ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

Nicotinic Acid Derivatives As Novel Noncompetitive α-Amylase and α-Glucosidase Inhibitors for Type 2 Diabetes Treatment

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Cite This: https://doi.org/10.1021/acsmedchemlett.4c00190 Read Online

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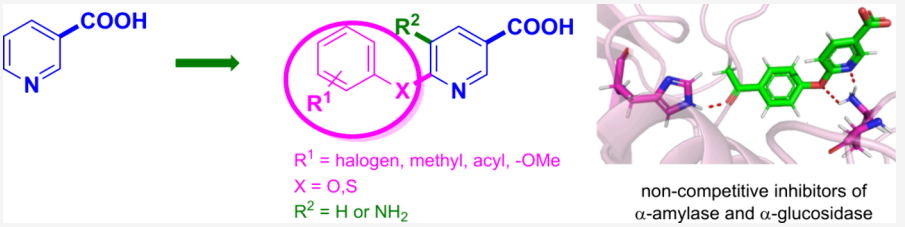


ABSTRACT: A library of novel nicotinic acid derivatives, focusing on the modification of position 6 of the pyridine ring with (thio)ether functionalities, was mostly produced through an innovative green synthetic approach (Cyrene-based) and evaluated for their α-amylase and α-glucosidase inhibitory activity. Compounds **8** and **44** demonstrated micromolar inhibition against α-amylase (IC_{50} of 20.5 and 58.1 μM, respectively), with **44** exhibiting a remarkable ∼72% enzyme inactivation level, surpassing the efficacy of the control compound, acarbose. Conversely, **35** and **39** exhibited comparable inhibition values to acarbose against α-glucosidase (IC_{50} of 32.9 and 26.4 μM, respectively) and a significant enhancement in enzyme inhibition at saturation (∼80−90%). Mechanistic studies revealed that the most promising compounds operated through a noncompetitive inhibition mechanism for both α-amylase and α-glucosidase, offering advantages for function regulation over competitive inhibitors. These inhibitors may open a new perspective for the development of improved hypoglycemic agents for type 2 diabetes treatment.

KEYWORDS: *synthesis, nicotinic acid, enzyme inhibitors, medicinal chemistry, organic chemistry*

Diabetes is a chronic metabolic disorder characterized by high blood sugar levels (hyperglycemia) over a prolonged period. This occurs due to either insufficient insulin production, insulin resistance, or both. Insulin is a pancreatic hormone that regulates blood sugar levels by facilitating the uptake of glucose from the bloodstream into cells to be used for energy or stored for future use. Currently, diabetes is one of the most important focal points in medical research, considering its significant social impact. Indeed, diabetes has been identified as one of the primary risk factors contributing to mortality worldwide.[1] Inadequate or ineffective treatment protocols can lead to various complications, such as stroke, cardiac arrest, limb amputation, vision loss, nervous system damage and an elevated risk of fetal death in poorly managed gestational forms of diabetes.[2]

There are several types of diabetes, but the most common ones are types 1 and 2. They share the similar symptom of elevated blood sugar levels but have different etiology. Type 1 is an autoimmune condition where the immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas.[3] In type 2, the body's cells become resistant to the action of insulin, and the pancreas may gradually lose its ability to produce enough insulin to compensate. As a result, unlike type 1, type 2 diabetes is considerably more manageable and preventable through lifestyle interventions, which could delay absorption of glucose after meals.[4] In recent years, researchers actively investigated hypoglycemic agents with several mechanisms of action, with the aim of identifying molecules able to balance blood sugar uptake and insulin secretion during the postprandial stage. In this context, two pivotal targets for antidiabetic therapy have long been considered: α-amylase and α-glucosidase, which are key enzymes involved in saccharide hydrolysis.[5−7] Thus, the quest for an ideal hypoglycemic agent may revolve around inhibition of these enzymatic targets to improve glucose regulation in type 2 diabetes, leading to a significant amelioration in lifestyle and increased patient's life expectancy. Nicotinic acid, also known as niacin or vitamin B3, is a pyridine derivative showing a plethora of biological activities and therapeutic effects, including lipid-lowering activity, anti-inflammatory effects, vasodilatory effects and treatment of

Received: April 25, 2024
Revised: July 22, 2024
Accepted: July 31, 2024

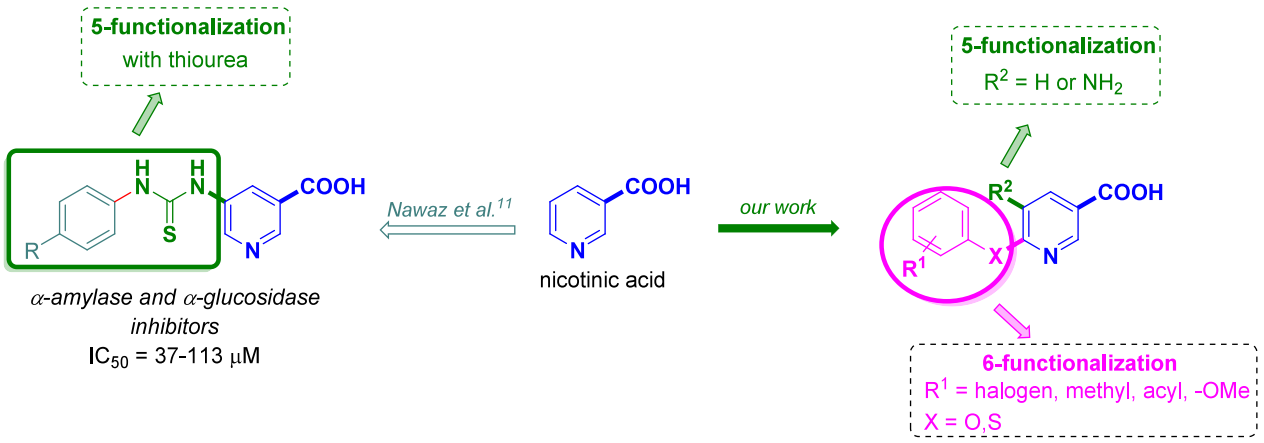
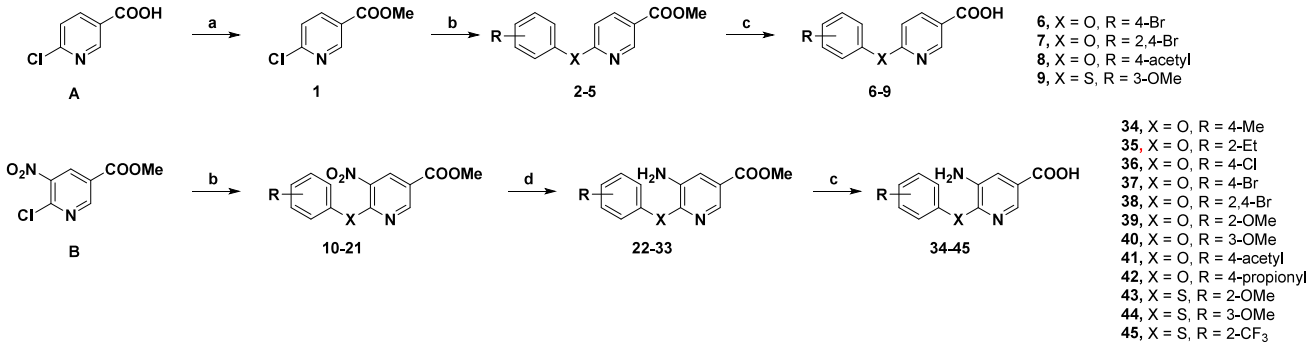


Figure 1. Design of the inhibitors. Chemical exploration of positions 5 and 6 of the nicotinic acid scaffold, proposed in this work, are shown in green and magenta, respectively (right side). Previously published thiourea moiety functionalization is shown in green (left side).

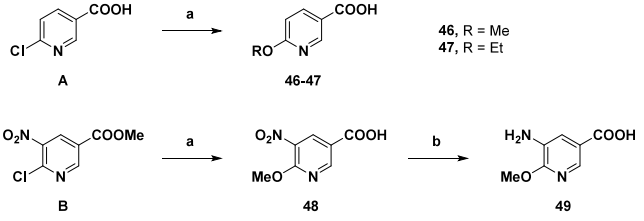
Scheme 1. Synthesis of Final Compounds 6−9 and 34−45[a]



[a]Reagents and conditions: (a) $TMSCHN_2$, toluene:MeOH 2:1 (*v*/*v*), rt, overnight, 98% yield; (b) appropriate phenol or thiophenol, NEt_3, Cyrene, 150 °C, sealed tube, 15−30 min, 60−95% yield; c) 1 M NaOH, MeOH, rt, 3−7 h, then 1 M $NaHSO_4$, 29−96% yield; d) Fe, NH_4Cl, EtOH:water 1:1 (*v*/*v*), 85 °C, 4 h, 23−88% yield.

pellagra.[8−10] Very recently nicotinic acid derivatives functionalized at position 5 with a thiourea moiety have been proposed as novel interesting α-amylase and α-glucosidase inhibitors.[11] Following our ongoing research about nicotinic acid derivatives,[12] we synthesized a library of 19 novel compounds and tested them for *in vitro* inhibition of α-amylase and α-glucosidase activity. Our chemical exploration was attempted both to position 5, keeping the hydrogen bond donor ($-NH_2$) as observed in the parental thiourea derivatives or removing it, and position 6 that was modified introducing (thio)ether

Scheme 2. Synthesis of Final Compounds 46, 47, and 49[a]



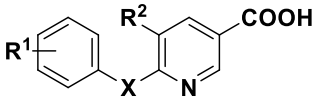
[a]Reagents and conditions: (a) MeONa or EtONa sol., refl, 24 h, *then* 1 M $NaHSO_4$, 17−49% yield; (b) Fe, NH_4Cl, EtOH:water 1:1 (*v*/*v*), 85 °C, 4 h, 35% yield.

moieties in order to explore available chemical space (Figure 1). In the case of aromatic ethers, phenols and thiophenols substituted with a plethora of electron withdrawing or electron donating groups were taken into consideration. Small substituents directly connected to the pyridine system, such as -OMe- or -OEt, were considered as aliphatic ether examples.

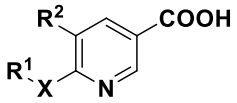
The synthesis of the target compounds bearing 6-phenoxy or 6-phenylthio fragments was conveniently carried out following the pathways reported in Scheme 1. The presence of a free carboxylic group functionality troubled the introduction of the phenol or thiophenol nucleophile at position 6, thus the starting material 6-chloro-nicotinic acid (A) was first converted into the corresponding methyl ester **1** using MeOH in the presence of (trimethylsilyl)diazomethane ($TMSCHN_2$). For the series of 5-amino nicotinic acids, the starting material 6-chloro-5-nitro nicotinic ester (B) was used directly as the methyl ester. A S_NAr reaction allowed the synthesis of **2−5** and **10−21** pyridyl-phenyl ethers or thioethers through an innovative green synthetic approach recently published by our research group.[12] Briefly, starting compounds A or B were reacted with the appropriate phenol or thiophenol in the presence of NEt_3 as the base using the green solvent Cyrene under heating at 150 °C for 15−30 min in a sealed tube, affording the products **2−5** and **10−21** in good to optimal yields (60−95%). The advantage of this Cyrene-mediated methodology is to avoid the use of toxic and dangerous solvents (such as DMF or DMSO) and reduce reaction times. Moreover, the use of tedious chromatographic purification techniques was circumvented, as the pure products precipi-

https://doi.org/10.1021/acsmedchemlett.4c00190
ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX

Table 1. *In Vitro* Inhibitory Activity (IC_{50}, μM) and Inactivation % of Compounds 6−9, 34−45, 46, 47, and 49 against α-Amylase and α-Glucosidase[a]



Compound	X	R^1	R^2	α-amylase IC_{50} (μM)	α-amylase inactivation (%)	α-glucosidase IC_{50} (μM)	α-glucosidase inactivation (%)
Acarbose	-	-	-	11.1 ± 3.9 [0.66; 1.0; 62][6]	53.5 [99.2][6]	19.6 ± 1.4 [4300][15] [750][5] [363][16]	50.8 [71.8][15]
Miglitol	-	-	-	n.i.	-	34.5 ± 2.9 [465][16]	43.6
Voglibose	-	-	-	n.i.	-	14.7 ± 1.3 [320][16]	32.5
6	O	4-Br	H	108.5 ± 13.1	49.1	394.6 ± 23.1	38.6
7	O	2,4-diBr	H	176.9 ± 7.4	73.2	n.i.	-
8	O	4-acetyl	H	20.5 ± 2.6	38.5	n.i.	-
9	S	2-OMe	H	240.6 ± 19.1	80.7	544.6 ± 39.1	36.3
34	O	4-Me	NH_2	438.6 ± 33.6	44.3	353.2 ± 33.6	26.6
35	O	2-Et	NH_2	166.7 ± 11.6	54.9	32.9 ± 2.8	79.3
36	O	4-Cl	NH_2	363.9 ± 9.7	59.9	607.8 ± 20.7	28.3
37	O	4-Br	NH_2	331.0 ± 25.4	81.3	526.0 ± 35.3	35.6
38	O	2,4-diBr	NH_2	201.5 ± 18.9	53.1	457.8 ± 20.1	46.2
39	O	2-OMe	NH_2	162.4 ± 9.7	55.2	26.4 ± 2.0	87.3
40	O	3-OMe	NH_2	197.5 ± 13.8	75.5	565.8 ± 15.8	51.2
41	O	4-acetyl	NH_2	383.4 ± 15.4	50.6	532.9 ± 45.4	34.5
42	O	4-propionyl	NH_2	355.5 ± 10.8	52.3	n.i.	-
43	S	2-OMe	NH_2	653.7 ± 48.4	48.6	206.5 ± 18.4	56.8
44	S	3-OMe	NH_2	58.1 ± 4.1	71.5	348.5 ± 11.4	32.8
45	S	2-CF_3	NH_2	199.5 ± 13.4	53.5	155.1 ± 10.3	43.7



46	O	Me	H	527.5 ± 19.4	87.4	878.8 ± 37.4	14.5
47	O	Et	H	236.9 ± 18.8	69.4	442.5 ± 28.7	27.5
49	O	Me	NH_2	281.3 ± 25.0	80.3	639.0 ± 35.2	27.9

[a]Notes: n.i. = no inhibition.

tated from the reaction mixture after treatment with ice water. The reaction reached completion in 30 min whenever A was used as starting material, while 15 min of reaction time was needed for B. The different reaction time is explained by the presence of the 5-nitro group, which accelerated the S_NAr reaction. Compounds **10**−**21** were then subjected to a conventional reduction of the nitro group in the presence of iron under acid conditions, to afford methyl 5-amino nicotinate derivatives (**22**−**33**) in moderate to good yields (23−88%). In this case as well, there was no need to perform any column chromatography purification step for obtaining the clean product (except for compound **33**). After the reaction had been completed, the solvents were removed under reduced pressure; treatment of the crude mixture with a saturated solution of K_2CO_3 (until slightly alkaline pH) resulted in the precipitation of the pure products. It is noteworthy that in some instances, the addition of drops of MeOH facilitated the precipitation process and led to increased yields. Finally, alkaline hydrolysis provided the target 6-substituted nicotinic (**6**−**9**) or 5-amino-nicotinic acid compounds (**34**−**45**) in moderate to good yields (29−96%). Noteworthy, the final nicotinic acid compounds precipitated from the crude mixture after acidification with a 1 M $NaHSO_4$ solution (pH 5.5).

The synthesis of the target compounds bearing 6-methoxy or 6-ethoxy fragments was carried out following similar pathways (Scheme 2). The S_NAr reaction in this case could not be developed using the methodology seen for phenols or thiophenols because the strongly basic conditions expected

https://doi.org/10.1021/acsmedchemlett.4c00190
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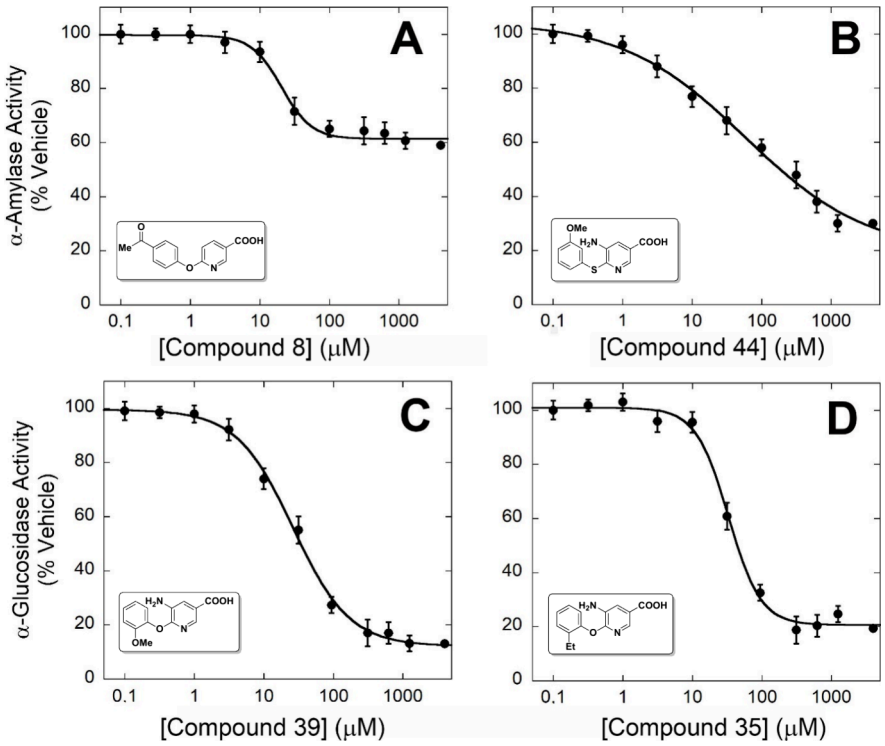

Figure 2. Enzyme inhibition assays performed on (A, B) α-amylase or (C, D) α-glucosidase by compounds **8**, **35**, **39**, and **44**. The enzymatic activity in the presence of different compound concentrations (in the 0−3500 μM range) was determined by colorimetric assays using an automated liquid-handler system. The plots display the mean values ± SD, n = 4.

from the presence of sodium alkoxides are incompatible with Cyrene, which is not stable and tends to polymerize.[13] However, it was possible to directly use the carboxylic acid as the starting material, thereby avoiding the subsequent hydrolysis step. Starting material A was reacted with alcoholic solutions of NaOMe or NaOEt at refluxing temperatures to provide **46** and **47** in low yields (17−35%). Starting material B was reacted with an alcoholic solution of NaOMe at refluxing temperatures to directly provide carboxylic acid derivative **48** in 49% yield. Finally, a reduction of the nitro group under the same reaction conditions observed before afforded **49** (35% yield). The structural confirmation and the purity of all the synthesized compounds was achieved by ^{1}H NMR, ^{13}C NMR, and HRMS. All compounds are >95% pure by HPLC analysis and representative HPLC traces are included in the Supporting Information.

The inhibitory activity of the target compounds **6**−**9**, **34**−**45**, **46**, **47** and **49** against α-amylase and α-glucosidase was measured by using an assay optimized from the one proposed by Nawaz et al.[11] The enzymes' source and the assay conditions are known to strongly affect the inhibition.[6] Acarbose was chosen as a standard control, and it showed a partial inhibition of both enzymes (~50%) and IC_{50} values in the 10−20 μM range (Table 1). Regarding α-amylase inhibition, the enzymatic activity was assayed in 20 mM potassium phosphate using soluble starch, and the reaction mixture was incubated at 95 °C for 10 min before recording the absorbance intensity (see the Supporting Information for details). It was noted that the synthesized compounds demonstrated varying degrees of α-amylase inhibitory activity with IC_{50} distributed over a wide range of values. Specifically, compounds **8** and **44** exhibited interesting α-amylase inhibition, with IC_{50} values of 20.5 ± 2.6 and 58.1 ± 4.1 μM, respectively (Table 1 and Figure 2A, B). Interestingly, **44** resulted in a high degree of inactivation of ~71.5% (*i.e.*, ~25% of residual enzymatic activity at saturation), a value significantly improved in comparison to that of acarbose (46.5% of residual enzymatic activity at saturation). These findings suggested that in the series of nicotinic acid derivatives, the presence of an acetyl group at the *para* position of the phenyl ring (**8**) was more conducive to α-amylase inhibition compared to other substituents. On the other hand, in the series of 5-amino nicotinic acid derivatives, a *meta*-substituted phenyl ring with an −OMe substituent (**44**), whenever connected to the pyridine core with a sulfur bridge, led to the best inhibition activity. An analogue assay against α-glucosidase showed various degrees of inhibition ranging mostly in the half millimolar range (Table 1), with the exception of ethers **35** and **39**, which showed IC_{50} values of 32.9 ± 2.8 and 26.4 ± 2.0 μM, respectively (Table 1 and Figure 2C, D). Enzyme inactivation at saturation for compounds **35** and **39** was higher than for acarbose (20.7% and 12.3% of residual enzymatic activity at saturation for **35** and **39**, instead of 49.2% for acarbose), showing a consistent improvement. These data demonstrated the significance of the NH_2 group presence at position 5 of the nicotinic acid scaffold for activity against α-glucosidase. Functionalization of the *ortho* position of the phenyl ring with electron-donating groups such as ethyl (**35**) and its isosteric replacement −OMe (**39**) led to compounds with remarkable activity. Furthermore, compounds **8**, **35** and **39** exhibited increased potency compared to the thiourea derivative disclosed by Nawaz et al. (range 37−113 μM),[11] indicating that introducing an ether or thioether functionality at position 6 was more effective in developing potent inhibitors. As further reference, miglitol and voglibose have been also evaluated: while both compounds did not

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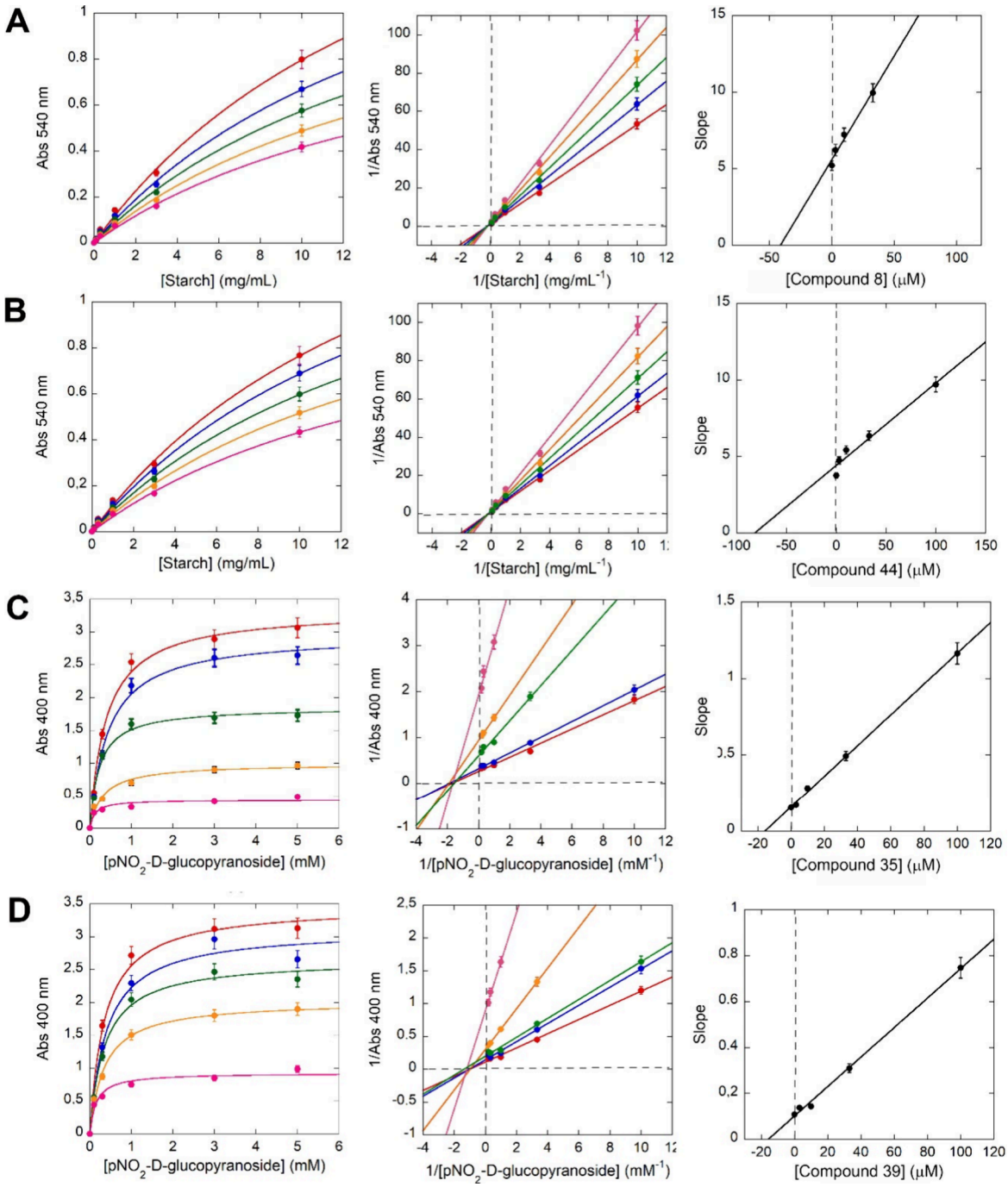

Figure 3. Inhibition of α-amylase (A,B) and α-glucosidase (C,D) by (A) **8**, (B) **44**, (C) **35**, and (D) **39**. The enzymatic activity was measured in the presence of increasing concentrations of inhibitor (0 μM, red line; 3 μM, blue line; 10 μM, green line; 33 μM, orange line; 100 μM, pink line) and different concentrations of (A, B) starch (0−10 mg/mL) or (C, D) *p*-nitrophenyl-α-D-glucopyranoside (0−5 mM, right panels). A Michaelis−Menten model of noncompetitive inhibition was globally fit: the Lineweaver−Burk equation was used to describe in a double reciprocal form the noncompetitive inhibition mechanism (central panels), and the K_i value was estimated by the tertiary plot of slope against compound concentration (linearly fitted, left panels). The plots display the mean values ± SD, n = 2.

modify the activity of α-amylase, in agreement with literature, a partial inhibition of α-glucosidase was determined.[14]

Then, the inhibitory mechanism of α-amylase by **8** and **44**, and of α-glucosidase by **35** and **39** was studied at different substrate and inhibitor concentrations using the same assays employed for IC_{50} estimation (the starch in the amylase activity assay could not be used at a saturating concentration because of the solubility limit). In detail, all compounds tested showed a decrease in apparent V_{max} values with minimal effect on apparent K_m ones (Figure 3 and Table S1 in the Supporting Information). This result is consistent with tested compounds being noncompetitive inhibitors. Kinetic eqs (1) and (2) (see Materials and Methods Section in the Supporting Information) were used to calculate the inhibitory constant K_i, as reported in Table 2. A good correlation between K_i and IC_{50} values for each compound was observed (see Tables 1 and 2) and these values were slightly lower for α-glucosidase in comparison with α-amylase. For sake of comparison, the inhibition of α-amylase

https://doi.org/10.1021/acsmedchemlett.4c00190
ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX

Table 2. Inhibition constants of α-amylase by compounds 8, 44 and acarbose, and of α-glucosidase by compounds 35 and 39

Enzyme	Compound	K_i (μM)
α-Amylase	8	41.2 ± 3.1
	44	81.9 ± 4.1
	acarbose	62.4 ± 2.4
α-Glucosidase	35	17.1 ± 1.4
	39	15.9 ± 1.3
	acarbose	90.7 ± 1.8

and α-glucosidase was studied for acarbose under our experimental conditions: in both cases, a noncompetitive inhibition was apparent, with K_i values in the 60−90 μM range (Table 2 and Table S1).

Molecular docking was carried out to elucidate the binding mode of the active compounds in the putative allosteric sites of α-amylase and α-glucosidase. Probable allosteric sites were identified by using the Maestro suite (Figure S1 in the Supporting Information). Docking of **8** and **44** in a common allosteric site of α-amylase is depicted in Figure 4A and B. **8** establishes significant interactions within the pocket: a bifurcated hydrogen bond is observed between the amino group of Lys53 and the nitrogen of the pyridine ring and the ether oxygen; additionally, the carbonyl group of the acetophenone moiety of **8** interacts via a hydrogen bond with His491. **44**, on the other hand, is oriented in such a way that the carbonyl oxygen attached to the pyridine system establishes two H-bonds with the amino groups of the side chains of Lys53 and Arg392, respectively. Moreover, the NH_2 of the pyridine ring acts as a H-bond donor toward the oxygen of the amide bond of Lys457. Figure 4C and D describe the docking poses of **35** and **39** within the common allosteric site of α-glucosidase. The amino group of the pyridine ring of compound **35** forms an H-bond with the carbonyl oxygen of the peptide backbone of Phe543. In contrast, for compound **39**, a hydrogen bond is observed between the carbonyl oxygen and a hydrogen of the amino group within the side chain of Lys523. These *in silico* results provide a first picture of a likely interaction of the noncompetitive inhibitors with unprecedented allosteric sites for both target enzymes and, whenever confirmed by mutagenesis experiment, will provide the bases for a rational development of the inhibitors. In the past, acarbose was reported as uncompetitive inhibitor of barley amylase, able to bind a secondary binding site to give an abortive ESI complex.[17]

The predicted drug-like properties of compounds **8**, **35**, **39**, and **44** were examined using SwissADME (Absorption, Distribution, Metabolism, Excretion) online tool and they displayed favorable pharmacokinetic properties as shown in Table 3. Concerning their physicochemical properties, all of the synthesized compounds showed good solubility in water according to ESOL solubility this favoring drug formulation. A <5 lipophilicity (log*P*) was predicted for all molecules, indicating good permeability to the target tissue. However, the tested compounds showed no blood−brain barrier penetration and are predicted to follow the Lipinski rule of 5. Compounds **8**, **35**, **39**, and **44** are predicted to have a high GI absorbance and a comparable bioavailability score of 0.56.

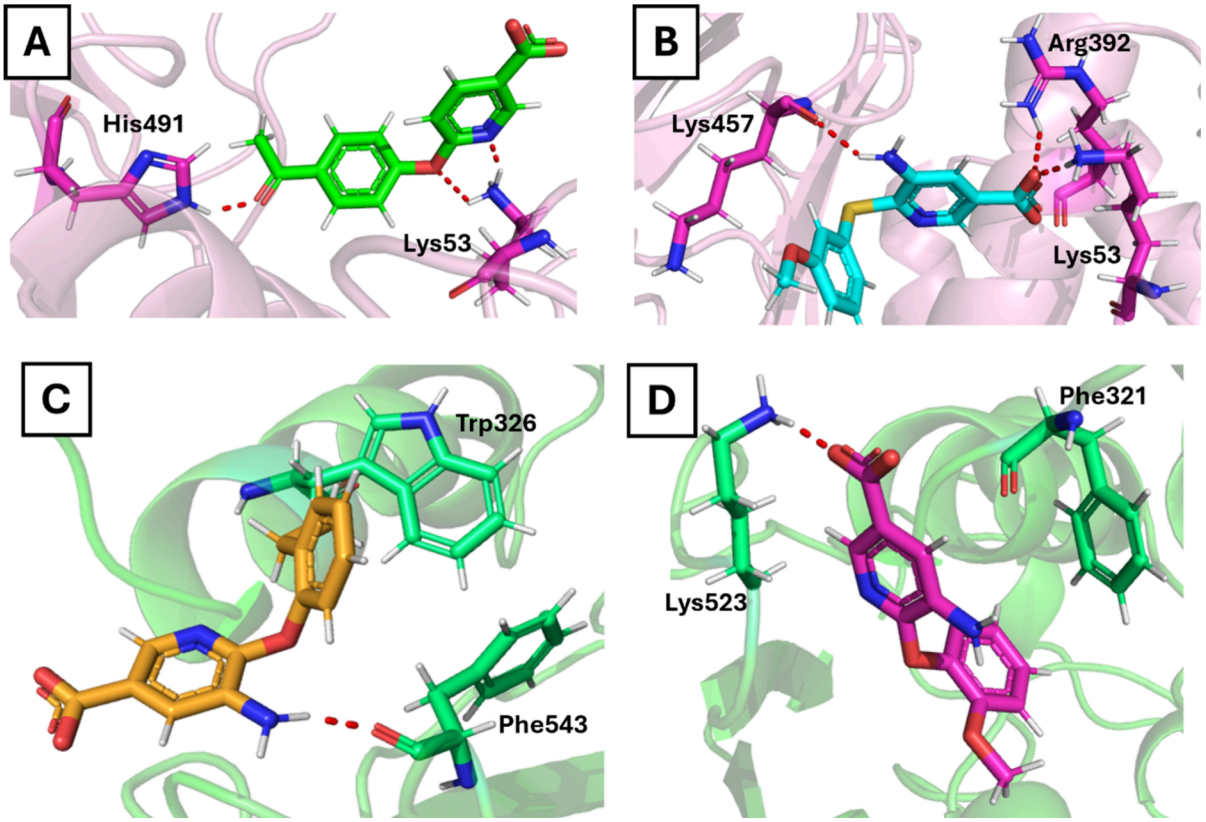

Figure 4. Binding modes of **8** (panel A) and **44** (panel B) into the putative allosteric site of α-amylase (PDB-code 1OSE) and binding modes of **35** (panel C) and **39** (panel D) into the putative allosteric site of α-glucosidase (PDB-code 3A4A). The residues involved in the interactions with the inhibitors are highlighted as sticks. H-bond interactions are displayed as red dashed lines.

https://doi.org/10.1021/acsmedchemlett.4c00190
ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX

Table 3. ADME and Drug-likeness of 8, 35, 39, and 44

Compound	Solubility (ESOL)	Consensus logP	H-bond acceptors	H-bond donors	Lipinski violations	GI absorption	BB Permeation	Bioavailability score
8	Soluble	1.8	5	1	No	High	No	0.56
35	Soluble	1.89	4	2	No	High	No	0.56
39	Soluble	1.25	5	2	No	High	No	0.56
44	Soluble	1.57	4	2	No	High	No	0.56

In conclusion, this work led to the discovery of novel nicotinic acid derivatives with the aim of investigating how modification of positions 5 and 6 could impact inhibitory activity against α-amylase and α-glucosidase. The target compounds were synthesized by employing a novel sustainable approach based on the use of the green solvent Cyrene. Remarkably, **8** and **44** exhibited micromolar inhibition values against α-amylase, with **44** demonstrating an ∼72% enzyme inactivation level, a superior outcome compared to the control, acarbose. Concerning α-glucosidase, on the other hand, both **35** and **39** showed inhibition values comparable to acarbose but displayed a significant enhancement in their ability to strongly deactivate the enzyme at saturation, by approximately ∼80−90% compared to the control. Notably, the inhibition mechanism of the most promising compounds turned out to be noncompetitive. This finding represents an important innovation since, tipically, inhibitors of α-amylase and α-glucosidase, used to alleviate postprandial glycemia, act *via* a reversible competitive mechanism.[6,7] In particular, this is also true for recently reported nicotinic-based inhibitors, showing the remarkable property to competitively inhibit both α-amylase and α-glucosidase.[11] The noncompetitive inhibition on both enzymes provided by our nicotinic acid 6-pyridine (thio)ether derivatives offers great advantages over a competitive inhibition due to the ability of the compounds to bind the enzymes at a site other than the active site, thereby not competing directly with the substrate. As a consequence, a noncompetitive inhibitor reduces the activity of the enzyme by binding equally well to the enzyme whether or not it has already bound to substrate, and its inhibition effect cannot be overcome by increasing substrate concentration. These preliminary results indicate that nicotinic acid scaffold could effectively be employed as an interesting pharmacophore in the design and optimization of new hypoglycemic drugs acting synergistically as noncompetitive inhibitors on both α-amylase and α-glucosidase, thus expanding the repertoires of potential strategies for type 2 diabetes treatment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.4c00190.

Material and methods; procedures for the synthesis of intermediates and final compounds; α-amylase and α-glucosidase inhibition assay protocols; copies of ^{1}H and ^{13}C NMR of final compounds; HPLC traces for representative compounds (PDF)

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Funding

This research was supported by PRIN2020 (Grant 2020K53E57) to Loredano Pollegioni and Marco Nardini. The support from Fondo di Ateneo per la Ricerca, Università degli Studi dell'Insubria, to Loredano Pollegioni and Elena Rosini is acknowledged.

Notes

The authors declare no competing financial interest.

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https://doi.org/10.1021/acsmedchemlett.4c00190
ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX