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Synthesis and bioactivity of 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-xylopyranosyl-1,3,4-oxa(thia)diazol-2-amines

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ABSTRACT

A series of new *N*′-[*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-[(1-aryl-1*H*-tetrazol-5-yl) sulfanyl]acetohydrazides **5a**–**5e** were synthesized rapidly in high yields from 2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl)acetohydrazides **3a**–**3e** and 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiocyanate **4**, then **5a**–**5e** were converted to a series of new 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amines **6a**–**6e** and 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amines **7a**–**7e**, respectively under mercuric acetate/alcohol system or acetic anhydride/phosphoric acid system, then deacetylated in the solution of CH_3ONa/CH_3OH. All of the novel compounds were characterized by IR, ^1H NMR, ^{13}C NMR, MS and elemental analysis. The structures of compounds **2e**, **3e**, 5a and **5c** have been determined by X-ray diffraction analysis. Some of the synthesized compounds displayed PTP1B inhibition and microorganism inhibition.

1. Introduction

Most heterocycles have a wide application as drugs in the pharmaceutical industry, as dyes or in agriculture. Tetrazoles, being an important class of heterocyclic compounds, can be used not only as precursors to a variety of nitrogen-containing heterocycles but also as materials with applications in diverse areas such as pharmaceuticals, explosives, information recording systems, and corrosion inhibitors.[1–3] 1,3,4-Oxadiazole compounds represent one of the most active classes of compounds possessing broad spectrum of biological activities as antibacterial, anti-fungal, analgesic, anti-inflammatory, anti-hypertension and muscle-relaxing activities.[4,5] A large number of 1,3,4-thiadiazoles have been applied in the agricultural field as herbicides,[6] fungicides[7] and bactericides.[8] In the medical field, one of the best known drugs based on a 1,3,4-thiadiazole is acetazolamide (acetazola),[9] a carbonic anhydrase inhibitor launched in 2003.[10] The lead compounds modified by saccharides and their derivatives can decrease the toxicity and side effect efficiently. They can also enhance the pharmaceutical effect. Therefore, it is a promising research project to modify lead compounds by saccharides.[11] Xylose is a non-caloric sweetener, used for diabetes and obesity.

Protein tyrosine phosphatase 1B (PTP1B) is a very important protein tyrosine phosphatase that has been implicated in the regulation of insulin action and in other signal transduction pathways.[12] The study indicates that protein tyrosine phosphatase 1B is a novel target for the treatment of diabetes and obesity. Inhibition of PTP1B's activity could improve the sensitivity of insulin signaling. To seek highly effective inhibitors of PTP1B has a promising application in diabetes and obesity therapy.

In the recent years, we had reported that various glycosyl isothiocyanates exhibited a high reactivity to the synthesis of carbohydrates and their derivatives.[13–28] Our intention was therefore to realize reinforcement of physiological activities by means of combining xylosyl and aryltetrazole with 1,3,4-oxadiazoles or 1,3,4-thiadiazoles. The synthetic route was shown in Scheme 1.

2. Results and discussion

2.1. Chemistry

In the process of the synthesis of *N*′-[*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl) acetohydrazides (**5a**–**5e**), anhydrous benzene was used as solvent to avoid the hydrolysis of 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiocyanate (**4**). The appropriate molar ratio of hydrazine hydrate with ethyl 2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl)acetates (**2a**–**2e**) for the synthesis of 2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl)

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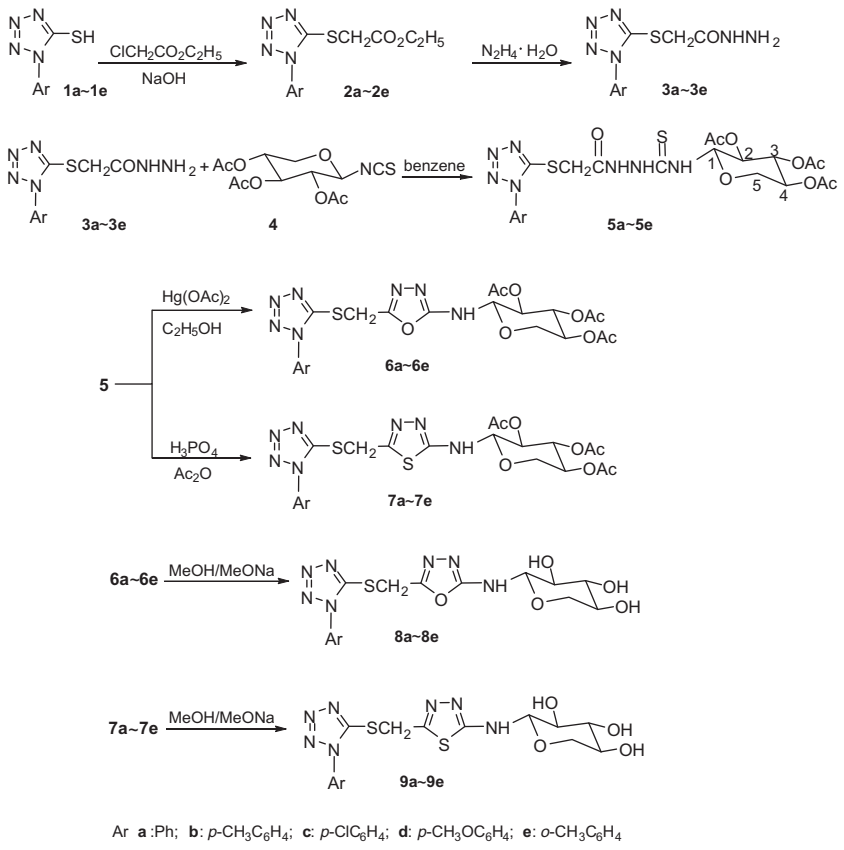

Scheme 1.

acetohydrazides (**3a**–**3e**) was 5:1. Then the yield was improved and the products were purified easily.

The 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amines (**6a**–**6e**) were prepared by cyclization of the intermediate of compounds **5a**–**5e** with mercury acetate in high yield. The 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amines (**7a**–**7e**) were obtained in high yield by the treatment compounds **5a**–**5e** with Ac_2O and phosphoric acid.

The structures of the compounds were established and confirmed on the basis of their elemental analyses and spectral data. The IR spectra of compounds **5a**–**5e** exhibited strong bands at about 1540 cm^{-1} which was attributed to characteristic absorption of NH–CS–NH. However, as to the target compounds **6a**–**6e** and **7a**–**7e**, the characteristic absorption of NH–CS–NH disappeared. These phenomena suggested the existence of the oxadiazole/thiadiazole. The signals at about 1745 cm^{-1} showed the absorption feature of C=O in the acetyl of sugar ring. However, in the target compounds **8a**–**8e** and **9a**–**9e**, the characteristic absorption of C=O disappeared, and the strong bands appeared at about 3300 cm^{-1} which was attributed to characteristic absorption of N–H and O–H. These indicated that the acetyl in the sugar ring had been removed. The medium band at about 910 cm^{-1} was the characteristic absorption of C1–H in the sugar ring, which indicated that all the compounds were β-anomer.

In the ^1H NMR spectra of compounds **6a**–**6e** and **7a**–**7e**, three single peaks appearing at about δ 2.00 were attributed to hydrogen atoms of acetyl in the sugar ring; while multiple peaks appearing at about δ 3.40–5.30 were attributed to hydrogen atoms of the sugar ring. Additionally, the signals of the sugar ring C1–H displayed at about δ 5.30 and revealed a triplet-peak for coupling with C2–H and N–H.

2.2. Crystal structures

To further understand the important effect of structural factors on their interactions, the crystal structure of compounds **2e**, **3e**, **5a** and **5c** were investigated. Transparent colorless crystals were obtained by slow evaporation from ethanol solution over several days. So far, attempts to obtain single crystals of **6a**–**6e**, **7a**–**7e**, **8a**–**8e** and **9a**–**9e** have been unsuccessful. The molecular structures of **2e**, **3e**, **5a** and **5c** are shown in Figures 1–4, respectively. Compound **2e** belongs to monoclinic system with space *P*2 (1)/*c* and unit cell parameters: a = 7.5908(15) Å, b = 17.547(4) Å, c = 10.757(2) Å, β = 103.48(3)°, Z = 4, D = 1.260 mg/m^3, μ = 0.234 mm^{-1}, F(0 0 0) = 528. Compound **3e** belongs to monoclinic system with space *P*2 (1)/*c* and unit cell parameters: a = 17.640(4) Å, b = 8.9326(18) Å, c = 7.8119(16) Å, β = 90.46(3)°, Z = 4, D = 1.361 mg/m^3, μ = 0.259 mm^{-1}, F(0 0 0) = 504. Compound **5e** belongs to Orthorhombic system with space *P*2(1)2(1)2(1) and unit cell parameters: a = 9.5924(19) Å, b = 12.641(3) Å, c = 23.292(5) Å, β = 103.48(3)°, Z = 4, D = 1.335 mg/m^3, μ = 0.243 mm^{-1}, F(0 0 0) = 1184. Compound **5c** belongs to Monoclinic system with space *P*2(1) and unit cell parameters: a = 9.7023(19) Å, b = 12.800(3) Å, c = 11.889(2) Å, β = 99.36(3)°, Z = 2, D = 1.407 mg/m^3, μ = 0.331 mm^{-1}, F(0 0 0) = 642.

2.3. Biological activities

Compounds **6a**–**6e**, **7a**–**7e**, **8a**–**8e** and **9a**–**9e** were evaluated in inhibition of PTP1B. The $NaVO_3$ was used as a reference of positive drug. The IC_{50} of $NaVO_3$ is 10 μmol/L. The bioassay results showed that compounds **6a**, **6b**, **6c**, **6e**, **8a** and **8e** had a very potent PTP1B inhibition activity. Compounds **6a**–**6e**, **7a**–**7e**, **8a**–**8e** and **9a**–**9e** were also tested for inhibition of microorganism include *Staphylococcus aureus*, *Colibacillus* and *Candida albicans*. The bioassay results