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A simple and efficient synthesis of novel inhibitors of alpha-glucosidase based on benzimidazole skeleton and molecular docking studies

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ABSTRACT

A novel series of benzimidazole derivatives were prepared starting from *o*-phenylenediamine and 4-nitro-*o*-phenylenediamine with iminoester hydrochlorides. Acidic proton in benzimidazole was exchanged with ethyl bromoacetate, then ethyl ester group was transformed into hydrazide group. Cyclization using CS_2/KOH leads to the corresponding 1,3,4-oxadiazole derivative, which was treated with phenyl isothiocyanate resulted in carbothioamide group, respectively. As the target compounds, triazole derivative was obtained under basic condition and thiadiazole derivative was obtained under acidic condition from cyclization of carbothioamide group. Most reactions were conducted using both the microwave and conventional methods to compare yields and reaction times. All compounds obtained in this study were investigated for α-glucosidase inhibitor activity. Compounds **6a**, **8a**, **4b**, **5b**, **6b** and **7b** were potent inhibitors with IC_{50} values ranging from 10.49 to 158.2 μM. This has described a new class of α-glucosidase inhibitors. Molecular docking studies were done for all compounds to identify important binding modes responsible for inhibition activity of α-glucosidase.

1. Introduction

The wide range of biological activities of benzimidazole has made it a preferred structure for the modern drug discovery [1,2]. Benzimidazole structures are classified under several ATC groups such as antineoplastic-abemaciclib, antibiotic-ridinilazole, histamine H4 receptor antagonist-toreforant and the proton pump inhibitor-tegoprazan, which represents substances used in both human and veterinary medicine [3,4] (Fig. 1). Thus, benzimidazoles of both synthetic and natural sources are the key components of many bioactive compounds [5–10].

In the literature, a number of synthetic routes have been developed in recent years to bring out new reagents for the synthesis of benzimidazoles. However, the major drawbacks of these methods are the harsh reaction conditions, unsatisfactory yields, use of expensive reagents and long reaction time [11–17]. Therefore, there is a need for an efficient synthetic route for benzimidazoles, which is short and economical. Also, the use of microwave irradiation in chemical reactions leads to easier work-up, higher yields, enhanced reaction rates, and sometimes, to selective conversions with a number of advantages of the eco-friendly approach in the framework of green chemistry [18–21].

The inhibitors of glucosidase enzyme are highly useful for medical therapies, such as diabetes, cancer, hyperlipoproteinemia, and obesity HIV [22–25]. α-Glucosidase inhibitors such as acarbose, miglitol, and voglibose are clinically used in the effective treatment of type-2 diabetes mellitus [26]. These inhibitors effectively decrease the postprandial glucose levels in type-2 diabetic patients [27]. However, they cause various side effects, such as diarrhea, abdominal and flatulence discomfort [28]. Therefore, designing of new α-glucosidase inhibitors with minimum side effects is still a reasonable claim [29]. The benzimidazole derivatives exhibited α-glucosidase [30–32] as well as antidiabetic [33] activity; hence it is important to obtain novel benzimidazole derivatives as antidiabetic compounds.

It would be worthwhile to design and synthesize some new benzimidazole derivatives bearing oxadiazole, triazole and thiadiazole moiety and to screen them for potential biological activities. In this study we obtained benzimidazoles from iminoester hydrochlorides by both microwave irradiation and conventional methods. In the next step, we synthesized benzimidazole derivatives containing ester, hydrazide, carbothioamide group, and oxadiazole, triazole, and thiadiazole ring. The biological properties of the synthesized compounds were evaluated in terms of

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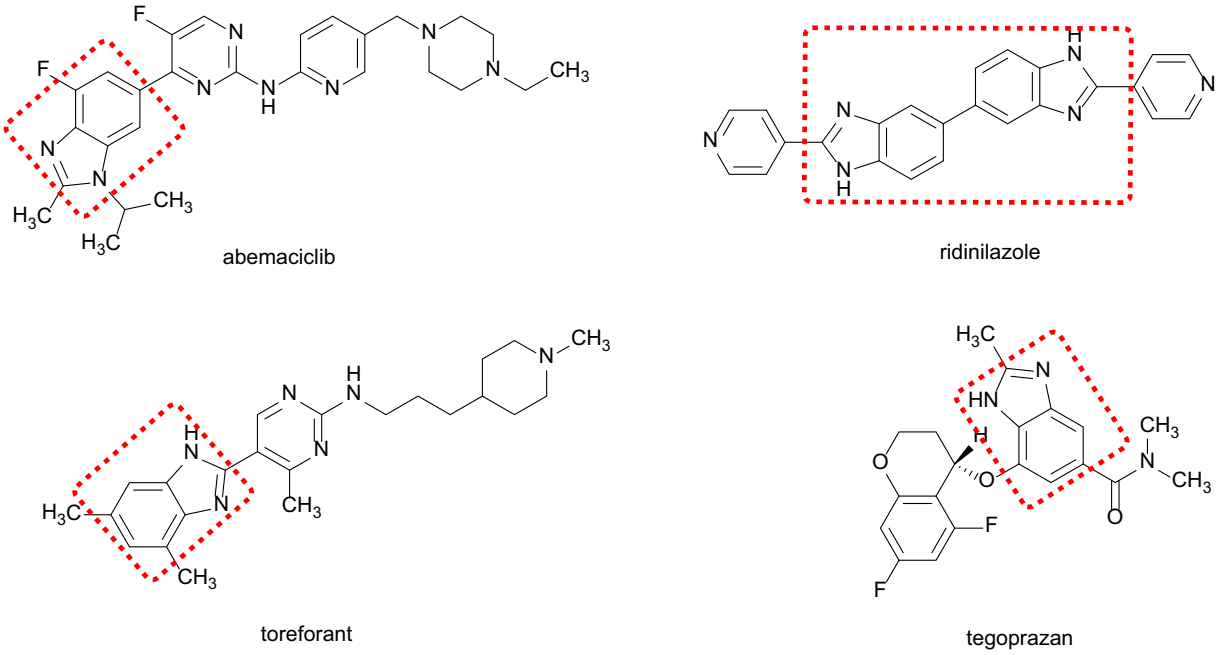

Fig. 1. Some drugs containing benzimidazole structure.

α-glucosidase inhibitory activities. In addition, docking studies were presented to explore their complementarity with the specified binding pockets as well.

2. Results and discussion

2.1. Chemistry

The synthetic process was started from the reaction of 2-(2,4-dichlorophenyl)acetonitrile with ethanol under $HCl_{(g)}$ producing ethyl 2-(2,4-dichlorophenyl)acetimidate hydrochloride (**1**) according to the literature [34]. Synthesis of benzimidazoles (**2a,b**) from ethyl 2-(2,4-dichlorophenyl) acetimidate hydrochloride (**1**) and *o*-phenylenediamine or 4-nitro-*o*-phenylenediamine in both conventional and microwave method, make the procedure a clean, efficient, and cheap method to afford a variety of useful heterocyclic compounds.

Compound **2a,b** reacted with ethyl bromoacetate under both microwave and conventional conditions to produce benzimidazole esters **3a,b**. Compound **3a,b** was further treated with an excess of hydrazine hydrate to produce hydrazide **4a,b** in moderate yield (68%, 81%) under conventional heating and in high yield (82%, 96%) under microwave heating. The reaction of compounds **4a,b** with carbon disulfide in an alkaline medium under conventional and microwave methods followed by acidification resulted in 1,3,4-oxadiazole ring closure producing benzimidazole thiols **5a,b**.

Thiosemicarbazides are known as miscellaneous compounds for the synthesis of different heterocyclic ring systems containing sulfur and nitrogen [35]. Compounds **6a,b** which were thiosemicarbazides derivatives prepared by the reaction of **4a,b** and phenyl isothiocyanate in ethanol, are useful intermediate for the synthesis of 1,3,4-thiadizaole and 1,2,4-triazole derivatives (Scheme 1).

The cyclization of compounds **6a,b** a with 2 N aqueous NaOH solution resulted in the formation of 5-{[2-(2,4-dichlorobenzyl)-(7-nitro)-1*H*-benzimidazol-1-yl]methyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**7a,b**) under both microwave irradiation and conventional method. On the other hand, the synthesis of 5-{[2-(2,4-dichlorobenzyl)-(6-nitro)-1*H*-benzimidazol-1-yl]methyl}-N-phenyl-1,3,4-thiadiazol-2-amine (**8a,b**) were realized through intramolecular cyclization of thiosemicarbazides **6a,b** in the presence of cold concentrated sulfuric acid (Scheme 1). As is known that compounds with the structures like **7a,b** can exist both in thiol and thione tautomeric forms, and the NH signal due to thione form is a more upfield singlet than the SH signal derived from thiol form [19]. According to the IR spectroscopic data of compounds **7a,b** the presence of S—H stretching band at 2663 and 2720 cm^{-1}, respectively, and the absence of an absorption at about 1260–1120 cm^{-1} region characteristic for the C=S stretching vibrations showed that these compounds were in the thiol form.

The structures of new compounds were confirmed by FT-IR, ^1H NMR, ^{13}C NMR spectroscopy and mass spectrometry. All synthesized compounds were screened for their biological activities.

2.2. α-Glucosidase inhibitory assay

All compounds were evaluated with regard to α-glucosidase inhibition and compounds **6a**, **8a**, **4b**, **5b**, **6b** and **7b** showed inhibition at various concentrations. No significant inhibitory effect was detected for other compounds. Among the tested compounds, **4b**, **5b** and **7b** showed the most significant α-glucosidase inhibition. These compounds inhibited α-glucosidase activity by 99 ± 1% at a concentration of 10 μM (Table 1). Acarbose, known as α-glucosidase inhibitor used as anti-diabetic drug, showed an inhibitory effect by 83.3 ± 1.5% at the same concentration. IC_{50} values of compounds **4b**, **5b** and **7b** were determined as 10.49 ± 0.91, 26.93 ± 1.43, and 40.45 ± 1.55 respectively (Table 1). These compounds have a considerable inhibition potential. It was concluded from the biological results for compounds **4b** (IC_{50} 10.49 ± 0.91), **5b** (IC_{50} 26.93 ± 1.43), and **7b** (IC_{50} 40.45 ± 1.55) that both electron donating groups *i.e.* —NH—, —NH_2, and —SH at hydrazide, oxadiazole, and triazole cyclics which are substituted at $N-1$ position of benzimidazole, as well as electron withdrawing group *i.e.* —NO_2 on benzimidazole ring play an effective role in this assay. The binding interactions of promising compounds (**4b**, **5b**, **7b**) were proved by using molecular docking.

Additionally, we have calculated the logP values of these compounds using the ClogP software to gain some insight on the