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Synthesis, α-glucosidase inhibition and molecular docking study of coumarin based derivatives

Muhammad Taha [a,*], Syed Adnan Ali Shah [b,c,*], Muhammad Afifi [b,c], Syahrul Imran [b,d], Sadia Sultan [b,c], Fazal Rahim [e], Khalid Mohammed Khan [f]

[a] Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia
[b] Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor D. E., Malaysia
[c] Faculty of Pharmacy, Universiti Tecknologi MARA Puncak Alam, 42300 Bandar Puncak Alam, Selangor D. E., Malaysia
[d] Faculty of Applied Science UiTM, 40450 Shah Alam, Selangor, Malaysia
[e] Department of Chemistry, Hazara University, Mansehra 21300, Pakistan
[f] H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan

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ABSTRACT

We have synthesized seventeen Coumarin based derivatives **(1–17)**, characterized by ^{1}HNMR, ^{13}CNMR and EI-MS and evaluated for α-glucosidase inhibitory potential. Among the series, all derivatives exhibited outstanding α-glucosidase inhibition with IC_{50} values ranging between 1.10 ± 0.01 and 36.46 ± 0.70 μM when compared with the standard inhibitor acarbose having IC_{50} value 39.45 ± 0.10 μM. The most potent derivative among the series is derivative **3** having IC_{50} value 1.10 ± 0.01 μM, which are many folds better than the standard acarbose. The structure activity relationship (SAR) was mainly based upon by bring about difference of substituent's on phenyl part. Molecular docking studies were carried out to understand the binding interaction of the most active compounds.

1. Introduction

More than 90% of diabetic patient suffers from type-2 diabetes, which is non-insulin dependent diabetes mellitus, which is characterized by insulin resistance and hyperglycemia [1]. Diabetes is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, expected to rise up to 220 million people by 2010 [2]. There has been an explosion of introduction of new classes of pharmacologic agents [3] including insulin and insulin analogs [4,5], sulfonylureas [6], bigunides [7], glitazones (thiazolidinediones) [8,9], and α-glucosidase inhibitors [10] are one of them.

α-Glucosidase belong to the glycosyl hydrolase-31, family of hydrolases and its major function is hydrolysis of terminal, non-reducing 1, 4-linked α-D-glucosidase with release of α-D-glucose. α-Glucosidase has drawn a special interest of the pharmaceutical research community because in earlier studies it was shown that the inhibition of its catalytic activity resulted in the retardation of glucose absorption and decrease in postprandial blood glucose level [11]. The α-glucosidase inhibitors might be a reasonable option as first-line drug in the treatment of patients with diabetes mellitus as it specifically targets postprandial hyperglycaemia. α-Glucosidase inhibitors are expected to cause no hypoglycaemic events or other life-threatening events, even at overdoses, and cause no weight gain [12]. Acarbose, The α-glucosidase inhibitor which delays the absorption of carbohydrate from the small intestine, reduces postprandial hyperglycemia in patients with type 2 diabetes [13].

Coumarin (1,2-benzopyrone) derivatives constitute one of the most common families of green plant secondary metabolites, several of them being reported to display multiple biological properties [14,15]. Many products which contain a coumarin subunit exhibit biological activities, such as molluscicidal, anthelmintic, hypnotic, and insecticidal activities [16]. Also, the medicinal properties of coumarins include inhibition of platelet aggregation, cytochrome P450 and steroid 5a-reductase [17,18].

Schiff bases represent an important group of organic compounds having various biological activities such as urease,

* Corresponding authors at: Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia (M. Taha).
E-mail addresses: taha_hej@yahoo.com, mtaha@iau.edu.sa (M. Taha), syedadnan@salam.uitm.edu.my, benzene301@yahoo.com (S.A.A. Shah).

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α-glucosidase, antiglycation and β-glucuronidase [19–28]. The study of novel biologically significant Schiff bases has been drawing attention of chemists and pharmacists [29]. Schiff basesfrom acyl-hyrazide having a wide range of biological actions are also reported i.e. Adriamycin immune conjugates, antiparasitic activity by inhibiting proteinase against Trypanosoma brucei, which causes sleeping sickness in humans, insecticidal, antimyco-bacterial and antileishmanial [30–34] and different analogs of *N*-cyanoethyl hydrazide also illustrated activity against β-glucuronidase enzyme [35].

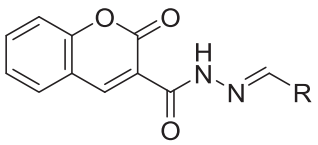
Here we are reporting synthesis of some new derivatives of coumarin based Schiff bases and their α-glucosidase inhibitory potential and molecular docking studies.

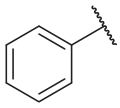
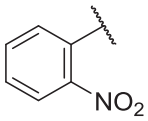
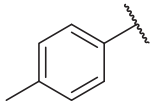
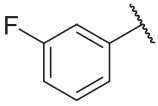
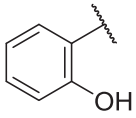
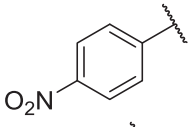
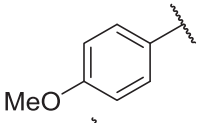
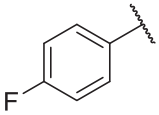
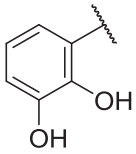
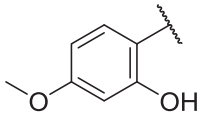
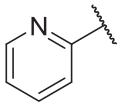
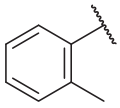
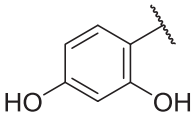
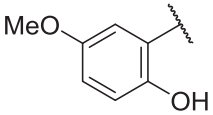
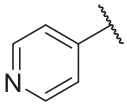
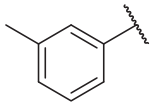
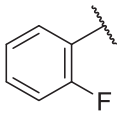
2. Results and discussion

2.1. Chemistry

Ethyl-3-coumarincarboxylate (Scheme 1) was added into round bottom flask which contains hydrazinium hydroxide (hydrazine hydrate) and methanol as the solvent. Reaction mixture was stirred for 24 h at room temperature. TLC is used to monitor progression of the reaction. On completion of reaction the solvent was evaporated and crude product was recrystallized in ethanol.

Seventeen **1**–**17** derivatives of 3-coumarincarbohydrazones were synthesized by refluxing 2-oxo-2H-chromene-3-carbohydrazide with various aldehydes in methanol. The general reaction scheme was described in Scheme 2.



No.	R	IC_{50} (μM ± SEM[a])	No.	R	IC_{50}(μM ± SEM[a])
1		29.14 ± 0.65	**10**		24.14 ± 0.55
2		7.58 ± 0.10	**11**		29.14 ± 0.65
3		1.10 ± 0.01	**12**		4.58 ± 0.10
4		4.26 ± 0.1	**13**		16.10 ± 0.25
5		3.15 ± 0.1	**14**		6.46 ± 0.10
6		6.10 ± 0.15	**15**		34.14 ± 0.25
7		4.58 ± 0.10	**16**		11.14 ± 0.35
8		16.10 ± 0.25	**17**		10.58 ± 0.30
9		36.46 ± 0.70	**Standard drug (acarbose)**		39.45 ± 0.10

[a] SEM Standard Error Mean.