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Synthesis and Molecular Docking studies of Some Tetrahydroimidazo[1,2-a]pyridine Derivatives as Potent α-Glucosidase Inhibitors

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Abstract

$KAl(SO_4)_2.12H_2O$ is found to efficiently and heterogeneously catalyze the one-pot three-component reaction of 2-(nitromethylene)imidazolidine, malononitrile and aldehydes under mild conditions to afford the corresponding tetrahydroimidazo[1,2-a]pyridine in good yields and short reaction times. Docking study of some compounds in the active site of α-glucosidase demonstrated that these compounds interacted with important active site residues with low binding energy in comparison to standard inhibitor acarbose.

Keywords: *Alum,Three-component reactions, Tetrahydroimidazo[1,2-a]pyridine, Molecular docking studies, α-glucosidase.*

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Introduction

Imidazo[1,2-a]pyridine is among important heterocyclic compounds with diverse biological properties, including antitumoral [1], antiviral [2], anti-ulcer [3], anti-inflammatory [4], antiprotozoal [5], antibacterial [6], antifungal [7], antitumor [8], and antiretroviral activities [9], and are also the core structures of many synthetic pharmaceuticals. In addition, tetrahydroimidazo[1,2-a]pyridines (THPs) have been reported as starting materials for the total synthesis of various drugs such as soraprazan, alpidem (a nonsedative anxiolytic), the PDE 3 inhibitor olprinone, and the sedative zolpidem [10-12].Several ameliorated procedures for the preparation of THPs and their derivatives [13-16] have been reported. Recently, many other methods indicate the use of Lewis acids [17, 18], protic acid (TFA) [19], or base ($NaHCO_3$) [20], piperidine (three-component reaction, 4h) [21], andpiperidine (four-component reaction, 12-14h)[22]for the synthesis of THPs.

Multi-component reactions (MCR) constitute a particularly attractive synthetic strategy for the preparation of highly functionalized organic compounds and important heterocycles for biological, pharmaceutical, and industrial applications in one-pot, a suitable, and atom-economical way [23-28]. Inhibition of α-glucosidase is a reliable approach for controlling post-prandial hyperglycemia in type 2 diabetes. Recently, compounds **A** and **B** with high inhibitory activity against α-glucosidase have been reported [29, 30].

Very recently, we reported the synthesis of *cis*-isoquinolinic acids [31], triamide [32], tetrahydropyridine [33], spirocyclopropane [34], and bis(quinazolinon-4(1*H*)-one) [35] all *via* multicomponent condensation. Moreover, we have designed the three-component one-step synthesis of tetrahydroimidazo[1,2-a]pyridines. In this direction, the use of alum, which is relatively nontoxic, inexpensive, and easily available is the center of our study [36, 37]. Due to the similarity of these compounds to α-glucosidase inhibitors A and B, some of tetrahydroimidazo[1,2-a]pyridine derivatives were studied in the active site of this enzyme by molecular modeling.

Experimental

*General procedure for the preparation of Tetrahydroimidazo[1,2-a]pyridine **4***

A mixture of ethylene 2-(nitromethylene)imidazolidine (1 mmol) **1**, malononitrile **2** (1 mmol), benzaldehyde **3**, alum (0.3 mmol, 0.15 g) and 10 mL EtOH in a 50 mL flask was stirred and refluxed for 130 minutes. After the completion of the reaction (monitored by TLC, ethylacetate/*n*-hexane, 4:1), the reaction mixture was allowed to cool down to room temperature, then the resulting solid was separated by filtration. Water (20 mL) was added to the resulting solid (for the separation of alum), the precipitates were filtered and washed with ethanol to give product **4**.

Docking study

Docking studyof some compounds was performed according to M. Adib et al work [38]

Spectral data for selected new products

5-amino-8-nitro-7-(3-nitrophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4i**)

Yield 88%. Yellow solid. MP: 248-250(dec). IR (KBr) (ν_{max}/cm^{-1}) 3406, 3365, 3203, 2183, 1656. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.81-3.83 (m, 2H, CH_2); 3.96-4.08 (m, 2H, CH_2); 4.83 (s, 1H, CH); 6.65 (s, 2H, NH_2); 7.58-7.73 (m, 2H, Ar); 8.0-8.10 (m, 2H, Ar); 9.61 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*) δc (ppm) 41.2; 43.8; 45.1; 58.3; 105.4; 121.1; 121.8; 122.1; 130.2; 134.5; 147.7; 148.1; 150.1; 151.9. MS (EI, 70 eV) *m/z*: 328 (M^+). Anal.Calcd for $C_{14}H_{12}N_6O_4$: C, 51.22; H, 3.68; N, 25.60%. Found: C, 51.10; H, 3.51; N, 25.45 %.

5-amino-7-(3,4-dichlorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4j**)

Yield 90%. Yellow solid. MP: 210-212. IR (KBr) (ν_{max}/cm^{-1}) 3429, 3348, 3241, 2177, 1659. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.79-3.85 (m, 2H, CH_2); 3.94-4.08 (m, 2H, CH_2); 4.66 (s, 1H, CH); 6.60 (s, 2H, NH_2);7.19-7.23 (m, 1H, arom); 7.43-7.44 (d, 1H, *J*=3 Hz, Ar); 7.53-7.56 (d, 1H, *J*=9 Hz, Ar); 9.57 (s,1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*) δc (ppm) 40.8; 43.8; 45.1; 58.4; 105.4; 121.2; 128.1; 129.4; 129.4; 130.7; 131.1; 145.6; 149.9; 151.9. MS (EI, 70 eV) *m/z*: 351(M^+), 353(M^{+2}). Anal.Calcd for $C_{14}H_{11}Cl_2N_5O_2$: C, 47.75; H, 3.15; N, 19.89%. Found: C, 47.61; H, 3.01; N, 19.73 %.

5-amino-7-(4-cyanophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4k**)

Yield 74%. Yellow solid. MP: 225-227(dec). IR (KBr) (ν_{max}/cm^{-1}) 3438, 3345, 3234, 2229, 2176, 1657. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.79-3.85 (m, 2H, CH_2); 3.94-4.05 (m, 2H, CH_2); 4.71 (s, 1H, CH); 6.61 (s, 2H, NH_2);7.39-7.41 (d, 2H, *J*=6 Hz Ar); 7.75-7.77 (d, 2H, *J*=6 Hz, Ar); 9.58 (s,1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*) δc (ppm) 41.5; 43.8; 45.1; 58.3; 105.3; 109.6; 119.4; 121.1; 128.5; 132.7; 150.0; 151.0; 152.0. MS (EI, 70 eV) *m/z*: 308 (M^+). Anal.Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92; N, 27.26%. Found: C, 58.30; H, 3.76; N, 27.08 %.

5-amino-7-(3-bromophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4l**)

Yield 72%. Yellow solid. MP: 208-210. IR (KBr) (ν_{max}/cm^{-1}) 3449, 3335, 3198, 2186, 1653. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.79-3.85 (m, 2H, CH_2); 3.93-4.09 (m, 2H, CH_2); 4.63 (s, 1H, CH); 6.57 (s, 2H, NH_2); 7.19-7.43 (m, 4H, Ar); 9.55 (s,1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*)

δc (ppm) 41.1; 43.7; 45.1; 58.8; 105.6; 121.2; 121.9; 126.7; 129.8; 130.0; 130.8; 148.2; 149.9; 151.9. MS (EI, 70 eV) *m/z*: 361(M^+), 363(M^{+2}). Anal.Calcd for $C_{14}H_{12}BrN_5O_2$: C, 46.43; H, 3.34; N, 19.34%. Found: C, 46.25; H, 3.20; N, 19.17 %.

5-amino-8-nitro-7-(2-nitrophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4m**)

Yield 92%. Yellow solid. MP: 220-222(dec). IR (KBr) (ν_{max}/cm^{-1}) 3461, 3352, 2186, 1653. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.79– 3.85 (m, 2H, CH_2); 4.01-4.08 (m, 2H, CH_2); 5.42 (s, 1H, CH); 6.67 (s, 2H, NH_2);7.40-7.80 (m, 4H, Ar); 9.55 (s,1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*) δc (ppm) 35.4; 43.8; 45.1; 57.7; 106.4; 120.7; 123.5; 128.1; 130.7; 133.7; 139.9; 149.6; 150.7; 151.6. MS (EI, 70 eV) *m/z*: 328 (M^+). Anal.Calcd for $C_{14}H_{12}N_6O_4$: C, 51.22; H, 3.68; N, 25.60%. Found: C, 51.05; H, 3.55; N, 25.46 %.

5-amino-7-(2-chlorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4n**)

Yield 77%. Yellow solid. MP: 270-272(dec). IR (KBr) (ν_{max}/cm^{-1}) 3450, 3337, 3198, 2188, 1657. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.80-3.86 (m, 2H, CH_2); 4.0-4.06 (m, 2H, CH_2); 5.16 (s, 1H, CH); 6.52 (s, 2H, NH_2); 7.17-7.43 (m, 4H, Ar); 9.55 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*) δc (ppm) 38.6; 43.7; 45.1; 58.1; 105.6; 120.9; 127.7; 128.4; 129.6; 130.2; 132.5; 142.6; 150.0; 152.2. MS (EI, 70 eV) *m/z*: 317(M^+), 319(M^{+2}). Anal.Calcd for $C_{14}H_{12}ClN_5O_2$: C, 52.92; H, 3.81; 11.16; N, 22.04%. Found: C, 52.78; H, 3.63; N, 21.86 %.

5-amino-7-(2,6-dichlorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4o**)

Yield 86%. Yellow solid. MP: 235-237(dec). IR (KBr) (ν_{max}/cm^{-1}) 3468, 3337, 3196, 2181, 1656. ^{1}H NMR (300MHz, DMS-*d*$_6$) δ_H (ppm) 3.79-3.86 (m, 2H, CH_2); 3.96-4.15 (m, 2H, CH_2); 5.71 (s, 1H, CH); 6.59 (s, 2H, NH_2); 7.20-7.44 (m, 3H, Ar); 9.61 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-*d6*) δc (ppm) 37.8; 43.7; 44.9; 55.1; 104.1; 120.5; 128.7; 129.0; 130.5; 134.2; 136.4; 137.2; 150.8; 152.8. MS (EI, 70 eV) *m/z*: 351(M^+), 353(M^{+2}). Anal.Calcd for $C_{14}H_{11}Cl_2N_5O_2$: C, 47.75; H, 3.15; N, 19.89%. Found: C, 47.56; H, 2.99; N, 19.72 %.

Results and discussion

When a mixture of ethylene2-(nitromethylene)imidazolidine **1**, malononitrile **2,** and benzaldehyde **3a** in ethanol was stirred and refluxed in the presence of a catalytic amount of 0.15 g alum, the reaction was completed within 130 min. studying the reaction mixture showed that DHP **4a** was prepared in 88% yield. (Scheme 1) The product **4a** structural features were characterized using IR,

^{1}H NMR, ^{13}C NMR, MS spectra and elemental analyses. Considering this successful synthesis, we developed the reaction of ethylene2-(nitromethylene)imidazolidine **1,** andmalononitrile **2,** with a range of otheraldehydes **3**, under similar conditions, obtaining the respective tetrahydroimidazo[1,2-a]pyridines **4b**-**o** in good yields. The optimized conditions are summarized in Table 1.

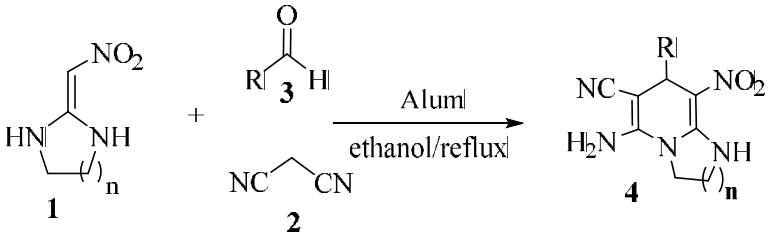
Table 1: Comparing the effect of different amounts of catalyst on the time and yield of the reaction of 2-(nitromethylene)imidazolidine **1** (1mmol), malononitrile **2** (1mmol), benzaldehyde **3a** (1mmol)to obtain 5-amino-8-nitro-7-phenyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbonitrile (**4a**).

Entry[a]	**Catalyst(g)**	**Time(min)**	**Yield(%)**
1	0.09g	130	77
2	0.12g	130	84
3	0.15g	130	88
4	0.18g	130	88
5	0.21	130	85
6	0.25	130	83

[a]For all the reactions, the catalyst is $KAl(SO_4)_2.12H_2O$, ethanol is used as the solvent, reflux at 50 mL flask.

As it can be seen in Table 1, 1 mmol of each reagent with 0.09g alum in 10 mL EtOH in a 50 mL flask was stirred at reflux for 130 min, which resulted in a 77% yield (Entry1). Increasing the amount of catalyst up 0.15 g improved the yield (Entry 2-6). Reaction conditions of entry 3 afforded compound 4with a synthetically useful yield in the same amount of time. Following the same pattern, fifteen other compounds were synthesized using the optimum conditions (Table 2 providing considerable yields (82%-94%)).

Table 2. The reaction of diaminal **1**, malononitrile **2**, and benzaldehyde **3** for the synthesis of tetrahydroimidazo[1,2-a]pyridine **4.**



products [a]	R	n	Time (min)	Yield (%)[b]	AE[c]	Mp (°C)	Lit. mp (°C)
4a	Ph	1	130	88	94.0	178-180	180[22]
4b	4-ClC_6H_4	1	140	85	94.6	270-272(dec)	270(dec)[22]
4c	4-BrC_6H_4	1	140	85	95.3	246-248(dec)	245-246(dec)[21]
4d	4-$NO_2C_6H_4$	1	120	86	94.8	246-248(dec)	244(dec) [22]
4e	Ph	2	140	84	94.3	246-248(dec)	247(dec) [22]
4f	4-ClC_6H_4	2	140	83	94.8	266-268(dec)	267(dec) [22]
4g	4-$NO_2C_6H_4$	2	130	85	95	226-228(dec)	225-226(dec)[21]
4h	4-BrC6H4	2	140	82	95.4	248-250(dec)	249-250(dec)[21]
4i	3-$NO_2C_6H_4$	1	120	88	94.8	248-250(dec)	-
4j	3,4-diClC_6H_3	1	110	92	96.2	210-212	-
4k	4-CNC_6H_4	1	120	84	94.5	225-227(dec)	-
4l	3-BrC_6H_4	1	140	85	95.3	208-210	-
4m	2-$NO_2C_6H_4$	1	110	94	94.8	220-222(dec)	-
4n	2-ClC_6H_4	1	130	87	94.6	270-272(dec)	-
4o	2,6-diClC_6H_3	1	130	92	96.2	235-237(dec)	-

[a]Reaction conditions: diaminal (1 mmol) , malononitrile (1 mmol), benzaldehyde, alum (0.3 mmol), 10 mL EtOH, reflux, [b]Yields based on aldehyde.[c]Atom-economic.

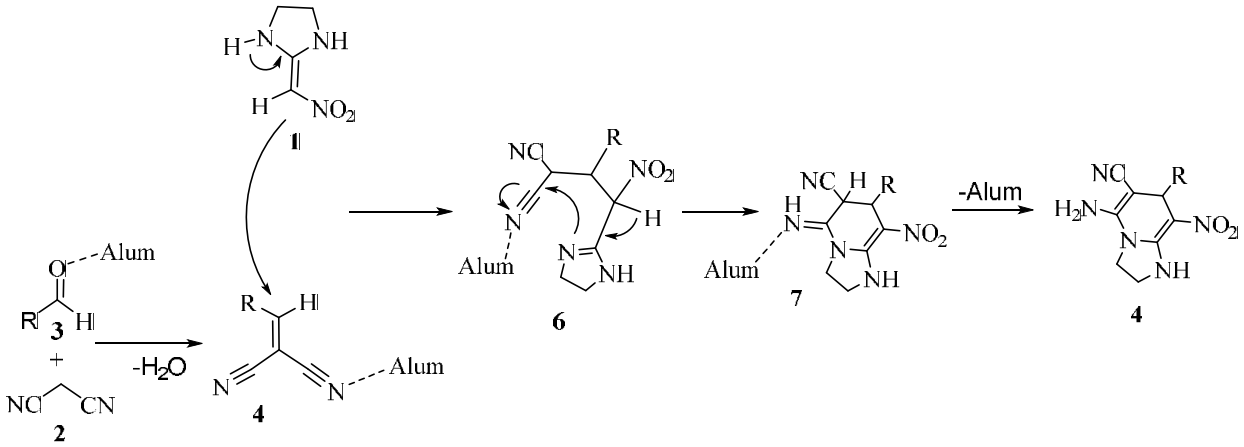
Interestingly, the heterogeneous catalyst was not deactivated and could be reused several times. Five consecutive runs of the reaction of 2-(nitromethylene)imidazolidine, malononitrile, and benzaldehyde with Alum were carried out (Table 3).

Table 3. Time and yield of the reaction for five consecutive runs in the reaction of 2-(nitromethylene)imidazolidine, malononitrile andbenzaldehyde with Alum.

Entry	Catalyst(g)	Time(min)	Yield(%)
1	0.15g	130	88
2	0.15g	130	88
3	0.15g	130	87
4	0.15g	130	86
5	0.15g	130	85

The results demonstrate that there is almost no significant change in the activity of the catalyst, so it could be used for at least five times successfully leading to high turn-over numbers (TONs).

A plausible mechanism for the synthesis of the product is shown in Scheme 1. It is conceivable that the reaction involves an initial formation of compound **4***via* knovenagel reaction between malononitrile **2** and aldehydes **3.** Thereaction of ketene diaminal **1** with compound **4** gives intermediate **6***via* Michael reaction. Then intermediate **6** would dehydrate spontaneously to give product **4**.



Scheme 1. Proposed mechanism for the formation of products **4a-o.**

As explained before, compounds A and B, with structural similarity to compounds 4a-o, exhibit high inhibitory activity against α-glucosidase. Therefore, we performed molecular modeling study of compounds **4a**, **4b** and **4k** in the active site of α-glucosidase to investigate their potent inhibitory activity (Figure 1).

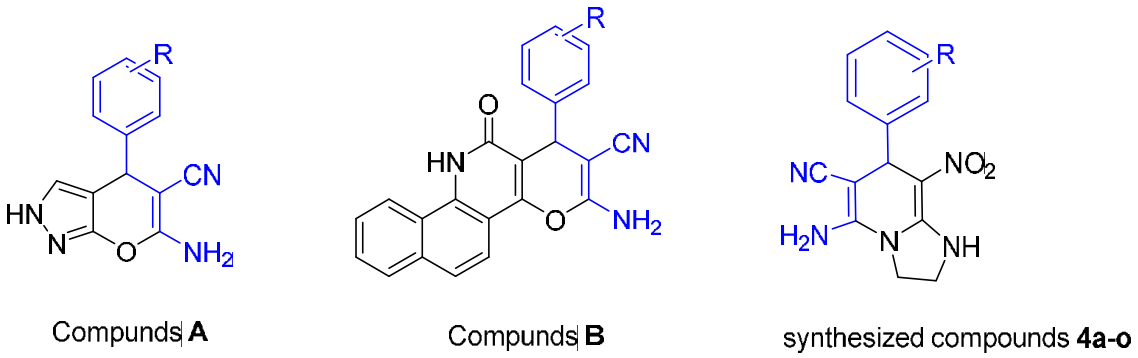
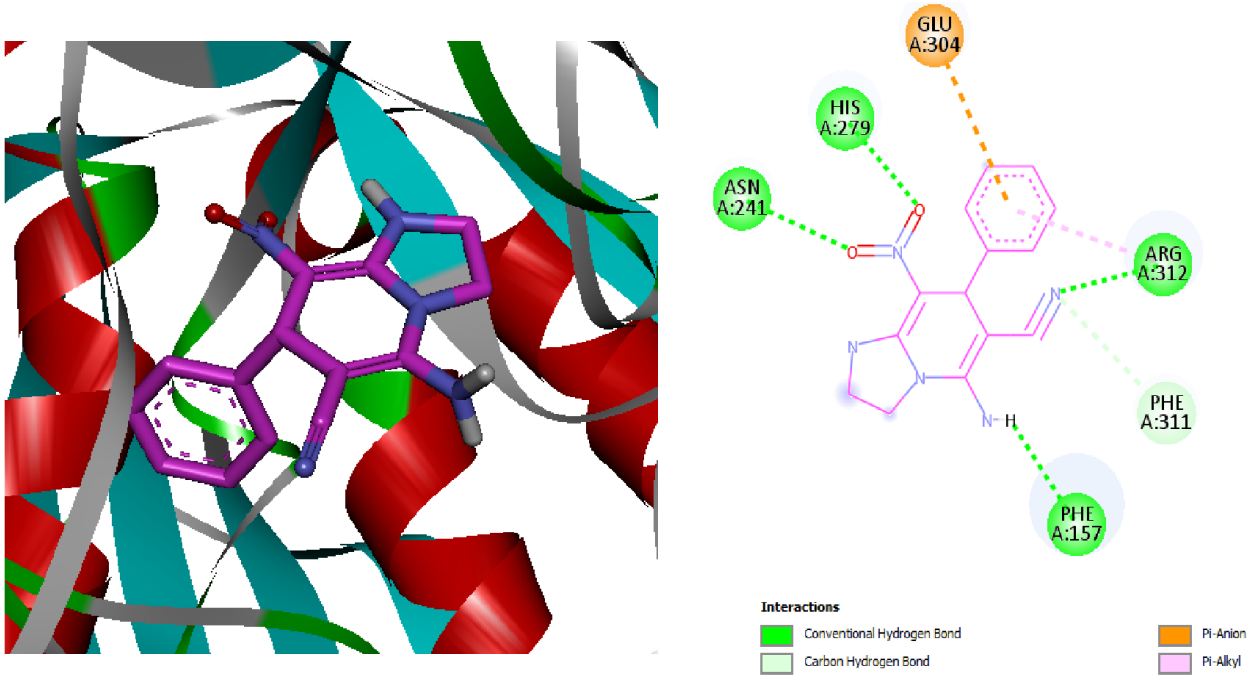


Figure 1. The similarity of synthesized compounds with compounds A and B.

Docking study of standard α-glucosidase inhibitor acarbose demonstrated that this drug with binding energy = -4.04 kcal/mol interacted with amino acids Asn241, His279, Thr301, Glu304, Thr307, Pro309, Ser308, Arg312, and Gln322 in the α-glucosidase active site.Docking study of un-substituted compound **4a** in the active site of α-glucosidase demonstrated that this compound interacted with important amino acids Asn241, His279, and Arg312 *via* hydrogen bond [38]. Arg312 also established a hydrophobic interaction with pendant phenyl ring. The latter ring also formed a π-anion interaction with Glu304. Furthermore, this compound formed a classic hydrogen bond with Phe157 and an un-classic hydrogen bond with Phe311. Bonding energy of compound 5a in the active site is -5.32 kcal/mol. This value showed that compound **4a** binds to the target enzyme easier than acarbose.

As can be seen in Figure 2, in 4-chloro derivative **4b** only one additional interaction formed in comparison to the un-substituted compound **4a**. Binding energy of this compound is -6.02 kcal/mol. Figure 2 also shows that the interaction mode of compounds 4a and 4-cyano derivative **4k** are similar while calculation of binding energy of compound **4k** demonstrated that this compound with a binding energy of -6.25 kcal/mol presumably creates stronger interactions with the active site.


GLU
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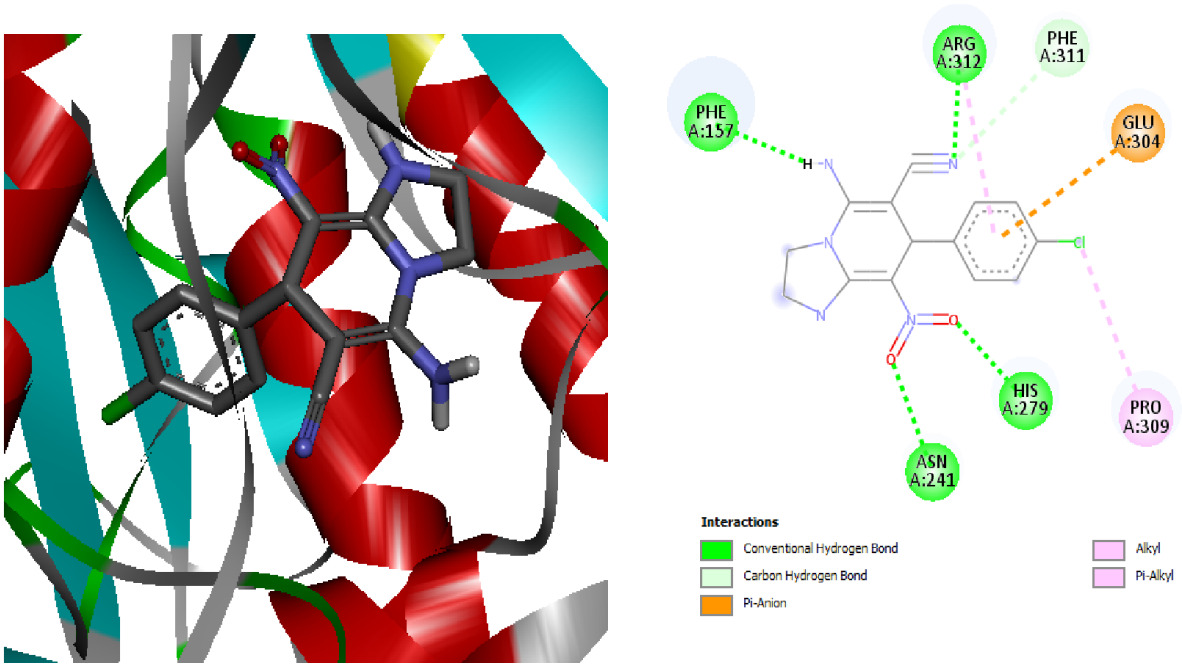
HIS
A:279
ASN
A:241
ARG
A:312
PHE
A:311
PHE
A:157
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Pi-Alkyl

4a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PHE
A:311
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GLU
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HIS
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PRO
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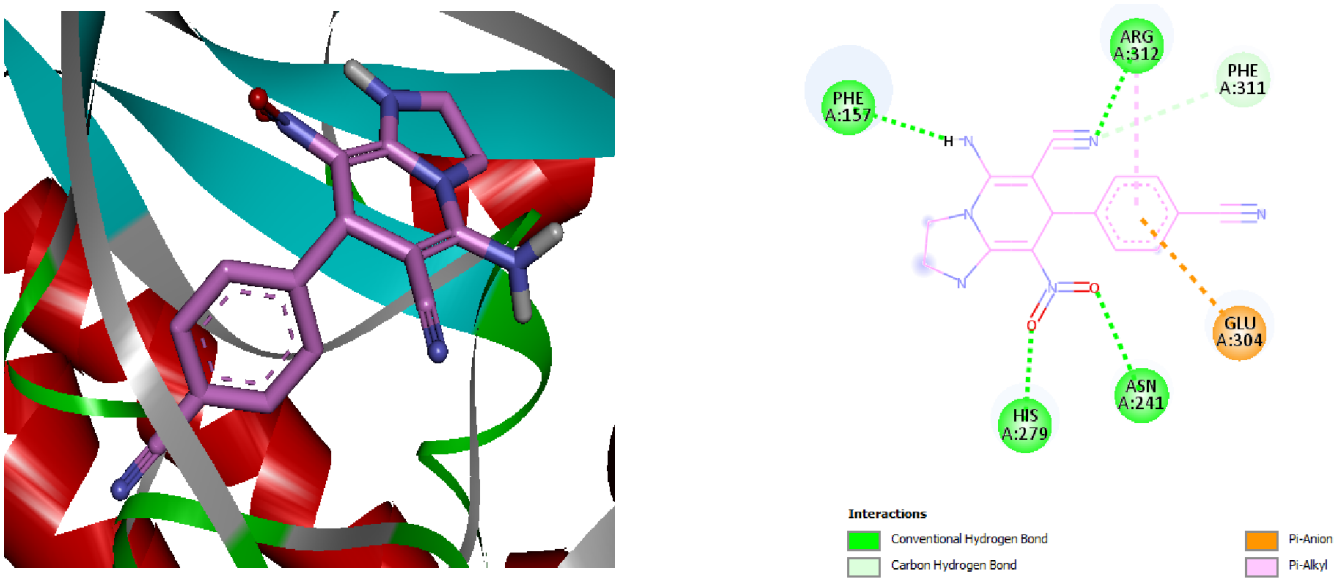
ASN
A:241
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Alkyl
Pi-Alkyl

4b



4k

Figure. 2. Interaction mode of compounds 4a, 4b, and 4k in the active site of α-glucosidase.

Conclusions

To summarize, a successful strategy, an efficient, and simple one-pot three-component synthesis was described for the preparation of tetrahydroimidazo[1,2-a]pyridine *via* cyclocondensation reaction of 2-(nitromethylene)imidazolidine, malononitrile and aldehydes. High yield of products, being atom-economic, and easy experimental procedure are among the several advantages offered by the proposed method. Docking study of these compounds in the active site of α-glucosidase revealed that these compounds could interact with important active site residues Asn241, His279, Arg312, and Glu304. This study also predicted new synthesized compounds with lower binding energies than standard α-glucosidase inhibitor acarbose attached to α-glucosidase active site.

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