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New indole based hybrid oxadiazole scaffolds with *N*-substituted acetamides: As potent anti-diabetic agents

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ABSTRACT

Current study is based on the sequential conversion of indolyl butanoic acid (**1**) into ethyl indolyl butanoate (**2**), indolyl butanohydrazide (**3**), and 1,3,4-oxadiazole-2-thiol analogs (**4**) by adopting chemical transformations. In a parallel series of reactions, 2-bromo-*N*-phenyl/arylacetamides (**7a-l**) were synthesized by reacting different amines derivatives (**5a-l**) with 2-bromoacetyl bromide (**6**) to serve as electrophile. Then, the synthesized electrophiles (**7a-l**) were treated with nucleophilic 1,3,4-oxadiazole-2-thiol analog (**4**) to afford a range of *N*-substituted derivatives (**8a-l**). The structural confirmation of all the synthetic compounds was carried out by IR, ^{1}H-, ^{13}C NMR, EI-MS, and CHN analysis data. All synthesized molecules (**8a-l**) were tested for their antidiabetic potential *via* inhibition of the α-glucosidase enzyme followed by their *in silico* study. Their cytotoxicity profile was also ascertained *via* hemolytic activity and all of them possessed very low cytotoxicity. Compounds **8h** and **8l** were found most active having IC_{50} values 9.46 ± 0.03 μM and 9.37 ± 0.03 μM, respectively. However, all other molecules also exhibited good to moderate inhibition potential with IC_{50} values between 12.68 ± 0.04–37.82 ± 0.07, compared to standard acarbose (IC_{50} = 37.38 ± 0.12 μM), hence can be used as lead molecules for further research in order to get better antidiabetic agents.

1. Introduction

α-Glucosidase enzyme (EC 3.2.1.20) belongs to the hydrolase family, found in the brush border surface membrane of small intestinal cells [1]. α-Glucosidase is one of the prime target for the development of anti-diabetic drugs for the patients suffering from type-2 diabetic mellitus. It is a fact that post-prandial hyperglycemia leads to the development of type-2 diabetes mellitus and complications associated with it such as neuropathy, nephropathy, micro and macroangiopathies [2].

Acarbose, voglibose, and miglitol are the α-glucosidase inhibitors which are being clinically used to treat the patients of type-2 diabetic mellitus and also used as anticancer and anti-HIV agents. Regrettably, some side effects such as diarrhea, abdominal discomfort, and flatulence are also linked to them. That's why, these clinical inhibitors are 50% less operative than other antidiabetic agents including metformin and sulfonylurea. Consequently, these drugs oftenly use in combination with other antidiabetic agents to improve the efficacy [3–9]. Identification of new therapies with no or lesser risk of side effects for the cure of type-2 diabetic mellitus is an appealing and interesting area of research for the medicinal chemist.

Indole is an aromatic heterocyclic compound, composed of a benzopyrrole scaffold in which the benzene ring fused with the 2- and 3-positions of pyrrole ring. Indole exhibits a distinctive reactivity and can be deprotonated at nitrogen of pyrrole ring. The resulting salts has proved to be good nucleophiles. Indole ring is found in many fungal

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metabolites, indole alkaloids, and marine natural products. Highly ionic salts (*e.g.* Li^+, K^+) favor the *N*-substitutions and softer counter ions favor C-3 substitution [10]. Indole is a highly conserved heterocyclic aromatic molecule, acts as a free radical scavenger. Indole analogs have a broad-spectrum of antioxidant activities. It also play crucial roles in the biological systems in the form of amino acid, alkaloids, and growth hormones. Many recent drugs used as antineoplastic, antihypertensive, and antimitotic agents, have indole ring as core scaffold. These drugs also have utilization for the treatment of chemotherapy-induced vomiting and nausea, and cluster headache [11–13].

1,3,4-Oxadiazole ring has a crucial important in heterocyclic chemistry and have extensive utilization in organic synthesis [14,15]. 1,3,4-Oxadiazole containing compounds have been gained considerable attention in pharmaceutical field due to their remarkable bioactivities. These compounds are effectively being utilized as antibacterial agents, anticancer, anti-Parkinson, anti-HIV, and anti-proliferative agents [16–21].

Our group has already reported lead compounds based on indole and oxadiazole scaffold as potent *α*-glucosidase inhibitors [22–28]. It is noteworthy that hybrid scaffold of indole with oxadiazole were also identified as significant inhibitors [25] (Fig. 1). Therefore, we decided to expand this study and further evaluate this class of compounds in order to get new and more powerful inhibitors. In the present investigation, the designed hybrid molecules were screened to explore their enzyme inhibitory potential against *α*-glucosidase enzyme. *In silico* studies were also carried out to ascertain various kinds of interactions with active pocket of *α*-glucosidase enzyme. Moreover, their cytotoxicity was also assessed to find their utility as possible drug candidates in drug discovery and development.

2. Results and discussion

2.1. Chemistry

First, the indolyl butanoic acid (**1**) was esterified by ethanol in the presence of catalytic volume of concentrated sulfuric acid. Ethanol was used as reactant and solvent in order to push the equilibrium towards product side, as it was a reversible reaction. The product was collected by solvent extraction after the addition of a weak base and excess of water. The base was added to neutralize the catalytic sulfuric acid and the unreacted carboxylic acid. During solvent extraction, salts of these acids were transferred to the aqueous layer while the resulted ester to the organic phase. Thus, ethyl indolyl butanoate (**2**) was obtained as brownish liquid (solid at refrigeration). The second step was performed to convert this ethyl ester to respective carbohydrazide (**3**), in the presence of hydrazine hydrate in methanol under reflux for 14 h. Thus, indolyl butanohydrazide (**3**) was obtained as a light brown solid. The third step was a cyclization to form heterocyclic ring by reaction with CS_2 in a basic alcoholic medium. The resulting product 1,3,4-oxadiazole-2-thiol analog (**4**) have a mercapto group at its second carbon. In a parallel sequence of reactions, different electrophiles were synthesized by reacting different amines derivatives (**5a-l**) with 2-bromoacetyl bromide (**6**) to afford 2-bromo-*N*-phenyl/arylacetamides (**7a-l**). Finally, in the last step, 1,3,4-oxadiazole-2-thiol analog (**4**) was reacted with the synthesized electrophiles (**7a-l**) (one in each reaction), in the presence of LiH using aprotic polar medium to get required derivatives (**8a-l**) (Scheme 1, Table 1).

2.2. Spectral studies of representative compound 8f

The molecule **8f** was obtained as light yellow solid. Formation of the desired compound was confirmed by molecular ion peak at *m/z* 450 in EI-MS spectrum. Further, structural confirmation was done by ^{1}H- and ^{13}C NMR. The CHN analysis data was also in agreement with the calculated values. Different Functional groups in the molecule were depicted by absorption bands in IR spectrum at υ 3274 (str., N—H), 2953 (aromatic str., C—H), 1761 (C=O ester str.), 1671 (C=O amide str.), 1650 (C=N str.), 1590 (aromatic str., C=C), 1531, 1489, 1452 (str. for oxadiazole), 1159 (str., C—O—C), 666 (str., C—S) cm^{-1}.

In ^{1}H NMR spectrum, the most downfield signal was observed at δ 10.80 for NH of the indole heterocyclic core. H-7 resonated at δ 7.48 as a doublet, showed *ortho* coupling (J = 7.8 Hz) with H-6. Another doublet of H-4 was appeared at δ 7.34, showed *ortho* coupling (J = 8.0 Hz) with H-5. A singlet for H-2 was resonated at δ 7.14. However, H-6 and H-5 resonated at δ 7.06 (J = 7.5 Hz) and δ 6.96 (J = 7.4 Hz), as triplets, respectively. Similarly, other aromatic protons also resonated in the usual range such as H-6‴′ and H-3‴′ appeared at δ 8.24 (J = 8.3 Hz) and δ 7.91 (J = 7.8 Hz), as doublets, and showed

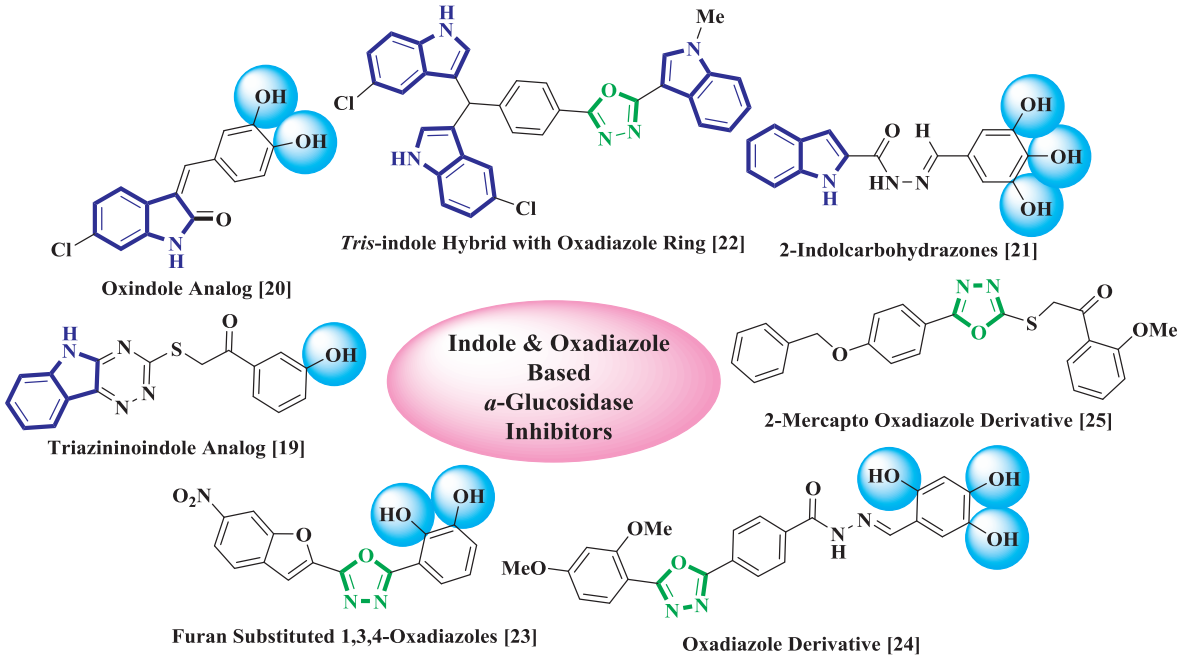

Fig. 1. Rationale of the current study.