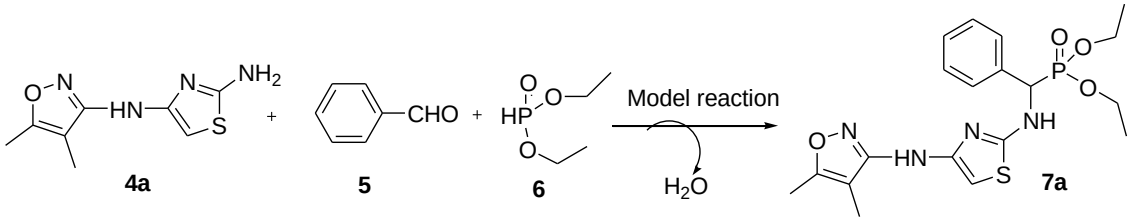
It was discovered that the yield of product **7a** increased from 39% to 60-72%, showing that the catalyst plays an important role in the process. Solid acidic catalysts, on the other hand, have grown in favour in organic synthesis. Nano TiO_2.SiO_2, in particular, has proven to be an efficient catalyst for a range of chemical reactions.[47-50] As a result, chempound**7a** was prepared using nano TiO_2.SiO_2 (5 mol%) in the model reaction. When THF was utilised as the solvent, a good yield (79%) (Table 1, entry9) of compound **7a** was achieved in 2.5 hours. Various solvents such as ethanol, toluene, and dichloromethane (DCM) were also used to investigate the effect of solvent on the process. There was no discernible yields of the products (72-79%) (Table 1, entry 10-12) observed in the investigation.

We then tried this process without the use of a solvent. In this scenario, a high yield (88%) of the product was attained in 1.5 hours (Table 1, entry 13). Further, the reaction mixture was MW irradiated (400 W) without solvent using nano TiO_2.SiO_2 (5 mol%) as catalyst to optimise the reaction conditions and to shorten the reaction time. In this situation, we were able to get a higher yield (94%) of **7a** in just 8 minutes (Table 1, entry 14). We also examined the effect of MW alone on the reaction without solvent and catalyst. We got good yield of the product (90%) within 15 minutes time. But we got better yield of the product **7a** with in less time, when the reaction was carried out in presence of catalyst nano TiO_2.SiO_2 (5 mol%) under solvent free condition using MW irradiation. So, we decided to proceed with this protocol for further optimization of reaction conditions.

The influence of catalyst (nano TiO_2.SiO_2) amount on the model reaction was also investigated, with catalyst levels ranging from 1 to 12.5 mol% (Table 2, entry 1-6). With a catalyst concentration of 7.5 mol%, a higher yield (95%) of compound **7a** was achieved. As a result, 7.5 mol% of the catalyst was validated using MW irradiation in a solvent-free environment. Table 2 is a summary of the findings. The reusability of nano TiO_2.SiO_2 (7.5 mol%) has also been investigated. After each run, the product was filtered and the residue cleaned with chloroform to

remove stains from the catalyst's surface, and it was repeated up to five times to make compound **7a** (Table 3, entry 1-5). As a result, nano $TiO_2.SiO_2$ (7.5 mol%) could efficiently catalyse the process in the absence of a solvent under MW irradiation.

Table 1. Synthesis of compound **7a** under various conditions[a]



4a **5** **6** **7a**

Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time	Yield[b] (%)
1	-----	THF	40	48h	39
2	$NiBr_2$ (5)	THF	40	8h	61
3	$AlCl_3$ (5)	THF	40	5h	63
4	$LaCl_3$ (5)	THF	40	6h	60
5	$CuCl_2$ (5)	THF	40	5h	66
6	$ZnCl_2$ (5)	THF	40	5h	64
7	$BF_3.Et_2O$ (5)	THF	40	4.5h	68
8	$BF_3.SiO_2$ (5)	THF	40	4 h	72
9	Nano $TiO_2.SiO_2$ (5)	THF	40	2.5h	79
10	Nano $TiO_2.SiO_2$ (5)	Ethanol	40	3h	73
11	Nano $TiO_2.SiO_2$ (5)	Toluene	60	4h	72
12	Nano $TiO_2.SiO_2$ (5)	DCM	40	3h	74
13	Nano $TiO_2.SiO_2$ (5)	Solvent-free	40	1.5h	88
14	Nano $TiO_2.SiO_2$ (5)	Solvent-free (MW)	Room temp.	8min	94
15	-----	Solvent-free (MW)	Room temp.	15min	90

[a]Reaction of N^4-(4,5-dimethylisoxazol-3-yl)thiazole-2,4-diamine, benzaldehyde and diethyl phosphite were selected as models to optimize reaction conditions
[b]Isolated yield

Table 2. The effect of the amount of the catalyst, nano $TiO_2.SiO_2$to promote the Kabachnik-Fields reaction[a]

Entry	Amount of Catalyst (mol%)	Time (min)	Yield[b] (%)
1	1	8	62
2	2.5	8	74
3	5	8	94
4	7.5	8	95
5	10	8	94
6	12.5	8	94

[a]Reaction of N^4-(4,5-dimethylisoxazol-3-yl)thiazole-2,4-diamine, benzaldehyde and diethyl phosphite were selected as models to optimize reaction conditions
[b]Isolated yield

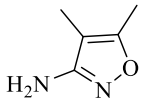
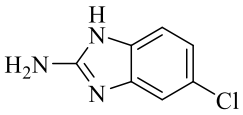
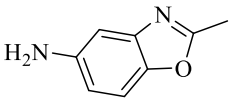
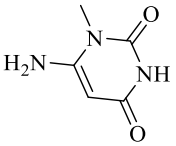
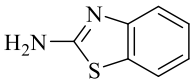
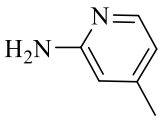
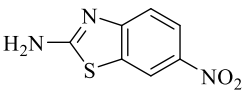
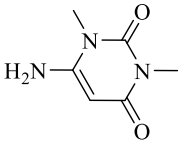
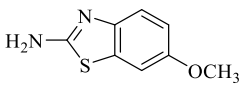
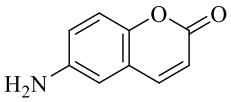
Table 3. Reusability of the catalyst, nano $TiO_2.SiO_2$ (7.5 mol%) for the synthesis of compound 7a[a]

Entry	Nano $TiO_2.SiO_2$ (7.5 mol%)	Time (min.)	Yield[b] (%)
1	1st run	8	94
2	2nd run	8	92
3	3rd run	8	91
4	4th run	8	88
5	5th run	8	82

[a]Reaction of *N*4-(4,5-dimethylisoxazol-3-yl)thiazole-2,4-diamine, benzaldehyde and diethyl phosphite were selected as models to optimize reaction conditions
[b]Isolated yield

After the reaction conditions were optimised, the generality of this process to synthesise*α*-Aps(**7b**-**j**) (Scheme 1) was investigated using MWI technique with a variety of amines (**4b**-**j**), benzaldehyde (**5**), and diethyl phosphite (**6**) in the presence of nano $TiO_2.SiO_2$ (7.5 mol%) without solvent. Figure S1 shows the detailed procedure for synthesizing novel *α*-Aps(**7a**-**j**). [See supporting information].

Table 4. MW mediated synthesis of *α*-aminophosphonates **(7a-j)**[a]

Compd.	Amine	Time (min)	Yield[b] (%)	Compd.	Amine	Time (min)	Yield[b] (%)
7a		8	95	**7f**		10	95
7b		6	92	**7g**		8	93
7c		10	94	**7h**		8	94
7d		12	90	**7i**		6	96
7e		10	92	**7j**		12	92

[a]Reaction of substituted amine, benzaldehyde and diethyl phosphite in presence of nano $TiO_2.SiO_2$ (7.5 mol%) without solvent under MWI.
[b]Isolated yield.

NMR (^{31}P, ^{1}H, ^{13}C), IR spectroscopy, mass, and elemental studies were used to elucidate the structures of the newly synthesised compounds **7a**-**j**. For the compounds **7a**-**j**, singlet ^{31}P NMR signals were found in the range of 23.6 to 16.5 ppm.[55,65] The signal attributable to the N-H proton of the thiazole ring and the NH proton linked to the methine group was seen at 9.41 and 5.52 ppm for **7a**-**j** in their ^{1}H-NMR spectra. The signals for aromatic protons of **7a**-**j** were found in the range 8.86 to 6.45 ppm. The proton signals of compounds **7a**-**j** emerged as multiplets for methylene protons at 4.17 ppm and as triplets for methyl protons at 1.24 ppm. The signal for methine proton

was found at 3.86 ppm. In ^{13}C NMR spectra, the chemical shifts for methine, methylene, and methyl carbons were found at 58.2, 61.3, and 14.2 ppm, respectively in compounds **7a-j**. The remaining carbons' chemical changes were observed within their respective ranges. An IR spectral investigation of the prepared compounds was conducted in order to confirm their functional groups. In IR spectra, the absorption band in the range 3349-3134 cm^{-1} is assigned to secondary amines of compounds **7a-j**. The stretching vibrations for P=O and P-O-Calip were noticed at 1228-1207 and 1019-1002 cm^{-1}, respectively. M+. ions were found as base peaks in all of the title compounds, as well as isotopic cluster peaks with the predicted ratio. The estimated elemental analysis values for the synthesized compounds were quite close to the empirical values. The Supplementary Materials contained typical spectra (^{1}H, ^{31}P, ^{13}C NMR, IR, mass and CHN analyses) of compound **7a** as representative of title compounds (Figure S2-S7).

3.2. Pharmacology

3.2.1. In Silico ADME Analysis

Compounds with high bioactivity and low toxicity are likely to be preferred during the drug discovery and development process. In silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) property screening based on molecular structure is one of the finest techniques to design new drug candidates. When ADME traits are predicted early in the drug development process, the rate of pharmacokinetic failure in clinical stages during the discovery phase is considerably reduced.[66] The ADME parameters of the proposed compounds were tested using SwissADME, which may be obtained at http://www.swissadme.ch. The physicochemical and structural advantages of the moieties were used to make the prediction. Table S1(See Supplemental materials)shows the physicochemical properties of the molecules 7a-j (molecular weight, heavy atoms, aromatic heavy atoms, ratio of sp3 hybridised carbons over the total carbon number of the molecule, rotatable bonds, H-bond acceptors and donors, molar refractivity, lipophilicity, and water solubility). These metrics were in good agreement with the applicable criteria for all of the compounds **7a-j** and had a satisfactory bioavailability score when compared to Acarbose. Table 6 lists the ADME parameters of the newly developed drugs. All of the substances were shown to have low gastrointestinal absorption (GI). The output of the BOILED-Egg model shows both passive blood-brain barrier (BBB) permeability and human gastrointestinal absorption (HIA).[67] The boiled egg diagram and the corresponding bioradar pictures of the molecules 7a-j are shown in Figure S8 and Figure S9.(See Supplemental materials for Figure S8 and S9) All of the examined molecules were identified outside the egg, showing that they were not absorbed and so were not BBB permeant. The reference drug, acarbose, was determined to be out of range. Active efflux in biological membranes is evaluated by knowing which chemicals are non-substrate or substrate of the permeability glycoprotein (PGP), notably for incidence from the gastrointestinal wall to the lumen.[68] The p-glycoprotein was projected to effluate molecules 1 (**7a**), 2 (**7b**), 3 (**7c**), 4 (**7d**), 5 (**7e**), 6 (**7f**), 8 (**7h**) and 10 (**7j**) (PGP+, red dots) from the central nervous system, but not molecules 7 (7g) and 9 (7i) (PGP+, blue dots).

It's important to predict if a chemical will cause substantial drug interactions by inhibiting cytochromes (CYPs) such CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, as well as which isoenzymes would be affected, in a pharmacokinetic study.[69,70] All the compounds were predicted to be CYP3A4 inhibitors. Except for **7b**, **7c**, **7e** and **7f** other compounds are non-inhibitors of CYP2D6. Except **7g**, all other molecules were predicted to be inhibitors of CYP2C9. Except 7g and 7i, remaining molecules were discovered to be CYP2C19 inhibitors. **7a**, **7b**, **7e** and **7f** were also found to be CYP1A2 inhibitors. The study also found that all of the compounds tested were CYP2C19, CYP2C9, and CYP3A4 inhibitors. The reference medication, acarbose, revealed that none of these isoenzymes are inhibitors. The reference drug had the least skin permeability and the highest log Kp of all the molecules studied, with the reference medication having the least skin permeability and the highest log Kp (-16.29). The results are presented in Table S2. (See supporting information)

Predicting drug-likeness variables can help with the qualitative identification of a chemical that turns out to be a high-bioavailability oral medicine. We employed five rules to evaluate the

produced compounds' drug-likeness and oral bioavailability: Lipinski[71], Ghose[72], Veber[73], Egan[74], and Muegge[75]. With a few exceptions, all of the molecules followed the five principles. The properties of compounds **7a-j** that relate to drug similarity are listed in Table 5. Except for acarbose (0.17), all of the drugs examined had a bioavailability score of 0.55, indicating good compliance. The cautions for pan assay interference chemicals (PAINS) are nil, indicating that the pharmacokinetic profile of the lead molecules is favourable. The majority of the compounds had good physicochemical, pharmacokinetic, and drug likeliness properties when compared to the reference drug, acarbose.

Table 5.Drug likeness properties of compounds **7a-j**

Compd.	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	B.S	PAINS alerts	S.A.
7a	0	0	0	1	0	0.55	0	4.82
7b	0	1	0	2	0	0.55	0	4.75
7c	0	1	1	2	2	0.55	0	4.61
7d	1	3	2	2	2	0.55	0	4.75
7e	1	3	2	2	2	0.55	0	4.71
7f	1	3	1	2	2	0.55	0	4.65
7g	0	0	1	1	1	0.55	0	4.63
7h	0	0	0	0	0	0.55	0	4.6
7i	0	0	1	1	1	0.55	0	4.77
7j	0	3	1	1	0	0.55	0	4.81
Acarbose	3	4	1	1	5	0.17	0	7.34

B.S.: Bioavailability Score; S.A.: Synthetic Accessibility

3.2.2. In silico Molecular Docking Study

All the designed molecules were screened further *in silico* for their ability to bind with pancreatic *α*-amylase enzyme using 1-click docking online server tool (http://mcule.com/apps/1-click-docking/) authorized by AutoDockVina docking algorithm.[75]The comprehensive data of binding energies and the corresponding bonding pose of complexes were shown in Table S4 (See Supplemental materials).

All the screened molecules (**7a**-**j**) have shown good docking with binding energies in the range -7.7 to -8.4 kcal/mol when on comparison with reference drug, acarbose (-8.2 kcal/mol). The docking score of the title compounds is in the order of **7e**>**7j**=**7g**=**7b**>**7i**>**7c**=**7f**=**7h**>**7d**>**7a**. Among the 10 molecules in this series, the molecule **7e** has shown the highest binding energywhen compared with the standard**.** Themolecule **7b**, **7g**, and **7j** have shown equal binding energies when compared with reference drug. The leftover molecules have shown significant binding interaction with the target enzyme. In compound **7e**, the benzothiazole and phenyl rings have formed π-π stacking with His201, Trp58 and Trp59. The NH attached to benzothiazole ring and the nitrogen of benzothiazoe ring has formed hydrogen bonding with Asp300 and His305 respectively. Additionally, the molecule formed hydrophobic interactions with residues such as Leu165, Leu162, Tyr 62, Trp59, Trp58, Ala307, Ile235, Val234, Ala198 and Tyr151. In molecule **7b**, oxygen atom of benzoxazole has formed hydrogen bonding with Gln63. The phenyl ring of 8b has formed π-π stacking with His201. Additionally, the molecule has also formed hydrophobic interaction with Tyr151, Leu165 and Leu162, Ala307, Val234, Ala198, Trp59 and Tyr62. In molecule **7g**, the 1,2,3,6-tetrahydro-3-methyl-2,6-dioxopyrimidin-4-ylamino group has formed π-π stacking with His201. The hydrophobic interactions are formed by this molecule with Tyr62, Trp59, Trp58, Tyr151, Ile235, Ala198, Leu162, and Leu165. In molecule 8i, oxygen atom of 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidin-4-ylamino ring has formed hydrogen bonding with Lys200. This ring also formed π-π stacking with His201. The molecule **7i** also formed hydrophobic connections with residues namely Trp58, Trp59, Tyr62, Tyr151, Ala198, Ile235, Val234, Leu162 and Leu165.

Hydrogen bonding is formed by NH group attached to 2-oxo-2H-chromen-6-ylamino ring and oxygen atom of ethoxy group with Asp300 and Tyr151 respectively. 2-oxo-2H-chromen-6-ylamino ring of **7j** also formed π-π stacking with Trp58. Besides, this molecule also formed hydrophobic contacts with Ala307, Leu162, Leu165, Trp59, Trp58, Tyr62, Ala198, Tyr151 and Ile235. In scientific literature,2D diagrams would be to recognize the binding interactions of the target proteinwith the ligands. The2D and 3D ligand interactiondiagrams of the molecules **7b**, **7e, 7g**, **7i**,and **7j** which depict their binding contacts with target enzyme has been developed by AutodockVinaprogram[77]and are presented inTable 6.

Table 6. 2D Lig Plot and 3D images of compounds **7b,7d, 7e, 7i,** and **7j**

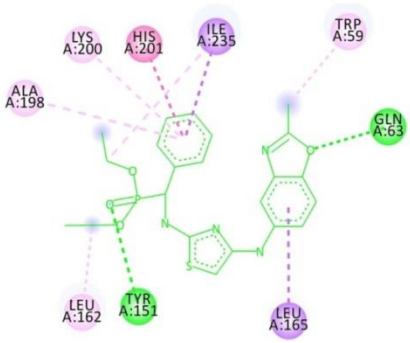
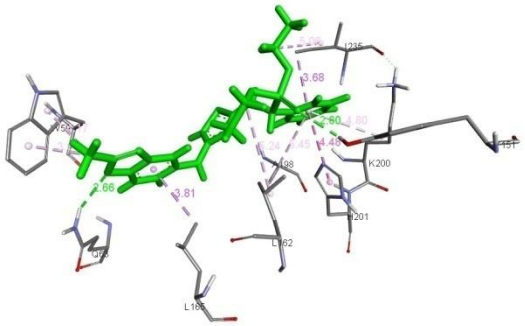
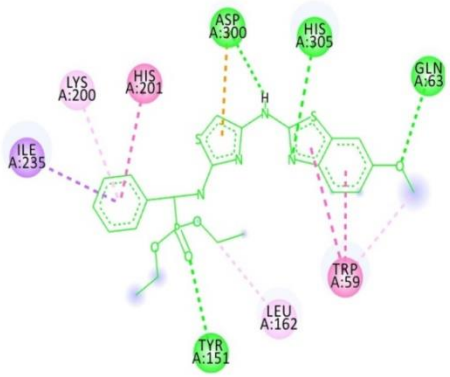
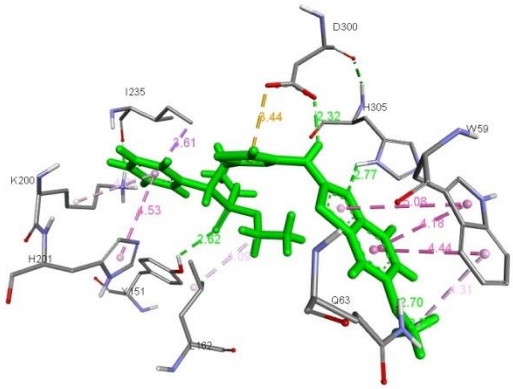
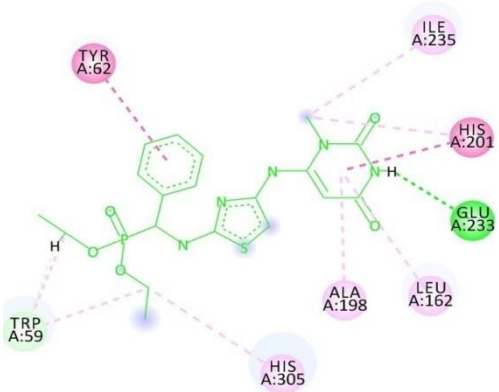
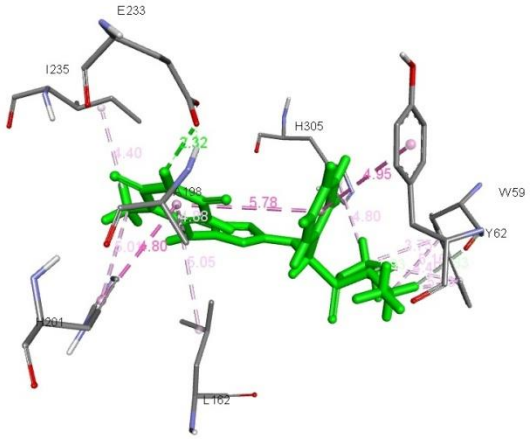
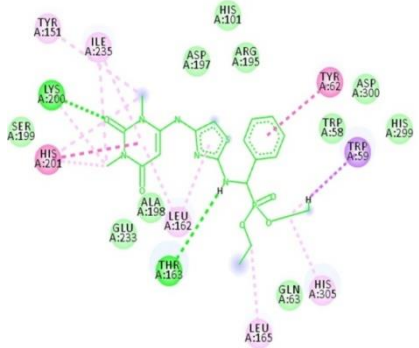
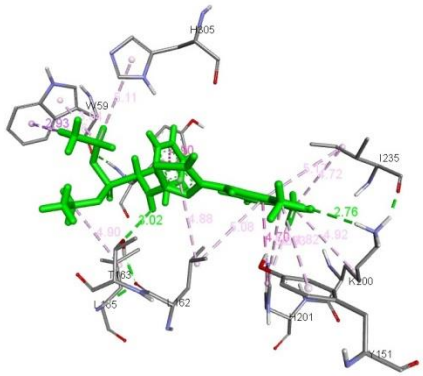
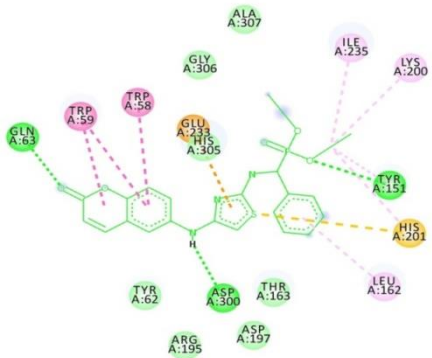
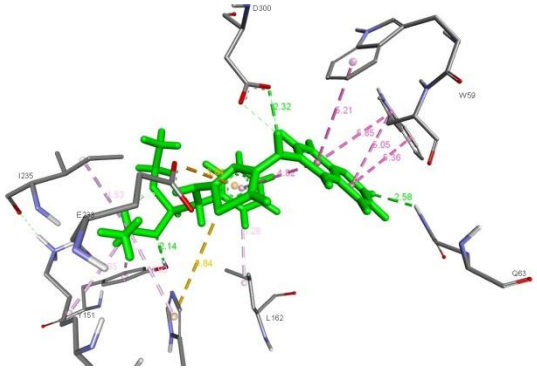
Compd.	2D structure	3D structure
7b		
7e		
7g		

Table 6 continued..

7i		
7j		

3.2.3. α-Amylase Inhibitory Activity

The synthesized compounds were screened *in vitro* for their ability to inhibit α-Amylase using a standard method[78, 79]with slight amendments. The screening was carried out at 25, 50, 100, 150, and 200 µg/mL concentrations. Majority of the compounds showed good inhibition towards the target enzyme. The inhibition effect of title compounds against *α*-Amylase decreased in the following order 7j>7e>7g>7h>7f>7i>7c>7b>7d. The compound **7j** bearing with 2-oxo-2H-chromen-6-ylamino)thiazol-2-ylamino moiety has shown the highest inhibitory activity amongst the screened compounds with IC_{50} value of 99.9±0.3 µg/mL. The compounds 7e bearing 6-methoxybenzo[d]thiazol-2-ylamino substituent has shown the second highest inhibition with IC_{50} value 102.0±0.7 µg/mL. The compound 7g having 1,2,3,6-tetrahydro-3-methyl-2,6-dioxopyrimidin-4-ylamino substituent has shown the third highest inhibition with IC_{50} value 106.7±0.4 µg/mL. The compounds 7h bearing with 4-methylpyridin-2-ylamino)thiazol-2-ylamino moiety has shown the inhibition next to these compounds with IC_{50} values 115.0±0.3 µg/mL and 119.2±0.7 µg/mL respectively. The remaining compoundsexhibited moderate inhibition on the enzyme with IC_{50} ranging 125.6±0.6 to 142.7±0.8 µg/mL. The reference drug, Acarbose has shown the IC_{50} value 102.6±0.8µg/mL.From the results, we observed that when methoxy substituent of benzothiazole moiety in compound **7e** is replaced by more electron withdrawing chloro (**7f,** IC_{50}: 118.9µg/mL) and nitro substituent (**7d,** IC_{50}: 154.36µg/mL), the inhibition effect of the concerned compounds against the target enzyme has been found to be decreased. The results pertaining to % inhibition and IC_{50} values of all the compounds **7a-j** are presented in Figures 1, and 2 respectively.

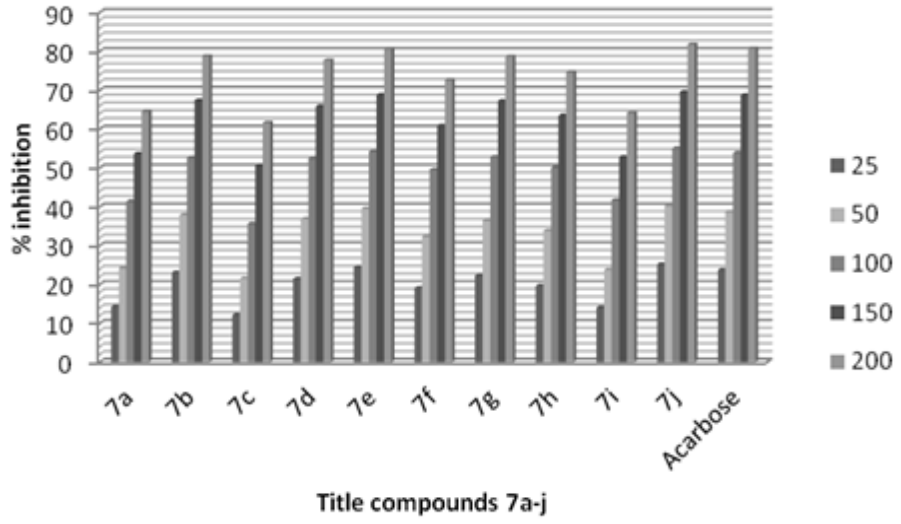


Figure 1. α-Amylase inhibition activity results of compounds **7a-j**

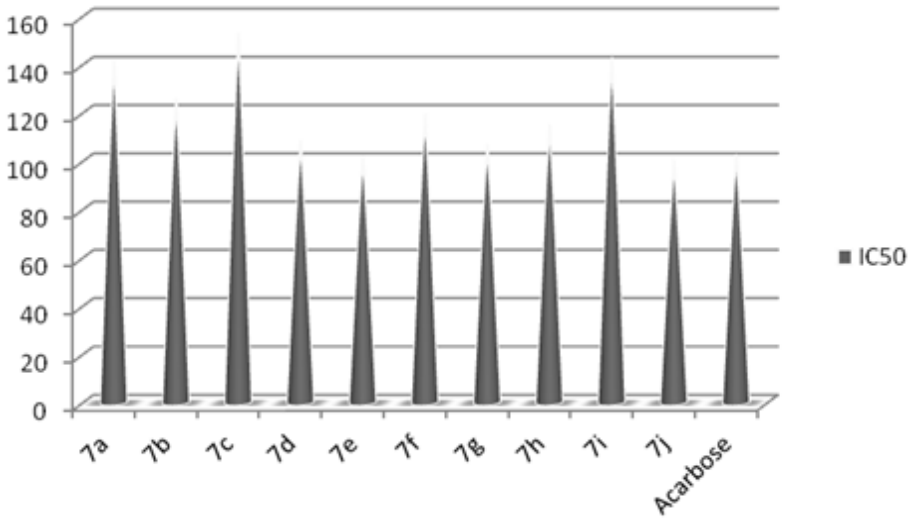


Figure 2. IC_{50} values of compounds **7a-j**

4. Conclusion

Using nano $TiO_2.SiO_2$as a reusable catalyst, a greener strategy was devised for the synthesis of novel α-Aps **7a-j***via* a one-pot K-F reaction in high yields under solvent-free conditions. Compounds were constructed to mimic ADMET and molecular docking prior to synthesis in order to find the most promising candidates for drug development. Molecules **7a-j**, which is predicted using the five principles and have a high oral bioavailability, were discovered in a library of drug-like molecules with good oral bioavailability. Because none of the chemicals are well absorbed through the GI tract and do not pass through the BBB, they are not P-glycoprotein substrates. The PAINS warnings are zero when compared to the reference medication, indicating that the lead compounds have an excellent pharmacokinetic profile. The results of the molecular docking analysis revealed that every drug tested inhibited the target enzyme effectively. The development of molecules having drug-like properties and the ability to inhibit the target enzyme, α-amylase, was prompted. This resulted in a reduction in medication development time, cost, and

chemical waste. All of the newly synthesised compounds were tested in vitro for *α*-amylase inhibitory activities using the spectrophotometric method. The chemical **7e** and **7j** inhibited the target enzyme more effectively than the reference drug. In comparison to a standard, the compounds **7b**, **7d**, **7f**, **7g**and**7h** have shown good inhibitory action on target. The findings of this study indicate that the synthesised compounds will be promising next-generation anti-diabetic drugs that can be used to effectively treat the symptoms of diabetes complications.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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