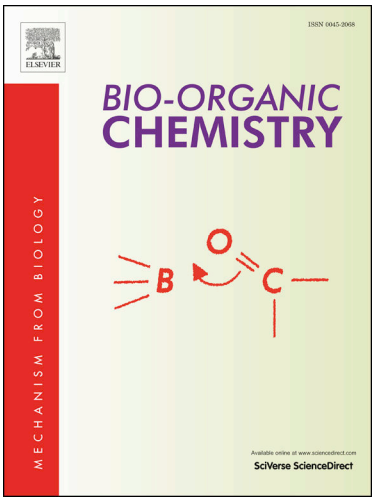

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Synthesis and molecular docking studies of imines as α-glucosidase and α-amylase inhibitors

Analy Aispuro-Pérez[a], Juan López-Ávalos[a], Fernando García-Páez[b], Julio Montes-Avila[a], Lorenzo A. Picos-Corrales[a], Adrián Ochoa-Terán[c], Pedro Bastidas[d], Sarita Montaño[a]; Loranda Calderón-Zamora[e]; Ulises Osuna-Martínez*[a] and Juan I. Sarmiento-Sánchez*[b]

[a] Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Sinaloa, Blvd. de las américas S/N, 80040, Campus Culiacán, Culiacán, Sinaloa, Mexico.

[b] Facultad de Ingeniería Culiacán, Universidad Autónoma de Sinaloa. Blvd. de las américas S/N, 80040, Culiacán, Sinaloa, Mexico. Tel./Fax: +52(667)7134043

[c] Centro de Graduados e Investigación en Química, Instituto Tecnológico de Tijuana. Blvd. Alberto Limón Padilla S/N, Mesa de Otay, 22500, Tijuana, B.C., Mexico.

[d] Laboratorio de Análisis de Residuos de Plaguicidas, Centro de Investigación en Alimentación y Desarrollo A.C., Carretera a El Dorado Km 5.5, Campo El Diez, Culiacán Sinaloa, 80129, Mexico.

[e] Facultad de Biología, Universidad Autónoma de Sinaloa, Blvd. de las américas S/N, 80040, Campus Culiacán, Culiacán, Sinaloa, México.

* Juan I. Sarmiento-Sánchez and Ulises Osuna-Martínez have contributed equally to this study. For questions, address to: chemical approach with Prof. Juan Sarmiento (jsarmiento@uas.edu.mx) and biological activities with Prof. Ulises Osuna (ulises.osuna@uas.edu.mx).

Abstract

Imine functionality is found in many compounds with important biological activity. Thus, the development of novel synthetic approaches for imines is important. In this work, it is propose an easy, eco-friendly and straightforward synthesis pathway of aryl imines under microwave irradiation catalyzed by Alumina-sulfuric acid. In addition, the *in vitro* enzymatic inhibition, antioxidant activity and molecular docking studies were performed. The aryl imines were isolated with yields in the range of 37-94%. All aryl imines synthesized were evaluated for *in vitro* inhibitory potential against α-glucosidase and α-amylase enzymes and the results exhibited that the most of the compounds displayed inhibitory activity against both enzymes. The (*E*)-1-(4-nitrophenyl)-*N*-(pyridin-2-yl)methanimine (**3d**) was 1.15-fold more active than acarbose against α-amylase whilst the (*E*)-1-phenyl-*N*-(pyridin-2-yl)methanimine (**3c**) displayed similar activity that acarbose against α-glucosidase. The molecular docking studies in α–glucosidase and α–amylase reveal that aryl imines mainly establish an H-bond with the R^2-subtituent and hydrophobic interactions with the R^1-subtituent. The docking analysis reveals these synthetic aryl imines **3d-i** interact in same active site than acarbose drug in both enzymes.

Keywords: aryl imines; *α*-glucosidase; *α*-amylase; antioxidant activity; docking

1. Introduction

Imines can be prepared by various methods including the classical way which involve the heating of an aldehyde with an amine in a polar solvent with dehydrating agents or removing the water azeotropically. Other approaches reported in the literature include condensation reactions promoted by ultrasound irradiation using SiO_2 [1], $Mg(ClO_4)_2$ [2], electrochemical oxidation of benzylic amines [3], SiO_2-$NaHSO_4$ [4], aniline with aryl aldehyde in water [5], basic alumina or poly-4-vinylpyridine [6], SiO_2-H_3PO_4 [7], aerobic oxidation of benzylic amines using graphite-supported gold nanoparticles [8], primary alcohols with amines using ruthenium(II) bis(benzimidazole)pyridine complex [9] or copper-aluminum mixed oxide [10] as catalyst, TiO_2-nanotubes under sunlight [11], SnO_2-doped silica nanospheres [12], K-10 clay [13], CaO-activated [14], SiO_2-P_2O_5 [15], MCM-41-SO_3H [16], grinding using H_2SO_4 as catalyst [17] and *p*-TsOH acid [18]. Such pathways often have complicated procedures, moisture sensitive catalysts or reagents, large volume of toxic solvents, expensive catalysts, high reaction temperatures and long reaction times. Imines are the intermediates to obtain some compounds as isoxazoline and pyrazolines [19], quinolones [20], α-alkylidene β-oxoamides [21] and 1,5-amino/ketoalcohols [22]. Imines are an important class of compounds because they exhibit a variety of applications in organic, inorganic and medicinal chemistry. The imine moiety is shown in bioactive compounds and exhibit a broad spectrum of biological activities as antioxidant [17], antidiabetic [23], α-glucosidase inhibitors [24,25], antimicrobial [26], anticancer [27,28], antifungal [29], anti-*Leishmania tropica* [30], among others.

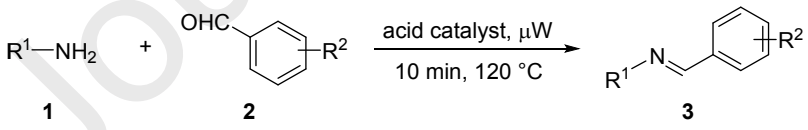
On the other hand, Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia. The main strategy for the treatment of diabetes is the drugs consumption to

control the glucose level in the blood. The glucose in the blood originates from the hydrolysis of carbohydrates and it is catalyzed by enzymes such as α-glucosidase and α-amylase. The α-glucosidase inhibitors reduce the absorption of glucose from the small intestine, and it is secreted by the pancreas and salivary glands to hydrolyze the oligosaccharides into simple sugar. The inhibition of α-amylase and α-glucosidase delays the glucose absorption, therefore, the postprandial blood glucose level is lowered, which is considered to be a therapeutic approach for the treatment of diabetes. Hence, due to the biological activity of imines and their use in organic field, the design of simple, efficient and eco-friendly ways for the imine synthesis has a great interest.

Currently, our research group is focused on the development of simple synthetic approaches for small compounds and the study of their potential biological activity. Recently, we have reported the synthesis of small compounds and their biological activity [31–35]. Here, we report an easy and efficient one-step microwave-assisted synthesis of aryl imines catalyzed by alumina-sulfuric acid (ASA) and their study as α-glucosidase and α-amylase inhibitors.

2. Result and discussion

2.1 Chemistry



Scheme 1. Synthetic route of aryl imines.

A series of aryl imines were obtained by reacting aryl amines with aryl aldehydes in the presence of an acid catalyst (scheme 1). In this regard, the initial efforts were devoted toward

the optimization of reaction conditions. The synthesis of *N*-benzylidene aniline (**3a**, BnA) under microwave irradiation was study as model reaction for this aim. The first studies were carried out setting the reaction conditions in 120 ºC and 10 minutes using some solvents (Table 1). These experiments display the higher yield with protic solvents as MeOH, EtOH and ^{i}PrOH (entry 3-5, Table 1) as it was expected. Lehn *et. al.*[36] report that traces of BnA were detected in water, nevertheless, the BnA under this approach was obtained in 69% yield (entry 2, Table 1) and lower time than in previous reports. [5,37]

Table 1. Yields for **3a** using different solvents

Entry	solvent	Yield (%)
1	-	68
2	H_2O	69
3	MeOH	88
4	EtOH	87
5	^{i}PrOH	83
6	1,4-dioxane	78
7	Benzene	78
8	Toluene	70
9	EtOAc	73
10	DMF	76
11	DMSO	70
12	THF	45
13	CH_3CN	78

In a second research step, a screening of commercial supports (entry 1-6, table 2) were used in order to find an efficient catalyst for the synthesis of imines (using 20 mg of catalyst) and these experiments showed better yield with acid alumina. Therefore, some tests varying temperature (80 to 140 ºC), time (2 to 15 minutes) and catalyst amount (10 to 150 mg) were carried out to establish the optimal conditions with acid alumina under solvent-free condition (supplementary material). The optimal conditions from these experiments were 120 ºC, 10

minutes and 100 mg of catalyst. Then, some acid catalysts as SBA-15-sulfuric acid, silica-sulfuric acid (SSA), alumina-sulfuric acid (ASA), metal hydrogen sulfates and alumina or acid silica were tested under the optimal conditions (entry 7-23, table 2). The higher yields were obtained with the alumina catalysts. Noteworthy, the ASA material was the most efficient catalyst giving a 94% yield during screening for efficiency (entry 10, Table 2).

Table 2. Synthesis of *N*-benzylidene aniline **3a** using various catalysts

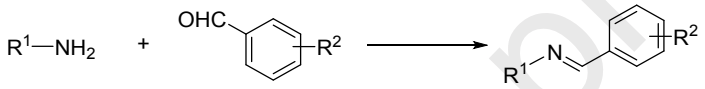
Entry	catalyst	Yield (%)[a]
1	neutral alumina	83
2	basic alumina	82
3	acid alumina	88
4	Silica gel	42
5	diatomaceous earth	50
6	sodium bisulfite	78
7	SBA-15	53
8	SBA-15-SO_3H	76
9	SSA	63
10	ASA	94
11	SiO_2-HCl	traces
12	SiO_2-H_2SO_4	traces
13	SiO_2-HNO_3	traces
14	SiO_2- H_3PO_4	5
15	Al_2O_3-HCl	53
16	Al_2O_3-H_2SO_4	80
17	Al_2O_3-HNO_3	5
18	Al_2O_3-H_3PO_4	82
19	$Zn(HSO_4)_2$	20
20	$Mg(HSO_4)_2$	traces
21	$Ca(HSO_4)_2$	traces
22	$Ba(HSO_4)_2$	traces
23	$Sn(HSO_4)_2$	16

[a]yield obtained using 100 mg of catalyst; SSA - silica sulfuric acid; ASA - alumina sulfuric acid.

Due to our interest in green chemistry and the above results that showed ASA as the best catalyst for the solvent-free synthesis of imines, this approach was used to investigate its

generality and feasibility and the synthesis of the desired compounds **3a-m** (Table 3) were produced in 37-94% yields. The structure of the imines were confirmed by NMR and GC-MS analyses. A structure-yield analysis reveals that lower yields are obtained when R^1 is a cycloalkyl substituent (**3b**, **3i** and **3l**, Table 3). If the 4-NO_2 analogous are compared (**3d-3j**), the highest yields are obtained with the *orto*-substituted aryl amines having a weak electron-donating group (EDG) (**3e** and **3h**).

Table 3. Yields of aryl imines **3a-3m** under μW irradiation



1 **2** **3**

	R^1	R^2	Yield (%)
3a	C_6H_5	H	94
3b	C_6H_{11}	H	37
3c	2-C_5H_4N	H	44
3d	2- C_5H_4N	4-NO_2	54
3e	2-$CH_3C_6H_4$	4-NO_2	82
3f	3-$CH_3C_6H_4$	4-NO_2	63
3g	4-$CH_3C_6H_4$	4-NO_2	50
3h	2,6-$(CH_3)_2C_6H_3$	4-NO_2	82
3i	C_6H_{11}	4-NO_2	40
3j	4-OHC_6H_4	4-NO_2	63
3k	4-OHC_6H_4	2-OH	82
3l	C_6H_{11}	4-Cl	39
3m	4-$CH_3C_6H_4$	3-OH	40

On the other hand, the recycling of heterogeneous catalyst is well reported. For this reason, we address the study to recyclability and reusability of the catalyst toward green chemistry approach. Upon the end of the reaction, the ASA was separated by filtration, washed with

isopropyl alcohol, dried and activate using μW irradiation under open vessel system (120 ºC, 10 minutes). The reactivated ASA was used in three additional cycles for the synthesis of compound **3a** and did not show a significant loss of yield (87, 85 and 80% yield, respectively).

2.2 Biological activities

The inhibitory potency of aryl imines **3a-m** against α-glucosidase and α-amylase was evaluated and compared with acarbose as a reference standard. All the synthesized aryl imines displayed inhibitory activity against α-glucosidase (αG), the compounds **3a** and **3c** were likewise active than acarbose. It is observed a better activity if R^1 is an aromatic ring as phenyl or pyridyl (**3a** and **3c**) compared with a non-aromatic ring as *c*-hexyl (**3b**). Furthermore, a weak or null inhibition is show with an electron-withdrawing group (EWG) on R^2 position (**3d-j**), even if pyridine ring is present as R^1 substituent (**3d**). When R^1 is a tolyl, the enzyme inhibition follows the reactivity order *meta* > *para* > *ortho* being 1.54- and 1.79-fold more active, respectively (**3e-g**). Nonetheless, the *p*-hydroxyphenyl (R^1-substituent) does not induce inhibition with an EWG as nitro in R^2 (**3j**), whilst an EDG as hydroxyl (**3k**) show 1.55-fold less inhibition than acarbose. From these results, we concluded that aryl imines with an EDG could be more active against αGI than those with a EWG as substituent.

Table 4. Biological activities of synthetic imines

	%AA (10 μg mL^{-1}) [a]	**IC_{50} (antioxidant)**	**IC_{50} (α-glucosidase)**	**IC_{50} (α-amylase)**
3a			25.37	-[b]
3b	2.990 ± 2.940	>100	53.87	-[b]

3c	3.089 ± 2.325	>100	24.02	-[b]
3d	5.224 ± 0.865	>100	35.05	28.53
3e	2.181 ± 0.644	>100	62.15	44.77
3f	13.130 ± 2.990	>100	34.68	37.56
3g	3.635 ± 0.708	>100	53.51	52.25
3h	3.998 ± 4.080	>100	36.32	126.4
3i	3.498 ± 0.982	>100	44.56	35.27
3j			-[b]	-[b]
3k			62.16	112.2
Acarbose			24.38	61.28
Vitamin C	56.84 ± 3.21	8.79		
Gallic acid	89.24 ± 13.78	4.08		

All IC_{50} are given in μg mL^{-1}; [a] value represents mean ± S.D.; [b] not inhibition

Based on the inhibitory activity against porcine pancreatic α-amylase (αA), the compounds **3d-g** and **3i** displayed the best activity. The compounds **3d**, **3e, 3f** and **3i** were found to be 1.15-, 0.37-, 0.63- and 0.74-fold more active than acarbose, respectively. The highest enzymatic inhibition was observed if R^1 is pyridine and R^2 is an EWG (**3d**), whilst the lack of substitution in R^2 leads to inactive compounds (**3a-c**). When R^1 is a tolyl, the enzymatic inhibition follows the reactivity order *meta* > *ortho* > *para* being 1.19- and 1.39-fold more active, respectively (**3e-g**). Nevertheless, when R^1 is a 4-hydroxypheyl there is not inhibition with a EWG as 4-NO_2 in R^2 (**3j**), whereas an EDG as 2-OH in R^2 (**3k**) show 0.83-fold less inhibition that acarbose. These results suggest that aryl imines substituted in R^2 and R^1 by EWG and weak EDG could be more active against αA.

On the other hand, all the synthetic imines behave as reducing agents over the DPPH• radical, the **3d** and **3f** compounds behave as the best antioxidants (Table 4). Based on the structure-

antioxidant activity relationship, the antioxidant activity can be related with the substitution on the aromatic ring; i.e., if R^1 is a non-aromatic ring (**3b**, **3i** and **3l**) or 2-pyridyl, the antioxidant activity increased with a EWG as substituent in the R^2 position. The compound **3f** displayed the best DPPH activity (13.130 ± 2.990%) at 100 μg mL^{-1} being 1.51-, 2.75- and 2.91-fold better than **3d**, **3i** and **3l**, respectively. However, all the synthesized aryl imines show poor antioxidant activity (IC_{50} >100 μg mL^{-1}) compared with vitamin C (IC_{50}= 8.79 μg mL^{-1}) or gallic acid (IC_{50}= 4.08 μg mL^{-1}).

2.3 Molecular docking studies

All the synthetic aryl imines (**3a-l**) were analyzed by molecular docking studies in order to find the binding interactions in the active pocket site of the enzyme. The X-ray structures of human pancreatic α-amylase (αA, pdb code: 5E0F) and human lysosomal acid-α-glucosidase (αG, pdb code: 5NN8) was selected as template for this purpose. The aryl imines (**3a-l**) docked within αA displayed the binding energies (ΔG_b) in the range of -5.82 at -7.37 kcal mol^{-1} being better than acarbose (-5.45 kcal mol^{-1}). The molecular docking analysis exhibited several interactions between the inhibitors and the αA upon binding in the active site residues. The binding energies calculated through the docking studies do not always show the biological response observed in the *in vitro* tests, the ligand-enzyme interactions could be used as a guide for the design of new drugs. In this sense, the compound **3d** which exhibit the highest *in vitro* activity against αA (IC_{50}= 28.53 μg mL^{-1}) is bound into the receptor site via a hydrophilic interaction establishing a H-bond between NO···H-N of Lys200 (2.58 Å, 111.9º) (Figure 1a). Other interactions result from other groups in the molecule, as the electrostatic interaction with the catalytic amino acid Glu233 (4.37 Å). Similarly, the

enzyme-ligand (E-L) complex for the active compounds **3e-g** are stabilized by H-bonds between the oxygen (NO_2) of the R^2-substituent with Lys200. In addition, they show other interactions that stabilize the E-L complex, as the electrostatic interaction with the catalytic amino acids Glu233. If the *in vitro* activities of compounds **3e-g** are observed, the docking studies reveals the lack of the H-bond with Ile235 as a probable cause of the decrease in the activity. Also, the docking parameters display the order **3e** > **3g > 3f**, suggesting a good approximation between the docking studies with the *in vitro* assay. The best docking parameters are exhibit when R^2 is a EWG, as is shown by the **3b** and **3i** activity. The same effect is observe for the aryl amines **3c** and **3d**. The docking studies against αA show the aryl amines **3a-c** as inactive compounds because of the absence of conventional H-bonds. Nonetheless, when R^1 is phenyl or pyridyl group another type of interactions were observed (T-shaped π-π, π-alkyl, π-sigma and stacked π-π). The molecular docking study revealed that all active compounds docked into the αA mainly display a H-bond with the oxygen of the R^2-subtituent, while the R^1-subtituent mainly exhibit hydrophobic interactions (T-shaped π-π, π-alkyl, π-sigma, alkyl and stacked π-π) and the substitution in R^1 with weak EDG leads to the best docking parameters.

On the other hand, the aryl imines (**3a-k**) docked within α-glucosidase displayed the binding energies (ΔG_b) in the range of -5.26 at -6.22 kcal mol^{-1} being better than acarbose (-4.42 kcal mol^{-1}). The aryl amines **3a** and **3c** displayed the highest *in vitro* activity against αG (IC_{50}= 25.37 and 24.02 μg mL^{-1}, respectively). Besides, the molecular docking against αG reveals that only compound **3c** (ΔG_b = -5.26 kcal mol^{-1}) form the interaction C=N···H-O of Ser676 (1.91 Å, 163.4º) and a hydrophobic interaction between ring B with Ser676 (3.36 Å). Otherwise, the aryl amine **3d** (ΔG_b = -6.19 kcal mol^{-1}) shows a similar activity than acarbose

against αG and αA enzymes, and it interacts in same binding site. Hence, the docking studies for **3d** in αG exhibited the interaction NO···H-N of Arg600 (2.01 Å, 141.2º) and a C-H bond with Arg600 (3.18 Å), an electrostatic (ring B···O of Asp616 at 3.55 Å) and hydrophobic interactions (T-shaped π- π with Trp376 and Phe649) (Figure 1b).

The enzyme-ligand (E-L) complex for the active compounds **3e-g** and **3i** are stabilized by H-bonds between NO···H-N of Arg600 similar to compound **3d**. In addition, they show other interaction that stabilize the E-L complex as electrostatic (ring B with Asp616), hydrophobic (T-shaped π-π with Trp376 and Phe649) and a C-H-O (NO···H-C of Arg600) interactions. The molecular docking studies in αG revealed, as in αA, that aryl imines mainly displayed H-bond in the R^2-subtituent and hydrophobic interactions on R^1-subtituent. In general, the docking studies show the interaction of these synthetic aryl imines **3d-i** in the same active pocket site that acarbose drug in α-glucosidase and α-amylase enzymes.

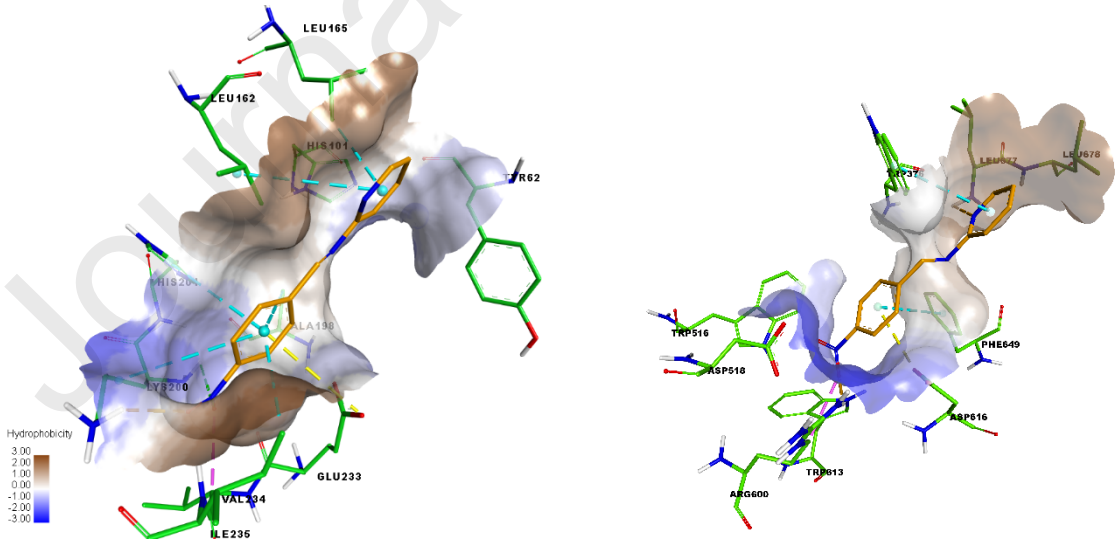


Figure 1. Putative binding interactions of compound **3d** against α-amylase (left) and α-glucosidase (right). Hydrogen, carbon Hydrogen, electrostatic and hydrophobic bonds are shown as orange, pink, yellow and blue pale dashed line. The atoms of nitrogen, polar hydrogen and oxygen are represented in blue, white and red, respectively.

3. Conclusion

An easy, efficient and ecofriendly approach for the synthesis for aryl imines using ASA as heterogeneous catalyst under microwave solvent-free conditions was developed. This approach affords aryl imines in short time using a simple workup procedure, avoiding purification methods for the final products. The molecular docking results encourage us to the design of novel aryl imines with potential antidiabetic activities and with better efficiency and selectivity. According with the results in the *in vitro* tests and the molecular docking studies, the aryl imines **3d**, **3f**, and **3i** have potential for *in vivo* antidiabetic evaluations.

4. Experimental

4.1 Chemistry

All reagents were purchased in the highest quality available and were used without further purification. Nuclear Magnetic Resonance of ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a Bruker 400 MHz Spectrometer in DMSO-d_6 with TMS as internal standard. Chemical Ionization Mass spectra were obtained at a GC-MS Agilent 7890B with ion trap, and the intensities were reported as a percentage relative to the base peak after the corresponding *m/z* value. Melting points were obtained on a Stuart apparatus model SMP30 (calibrated before use with phenolphthalein) and were uncorrected. The values are report as an average of three separated experiments. All reactions described herein were conducted in Pyrex tubes sealed with a silicon septum in a single-mode microwave reactor (Discover-SP model 909150 equipped with an Explorer 12 hybrid model 909505, with 725 W of maximum power, CEM Corp.) with 100 W of initial power.

Preparation of alumina-sulfuric acid

Alumina-sulfuric acid was prepared following the same methodology reported by Pramanik *et al.* [38] The concentration of H^+ on alumina-sulfuric acid for this procedure is $3x10^{-4}$ mol g^{-1}.

General procedure for the Imines synthesis

To a microwave reactor vessel (10 mL) was added an aldehyde (1.0 mmol), a primary amine (1.1 mmol) and alumina-sulfuric acid (100 mg). Mixture was heated at 120 ºC for 10 min, and then cooled to room temperature. The resulting mixture was filtered using methanol (5 mL), ethyl acetate or DCM and concentrated under vacuum. The solid formed was washed with diethyl ether (2 x 2 mL) and imines were obtained. Characterization data are similar to those reported in the literature.

(*E*)-*N*,1-diphenylmethanimine (3a). lit. [39,40]; yield 94%; Pale yellow solid; ^{1}H-NMR (400 MHz, *DMSO-d_6*): δ 8.63 (s, 1H, imidic H), 7.94 (m, 2H, ArH), 7.53 (m, 3H, ArH), 7.43 (dd, 2H, *J* = 7.3, 6.8 Hz, ArH), 7.29 (m, 3H, ArH); ^{13}C-NMR (100 MHz, *DMSO-d_6*): δ 160.5 (CH, imidic), 151.3 (C-N, Ar), 139.5 (C, Ar), 131.4 (CH, Ar), 129.1(2xCH, Ar), 129.0 (2xCH, Ar), 128.8 (2xCH, Ar), 125.9(CH, Ar), 120.9 (2xCH, Ar). GC-MS (CI) *m/z*: 182 $[M+H]^+$. **(*E*)-*N*-cyclohexyl-1-phenylmethanimine (3b).** lit. [9]; yield 37%; white solid; ^{1}H-NMR (400 MHz, *DMSO-d_6*): δ 8.36 (s, 1H, iminic H), 7.87 (d, *J* = 6.1 Hz, 1H, ArH), 7.71 (m, 1H, ArH), 7.40 (m, 3H, ArH), 3.21 (m, 1H, CH-N), 1.52 (m, 10H, -CH_2); ^{13}C-NMR (100 MHz, *DMSO-d_6*): δ 158.2 (CH, imidic), 136.6 (C, Ar), 130.3 (CH, Ar), 128.5 (2xCH, Ar), 127.7 (2xCH, Ar), 68.5 (CH-N), 34.0 (2xCH_2), 25.2 (CH_2), 24.1 (2xCH_2). GC-MS (CI) *m/z*: 188 $[M+H]^+$.

(*E*)-1-phenyl-*N*-(pyridin-2-yl)methanimine (3c). lit. [41]; yield 40%; white solid; ^{1}H-NMR (400 MHz, *DMSO-d*$_6$): δ 9.17 (s, 1H, iminic H), 8.51 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H, Py-H), 7.92 (dd, *J* = 6.8, 1.2 Hz, 2H, ArH), 7.72 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H, Py-H), 7.54 (m, 3H, ArH), 7.38 (dd, *J* = 8.4, 1.8 Hz, 1H, Py-H), 7.25 (dd, *J* = 7.3, 1.22 Hz, 1H, Py-H); ^{13}C-NMR (100 MHz, *DMSO-d*$_6$): δ 162.5 (CH, imidic), 160.4 (C-N, Py), 148.7 (CH-N, Py), 138.4 (CH, Py), 135.5 (C, Ar), 132.0 (CH, Ar), 129.2 (2xCH, Ar), 128.8 (2xCH, Ar), 122.1 (CH, Py), 119.3 (CH, Py). GC-MS (CI) *m/z*: 183 $[M+H]^+$.

(*E*)-1-(4-nitrophenyl)-*N*-(pyridin-2-yl)methanimine (3d). lit. [41]; yield 54%; pale yellow solid; ^{1}H-NMR (400 MHz, *DMSO-d*$_6$): δ 9.33 (s, 1H, iminic H), 8.54 (dd, *J* = 4.9, 1.2 Hz, 1H, Py-H), 8.24 (dd, *J* = 8.8, 4.1 Hz, 2H, ArH), 8.17 (dd, *J* = 8.8, 4.1 Hz, 2H, ArH), 7.74 (d, *J* = 9.1 Hz, 1H, Py-H), 7.71 (ddd, *J* = 8.5, 6.9, 1.9 Hz, 2H, Py-H);); ^{13}C-NMR (100 MHz, *DMSO-d*$_6$): δ 160.8 (CH, imidic), 159.7 (C-N, Py), 150.4 (C-NO_2, Ar), 148.9 (CH-N, Py), 146.6 (C, Ar), 140.1 (CH, Py), 130.6 (2xCH, Ar), 124.2 (2xCH, Ar), 123.3 (CH, Py), 120.0 (CH, Py). GC-MS (CI) *m/z*: 228 $[M+H]^+$.

(*E*)-1-(4-nitrophenyl)-*N*-(*o*-tolyl)methanimine (3e). lit. [42]; yield 82%; yellow crystals; ^{1}H-NMR (400 MHz, *CDCl*$_3$-*d*): δ 8.47 (s, 1H, iminic H), 8.32 (d, *J* = 8.6 Hz, 2H, ArH), 8.08 (d, *J* = 8.6 Hz, 2H, ArH), 7.21 (m, 3H, ArH), 6.96 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 2.39 (s, 3H, -CH_3); ^{13}C-NMR (400 MHz, *CDCl*$_3$-*d*): δ 156.4 (CH=N), 149.9 (C-N, Ar), 149.2 (C-NO_2, Ar), 141.8 (C-CH_3, Ar), 132.6 (C-CH, Ar), 130.5 (2xCH, Ar), 129.3 (2xCH, Ar), 126.8 (CH, Ar), 124.0 (2xCH, Ar), 117.1 (CH, Ar), 17.8 (-CH_3). GC-MS (CI) *m/z*: 241 $[M+H]^+$.

(*E*)-1-(4-nitrophenyl)-*N*-(*m*-tolyl)methanimine (3f). lit. [43]; yield 63%; yellow crystals; ^{1}H-NMR (400 MHz, *CDCl*$_3$-*d*): δ 8.47 (s, 1H, iminic H), 8.32 (d, *J* = 8.6 Hz, 2H, ArH), 8.08 (d, *J* = 8.6 Hz, 2H, ArH), 7.22 (m, 3H, ArH), 6.97 (dd, *J* = 7.6, 1.5 Hz, 1H, ArH), 2.39 (s,

3H, -CH_3); ^{13}C-NMR (100 MHz, *CDCl$_3$-d*): δ 156.4 (CH, imidic), 149.9 (C-NO_2, Ar), 149.3 (C-N, Ar), 141.8 (2xC, Ar), 132.6 (CH, Ar), 130.6 (CH, Ar), 129.3 (2xCH, Ar), 126.8 (CH, Ar), 124.0 (2xCH, Ar), 117.2 (CH, Ar), 17.8 (-CH_3). GC-MS (CI) *m/z*: 241 $[M+H]^+$.

(*E*)-*N*-(4-nitrophenyl)-1-(*p*-tolyl)methanimine (3g). lit. [44]; yield 50%; yellow crystals; ^{1}H-NMR (400 MHz, *DMSO-d$_6$*): δ 8.80 (s, 1H, iminic H), 8.34 (dt, *J* = 8.8, 2.2 Hz, 2H, ArH), 8.17 (dt, *J* = 8.8, 2.2 Hz, 1H, ArH), 7.27 (dd, *J* = 8.5, 3.1 Hz, 4H, ArH), 2.34 (s, 3H, -CH_3); ^{13}C-NMR (100 MHz, *CDCl$_3$-d*): δ 157.5 (CH, imidic), 148.6 (C-N, Ar), 147.8 (C-NO_2, Ar), 141.6 (C, Ar), 136.5 (C-CH_3, Ar), 129.7 (2xCH, Ar), 129.4 (2xCH, Ar), 123.9 (2xCH, Ar), 121.2 (2xCH, Ar), 20.5 (-CH_3). GC-MS (CI) *m/z*: 241 $[M+H]^+$.

(*E*)-*N*-(2,6-dimethylphenyl)-1-(4-nitrophenyl)methanimine (3h). lit. [45]; yield 82%; yellow crystals; ^{1}H-NMR (400 MHz, *DMSO-d$_6$*): δ 8.53 (s, 1H, iminic H), 8.39 (d, *J* = 8.8 Hz, 2H, ArH), 8.21 (d, *J* = 9.0 Hz, 2H, ArH), 7.09 (dd, *J* = 7.6, 0.5 Hz, 2H, ArH), 6.98 (t, *J* = 7.1 Hz, 1H, ArH), 2.09 (s, 6H, 2xCH_3); ^{13}C-NMR (100 MHz, *DMSO-d$_6$*): δ 161.7 (CH, imidic), 150.2 (C-N, Ar), 149.0 (C-NO_2, Ar), 141.1 (C, Ar), 129.3 (2xCH, Ar), 127.9 (2xCH, Ar), 126.2 (2xC-CH_3, Ar), 123.9 (2xCH, Ar), 123.9 (CH, Ar), 17.8 (-CH_3). GC-MS (CI) *m/z*: 255 $[M+H]^+$.

(*E*)-*N*-cyclohexyl-1-(4-nitrophenyl)methanimine (3i). lit. [8]; yield 40%; white solid; ^{1}H-NMR (400 MHz, *DMSO-d$_6$*): δ 8.52 (s, 1H, iminic H), 8.28 (d, *J* = 9.0 Hz, 2H, ArH), 7.98 (d, *J* = 9.0 Hz, 2H, ArH), 3.32 (m, 1H, CH-N), 1.75 (m, 6H, CH_2), 1.25 (m, 4H, CH_2); ^{13}C-NMR (100 MHz, *DMSO-d$_6$*): δ 157.9 (CH, imidic), 148.3 (C-NO_2, Ar), 141.9 (C, Ar), 128.7 (2xCH, Ar), 123.8 (2xCH, Ar), 68.5 (CH-N), 33.8 (2xCH_2), 25.1 (CH_2), 23.9 (2xCH_2). GC-MS (CI) *m/z*: 232 $[M+H]^+$.

(*E*)-4-((4-nitrobenzylidene)amino)phenol (3j). lit. [46]; yield 63%; ^{1}H-NMR (400 MHz, *DMSO-d_6*): δ 8.76 (s, 1H, iminico H), 8.30 (d, *J* = 8.8 Hz, 2H, ArH), 8.11 (d, *J* = 8.8 Hz, 2H, ArH), 7.30 (d, *J* = 8.6 Hz, 2H, ArH), 6.84 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, *DMSO-d_6*): δ 157.2 (CH=N, imidico), 154.6 (C-OH, Ar), 148.3 (C-NO2, Ar), 142.1 (C-N, Ar), 141.6 (C, Ar), 129.0 (2xCH, Ar), 123.8 (2xCH, Ar), 123.0 (2xCH, Ar), 115.8 (2xCH, Ar). GC-MS (CI) *m/z*: 243 $[M+H]^+$.

(*E*)-2-(((4-hydroxyphenyl)imino)methyl)phenol (3k). lit. [47]; yield 82%; white solid; ^{1}H-NMR (400 MHz, *DMSO-d_6*): δ 8.85 (s, 1H, iminic H), 7.59 (dd, *J* = 7.7, 1.6 Hz, 1H, ArH), 7.47 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1H, ArH), 7.15 (d, *J* = 8.8 Hz, 1H, ArH), 7.02 (d, *J* = 8.1 Hz, 1H, ArH), 6.97 (t, *J* = 7.6 Hz, 1H, ArH), 6.85 (d, *J* = 8.8 Hz, 2H, ArH). GC-MS (CI) *m/z*: 214 $[M+H]^+$.

(*E*)-1-(4-chlorophenyl)-*N*-cyclohexylmethanimine (3l). lit. [3]; yield 40%; white solid; ^{1}H-NMR (400 MHz, *DMSO-d_6*): δ 8.36 (s, 1H, iminic H), 7.73 (d, *J* = 8.3 Hz, 2H, ArH), 7.49 (d, *J* = 8.3 Hz, 2H, ArH), 3.23 (s, 1H, CH-N), 1.71 (m, 5H, CH_2), 1.37 (m, 5H, CH_2);); ^{13}C-NMR (100 MHz, *DMSO-d_6*): δ 157.1 (CH, imidic), 135.1 (C, Ar), 134.8 (C-Cl, Ar), 129.3 (2xCH, Ar), 128.5 (2xCH, Ar), 68.3 (CH-N), 33.9 (2xCH_2), 25.1 (CH_2), 24.0 (2xCH_2). GC-MS (CI) *m/z*: 221 $[M+H]^+$.

(*E*)-3-((*p*-tolylimino)methyl)phenol (3m). lit. [48]; yield 40%; yellow crystals; ^{1}H-NMR (400 MHz, *$CDCl_3$*): δ 13.35 (s, 1H, OH-phenolic), 8.61 (s, 1H, imidic H), 7.36 (t, 2H, ArH), 7.21 (m, 4H, ArH), 7.01 (d, 1H, *J* = 7.5 Hz, ArH), 6.92 (td, 1H, *J* = 7.4, 1.2 Hz, ArH), 2.37 (s, 3H, -CH_3); ^{13}C-NMR (100 MHz, *$CDCl_3$*): δ 161.6 (CH, imidic), 161.1 (C-OH, Ar), 145.9 (C-N, Ar), 136.8 (CH, Ar), 132.8 (C-CH_3, Ar), 132.1 (C, Ar), 129.9 (2xCH, Ar), 120.9

(2xCH, Ar), 119.3 (CH, Ar), 118.9 (CH, Ar), 117.2 (CH, Ar), 21.0 (-CH_3). GC-MS (CI) *m/z*: 212 $[M+H]^+$.

4.2 *α*-Amylase inhibitory activity

The α-amylase activity of the synthetic quinazoline-2,4(1*H*,3*H*)-diones was assessed as described by Adisakwattana *et al.* with slight modification.[49] Porcine pancreatic α-amylase (EC 3.2.1.1) was dissolved in 0.1 M phosphate buffer at pH 6.9 (concentration of 0.5 mg mL^{-1}). In a 96-well flat-bottom plate, 75 µL of the enzyme solution and 75 µL of quinazoline-2,4(1*H*,3*H*)-diones solution (concentrations of 1, 10, 100, 500, 1000 µg mL^{-1} in methanol) were added. After 10 minutes of incubation at 25 °C, 75 µL of the starch solution (0.1% p/v in 0.1 M phosphate buffer at pH 6.9) was added to start the reaction and the mixture were incubated for 10 minutes at 25 °C. The reaction was stopped by adding 62.5 µL dinitrosalicylic (DNS) reagent (1% 3,5-dinitrosalicylic acid, 0.2% phenol, 0.05% Na_2SO_3 and 1% NaOH in aqueous solution) to the reaction mixture. The mixtures were heated at 100°C for 5 minutes in order to stop the reaction. After cooling to room temperature, the absorbance was recorded at 580 nm using a microplate reader. The α-amylase inhibitory activity was expressed as percentage inhibition and was calculated as follows:

$$\%\ Inhibition = \frac{Abs_{control} - Abs_{samples}}{Abs_{control}} x100$$

Where $Abs_{control}$ was the absorbance without sample, $Abs_{samples}$ was the absorbance of the sample at different concentrations.

4.3 *α*-Glucosidase inhibitory activity

The α-glucosidase (EC 3.2.1.20) activity of the synthetic quinazoline-2,4(1*H*,3*H*)-diones was assessed as described by Kwon *et al.* with slight modification. [50] In a 96-well flat-bottom

plate, 100 µL of the enzyme solution (1 U mL^{-1} in 0.1 M of phosphate buffer at pH 7.0) and 50 µL of quinazoline-2,4(1*H*,3*H*)-diones solution (concentrations of 1, 10, 100, 500, 1000 µg mL^{-1} in methanol) were added. After 10 minutes of incubation at 25 °C, 50 µL of 5 mM *p*-nitro-phenyl-α-D-glucopyranoside solution in 0.1 M phosphate buffer (pH 7.0) was added and the mixture were incubated at 25 °C for 5 minutes. After, the absorbance was recorded at 405 nm using a microplate reader. The α-glucosidase inhibitory activity was expressed as percentage inhibition and was calculated as follows:

$$\%\ Inhibition = \frac{Abs_{control} - Abs_{samples}}{Abs_{control}} x100$$

Where $Abs_{control}$ was the absorbance without sample, $Abs_{samples}$ was the absorbance of the sample at different concentrations.

4.4 DPPH-scavenging Activity

The DPPH• scavenging activities of the imines were assessed as described by Clarke *et. al.* [51] with slight modifications. This method is based on the reduction of DPPH in the presence of antioxidants, the antioxidant activity is detected as a change from purple to yellow color in the solution. In a 96-well flat-bottom plate, 20 µL of the imines (0.1 to 100 µg mL^{-1} in methanol) and 180 µL of DPPH solution (150 µM in methanol) were added. The mixture was shaken, incubated for 20 min at room temperature in darkness conditions, and the absorbance was measured at 532 nm. The DPPH•-scavenging activity of the imines was calculated as follows:

$$DPPH - scavenging\ effect\ (\%) = \frac{A_0 - A_1}{A_0} x100$$

Where: A_0 was the absorbance of control; and A_1 was the absorbance in the presence of the imines. Vitamin C and gallic acid were used as standard (0.1 to 10 μg mL^{-1}). Calculated values corresponded to the mean ± standard deviation of two experiment by triplicate and were determined by GraphPad Prism V6 software.

4.5 Molecular docking [52–54]

The automated molecular docking studies were carried out using AutoDock Tool v1.5.6 and were guided to active site of the enzyme [55]. First, the aryl imines (ligands) were design using ChemDraw V16 and Spartan V14 was used for 3D optimization using MMFF94s for the optimization to lowest energy geometry including water phase for all ligand. Later, the structures were saved as SYBYL mol2 file format and *Gasteiger* charges were assigned to the ligands. Second, the crystal structure for human pancreatic α-amylase (pdb code: 5E0F) and human lysosomal acid-α-glucosidase (pdb code: 5NN8) was downloaded from RCSB protein data bank. Before of docking calculations, all water molecules, ligands and cations were removed from protein. Later, polar hydrogens and the *Kollman* charges were assigned for the protein. Then, the grid box site was set for human pancreatic α-amylase in -7.946, 10.438 and -21.863 Å (x, y and z) with a grid of 80, 72 and 66 point (x, y and z). For human lysosomal acid-α-glucosidase the grid box site was set at -12.175, -35.415 and 88.753 Å (x, y and z) with a grid of 74, 70 and 90 point (x, y and z) with 0.375 Å spacing. Docking calculations were performed using Lamarckian genetic algorithm for ligands conformational searching. The docking for the ligands consisted of a total of 200 runs that were carried out with a population size of 150 individuals, a maximum of 25 million energies evaluations, a maximum of 270,000 generations, a gene mutation rate of 0.02 and a crossover rate of 0.8.

Cluster analysis was performed on the docked results using a root mean square (RMS) tolerance of 0.5 Å.

The conformation with the lowest binding energy was examined by Accelrys, Discovery Studio Visualizer v17.2.0.16349 [Accelrys Inc., San Diego, CA (2007)] to determine their binding orientations, molecular modeling, evaluation of the hydrogen bonds and other interactions.

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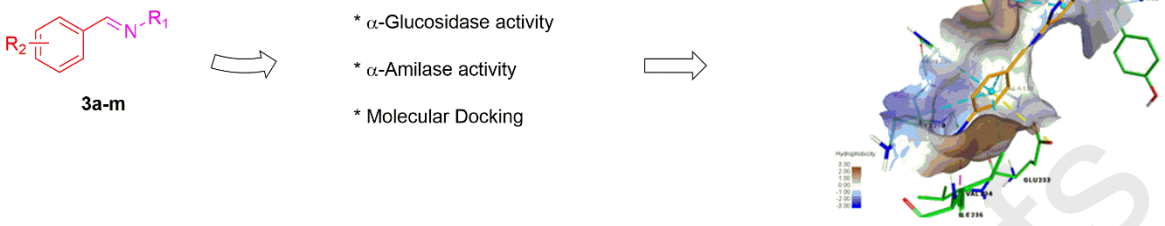
Graphical abstract



Highlights

• Alumina-Sulfuric acid is an efficient catalyst for aryl imines synthesis.

• Aryl imines synthesized displayed significant a-amylase inhibition with IC_{50} values of 28.53 - 126.40 μg mL^{-1}.

• Aryl imines synthesized displayed significant a-glucosidase inhibition with IC_{50} values of 24.02 - 62.16 μg mL^{-1}.

• Molecular docking studies were performed to find the binding interactions at the active pocket site of the enzyme.

Conflict of Interest

November 22th, 2019

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Dear Editor

We confirm that the manuscript entitled " Synthesis and molecular docking studies of imines as α-glucosidase and α-amylase inhibitors" has been read and approved by all authors and that there are no other persons who satisfied the criteria for authorship. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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Moreover, the principal author signing on behalf of all co-authors of the manuscript.

Dr. Juan I. Sarmiento Sánchez
Professor of Engineering School
Autonomous University of Sinaloa
Américas Boulevard, University City
Culiacán, Sinaloa 80040, México
E-mail: jsarmiento@uas.edu.mx