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Synthesis of alpha amylase inhibitors based on privileged indole scaffold

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ABSTRACT

Twenty five derivatives of indole carbohydrazide (**1**–**25**) had been synthesized. These compounds were characterized using ^{1}H NMR and EI-MS, and further evaluated for their α-amylase inhibitory potential. The analogs (**1**–**25**) showed varying degree of α-amylase inhibitory potential.

ranging between 9.28 and 599.0 μM when compared with standard acarbose having IC_{50} value 8.78 ± 0.16 μM. Six analogs, **25** (IC_{50} = 9.28 ± 0.153 μM), **22** (IC_{50} = 9.79 ± 0.43 μM), **4** (IC_{50} = 11.08 ± 0.357 μM), **1** (IC_{50} = 12.65 ± 0.169 μM), **8** (IC_{50} = 21.37 ± 0.07 μM) and **14** (IC_{50} = 43.21 ± 0.14 μM) showed potent α-amylase inhibition as compared to the standard acarbose (IC_{50} = 8.78 ± 0.16 μM). All other analogs displayed good to moderate inhibitory potential. Structure-activity relationship was established through the interaction of the active compounds with enzyme active site with the help of docking studies.

1. Introduction

Alpha-amylase is an enzyme (EC.3.2.1.1) that hydrolyses alpha bonds of large alpha-linked polysaccharides such as starch and glycogen yielding glucose and maltose [1,2]. Alpha-amylase enzyme is calcium metallo-enzyme that can be found in normal serum, urine and saliva of human. In clinical chemistry, the activity of α-amylase in serum and urine indicates the presence of parotitis and pancreatitis [3]. α-Amylase is one of the most important industrial endoamylases that is capable of hydrolyzing the internal α-1,4 glycosidic linkages to glucose, maltose and dextrin while retaining the α-anomeric configuration in the products [4]. As a ubiquitous enzyme, α-amylase is produced by many species, including animals, plants and microorganisms. From all these species, α-amylase from microorganisms are preferred because of their plasticity for genetic manipulation and potential for economical bulk production [5]. A large number of microbial α-amylase of different origins had been widely studied and extensively applied in a vast spectrum of industries ranging from food to textile, detergent, biofuel and paper industries. Furthermore, ground-breaking clinical applications had been realized in medicine and in the elimination of environmental pollutants [6,7]. Coleopteran, Indole, methyl acarviosin, Isoflavonoids and flavonoids recently reported inhibitors for alpha amylase [8–11]. Inhibitors of this enzyme can slow down carbohydrate absorption prolonging total carbohydrate absorption time, decreasing the rate of glucose absorption and, subsequently, reducing the postprandial plasma glucose increase. Clinically used diabetes control inhibitors are acarbose and miglitol [12,13].

The indole moiety is probably the most widely spread nitrogen heterocyclic moiety in nature. It is an essential part of the amino acid tryptophan and the neurotransmitter serotonin. The indole scaffold can also be found in numerous naturally occurring plant based alkaloids. The biological importance of indole heterocycles and their pharmacological and medical potential had made them extremely attractive and rewarding research targets and these

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qualities have motivated countless researchers to study their synthesis and pharmacological properties [14]. The biological activities of indoles cover a wide spectrum, including anticancer [15], antibacterial and antimicrobial [16], anti-inflammatory [17], antimalarial and cytotoxic [18] and antitubercular [19] activities. We found that few natural products having indole moiety showed good activity [20–22], which excited us to design and synthesize cost effective indole derivatives for α-amylase inhibitory potential.

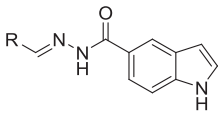
2. Result and discussions

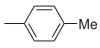
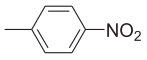
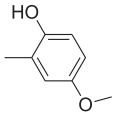
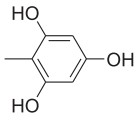
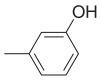
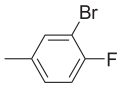
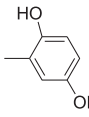
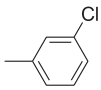
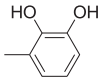
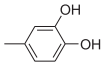
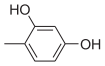
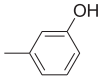
2.1. Chemistry

1*H*-Indole-5-carbohydrazide was obtained from methyl-1*H*-indole-5-carboxylate after refluxing it with hydrazine hydrate. 5-Indole hydrazones were synthesized by condensation with various aromatic aldehydes. The crude solid products were recrystallized from methanol with good yields, *i.e.* 74–86%. Constructions of prepared compounds (**1**–**25)** were established by a variety of spectroscopic techniques and CHN analysis. Elemental analyses were found to be in good agreement with the calculated values for all the compounds scheme 1 [23].

3. *In vitro* α-amylase inhibitory potential

In continuation of our research on potent enzyme inhibitors [24–33]. We have synthesized twenty five indole carbohydrazide analogs (**1**–**25)** and evaluated against α-amylase inhibitory potential. Among the series, all analogs showed varying degree of α-amylase inhibitory potential ranging between 9.28 ± 0.153 μM and 599.0 ± 0.21 μM when compared with standard acarbose having IC_{50} value 8.78 ± 0.16 μM. Six analogs, such as analog **25** (IC_{50} = 9.28 ± 0.153 μM), analog **22** (IC_{50} = 9.79 ± 0.43 μM), analog **4** (IC_{50} = 11.08 ± 0.357 μM), analog **1** (IC_{50} = 12.65 ± 0.169 μM), analog **8** (IC_{50} = 21.37 ± 0.07 μM) and analog **14** (IC_{50} = 43.21 ± 0.14 μM) showed potent α-amylase inhibition as compared to the standard acarbose. Eleven analogs, such as analog **10** (IC_{50} = 50.38 ± 0.097 μM), analog **17** (IC_{50} = 56.32 ± 0.11 μM), analog **15** (IC_{50} = 62.36 ± 0.05 μM), analog **23** (IC_{50} = 64.26 ± 0.104 μM), analog **11** (IC_{50} = 71.21 ± 0.268 μM), analog **9** (IC_{50} = 83.49 ± 0.19 μM),



S. no.	R	IC_{50} ± SEM[a]	S. no.	R	IC_{50} ± SEM[a]
1		12.65 ± 0.169	**14**		43.21±0.14
2		532.1 ± 1.8	**15**		62.36±0.05
3		152.1 ± 0.09	**16**		130.0±0.04
4		11.08 ± 0.357	**17**		56.32.±0.11
5		94.82 ± 0.12	**18**		294.8±0.12
6		219.5 ± 0.07	**19**		202.7±0.07
7		92.29 ± 0.08	**20**		599.0±0.21
8		21.37 ± 0.07	**21**		84.61±0.123
9		83.49 ± 0.19	**22**		9.79±0.43

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