

Some novel piperidine analogues having strong alpha glucosidase inhibition

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Abstract: The idea of this study is based on the marvelous fact of nojirimycin and deoxy nojirimycin, naturally occurring from piperidine class and having their role as alpha glucosidase inhibitors. In the present work some hydroxy piperidine analogues have been synthesized and analysed for their hypoglycemic effect through glucosidase inhibition owing to the structural resemblance with nojirimycin. The activity was done by spectral absorbance analysis using acarbose as standard. Two analogues (I & IV) were found to pose excellent activity having 87.4 and 54.7% inhibition respectively, hence strengthening the idea of studying piperidine analogues as glucosidase inhibitors due to structural similarity with nojirimycin.

Keywords: Nojirimycin, Piperidine, Analogues, hypoglycemic, glucosidase.

INTRODUCTION

Disturbance in glucose metabolism is a specific characteristic of diabetes and is manifested by an elevated blood glucose level along with other symptoms (Tominaga *et al.*, 1999; Monnier *et al.*, 2002). The disease is found to be affecting globally millions of population and consequently causing an increased death rate due to inappropriate treatment. Due to diabetes complications of kidneys, eye and neurons have become highly considerable and demand management of diabetes (Wang *et al.* 2005, Chan *et al.*, 2009; Tian *et al.*, 2006). Alpha-glucosidase, a hydrolytic enzyme present in intestinal mucosa, responsible for converting polysaccharides into monosaccharides and as a result enhancing glucose absorption, accordingly causes high blood glucose levels. For treating diabetes α -glucosidase suppression is made a target for delaying sugar digestion and reducing glucose absorption and subsequently postprandial insulin release (Harold *et al.*, 1997; Ye *et al.*, 2002; Tattersall *et al.*, 1993). Consequently the drugs having the ability of alpha-glucosidase inhibition (AGI) prove an excellent remedy for controlling glucose levels in diabetic patients (Truscheit *et al.*, 1981; Tundis, 2010) and drugs like acarbose, voglibose, miglitol are the choice of medicine regarding the management of diabetes type 2 (Braun *et al.*, 1996; Buse *et al.*, 2004). Moreover tremendous fact data reveals that these moieties are also excellent campaigner against HDL and LDL cholesterol and produce declining effect of triglycerides with a subsequent reduction in occurrence of myocardial

infarctions in type 2 diabetic patients (Mughal *et al.*, 2000; Hanefeld *et al.*, 2004). Many naturally occurring molecule have also proven wonderful glucosidase inhibitors. Among this group of compounds, Piperidine occupies an important position and is among the major classes of iminosugars. Deoxynojirimycin and nojirimycin are piperidine ring containing molecules, isolated from both plant and microbial sources. Nojirimycin is an approved glucosidase inhibitor (Asano, 2009; Hanefeld *et al.*, 2008). Thirty synthetic analogues of deoxynojirimycin have been developed. Furthermore a very stereocontrolled synthesis of (+)-1-deoxynojirimycin was carried out to establish the all-trans cyclic triol. Polyhydroxylated piperidines is a group of moieties that has also shown good glucosidase inhibition. Through a hundreds hits and trials moieties having piperidine and pyrrolidine ring, were assessed for their remarkable achievement for controlling the plasma glucose level (Monica *et al.*, 2004). As an outcome a novel candidate series of pyrrolidine-constrained phenethylamines was developed as Dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Sitagliptin and vildagliptin are most important and promising as antidiabetic agents of the series (Mushtaq *et al.*, 2010; Wiedeman, 2003; Richter *et al.*, 2008). A new piperidine derivative 2-hydroxymethyl-3,4,5-trihydroxy-piperidine compounds is proved as a good medicaments for influencing carbohydrate metabolism. *Commelina communis*, a traditional herbal medicine has been used for the treatment of diabetes. Methanolic extract of the herb was found to prove strong candidate for controlling alpha-glucosidase activity. Furthermore due to having promising response various other piperidine analogues

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like 1-deoxymannojirimycin, alpha-homonojirimycin, 1-deoxynojirimycin and 7-O-beta-D-glucopyranosyl alpha-homonojirimycin were fractionated (Kim *et al.*, 1999; Haider *et al.* 2014). The mentioned specifics are credited for the current study, in which different piperidine derivatives were synthesized and evaluated for their alpha glucosidase inhibition.

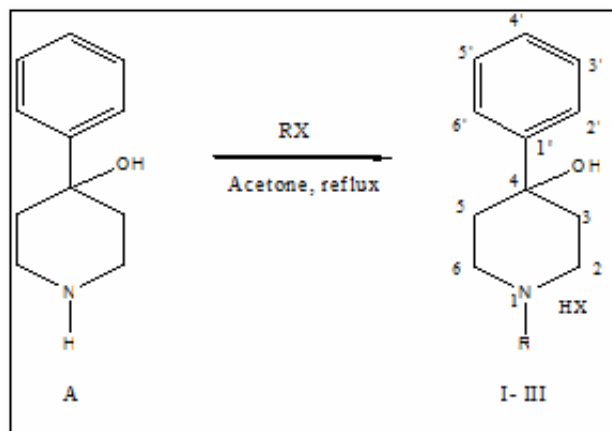


Fig. 1: Reaction method of 4-hydroxy-4-phenyl piperidine derivatives.

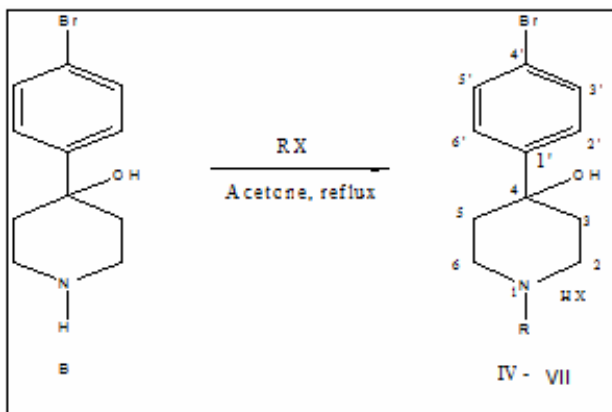


Fig. 2: Reaction method of 4-(4'-Bromophenyl)-4-hydroxy piperidine derivatives

Method

In the present study the analogues of 4-Hydroxy-4-phenyl piperidine, 4-(4'-Bromophenyl)-4-hydroxypiperidine and 4-(4'-Chlorophenyl)-4-hydroxy piperidine were synthesized by reacting with different phenacyl halides according to the designed reaction scheme (tables 1-3, figs. 1-3) and further examined for the antidiabetic activity by alpha glucosidase inhibition.

Alpha glucosidase inhibition

The present activity was done by Spectra Max340 (Molecular Device, USA). Through 96 well micro plate. Alpha Glucosidase enzyme and p-nitrophenyl α-glucopyranoside (PNP-G, as a substrate) were obtained from Sigma (St. Louis, Mo, USA) and E. Merck respectively. Buffers and other chemicals were of

analytical grades. The inhibition activity of enzyme was done in 5 mM phosphate buffer pH 8 and containing sodium chloride (Matsu *et al.*, 1996). Afterwards 20 μl of enzyme solution and 25 μl of substrate in phosphate buffer was kept in incubation with a range of concentrations of synthesized compounds in DMSO as reaction solvent, at 37°C. The activity results were observed by quantifying the variance in absorbance at 400 nm for 30 minutes. Acarbose was used as the standard drug. Through the following formula percent inhibition of the enzyme and IC₅₀ values of the under study compounds were estimated.

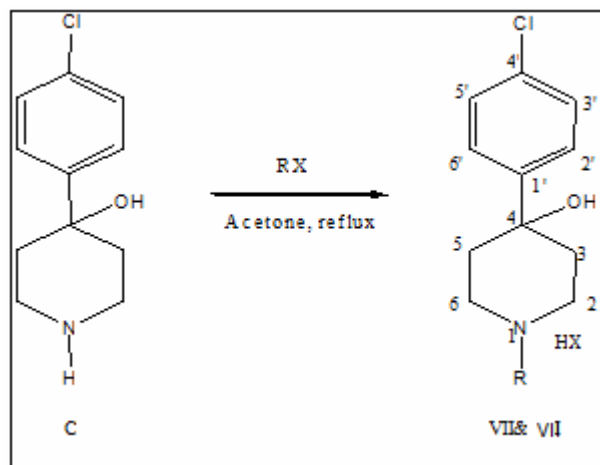


Fig. 3: Reaction method of 4-(4'-Chlorophenyl)-4-hydroxy piperidine derivatives

$$\% \text{ Inhibition} = (A_c - A_s) / (A_c - A_b) \times 100$$

Whereas,

A_c = absorbance of control

A_s = absorbance of sample

A_b = absorbance of blank

Results

The outstanding position of piperidine and its derivatives has approved the moiety as an important nucleus in numerous pharmaceuticals. Accordingly more work is on the way on this successful moiety and the present one is the continuation of the previous and continuous efforts. The current activity frames the study of antidiabetic aptitude of piperidine derivatives by suppressing the alpha glucosidase enzyme. The conducted α-Glucosidase inhibition activity of the synthesized derivatives (I-VIII) is presented in table-4. According to the results, derivative of 4-Hydroxy-4-phenyl piperidine (I), 1''-Phenoxypropyl)-4-Phenyl-4-hydroxy piperidinium Hydrobromide (I) inhibited the α-glucosidase enzyme strongly and has shown more potential than the standard drug Acarbose, whereas the compounds (II & III) that is 1-(1''-Propiophenone)-4-phenyl-4-hydroxy piperidinium Hydrochloride and 1-(1''-Ethyl phthalamide)-4-phenyl-4-hydroxy piperidinium Hydrobromide respectively exhibited slight inhibition with no prominent effect. In addition to this when the derivatives of 4-(4'-

Bromophenyl)-4-hydroxy piperidine (B) were tested, among them only compound (V), 1-(1''-Phenoxypropyl)-4-(4'-bromophenyl)-4-hydroxy piperidinium Hydrobromide responded for the inhibition of α -glucosidase enzyme equivalent to that of standard whereas the rest of compounds did not show any significant response. Furthermore no derivative of 4-(4'-Chlorophenyl)-4-hydroxy piperidine was found to exhibit α glucosidase inhibition activity.

Discussion

The occurrence of piperidine in black pepper is responsible for its spicy and pungent taste. Piperidine ring containing compounds have displayed a verity of biological properties and proved potent for various

activities such as antidiabetic, antinociception, anti-inflammation and for amylase and protease inhibition. In the field of medicinal chemistry the molecules are worked out for their accurate pharmacological response. As such Piperidine moiety is of utmost attraction for the drug designer due to its novelty and promising therapeutic responses. In the last few decades extensive research has been carried out on piperidine ring containing compounds (Kauffman *et al.*, 2009; Watson *et al.*, 2000; Dodson *et al.*, 2000). Consequently the present research work endorsed the strong antidiabetic response of piperidine derivatives through glucosidase inhibition. Highly prominent effects were observed from 1-(1''-Phenoxypropyl)-4-phenyl-4-hydroxy piperidinium Hydrobromide (I) and 1-(1''-phenoxypropyl)-4-(4'-

Table 1: Substituents of 4-Hydroxy-4-phenyl piperidine

Compound No.	R	X
I	OC ₉ H ₁₁	Br
II	OC ₈ H ₇	Cl
III	O ₂ C ₁₀ H ₈ N	Br

Table 2: Substituent of 4-(4'-Bromophenyl)-4-hydroxy piperidine

Compound No.	R	X
IV	OC ₁₂ H ₁₇	Br
V	OC ₉ H ₁₁	Br
VI	O ₂ C ₃ H ₅ N ₂	Cl

Table 3: Substituents of 4-(4'-Chlorophenyl)-4-hydroxy piperidine

Compound No	R	X
VII	OC ₁₂ H ₁₇	Br
VIII	O ₂ C ₅ H ₅ N ₂	Cl

Table 4: Alpha-glucosidase inhibition activity of synthesized piperidine analogues

Compounds	Conc. (mM)	α -Glucosidase Inhibition Activity (%)	IC ₅₀ ± SEM [μ M]
1-(1''-Phenoxypropyl)-4-phenyl-4-hydroxy piperidinium Hydrobromide (I)	0.250	87.4	113±8.46
1-(1''-Propiophenone)-4-phenyl-4-hydroxy piperidinium Hydrochloride (II)	0.500	21.8	N. A.
1-(1''-Ethyl phthalamide)-4- phenyl-4-hydroxy piperidinium Hydrobromide (III)	0.500	-2.6	N. A.
1-(1''-Adamantan acyl)-4-(4'-bromophenyl)-4-hydroxy piperidinium Hydrobromide (IV)	0.500	N. A.	N. A.
1-(1''-Phenoxypropyl)-4-(4'-bromophenyl)-4-hydroxy piperidinium Hydrobromide (V)	0.500	54.7	463.9±12.3
1-(6''-Methyluracil)-4-(4'-bromophenyl)-4-hydroxy piperidinium Hydrochloride (VI)	0.500	N. A.	N. A.
1-(1''-Adamantan acyl)-4-(4'chlorophenyl)-4-hydroxy piperidinium Hydrobromide (VII)	0.500	N. A.	N. A.
1-(6''- Methyluracil)-4-(4'-chlorophenyl)-4-hydroxy piperidinium Hydrochloride (VIII)	0.500	N. A.	N. A.
Acarbose	1.00	54.3	906±6.387

Activity Key: N. A. = Not active

bromophenyl)-4-hydroxy piperidinim Hydro bromide (V) for glucosidase inhibition. At molecular level the structural activity relationship reveals that the placement of carbonyl group at the nitrogen of piperidine ring is accountable for the activity in compound 1-(1''-Phenoxypropyl)-4-phenyl-4-hydroxy piperidinium Hydro bromide (I) and 1-(1''-phenoxypropyl)-4-(4'-bromophenyl)-4-hydroxy piperidinim Hydro bromide (V). The SAR analysis may lead to the designing and synthesizing of compounds to develop further potent glucosidase inhibitors.

CONCLUSION

The structural activity relationship reveals that the placement of carbonyl group at nitrogen of piperidine ring is accountable for the activity in compound 1-(1''-Phenoxypropyl)-4-phenyl-4-hydroxy piperidinium Hydro bromide (I) and 1-(1''-phenoxypropyl)-4-(4'-bromophenyl)-4-hydroxy piperidinim Hydro bromide (V). Hence it was concluded that these compounds will cause a decline in α -glucosidase enzyme and will be able to demonstrate good antidiabetic activity, hence these compounds can be considered as selective inhibitor for alpha glucosidase enzyme.

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