SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED 2-PHENOXY-NICOTINALDEHYDES AS *α*-AMYLASE INHIBITORS

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Diabetes mellitus is a chronic endocrine disorder that affects the metabolism of carbohydrates, proteins, fat, electrolytes and water. *α*-Amylase and *α*-glucosidase are the crucial enzymes required for the digestion of the carbohydrate. These enzymes play a vital role in the breakdown of starch in the diet and its activity has been correlated to postprandial blood glucose levels, the control of which is essential for maintaining the quality of life for diabetic patients. We report the synthesis, characterization and biological evaluation of new substituted 2-phenoxynicotinaldehydes as *α*-amylase inhibitors. A new general method based on the aromatic nucleophilic substitution reactions of 2-chloronicotinaldehyde with differently substituted phenols in the presence of K_2CO_3 in dry dioxane was developed to furnish the corresponding substituted 2-phenoxynicontinaldehydes with 70-80% yields.

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Introduction

Diabetes Mellitus (DM) is an extended metabolic disease of several etiologies characterized by chronic hyperglycemia with a disorder of carbohydrate, fat and also protein metabolism. It includes a group of metabolic diseases characterized by hyperglycemia, in which blood sugar levels are elevated either from defects in insulin secretion, insulin action or both of them.[1] Therefore, it is necessary to decrease postprandial hyperglycemia to treat diabetes.[2] This can be achieved by the inhibition of carbohydrate-hydrolyzing enzymes like *α*-amylase and *α*-glucosidase.[3]

α-Amylase is responsible for the breakdown of long chain carbohydrates and *α*-glucosidase breaks down starch and disaccharides to glucose. They serve as the primary digestive enzymes and support in intestinal absorption. Both these enzymes are the potential targets in the development of lead compounds for the treatment of diabetes.[4]

Many natural products from plants have been used for the treatment of diabetes.[5-8] Various drugs are available for the cure of Type 2 diabetes like acarbose, biguanides, sulphonylureas, thiozolidinediones, etc.[9,10] But they have also exhibited many undesired side effects like gastrointestinal side effects and thus signifying other effective substitutes.[11]

The pyridine substructure is one of the most predominant heterocycles found in natural products, pharmaceuticals, and functional materials.[12] In the recent past, novel derivatives of pyridine have been developed and found to have a large number of biological activities.[13-20] The pyridine structure is found in natural compounds like nicotinic acid (vitamin B_3) and pyridoxine (vitamin B_6). Over 100 medications on the market today include pyridine rings, such as Lunesta, commonly used to treat insomnia,

Singulair, widely used to treat asthma, Nexium, widely used to treat acid reflux, and Actos, widely used to treat Type II diabetes (Figure 1).[21]

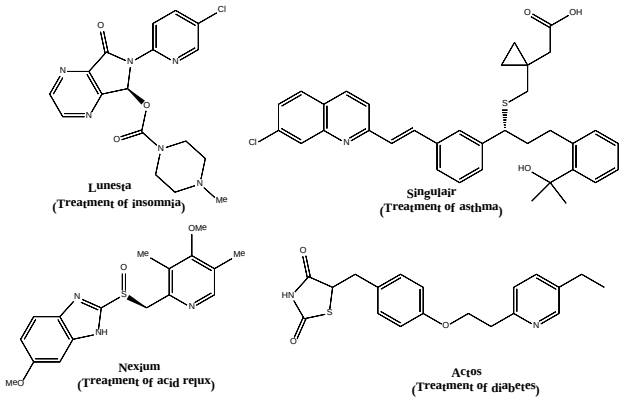


Figure 1. Some representative pyridine containing drugs

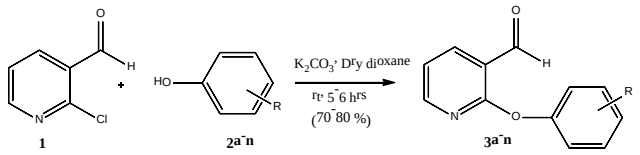
The pyridine moiety is also found in structurally simple drugs like isoniazid[22] and ethionamide[23] (both prodrugs for inhibitors of inter alia enoyl-acyl carrier protein reductase; tuberculosis), amrinone (phosphodiesterase 3 inhibitor; heart failure) and bupicomide (dopamine *β*-hydroxylase inhibitor; hypertension).

The high reactivity of pyridine allows for many possible chemical reactions.[24-25] In continuation with our efforts on the synthesis of bioactive heterocyclic compounds,[26-32] the present study was carried out to investigate the inhibitory potentials of substituted 2-phenoxynicotinaldehydes.

Results and discussion

We have synthesized a series of substituted 2-phenoxynicotinaldehydes by developing new reaction conditions. In the literature, various methods are reported for the aromatic nucleophilic substitution of 2-chloronicotinaldehydes by substituted phenols.[33-39] All these reported methods have some limitations. It requires high temperature and longer reaction time. Hence, there was a need to develop better reaction conditions for the synthesis of substituted 2-phenoxynicotinaldehydes from 2-chloronicotinaldehydes. In accordance with our aim, we performed the reaction of 2-chloronicotinaldehyde (**1**, 10 mmol) with phenol (**2l,** 10 mmol) in the presence of anhydrous K_2CO_3 (15 mmol) in dry dioxane at room temperature and exclusively obtained the corresponding 2-phenoxynicotinaldehyde (**3l**) with 75 % yield. In the same conversion, use of 10 mmol (1 equiv.) of K_2CO_3 also furnished the 2-phenoxynicotinaldehyde (**3l**) but less than 60 % yield, revealing that 15 mmol (1.5 equiv.) of K_2CO_3 is necessary for quantitative conversion of 2-chl**o**ronicotinaldehydes to corresponding substituted 2-phenoxynicotinaldehydes.

To establish the generality of this new set of reaction condition, we performed the aromatic nucleophilic substitution reactions of 2-chloro-nicotinaldehyde with differently substituted phenols in the presence of K_2CO_3 in dry dioxane to furnish the corresponding substituted 2-phenoxynicontinaldehydes with 70-80% yields (Scheme 1). ^1H and ^{13}C NMR spectral data confirmed the structures of all the synthesized substituted 2-phenoxynicontinaldehydes.



3a : R = 4-Cl; **3b** : R = 2, 4-Cl, Cl; **3c** : R = 2, 5-Cl, Cl; **3d** : R = 4-CH_3; **3e** : R = 2-Br; **3f** : R = 2-CH_3; **3g** : R = 3, 4-Cl, Cl; **3h** : R = 3-CH_3; **3i** : R = 2-CF_3; **3j** : R = 3, 5-Cl, Cl; **3k** : R = 2-CF3; **3l** : R = H; **3m** : R = 2-Cl; **3n** : R = 3-Cl

Scheme 1. Synthesis of substituted 2-phenoxy nicotinaldehydes

Biological activity

The enzyme inhibition activity was studied by agar diffusion method with some modifications.[40] For evaluating the enzyme inhibitory activity, commercially available *α*-amylase sample (from Hi media laboratory) was used. The synthesized compounds were dissolved in DMSO at 25 mg per ml concentration. A paper disc of 6 mm diameter from Hi media was impregnated with 10 µL of 1 % *α*-amylase solution. Subsequently, 10 µL of test compound solution was also impregnated to the enzyme discs. Control discs were prepared by adding 10 µL of DMSO only. Control and test discs were placed on 1 % starch containing Agar gel plates (pH 6.5). These plates were incubated at 37 ^{0}C for 24 h. After 24 h the plates were developed by Gram's iodine solution to observe the zone of clearance. Each zone was measured in millimetre (Table 1).

Table 1. Disc and medium preparation

Parameter	Magnitude
Concentration of enzyme	10 mg in 1 mL
Concentration of test compound	25 mg in 1 mL
Concentration of starch (substrate)	10 mg in 1 mL
Volume of the substrate in each plate	8 mL
Amount of substrate in each plate	80 mg
Diameter of zone (mm) for blank without enzyme with DMSO	Nil

The zone of control was used to calculate the amount of starch hydrolyzed. The amount of starch hydrolyzed was calculated as shown in Table 2. The zone of clearance indicated the amount of starch hydrolyzed in milligrams. The amount of starch hydrolyzed by control was considered as 100 % activity and accordingly, % change in activity was measured.

From Table 3, it is observed that all the tested compounds showed anti-*α*-amylase activity in the range from 25 % to 59 %. Among these compounds **2i** showed the least inhibition at 25.33 %, while compounds **2a**, **2e**, and **2g** showed higher inhibition of more than 59 %.

Table 2. Calculation for substrate consumed by control

Value of π	3.14
Thickness of medium, mm	1.01
Diameter of zone (mm) for control (with only amylase and DMSO)	22
Radius of zone (mm)	11
Volume of the reaction zone, mm^3, [πr^2*h (thickness of medium)]	383.7394
Amount of substrate consumed in control mg	383.7394/100

Table 3. Calculation of percent reduction in *α*-amylase activity

Entry	Diameter of the zone, mm	Consumed substrate, mg	Acti-vity, %	Activity fall, %
Control	22	3.83	100	0.00
2a	14	1.54	40.2	59.8
2b	15.5	1.89	49.34	50.66
2c	15.5	1.89	49.34	50.66
2d	16	2.01	52.48	47.52
2e	14	1.54	40.2	59.8
2f	16.5	2.14	55.87	44.13
2g	14	1.55	40.47	59.53
2h	15.5	1.9	49.6	50.4
2i	19	2.86	74.67	25.33
2j	15.5	1.89	49.34	50.66
2k	16.5	2.14	55.87	44.13
2l	17	2.27	59.26	40.74
2m	18.2	2.6	67.88	32.12
2n	17.6	2.43	63.44	36.56

Experimental

General procedure for the synthesis substituted 2-phenoxy-nicotinaldehydes

2-Chloronicotinaldehyde (10 mmol), substituted phenols (10 mmol) and potassium carbonate (15 mmol) in dry dioxane were stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated on a rotary evaporator. The reaction mixture was extracted by ethyl acetate. The crude product obtained was purified by recrystallization in ethanol to furnish the corresponding substituted 2-phenoxynicotinaldehydes with 70-80% yields.

2-(4-Chlorophenoxy)nicotinaldehyde (3a).

Yield: 74 %; M.p.: 80-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.15-7.19 (m, 3H), 7.41-7.45 (m, 2H), 8.27 (dd, *J* = 8 and 2 Hz, 1H), 8.36 (dd, *J* = 7 and 2 Hz, 1H), 10.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 119.32, 119.52, 123.12, 129.80, 130.83, 138.34, 151.46, 152.99, 163.72, 188.52.

2-(2,4-Dichlorophenoxy)nicotinaldehyde (3b)

Yield: 70 %; M.P.: 122-124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.17-7.20 (m, 1H), 7.26-7.28 (m, 1H), 7.34-7.37 (m, 1H), 7.51-7.52 (m, 1H), 8.28 (dd, *J* = 8 and 2 Hz, 1H), 8.31 (dd, *J* = 7 and 2 Hz, 1H), 10.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 119.10, 119.58, 125.15, 128.18, 128.32, 130.41, 131.65, 138.41, 147.71, 152.85, 163.05, 188.33.

2-(2,5-Dichlorophenoxy)nicotinaldehyde (3c)

Yield: 70 %; M.P.: 88-90 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm = 7.38 (dd, *J* = 8 and 5 Hz, 1H), 7.44 (dd, *J* = 8 and 2 Hz, 1H), 7.66-7.68 (m, 2H), 8.30 (dd, *J* = 8 and 2 Hz, 1H), 8.40 (dd, *J* = 5 and 2 Hz, 1H), 10.44 (s, 1H).

2-(*p*-Tolyloxy)nicotinaldehyde (3d)

Yield: 80 %; M.P.: 78-80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 2.41 (s, 3H), 7.10-7.14 (m, 3H), 7.26-7.28 (m, 2H), 8.26 (dd, *J* = 8 and 2 Hz, 1H), 8.37 (dd, *J* = 5 and 2 Hz, 1H), 10.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 20.94, 118.79, 119.45, 121.45, 130.31, 135.13, 138.04, 150.73, 153.19, 164.36, 188.94.

2-(2-Bromophenoxy)nicotinaldehyde (3e)

Yield: 76 %; M.P.: 83-85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.15-7.22 (m, 2H), 7.23-7.34 (m, 1H), 7.42-7.46 (m, 1H), 7.68-7.70 (m, 1H), 8.28-8.34 (m, 2H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 116.68, 119.23, 119.29, 124.38, 127.14, 128.67, 133.72, 138.21, 150.18, 152.95, 163.36, 188.68.

2-(*o*-Tolyloxy)nicotinaldehyde (3f)

Yield: 78 %; M.P.: Thick oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 2.23 (s, 3H), 7.10-7.20 (m, 2H), 7.22-7.34 (m, 3H), 8.27 (dd, *J* = 8 and 2 Hz, 1H), 8.34 (dd, *J* = 5 and 2 Hz, 1H), 10.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 16.51, 118.74, 119.13, 122.13, 125.86, 127.20, 130.75, 131.46, 138.17, 151.44, 153.30, 163.98, 188.77.

2-(3,4-Dichlorophenoxy)nicotinaldehyde (3g)

Yield: 72 %; M.P.: 82-84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.09-7.20 (m, 1H), 7.20-7.22 (m, 1H), 7.37 (d, *J* = 2 Hz, 1H),7.52 (d, *J* = 8Hz, 1H), 8.28 (dd, *J* = 8 and 2 Hz, 1H), 8.36 (dd, *J* = 5 & 2Hz, 1H), 10.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 119.51, 119.72, 121.45, 124.04, 129.32, 130.97, 133.23, 138.52, 151.68, 152.92, 163.23, 188.18.

2-(*m*-Tolyloxy)nicotinaldehyde (3h).

Yield: 75 %; M.P.: 54-56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 2.42 (s, 3H), 7.01-7.10 (m, 2H), 7.12-7.16 (m, 2H), 7.34-7.38 (m, 1H), 8.26 (dd, *J* = 8 and 2Hz, 1H), 8.37 (dd, *J* = 5 and 2 Hz, 1H), 10.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 21.43, 118.59, 118.91, 119.57, 122.19, 126.33, 129.46, 138.06, 140.00, 153.07, 153.23, 164.23, 188.90.

2-(3-(Trifluoromethyl)phenoxy)nicotinaldehyde (3i)

Yield: 70 %; M.P.: 50-52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.19-7.22 (m, 1H), 7.29-7.62 (m, 4H), 8.29 (dd, *J* = 8 and 2Hz, 1H), 8.37 (dd, *J* = 5 and 2 Hz, 1H), 10.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 118.92, 119.00, 119.60, 119.63, 122.17, 122.24, 125.26, 130.24, 138.47, 152.94, 153.13, 163.36, 188.31.

2-(3,5-Dichlorophenoxy)nicotinaldehyde (3j)

Yield: 70 %; M.P.: 110-112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.17-7.22 (m, 2H), 7.23-7.24 (m, 1H), 7.29-7.30 (m, 1H), 8.28 (dd, *J* = 8 and 2 Hz, 1H), 8.39 (dd, *J* = 5 and 2 Hz, 1H), 10.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 119.62, 119.95, 120.83, 125.84, 135.50, 138.57, 152.96, 153.80, 162.98, 188.04.

2-(2-(Trifluoromethyl)phenoxy)nicotinaldehyde (3k)

Yield: 77 %; M.P.: 50-52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.17-7.21 (m, 1H), 7.39-7.43 (m, 2H), 7.65-7.67 (m, 1H), 7.69-7.78 (m, 1H), 8.29 (dd, *J* = 8 and 2 Hz, 1H), 8.34 (dd, *J* = 5 and 2 Hz, 1H), 10.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 119.57, 121.76, 124.47, 125.52, 127.18, 127.23, 127.28, 133.03, 138.24, 150.32, 152.77, 163.43, 188.47.

2-Phenoxynicotinaldehyde (3l)

Yield: 75 %; M.P.: 58-60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.11-7.14 (m, 1H), 7.18-7.19 (m, 1H), 7.20-7.21 (m, 1H), 7.26-7.30 (m, 1H), 7.44-7.48 (m, 2H), 8.25 (dd, J = 8 and 2 Hz, 1H), 8.35 (dd, J = 5 and 2 Hz, 1H), 10.57 (s, 1H).

2-(2-Chlorophenoxy)nicotinaldehyde (3m)

Yield: 70 %; M.P.: 63-65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.13-7.16 (m, 1H), 7.23-7.27 (m, 1H), 7.27-7.32 (m, 1H), 7.35-7.38 (m, 1H), 7.50-7.52 (m, 1H), 8.27 (dd, J = 8 and 2 Hz, 1H), 8.31 (dd, J = 5 and 2 Hz, 1H), 10.62 (s, 1H).

2-(3-Chlorophenoxy)nicotinaldehyde (3n)

Yield: 70 %; M.P.: 56-58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 7.01-7.13 (m, 1H), 7.15-7.19 (m, 1H), 7.23-7.25 (m, 1H), 7.26-7.27 (m, 1H), 7.35-7.40 (m, 1H), 8.26 (dd, J = 8 and 2 Hz, 1H), 8.36 (dd, J = 5 and 2 Hz, 1H), 10.53 (s, 1H).

Conclusions

We have reported a new method for aromatic nucleophilic substitution of 2-chloronicotinaldehyde by substituted phenols to furnish the corresponding substituted 2-phenoxynicotinaldehydes. All the synthesized compounds showed anti-α-amylase activity. Among these compounds **2a**, **2e** and **2g** showed very good inhibition of more than 59%. These three compounds can be subjected to *in-vivo* studies.

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