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Original article

Synthesis of novel derivatives of 4-methylbenzimidazole and evaluation of their biological activities

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ABSTRACT

4-Methylbenzimidazole **1**–**28** novel derivatives were synthesized and evaluated for their antiglycation and antioxidant activities. Compounds **1**–**7** and **11** showed excellent activities ranged 140–280 μM, better than standard drug rutin (294.46 ± 1.50 μM). Compound **1**–**28** were also evaluated for DPPH activities. Compounds **1**–**8** showed excellent activities, ranging 12–29 μM, better than standard drug *n*-propylgallate (IC_{50} = 30.30 ± 0.40 μM). For superoxide anion scavenging activity, compounds **1**–**7** showed better activity than standard *n*-propylgallate (IC_{50} = 106.34 ± 1.6 μM), ranged 82–104 μM. These compounds were found to be nontoxic to THP-1 cells.

1. Introduction

Benzimidazole is a versatile heterocyclic pharmacophore with diverse range of medicinal properties as evaluated by numerous research groups [1]. A number of commercially available drugs that contain benzimidazole ring are proton pump inhibitors [2] anti-helmintics [3] antidopaminergics [4] antipsychotics [5] ionodilators [6] and anticancers [7].

Hydrazone derivatives are widely used in pharmaceutical industry [8,9], such as Isonicotinhydrazide and its N-isopropyl acylhydrazone have been used as effective therapeutics for tuberculosis [10]. The hydrazones also reported for their bactericidal [11,12], anti-convulsant [13], analgesic [14], anti-inflammatory [15] and vasodilator [16] activities.

Metal complexes of hydrazones also drew considerable attention due to their medicinal and catalytic properties [17,18].

Discovery of glycation inhibitor is a main advancement for the treatment of late diabetic complications. At present, number of efficient glycation inhibitors is few; the requirement of novel glycation inhibitors is still unmet [19]. Horrible incident of type-2 diabetes is increasing; its harmful effects are mostly endorsed to the formation of sugar derived substances called advanced glycation end products (AGEPs) [20]. AGEPs are important pathogenic mediators of approximately all diabetic complications [21]. A lot of efforts have been focused on reversing the glycation process by discovering potential new glycation inhibitors [22]. These

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molecular inhibitors can cleave AGEPs cross-links and possibly opens the opportunity to reverse the steady process of diabetic complications [23]. On the other hand, AGEPs receptor binding induces the production of reactive oxygen species (ROS), which results in the activation of pleiotropic transcription factor nuclear factor NF-κB, thus causing multiple pathological alterations in gene expression [24].

Results suggest that oxidative stress has significant role in the development of diabetic complications, both microvascular and cardiovascular. It has been shown that the metabolic abnormalities associated with diabetes results in mitochondrial superoxide overproduction. This increased superoxide production is vital mediator of diabetes tissue damage, which is involved in the activation of 5 pathways leading to the pathogenesis of complications and direct inactivation of 2 antiatherosclerotic enzymes, eNOS and prostacyclin synthase [25].

In the continuation of our research on medicinal chemistry, we have synthesized a series of benzimidazoles **1**–**28** with benzohydrazide moiety. Our previous studies suggested that benzohydrazide moiety has potent antioxidant, antiglycation and antileishmanial activities [26]. In view of the potential of these classes of organic compounds we proposed if benzimidazole ring and benzohydrazide moieties are combined in a single molecule to see whether it improves their efficacy or not.

Antiglycation agents with antioxidant properties may serve as viable lead compounds for the development of new antidiabetic drugs which will possibly not only reverse the glycation process but will also assist to eradicate glycation induced oxidative stress.

2. Results and discussion

2.1. Chemistry

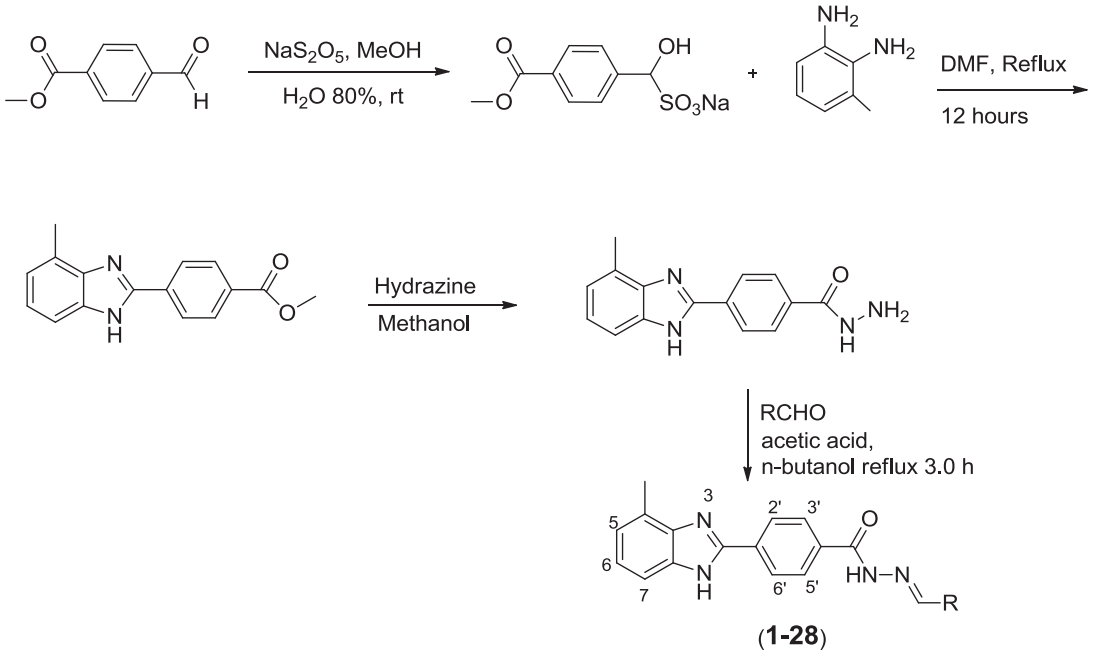
The synthesis of novel derivatives of 4-benzimidazole are commenced with the synthesis of sodium metasulfite adduct according to literature protocol [27]. The resulting sulfite adduct was refluxed with 3-methyl-1,2-diaminobenzene in DMF for 6 h to give the arylester substituted benzimidazole. The benzohydrazide of benzimidazole was formed by refluxing arylester of benzimidazole with methanolic hydrazine hydrate (Scheme 1).

The synthesis of benzimidazole benzohydrazide Schiff bases (**1**–**28**) was accomplished by reacting different aldehydes with benzimidazole benzohydrazide in *n*-butanol in the presence of catalytic amount of acetic acid as shown in Scheme 1.

2.2. DFT study over configuration (Z/E)

The stereochemical configuration of double bond −N═CH-R in 4-methylbenzimidazoles **1**–**28** (Scheme 1) may be assigned as *Z* or *E*. Electronic energies and vibration modes *i.e*, $\nu_{C=O}$, $\nu_{N=C}$ and ν_{CH} (CH in −N═**CH**-R), have been calculated for randomly selected five compounds (**3**, **5**, **8**, **16** and **2**5) using DFT calculations at the b3lyp/6-311++G(d,p) level to determine the configuration. The calculated electronic energies showed that the *E* configuration is relatively more stable than *Z* by (5, 9, and 8 kcal/mol) for **3**, **5** and **8** compounds, respectively. However, for compound **16** and **25**, the hydrogen bond formation between −CO−**NH**− group and (i) nitrogen atom of pyridine ring in **16** ($d = 1.93$ Å) and (ii) oxygen atom of furan moiety in **25** stabilize the *Z* configuration by 7 and 2 kcal/mol with regard to *E* configuration, respectively (Fig. 1).

To confirm these results, the vibration modes of $\nu_{C=O}$, $\nu_{N=C}$ and ν_{CH} (CH in −N═**CH**-R) were calculated at the same level of theory and compared the corresponding experimental data (Table 1). The variation of vibrational modes $\Delta\nu_{C=O}$ ($\Delta\nu_{N=C}$) between the calculated and experimental values was very small for *E* and *Z* configurations, respectively. However, the large variation of vibration modes of ν_{CH} (CH in −N═**CH**-R) between the *E* and *Z* configuration allow a better assignment of absolute configuration. On one hand, the *E* configurations for the compounds **3**, **5** and **8** showed a variation of 3–15 cm^{-1} to experimental mode; while for *Z* configuration the variation vary from 105 to 132 cm^{-1}. These results are in good agreement with electronic energies obtained above. Therefore, the stereochemistry of −N═CH− double bond for **3**, **5** and **8** is *E* configuration. On the other, based on the electronic energy, the *Z* configurations of **16** and **25** are more stable than E ones. The stable configuration of **16** and **25** is confirmed by ν_{CH} (CH in −N═**CH**-R)



Scheme 1. synthesis of benzimidazole benzohydrazide **1**–**28**.