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Synthesis, α-amylase inhibitory potential and molecular docking study of indole derivatives

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ABSTRACT

In search of potent α-amylase inhibitor we have synthesized eighteen indole analogs (**1**–**18**), characterized by NMR and HR-EIMS and screened for α-amylase inhibitory activity. All analogs exhibited a variable degree of α-amylase inhibition with IC_{50} values ranging between 2.031 ± 0.11 and 2.633 ± 0.05 μM when compared with standard acarbose having IC_{50} values 1.927 ± 0.17 μM. All compounds showed good *α*-amylase inhibition. Compound **14** was found to be the most potent analog among the series. Structure-activity relationship has been established for all compounds mainly based on bringing about the difference of substituents on phenyl ring. To understand the binding interaction of the most active analogs molecular docking study was performed.

1. Introduction

α-Amylase is an endoamylase that catalyze the initial hydrolysis of starch into shorter oligosaccharides through the cleavage of internal *α*-D-(1-4) glyosidic bonds resulting in *α*-anomeric products [1–3]. It should be noted that neither terminal glucose residues nor *α*-D-(1-6) linkages can be cleaved by *α*-amylase. Therefore, the resulting products of *α*-amylase action are the dextrin's and oligosaccharides [1]. Nearly 95% of diabetes cases are regarded as by changing blood glucose level due to insulin resistance. This condition leads various obstacles such as cardiovascular diseases, stroke, high blood pressure, blindness, and kidney failure [4,5]. In T2DM, the post-prandial blood glucose level rises uncontrollably leading to hyperglycemic conditions causing metabolic derangements in the body. Treatment for hyperglycemia mainly focuses on stimulating insulin secretion from the ß-cells of pancreatic islets, inhibiting the insulin degradation process, repairing or regenerating pancreatic beta cells, and inhibiting the starch hydrolases, *α*-amylase and *α*-glucosidase [6]. Therefore, *α*-amylase is one of the enzymes of great concern to the medical practitioners and researchers in controlling T2DM. (see Table 1.).

The indole moiety is probably the most widely spread nitrogen heterocycle in nature. It is an essential part of the amino acid tryptophan and the neurotransmitter serotonin, and the indole scaffold is also found in numerous naturally occurring plant based alkaloids. The biological importance of indole heterocycles and their pharmacological and medical potential have made them extremely attractive and rewarding research targets. These qualities have motivated countless researchers to study their synthesis and pharmacological properties [7]. The biological activities of indoles cover a wide spectrum, including anticancer [8], antimicrobial [9], anti-inflammatory [10], antimalarial [11], cytotoxic [11] and antitubercular [12] activities. We have reported indole-based derivatives as anti-diabetic [13] as well as we

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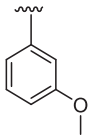
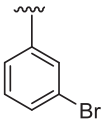
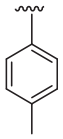
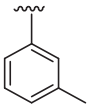
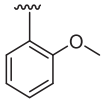
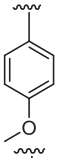
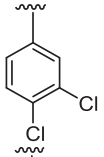
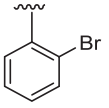
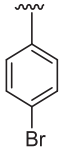
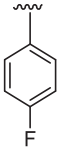
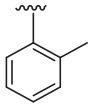
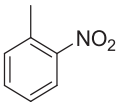
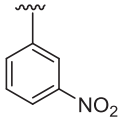
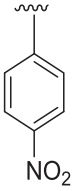
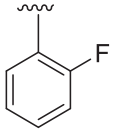
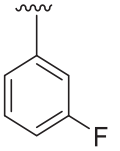
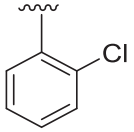
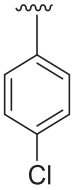
Table 1
α-Amylase inhibitory activity of synthetic compounds (1–18).

S. No	Structure	IC_{50} ± SEM[a]	S. No	Structure	IC_{50} ± SEM[a]
1		2.63 ± 0.05	10		2.10 ± 0.17
2		2.46 ± 0.03	11		2.51 ± 0.013
3		2.05 ± 0.11	12		2.50 ± 0.07
4		2.44 ± 0.07	13		2.55 ± 0.21
5		2.33 ± 0.09	14		2.03 ± 0.11
6		2.06 ± 0.09	15		2.42 ± 0.041
7		2.45 ± 0.06	16		2.29 ± 0.06
8		2.54 ± 0.02	17		2.20 ± 0.02
9		2.10 ± 0.21	18		2.15 ± 0.06
	Acarbose	1.927 ± 0.17			

[a] Standard error mean.

found in literature that few natural products possessing indole moiety exhibit good biological potential [14]. So, we thought to investigate by varying functionality in the molecule through designing and synthesizing cost-effective indole derivatives for α-amylase inhibitory potential.

In continuation of our ongoing research on the chemistry and bioactivity of new heterocyclic compounds [14–18], we carried out the synthesis of indole derivatives which is reported here in.

Previously we have reported indole Schiff bases for the α-Amylase inhibition [15]; this time we are reporting thiosemicarbazide derivatives of indole as new α-Amylase inhibitors.

2. Results and discussion

2.1. Chemistry

The compounds (**1–18**) were synthesized from 5-chloro-1H-indole-2-carbohydrazide and arylisothiocyanate. In first step, indole hydrazide was synthesized from ethyl 5-chloro-1H-indole-2-carboxylate through reaction with hydrazine hydrate in ethanol upon reflux for 6 h. The

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