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Design, synthesis of novel azolyl flavonoids and their protein tyrosine Phosphatase-1B inhibitory activities

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ABSTRACT

A series of azolyl flavonoids were synthesized and characterized by NMR, IR, MS and HRMS spectra. All the newly prepared compounds were screened for their potential protein tyrosine phosphatase inhibitory activities. Bioactive assay manifested that most of the azolyl flavonoids exhibited good protein phosphatase 1B (PTP1B) inhibitory activities. Especially, triazolyl flavonoid **6a** displayed the best inhibitory activity (IC_{50} = 1.6 μM) with 9.9-fold selectivity for PTP1B over the closely related T-cell protein tyrosine phosphatase (TCPTP). Cell viability assays indicated **6a** has lower cytotoxicity. Molecular modeling and dynamics studies revealed the reason of selectivity for PTP1B over TCPTP. Quantum chemical studies were carried out on these compounds to understand the structural features essential for activity.

1. Introduction

Protein tyrosine phosphatases (PTPs) play an important role in modulation several cellular signal transduction pathways and catalysis protein tyrosine dephosphorylation [1]. Dysregulation of PTPs activities lead to the pathogenesis of many human diseases such as obesity, autoimmune disorders, cancers and diabetes [2]. Protein tyrosine phosphatases 1B (PTP1B), a key member of the PTP family, could regulate the insulin sensitivity and act by directly inactivating insulin receptor (IR) through dephosphorylation tyrosine residues in the regulatory domain. Insulin exerts an important effect in glucose uptake. Resistance of insulin results in reduced glucose intake and increased hepatic glucose output, which led to the increase of the blood glucose level [3]. A number of synthetic PTP1B inhibitors have been discovered [4–6]. Compound **1** was a classic PTP1B inhibitor (IC_{50} = 32 nM) designed on the basis of catalytic pocket characteristics and demonstrated modest caco-2 permeability (0.4×10^{-6} cm/s), but without selectivity (Fig. 1). Compound **2** derived from natural products has also been proved to be active against PTP1B with micromolar level of activity (IC_{50} = 2.42 μM), however, the selectivity or membrane permeability was not further reported [7]. PTP inhibitors especially that can inhibit the particular PTP with good permeability received much attention [8].

Flavonoids, a type of plant phenolic compounds, are widely found in nature with large potentiality in the treatment of cancer, car-diovascular disease and neurodegenerative disorders. Recently, these natural flavones have drawn special attention as they are found to be good PTP1B inhibitors with low toxicity and high hypoglycemic effects [9]. It has disclosed that they could inhibit PTP1B activity in a non-competitive way different to the traditional drugs [10]. More and more flavonoids received much attention due to their unique properties in the inhibition of PTP1B (Fig. 1).

Azoles (thiazoles, oxazoles, carbazoles, imidazoles, benz-imidazoles, triazoles, tetrazoles etc.) are an important type of nitrogen heterocycles with aromaticity and electron rich properties. The special structure enables their derivatives to easily bind with the enzymes and receptors in organisms through noncovalent interactions such as coordination and hydrogen bonds, thereby giving them various medicinal applications. Recently, research has established that the introduction of nitrogen-containing heterocyclic moieties into the flavonoid backbone can improve bioactivity [11–14]. Especially, it reported that presence of azole ring is beneficial to improve the PTP1B inhibitory activity [15,16]. However, to the best of our knowledge, azolyl flavonoids have been rarely reported. In view of the above observations herein we incorporated different azole fragments into the O-7 position of flavonoid to generate a novel class of azolyl flavonoids. It evidenced that alkyl linkers can modulate physico-chemical properties and thus improve biological potency [17]. With the aim of better understanding structure–activity relationships and increasing flexibility, different lengths of alkyl chains were introduced into the target compounds to investigate the influence of linkers on bioactivities.

The designed structures of this series of novel azolyl flavonoids are shown in Scheme 1. All the newly synthesized compounds were

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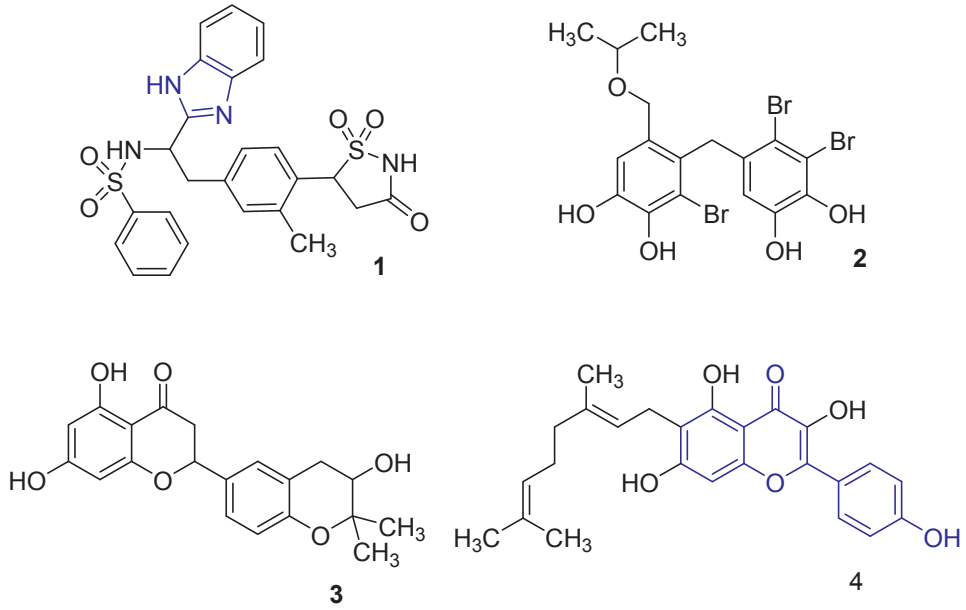
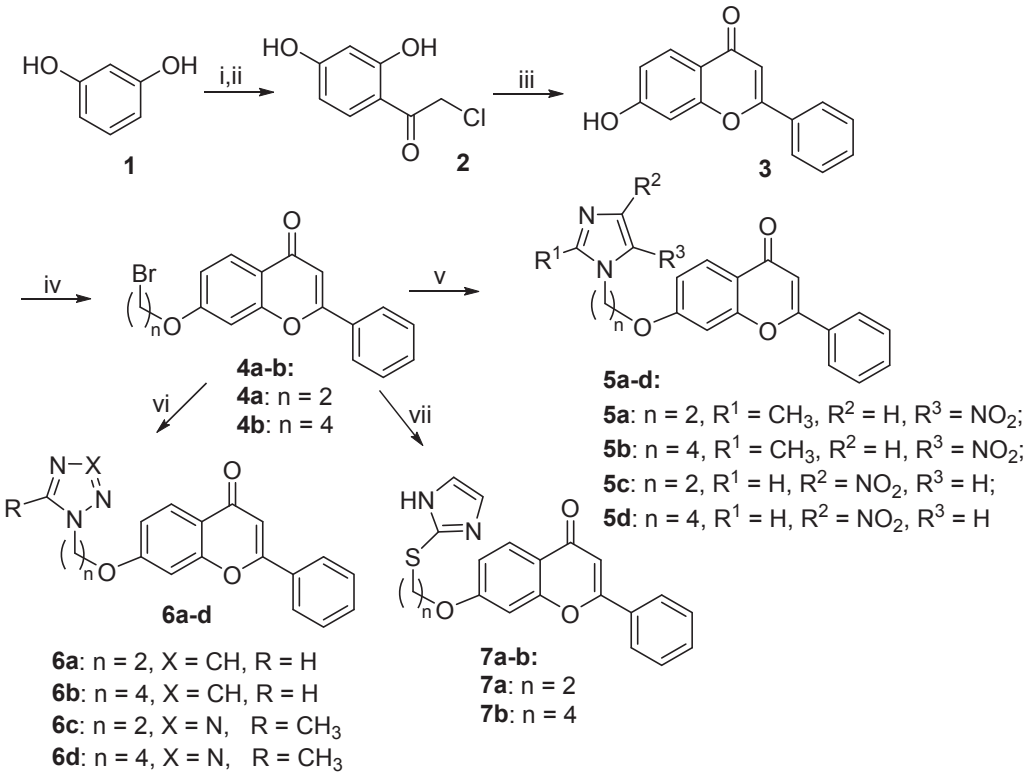


Fig. 1. Some reported PTP1B inhibitors.



Scheme 1. Synthetic routes of azolyl flavonoids. Reagents and conditions: (i) $ClCH_2CN$, EtOEt, HCl (g), 0 °C; (ii) 1 mol/L HCl, H_2O, reflux; (iii) benzaldehyde, 10%NaOH, rt, EtOH; (iv) alkyl dibromides, K_2CO_3, acetone, 50 °C; (v) 2-methyl-5-nitroimidazole or 4-nitroimidazole, K_2CO_3, acetonitrile, 50 °C; (vi) triazole or 5-methyl tetrazole, K_2CO_3, acetonitrile, 50 °C; (vii) imidazole-thiol, K_2CO_3, acetonitrile, 50 °C.

characterized by spectral analysis and evaluated for their inhibition of PTP1B *in vitro*. Molecular modeling, molecular dynamics, energies and plots of HOMO and LUMO, and plots of MEP were also investigated by quantum chemical calculation to understand the structural features essential for activity.

2. Results and discussion

2.1. Chemistry

The target azolyl flavonoids were synthesized according to the synthetic route outlined in Scheme 1. Condensation of 1,3-benzenediol with chloro-acetonitrile in the presence of $ZnCl_2$ in ether was followed by hydrolysis in water and produced ketone **2** in 86% yield. The resulting **2** was reacted with benzaldehyde in ethanol with 10% NaOH, was followed by acidification with aqueous HCl to afford intermediate **3** in satisfactory yields [18]. Compound **3** was then further treated with alkyl dibromides in acetone using potassium carbonate as base to afford bromides **4a-b** with yields of 50–76% [19]. The target azolyl flavonoids **5a–d**, **6a–d** and **7a–b** were conveniently and efficiently obtained in 50–67% yields by the reaction of bromides **4a–b** respectively with 2-methyl-5-nitroimidazole, 4-nitroimidazole, triazole, tetrazole or