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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

Yao-Wu He [a,b,d], Ling-Hua Cao [a,b,*], Jian-Bin Zhang [c], Duo-Zhi Wang [b], Haji Akber Aisa [a,*]

[a] Key Laboratory of Chemistry of Plant Resources in Arid Regions, Chinese Academy of Sciences, Xinjiang Technical Institute of Physics and Chemistry, Urumqi 830011, PR China
[b] College of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, PR China
[c] Physics and Chemistry Test Center of Xinjiang University, Urumqi 830046, PR China
[d] Graduate University of the Chinese Academy of Sciences, Beijing 100049, PR China

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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)

* Corresponding authors.
*E-mail addresses:* clhxj@xju.edu.cn (L.-H. Cao), haji@ms.xjb.ac.cn (H.A. Aisa).

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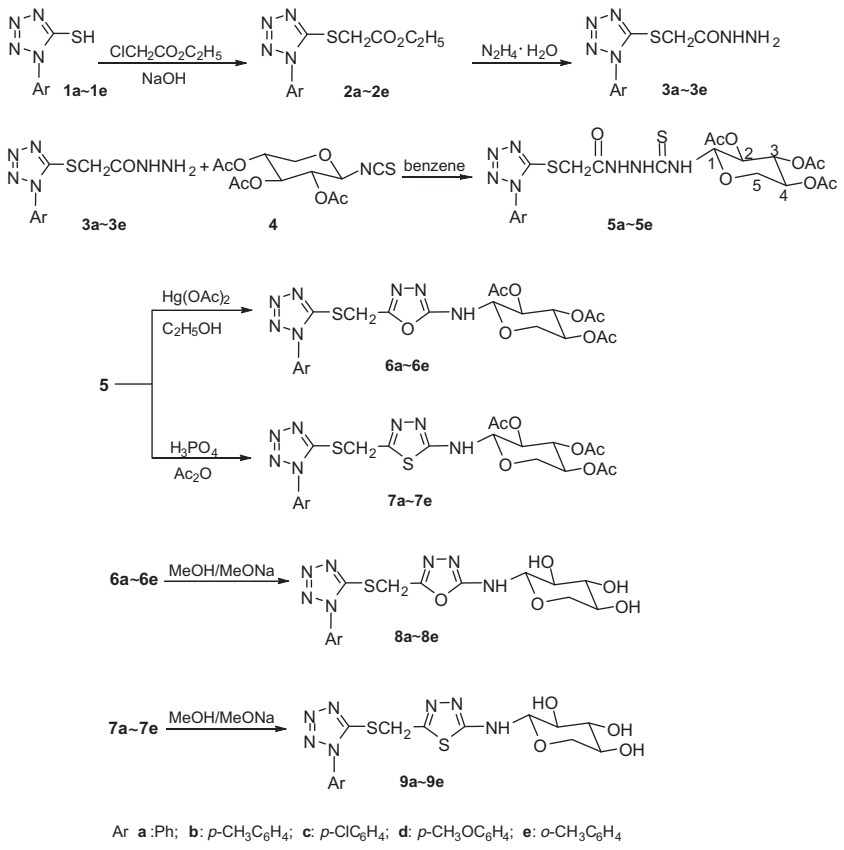


**Scheme 1.**

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 $\delta$ 2.00 were attributed to hydrogen atoms of acetyl in the sugar ring; while multiple peaks appearing at about $\delta$ 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 $\delta$ 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, $\beta$ = 103.48(3)°, $Z$ = 4, $D$ = 1.260 mg/$m^3$, $\mu$ = 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, $\beta$ = 90.46(3)°, $Z$ = 4, $D$ = 1.361 mg/$m^3$, $\mu$ = 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, $\beta$ = 103.48(3)°, $Z$ = 4, $D$ = 1.335 mg/$m^3$, $\mu$ = 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, $\beta$ = 99.36(3)°, $Z$ = 2, $D$ = 1.407 mg/$m^3$, $\mu$ = 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

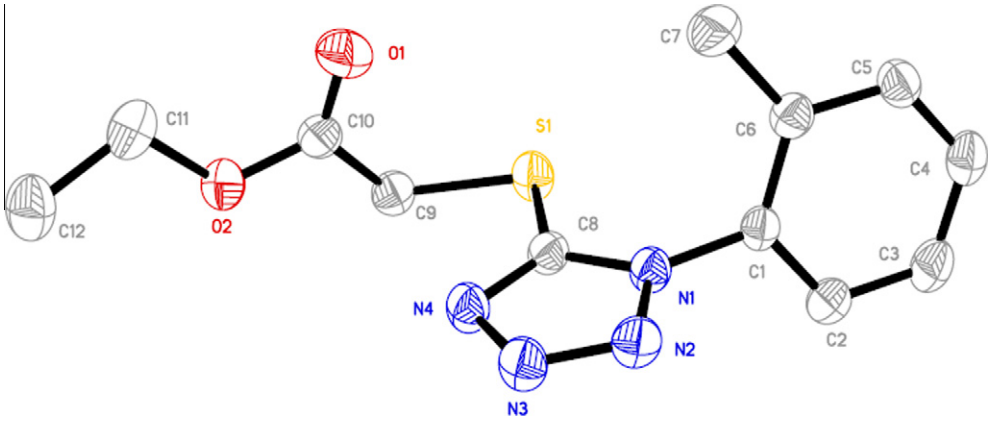


**Figure 1.** X-ray crystallographic structure of compound **2e**.

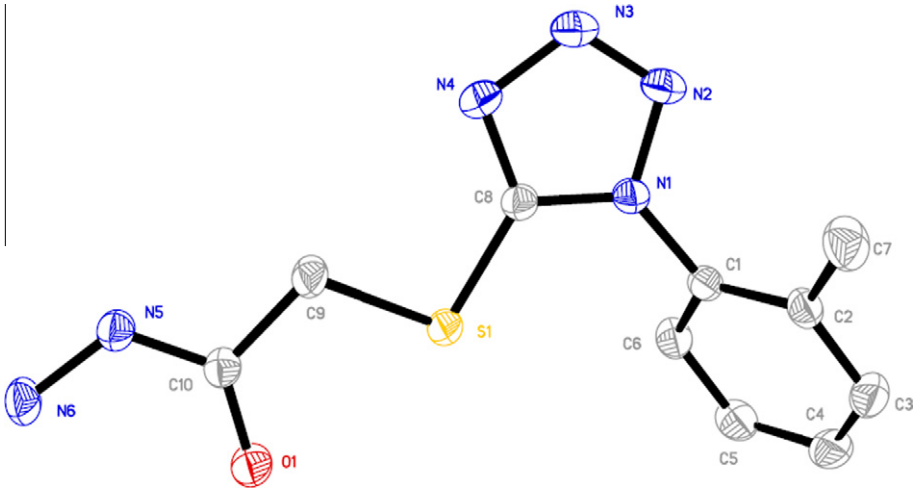


**Figure 2.** X-ray crystallographic structure of compound **3e**.

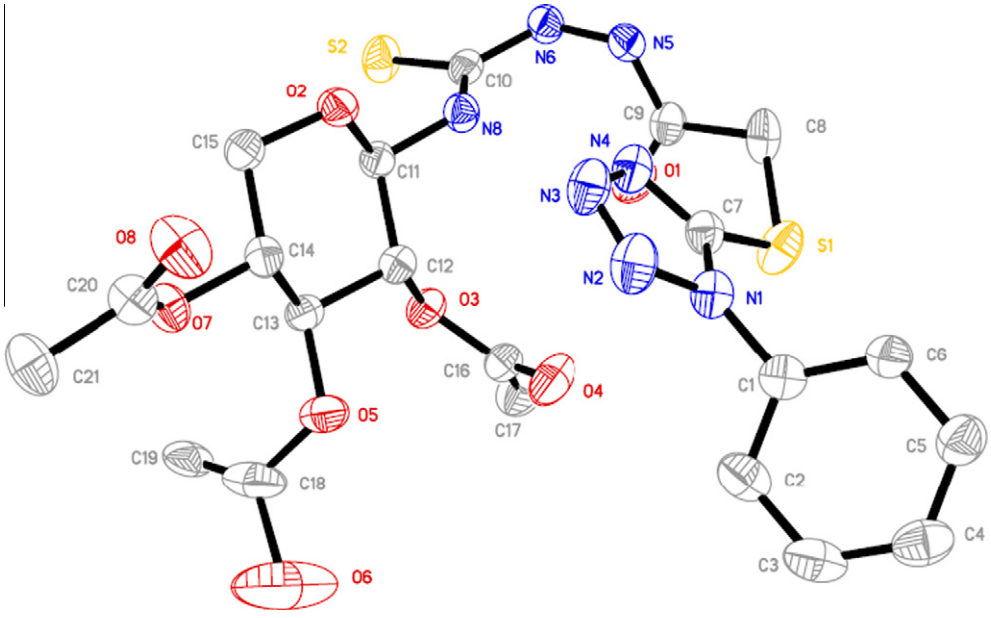


**Figure 3.** X-ray crystallographic structure of compound **5a**.

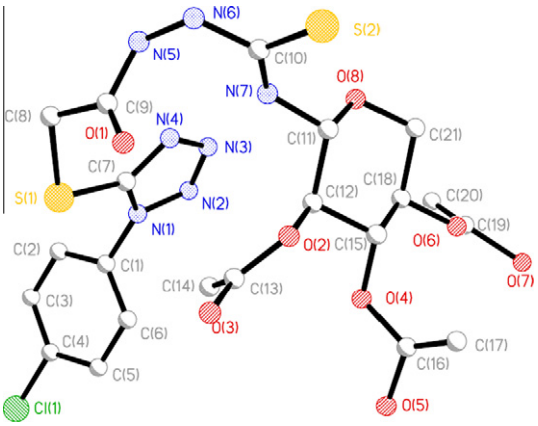


**Figure 4.** X-ray crystallographic structure of compound **5c**.

showed that compounds **6a**, **6b**, **6c**, **6e**, **8a**, **8c**, **8e** and **9e** had a rather *S. aureus* inhibition activity, and compounds **6b**, **6c**, **6e** and **8e** had some *Colibacillus inhibition* activity, but no compounds displayed significantly *C. albicans* inhibition activity. The activity results were shown in Table 1. These results revealed that the synthesized oxadiazole derivatives had higher inhibition activity than thiadiazole derivatives, and the acetylated compounds had better inhibition activity than the deacetylated compounds. The α 1B adrenergic receptor agonist activity of **6d** and **7d** was tested, but they did not show significant activity.

## 3. Experimental

### 3.1. General methods

Melting points were determined on a Yanaco MP-S3 micro melting point apparatus and are corrected. The $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on a Varian Inova-400 or Varian Inova-600 (using TMS as internal standard). Chemical shifts are expressed as $\delta$ units, using $CDCl_3$, DMSO-$d_6$ or $CD_3OD$ as solvent. The IR spectra were recorded as KBr pellets on a Bruker FT-IR Equinox 55 instrument. ESI-MS data were obtained in an HP 1100 LC/MS instrument. Elemental analyses were performed on a Thermo Flash EA-1112 analyzer. The crystal structure of compounds was determined on an R-AXIS SPIDER X-ray diffractometer. Analytical thin-layer chromatography (TLC) was performed on silica gel $GF_{254}$ (Qingdao, China) and 0.5% CMC, and detected by UV light or iodine vapor. Column chromatography was performed on silica gel (100–200 mesh). All reagents were commercial products of analytical grade and were used directly without processing unless noted otherwise. The boiling point range of petroleum ether was 60–90 °C.

**Table 1**
Activity results of tested compounds

| Compd | PTP1B[a] inhibition | | Microorganism inhibition | |
|---|---|---|---|---|
| | $IC_{50}$ (μmol/L) | *Staphylococcus aureus* | *Colibacillus* | *Candida albicans* |
| **6a** | 12.64 | ++∼+++ | — | — |
| **6b** | 2.76 | ++∼+++ | + | — |
| **6c** | 3.98 | ++∼+++ | ±∼+ | — |
| **6d** | — | — | — | — |
| **6e** | 15.71 | ++ | ±∼+ | — |
| **7a** | — | — | — | — |
| **7b** | 220.54 | — | — | — |
| **7c** | — | — | — | — |
| **7d** | 193.09 | — | — | — |
| **7e** | — | — | — | — |
| **8a** | 28.06 | + | ±∼+ | — |
| **8b** | 117.25 | — | — | — |
| **8c** | 111.01 | + | — | — |
| **8d** | 539.68 | — | — | — |
| **8e** | 18.54 | +∼++ | — | — |
| **9a** | 70.34 | — | — | — |
| **9b** | — | — | — | — |
| **9c** | 166.85 | — | — | — |
| **9d** | 227.43 | — | — | — |
| **9e** | 94.46 | +∼++ | — | — |
| $NaVO_3$ | 10 | | | |

±∼+: Diameter of antibacterial circle <4 mm; +: diameter of antibacterial circle 4–5 mm; ++: diameter of antibacterial circle 5–7 mm; +++: diameter of antibacterial circle 7–9 mm; ++++: diameter of antibacterial circle ⩾10 mm.

[a] PTP1B: Protein tyrosine phosphatase 1B; $IC_{50}$: 50% inhibiting concentration.

### 3.2. Compounds 1a–1e were prepared by the published procedure[29]

Compound **1a:** White solid, yield 90%; mp 162–164 °C (lit.[29] yield 96%, mp 155–156 °C).
Compound **1b:** White solid, yield 89%; mp 166–168 °C.
Compound **1c:** White solid, yield 90%; mp 178–180 °C.
Compound **1d:** White solid, yield 87%; mp 172–173 °C.
Compound **1e:** White solid, yield 90%; mp 139–141 °C.

### 3.3. Preparation of ethyl 2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl) acetates 2a–2e in terms of the literature[10]

Compounds **2a**–**2e** were prepared according to the literature while using ethyl chloroacetate replaces methyl chloroacetate as a material.
Compound **2a:** White solid, yield 72%, mp 79–80 °C.
Compound **2b:** White solid, yield 61%, mp73–74.5 °C.
Compound **2c:** White solid, yield 65%, mp 74–77 °C.
Compound **2d:** White solid, yield 62%, mp 61–62 °C.
Compound **2e:** White solid, yield 70%, mp 77–78 °C.

### 3.4. Preparation of compounds 2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl)acetohydrazides 3a–3e

A solution of 1 mmol compounds **2a**–**2e** and 5 mmol hydrazine hydrate in 10 mL of ethanol was stirred and refluxed for about 4 h. The solvent was removed to give a residue that was recrystallized from ethanol.
Compound **3a:** White solid, yield 80%, mp 161–163 °C (lit.[29] mp 158–159 °C).
Compound **3b:** White solid, yield 76%, mp 181–183 °C.
Compound **3c:** White solid, yield 70%, mp 175–176 °C.
Compound **3d:** White solid, yield 81%, mp178–179.5 °C.
Compound **3e:** White solid, yield 78%, mp 102–104 °C.

### 3.5. 2,3,4-Tri-*O*-acetyl-xylopyranosyl isothiocyanate 4 was prepared by the published procedure[30]

#### 3.5.1. 2,3,4-Tri-*O*-acetyl-xylopyranosyl isothiocyanate 4

Yield 40%, mp 85–86 °C (lit.[30] yield 41%, mp 88–90 °C).

### 3.6. General procedure for the preparation of *N*′-[*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-(1-aryl-1*H*-tetrazol-5-ylsulfanyl)acetohydrazides 5a–5e

An equimolecular mixture of **4** (5 mmol) and **3a**–**3e** (5 mmol) in 20 mL of dry benzene was heated under reflux about 4 h. After the reaction was completed (TLC, expended matter: EtOAc–petroleum ether 3:1, v/v), the mixture was concentrated. The pure production was obtained by recrystallization from ethanol.

#### 3.6.1. *N*′-[*N*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)acetohydrazide (5a)

White solid, yield 75%, mp 178–180 °C; $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ 2.03, 2.05, 2.06 (3s, 9H, $CH_3CO$), 3.41 (t, $J$ = 11 Hz, 1H, C4–H), 3.87 (dd, $J$ = 11.1, 5.6 Hz, 1H, C5–Ha), 4.10 (d, $J$ = 15.6 Hz, 1H, $SCH_a$), 4.15 (d, $J$ = 15.6 Hz, 1H, $SCH_b$), 4.76 (m, 1H, C5–Hb), 4.97 (t, $J$ = 9.3 Hz, 1H, C2–H), 5.29 (t, $J$ = 9.6 Hz, 1H, C3–H), 5.53 (t, $J$ = 9.3 Hz, 1H, C1–H), 7.62–7.71 (m, 5H, ArH); 8.16 (d, $J$ = 9.1 Hz, 1H, NH), 10.01 (s, 1H, NH), 10.54 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150 MHz): $\delta$ 184.75 (C=S), 172.13, 171.86, 170.23, 167.83 (C=O), 166.56 (C=N), 157.24, 138.14, 134.56 (Phenyl-C), 86.17 (C1), 75.41 (C3), 68.79 (C5), 54.26 (C4), 43.35 (C2), 27.18, 20.96, 19.67 ($CH_3$); IR (KBr) $v$: 3327, 3220 (N–H), 1742 (C=O), 1502 (C=N, Aryl), 1535 (NH–CS–NH), 1234 (N–N=C), 1039 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 590 (15, [M+23]$^+$), 568 (32, [M+H]$^+$). Anal. Calcd for $C_{21}H_{25}N_7O_8S_2$: C, 44.44; H, 4.44; N, 17.27. Found: C, 44.52; H, 4.42; N, 17.32.

#### 3.6.2. *N*′-[*N*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl) thiocarbamoyl]-2-[1-(4-methylphenyl)-1*H*-tetrazol-5-ylsulfanyl]acetohydrazide (5b)

White solid, yield 73%, mp 188.5–190 °C; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 1.99, 2.01, 2.04 (3s, 9H, $CH_3CO$), 2.53 (s, 3H, $CH_3$), 3.46 (t, $J$ = 11.1 Hz, 1H, C4–H), 3.91 (dd, $J$ = 11.4, 5.4 Hz, 1H, C5–Ha), 4.79 (s, 2H, $SCH_2$), 4.85 (m, 1H, C5–Hb), 4.93 (t, $J$ = 9.0 Hz, 1H, C2–H), 5.22 (t, $J$ = 9.6 Hz, 1H, C3–H), 5.41 (t, $J$ = 9.0 Hz, 1H, C1–H), 7.27–7.36 (m, 4H, ArH), 8.37 (d, $J$ = 9.8 Hz, 1H, NH), 9.75 (s, 1H, NH), 10.22 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 181.25 (C=S), 171.58, 170.24, 160.31, 159.56 (C=O), 155.43 (C=N), 136.78, 120.18, 117.85 (Phenyl-C), 82.14 (C1), 60.17 (C3), 42.55 (C5), 35.41 (C4), 25.78, 23.44, 21.09, 19.97 ($CH_3$); IR (KBr) $v$: 3321, 3235 (N–H), 1740 (C=O), 1634, 1596, 1499 (C=N, Aryl), 1560 (NH–CS–NH), 1221 (N–N=C), 1060 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 604 (16, [M+23]$^+$), 582 (30, [M+H]$^+$). Anal. Calcd for $C_{22}H_{27}N_7O_8S_2$: C, 45.43; H, 4.68; N, 16.86. Found: C, 45.50; H, 4.70; N, 16.91.

#### 3.6.3. *N*′-[*N*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-[1-(4-chlorophenyl)-1*H*-tetrazol-5-ylsulfanyl]acetohydrazide (5c)

White solid, yield 79%, mp 199–201 °C; $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ 1.88, 1.94, 1.99 (3s, 9H, $CH_3CO$), 3.48 (t, $J$ = 10.8 Hz, 1H, C4–H), 3.93 (dd, $J$ = 11.1, 5.1 Hz, 1H, C5–Ha), 4.12 (d, $J$ = 15.6 Hz, 1H, $SCH_a$), 4.17 (d, $J$ = 15.6 Hz, 1H, $SCH_b$), 4.81–4.85 (m, 1H, C5–Hb), 4.95 (t, $J$ = 9.3 Hz, 1H, C2–H), 5.25 (t, $J$ = 9.6 Hz, 1H, C3–H), 5.76 (t, $J$ = 9.3 Hz, 1H, C1–H), 7.74–7.79 (m, 4H, ArH); 8.23 (d, $J$ = 9 Hz, 1H, NH), 9.94 (s, 1H, NH), 10.40 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150 MHz): $\delta$ 183.66 (C=S), 170.27, 170.18, 169.91, 166.56 (C=O), 155.01 (C=N), 136.04, 132.49, 130.83, 127.09 (phenyl-C), 83.08 (C1), 73.21 (C3), 71.05 (C5), 69.17 (C4), 64.17 (C2), 35.69 ($SCH_2$), 21.16, 21.06, 20.99 ($CH_3$); IR (KBr) $v$: 3335, 3237 (N–H), 1737 (C=O), 1496, 1473 (C=N, Aryl), 1553 (NH–CS–NH), 1239 (N–N=C), 1059 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 624 (17, [M+23]$^+$), 602 (37, [M+H]$^+$). Anal. Calcd for $C_{21}H_{24}ClN_7O_8S_2$: C, 41.89; H, 4.02; N, 16.29. Found: C, 41.92; H, 4.04; N, 16.24.

#### 3.6.4. *N*′-[*N*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-[1-(4-methoxyphenyl)-1*H*-tetrazol-5-ylsulfanyl]acetohydrazide (5d)

White solid, yield 80%, mp 203–205 °C; $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ 1.97, 1.99, 2.04 (3s, 9H, $CH_3CO$), 3.73 (s, 3H, $OCH_3$), 3.38 (t, $J$ = 11.1 Hz, 1H, C4–H), 3.84 (dd, $J$ = 11.7, 5.4 Hz, 1H, C5–Ha), 4.91 (s, 2H, $SCH_2$), 4.92–4.97 (m, 1H, C5–Hb), 5.00 (t, $J$ = 9.0 Hz, 1H, C2–H), 5.34 (t, $J$ = 9.6 Hz, 1H, C3–H), 5.41 (t, $J$ = 9.0 Hz, 1H, C1–H), 7.13–7.54 (m, 4H, ArH), 8.16 (d, $J$ = 9.2 Hz, 1H, NH), 9.86 (s, 1H, NH), 10.54 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150 MHz): $\delta$ 171.84, 170.48, 169.97, 163.29 (C=O), 158.72 (C=N), 135.51, 128.57, 118.63 (phenyl–C), 80.27 (C1), 68.81 (C3), 68.45 (C5), 65.18 (C4), 28.69, 22.80, 22.56, 21.37 ($CH_3$); IR (KBr) $v$: 3335, 3240 (N–H), 1744 (C=O), 1503, 1469, 1394 (C=N, Aryl), 1551 (NH–CS–NH), 1231 (N–N=C), 1062 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 620 (21, [M+23]$^+$), 598 (38, [M+H]$^+$). Anal. Calcd for $C_{22}H_{27}N_7O_9S_2$: C, 44.21; H, 4.55; N, 16.41. Found: C, 44.34; H, 4.53; N, 16.47.

#### 3.6.5. *N*′-[*N*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)thiocarbamoyl]-2-[1-(2-methylphenyl)-1*H*-tetrazol-5-ylsulfanyl]acetohydrazide (5e)

White bulk crystals, yield 67%, mp 193–195 °C; $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ 1.94, 2.00, 2.05 (3s, 9H, $CH_3CO$), 3.48 (t, $J$ = 11.1 Hz, 1H, C4–H), 3.92 (dd, $J$ = 11.4, 5.4 Hz, 1H, C5–Ha), 4.11 (d, $J$ = 15.6 Hz, 1H, $SCH_a$), 4.17 (d, $J$ = 15.6 Hz, 1H, $SCH_b$), 4.81–4.84 (m, 1H, C5–Hb), 5.00 (t, $J$ = 9.3 Hz, 1H, C2–H), 5.25 (t, $J$ = 9.6 Hz, 1H, C3–H), 5.76 (t, $J$ = 9.3 Hz, 1H, C1–H), 7.47–7.62 (m, 4H, ArH); 8.27 (d, $J$ = 9.6 Hz, 1H, NH), 9.93 (s, 1H, NH), 10.39 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150 MHz): $\delta$ 183.67 (C=S), 170.29, 170.21, 169.87, 166.56 (C=O), 155.93 (C=N), 135.60, 132.41, 132.25, 128.22, 127.78, 127.69 (Phenyl-C), 83.08 (C1), 73.19 (C3), 71.07 (C5), 69.15(C4), 64.16 (C2), 35.19 ($SCH_2$), 21.16, 21.05, 20.98, 17.39 ($CH_3$); IR (KBr) $v$: 3339, 3245 (N–H), 1746 (C=O), 1508, 1447, (C=N, Aryl), 1546 (NH–CS–NH), 1235 (N–N=C), 1083 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 604 (20, [M+23]$^+$), 582 (35, [M+H]$^+$). Anal. Calcd for $C_{22}H_{27}N_7O_8S_2$: C, 45.43; H, 4.68; N, 16.86. Found: C, 45.53; H, 4.66; N, 16.93.

### 3.7. General procedure for the preparation of 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

The $Hg(OAc)_2$ (0.6 mmol) was added to a solution of the corresponding compounds **5a–5e** (0.5 mmol) in EtOH (20 mL), then the reaction mixture was stirred and refluxed for 3–4 h until TLC (EtOAc/petroleum ether, 3:1, v/v) revealed complete consumption of the starting material. EtOAc (20 mL) was added to the reaction mixture. The precipitate was filtered off and the filtrate was concentrated. The pure production was obtained by recrystallization from ethanol.

#### 3.7.1. 5-(1-Phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amine (6a)

White solid, yield 51%, mp 202.5–203.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.03. 2.04, 2.06 (3s, 9H, $CH_3CO$), 3.36 (t, 1H, $J$ = 10.8 Hz, C4–H), 4.21 (dd, $J$ = 11.1, 5.2 Hz, 1H, C5–Ha), 4.71 (s, 2H, $SCH_2$), 4.91–4.96 (m, 2H, C5–Hb, C2–H), 4.98–5.02 (m, 1H, C3–H), 5.24–5.31 (m, 1H, C1–H), 5.74 (br 1H, NH), 7.58 (s, 5H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 175.57, 170.93, 169.21 (C=O), 160.43, 155.73, 147.22 (C=N), 136.58, 127.34, 119.39 (phenyl-C), 80.00 (C1), 78.19 (C5), 67.69 (C3), 67.18 (C4), 59.74 (C2), 38.14 ($SCH_2$), 23.86, 21.44, 19.57 ($CH_3$); IR (KBr) $v$: 3182 (N–H), 1740 (C=O), 1629, 1585, 1500 (C=N Aryl), 1264 (N–N=C), 1040 (C–O–C), 910 (C1–H) cm$^{-1}$; ESIMS: $m/z$ (%) 556 (23, [M+23]$^+$), 534 (33, [M+H]$^+$). Anal. Calcd for $C_{21}H_{23}N_7O_8S$: C, 47.28; H, 4.35; N, 18.38. Found: C, 47.36; H, 4.33; N, 18.34.

#### 3.7.2. 5-[1-(4-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amine (6b)

White acicular crystal, yield 57%, mp 198–199 °C; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 2.05, 2.06, 2.07 (3s, 9H, $CH_3CO$), 2.46 (s, 3H, $CH_3$), 3.45 (t, $J$ = 11 Hz, 1H, C4–H), 4.10 (dd, $J$ = 11.4, 6.0 Hz, 1H, C5–Ha), 4.71 (s, 2H, $SCH_2$), 4.95–4.96 (m, 2H, C5–Hb, C2–H),

4.98–5.03 (m, 1H, C3–H), 5.30–5.34 (m, 1H, C1–H), 5.97 (br, 1H, NH), 7.26–7.43 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 178.42, 170.96, 169.83 (C=O), 169.76, 162.14, 156.96 (C=N), 152.31, 145.38, 141.05, 130.54, 123.77, 113.65 (phenyl-C), 81.88 (C1), 70.68 (C5), 68.87 (C3), 64.32 (C4), 51.16 (C2), 36.25 ($SCH_2$), 20.65, 20.61, 19.52 ($CH_3$); IR (KBr) $\nu$: 3186 (N–H), 1739 (C=O), 1635, 1586, 1518 (C=N, Aryl), 1235 (N–N=C), 1038 (C–O–C), 901 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 570 (19, [M+23]$^+$), 548 (31, [M+H]$^+$). Anal. Calcd for $C_{22}H_{25}N_7O_8S$: C, 48.26; H, 4.60; N, 17.91. Found: C, 48.40; H, 4.58; N, 17.87.

### 3.7.3. 5-[1-(4-Chlorophenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amine (6c)

White solid, yield 62%, mp 200–201 °C; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 2.05, 2.06, 2.07 (3s, 9H, $CH_3CO$), 3.44 (t, $J$ = 11 Hz, 1H, C4–H), 4.12 (dd, $J$ = 10.7, 5.4 Hz, 1H, C5–Ha), 4.71 (d, $J$ = 15.6 Hz, 1H, $SCH_a$), 4.74 (d, $J$ = 15.6 Hz, 1H, $SCH_b$), 4.93 (s, 1H, C5–Hb), 4.95–4.98 (m, 1H, C2–H), 4.99–5.03 (m, 1H, C3-H), 5.31–5.34 (m, 1H, C1–H), 6.06 (br, 1H, NH), 7.27–7.58 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 171.01, 169.85, 169.78 (C=O), 162.12, 156.76, 152.35 (C=N), 136.78, 131.70, 130.32, 125.17, 116.66 (phenyl-C), 83.16 (C1), 71.96 (C5), 70.65 (C3), 68.84 (C4), 64.34 (C2), 26.68 ($SCH_2$), 20.72, 20.68, 20.63 ($CH_3$); IR (KBr) $\nu$: 3226 (N–H), 1744 (C=O), 1631, 1585, 1497, 1428 (C=N, Aryl), 1262 (N–N=C), 1040 (C–O–C), 905 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 590 (28, [M+23]$^+$), 568 (26, [M+H]$^+$). Anal. Calcd for $C_{21}H_{22}ClN_7O_8S$: C, 44.41; H, 3.90; N, 17.26. Found: C, 44.27; H, 3.91; N, 17.22.

### 3.7.4. 5-[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amine (6d)

White solid, yield 58%, mp 192.5–194 °C; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 2.05, 2.06, 2.07 (3s, 9H, $CH_3CO$), 3.45 (t, $J$ = 10.8 Hz, 1H, C4–H), 3.89 (s, 3H, $OCH_3$), 4.10 (dd, $J$ = 10.7, 5.4 Hz, 1H, C5–Ha), 4.69 (s, 2H, $SCH_2$), 4.96–4.98 (m, 2H, C5–Hb, C2–H), 4.99–5.03 (m, 1H, C3–H), 5.32 (t, $J$ = 8.7 Hz, 1H, C1–H), 6.06 (br, 1H, NH), 7.05–7.45 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 170.92, 169.86, 169.78 (C=O), 162.21, 161.09, 156.92 (C=N), 152.48, 125.85, 125.61, 115.08 (phenyl-C), 83.13 (C1), 70.65(C5), 68.84 (C3), 64.28 (C4), 55.72 (C2), 26.51, 20.70, 20.66, 20.60 ($CH_3$); IR (KBr) $\nu$: 3221, 3051 (N–H), 1750 (C=O), 1630, 1583, 1514 (C=N, Aryl), 1249 (N–N=C), 1079 (C–O–C), 903 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 586 (21, [M+23]$^+$), 564 (36, [M+H]$^+$). Anal. Calcd for $C_{22}H_{25}N_7O_9S$: C, 46.89; H, 4.47; N, 17.40. Found: C, 47.01; H, 4.49; N, 17.45.

### 3.7.5. 5-[1-(2-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxadiazole-2-amine (6e)

White solid, yield 54%, mp 207–209 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.99, 2.03, 2.05 (3s, 9H, $CH_3CO$), 2.30 (s, 3H, $CH_3$), 3.44 (t, $J$ = 11 Hz, 1H, C4–H), 4.10 (dd, $J$ = 11.1, 5.4 Hz, 1H, C5–Ha), 4.77 (s, 2H, $SCH_2$), 4.93–4.96 (m, 2H, C5–Hb, C2–H), 5.00–5.04 (m, 1H, C3–H), 5.35–5.43 (m, 1H, C1–H), 5.92 (br, 1H, NH), 7.06–7.48 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 171.35, 170.81, 169.97 (C=O), 166.36, 155.49 (C=N), 138.12, 135.74, 133.16, 129.27, 117.42 (phenyl-C), 83.52 (C1), 70.86 (C5), 70.51 (C3), 65.17 (C4), 41.2 (C2), 33.69 ($SCH_2$), 26.17, 20.54, 19.37 ($CH_3$); IR (KBr) $\nu$: 3184 (N–H), 1742 (C=O), 1629, 1586, 1498 (C=N, Aryl), 1226 (N–N=C), 1039 (C–O–C), 908 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 570 (24, [M+23]$^+$), 548 (28, [M+H]$^+$). Anal. Calcd for $C_{22}H_{25}N_7O_8S$: C, 48.26; H, 4.60; N, 17.91. Found: C, 48.17; H, 4.58; N, 17.94.

### 3.8. General procedure for the preparation of 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amine 7a–7e

A mixture of **5a–5e** (1 mmol), $Ac_2O$ (10 mL) and 85% $H_3PO_4$ (0.5 mL) was stirred at room temperature for 24 h. EtOAc (20 mL) was added to the reaction mixture. The mixture was successively washed with brine, saturated with $NaHCO_3$ solution, and water, then dried with $Na_2SO_4$, and concentrated under reduced pressure to afford the yellow syrup. The crude product was further purified by flash chromatography on a silica gel column chromatograph (eluent: $CHCl_3$/EtOAc, 5:1, v/v) to obtain **7a–7e**.

### 3.8.1. 5-(1-Phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amine (7a)

White solid, yield 54%, mp 197–198 °C; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 2.06 (1s, 3H, $CH_3CO$), 2.07 (2s, 6H, $CH_3CO$), 3.48 (t, $J$ = 11.1 Hz, 1H, C4–H), 4.13 (dd, $J$ = 12.0, 5.4 Hz, 1H, C5–Ha), 4.86 (d, $J$ = 15.0 Hz, 1H, $SCH_a$), 4.89 (d, $J$ = 15.0 Hz, 1H, $SCH_b$), 4.96–4.99 (m, 2H, C5–Hb, C2–H), 5.00–5.04 (m, 1H, C3–H), 5.31–5.36 (m, 1H, C1–H), 6.37 (br, 1H, NH), 7.28–7.60 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 170.91, 169.82, 169.78 (C=O), 168.75, 155.89, 153.04 (C=N), 133.35, 130.46, 130.01, 123.65 (phenyl-C), 84.90 (C1), 71.97 (C5), 70.83 (C3), 68.87 (C4), 64.13 (C2), 31.46 ($SCH_2$), 20.66, 20.63 ($CH_3$); IR (KBr) $\nu$: 3222 (N–H), 1740 (C=O), 1555, 1511 (C=N, Aryl), 1223 (N–N=C), 1040 (C–O–C), 909 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 572 (25, [M+23]$^+$), 550 (18, [M+H]$^+$). Anal. Calcd for $C_{21}H_{23}N_7O_7S_2$: C, 45.89; H, 4.22; N, 17.84. Found: C, 45.81; H, 4.24; N, 17.89.

### 3.8.2. 5-[1-(4-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amine (7b)

White solid, yield 47%, mp 205.5–206.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.03, 2.05, 2.08 (3s, 9H, $CH_3CO$), 2.46 (s, 3H, $CH_3$), 3.53 (t, $J$ = 11 Hz, 1H, C4–H), 4.13 (dd, $J$ = 11.4, 5.4 Hz, 1H, C5–Ha), 4.82 (s, 2H, $SCH_2$), 4.90–4.92 (m, 2H, C5–Hb, C2–H), 4.97–5.01 (m, 1H, C3–H), 5.21–5.25 (m, 1H, C1–H), 5.73 (br 1H, NH), 7.38–7.56 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 172.47, 170.32, 169.83 (C=O), 160.58, 154.57, 147.28 (C=N), 131.54, 120.24, 118.76 (phenyl-C), 82.46 (C1), 73.63 (C5), 70.85 (C3), 69.78 (C4), 51.16 (C2), 33.45 ($SCH_2$), 27.69, 18.73 ($CH_3$); IR (KBr) $\nu$: 3235 (N–H), 1741 (C=O), 1515, 1430 (C=N, Aryl), 1223 (N–N=C), 1040 (C–O–C), 906 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 586 (19, [M+23]$^+$), 564 (12, [M+H]$^+$). Anal Calcd for $C_{22}H_{25}N_7O_7S_2$: C, 46.88; H, 4.47; N, 17.40. Found: C, 47.03; H, 4.45; N, 17.35.

### 3.8.3. 5-[1-(4-Chlorophenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amine (7c)

White solid, yield 38%, mp 208–209 °C; $^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ 1.95, 2.01, 2.10 (3s, 9H, $CH_3CO$), 3.47 (t, $J$ = 11.1 Hz, 1H, C4–H), 4.13 (dd, $J$ = 11.7, 5.4 Hz, 1H, C5–Ha), 4.85 (d, $J$ = 15 Hz, 1H, $SCH_a$), 4.88 (d, $J$ = 15 Hz, 1H, $SCH_b$), 4.91–4.96 (m, 2H, C5–Hb, C2–H), 4.98–5.02 (m, 1H, C3–H), 5.23–5.36 (m, 1H, C1–H), 6.46 (br, 1H, NH), 7.26–7.57 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 170.91, 169.75, 168.72 (C=O), 155.59, 153.03, 136.67 (C=N), 131.75, 130.31, 124.89 (phenyl-C), 84.84 (C1), 71.82 (C5), 70.73 (C3), 68.79 (C4), 64.11 (C2), 31.52 ($SCH_2$), 20.65 ($CH_3$); IR (KBr) $\nu$: 3247 (N–H), 1743 (C=O), 1554, 1495 (C=N, Aryl), 1230 (N–N=C), 1040 (C–O–C), 905 (C1–H) cm$^{-1}$; ESIMS: *m/z* (%) 606 (21, [M+23]$^+$), 584 (8, [M+H]$^+$). Anal Calcd for $C_{21}H_{22}ClN_7O_7S_2$: C, 43.19; H, 3.80; N, 16.79. Found: C, 43.23; H, 3.79; N, 16.83.

#### 3.8.4. 5-[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amine (7d)

White solid, yield 41%, mp 202–203.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.97, 2.05, 2.06 (3s, 9H, $CH_3CO$), 3.53 (t, $J$ = 10.8 Hz, 1H, C4–H), 3.88 (s, 3H, $OCH_3$), 4.12 (dd, $J$ = 11.1, 6 Hz, 1H, C5–Ha), 4.82 (s, 2H, $SCH_2$), 4.95–4.98 (m, 2H, C5–Hb, C2–H), 5.01–5.04 (m, 1H, C3–H), 5.31(m, 1H, C1–H), 5.78 (br, 1H, NH), 7.04–7.45 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 176.87, 174.35, 170.77 (C=O), 165.43, 154.36, 147.52 (C=N), 131.55, 129.14, 112.22 (phenyl-C), 80.29 (C1), 70.65 (C5), 65.42 (C3), 61.38 (C4), 53.17 (C2), 31.45 ($SCH_2$), 24.64, 21.76, 20.12 ($CH_3$); IR (KBr) $\nu$: 3250 (N–H), 1745 (C=O), 1553, 1490, 1429 (C=N, Aryl), 1224 (N–N=C), 1037 (C–O–C), 905 (C1–H) cm$^{-1}$; ESIMS: $m/z$ (%) 602 (17, [M+23]$^+$), 580 (14, [M+H]$^+$). Anal. Calcd for $C_{22}H_{25}N_7O_8S_2$: C, 45.59; H, 4.35; N, 16.92. Found: C, 45.50; H, 4.37; N, 16.87.

#### 3.8.5. 5-[1-(2-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-thiadiazole-2-amine (7e)

White solid, yield 38%, mp 194–196 °C; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.96, 2.08, 2.17 (3s, 9H, $CH_3CO$), 2.48 (s, 3H, $CH_3$), 3.49 (t, $J$ = 10.8 Hz, 1H, C4–H), 4.14 (dd, $J$ = 11.7, 5.7 Hz, 1H, C5–Ha), 4.80 (d, $J$ = 15 Hz, 1H, $SCH_a$), 4.84 (d, $J$ = 15 Hz, 1H, $SCH_b$), 4.96–4.97 (m, 2H, C5–Hb, C2–H), 4.99–5.03 (m, 1H, C3–H), 5.31–5.35 (m, 1H, C1–H), 6.50 (br, 1H, NH), 7.23–7.52 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ 170.88, 169.79, 169.76 (C=O), 168.69, 155.97, 154.49 (C=N), 135.32, 131.89, 131.68, 131.56, 127.36, 126.65 (phenyl-C), 84.81(C1), 71.76(C5), 70.68 (C3), 68.77 (C4), 64.09 (C2), 31.15 ($SCH_2$), 20.69, 20.65, 17.45 ($CH_3$); IR (KBr) $\nu$: 3224 (N–H), 1742 (C=O), 1566, 1510 (C=N, Aryl), 1223 (N–N=C), 1037 (C–O–C), 908 (C1–H) cm$^{-1}$; ESIMS: $m/z$ (%) 586 (28, [M+23]$^+$), 564 (20, [M+H]$^+$). Anal. Calcd for $C_{22}H_{25}N_7O_7S_2$: C, 46.88; H, 4.47; N, 17.40. Found: C, 46.81; H, 4.45; N, 17.45.

### 3.9. General procedure for the preparation of 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-xylopyranosyl-1,3,4-oxadiazol-2-amine 8a–8e and 5-(1-aryl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-xylopyranosyl-1,3,4-thiadiazole-2-amine 9a–9e

To a solution of the corresponding compounds **6** and **7** (0.05 mmol) in MeOH (5 mL) was added NaOMe (0.1 M, 0.2 mL), and the reaction mixture was stirred at room temperature for 0.5 h until TLC ($CHCl_3$/MeOH 5:1, v/v) revealed complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to afford the White solid. The crude product was further purified by flash chromatography on a silica gel column chromatograph (eluent: $CHCl_3$–MeOH, 4:1, v/v) to obtain **8**–**9**.

#### 3.9.1. 5-(1-Phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-xylopyranosyl-1,3,4-oxadiazol-2-amine (8a)

White solid, yield 59%, mp 170–172 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 1.20–3.10 (m, 3H, O–H); 3.81 (t, $J$ = 11.1 Hz, 1H, C4–H), 4.15–4.17 (m, 1H, C5–Ha), 4.78 (s, 2H, $SCH_2$), 4.95–4.98 (m, 2H, C5–Hb, C2–H), 5.00–5.04 (m, 1H, C3–H), 5.19–5.22 (m, 1H, C1–H), 7.57–7.74 (m, 5H, ArH), 8.11 (br, 1H, NH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 163.54, 155.74, 149.36 (C=N), 139.11, 130.70, 127.65 (phenyl-C), 80.45 (C1), 75.24 (C3), 70.18 (C5), 60.55 (C4), 56.13 (C2), 50.21 ($SCH_2$); IR (KBr) $\nu$: 3339 (O–H, N–H), 1595, 1556, 1504, 1459 (C=N, Aryl), 1287 (N–N=C), 1049 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 424 (39, [M+H]$^+$), 446 (62, [M+23]$^+$); Anal. Calcd for $C_{15}H_{17}N_7O_4S_2$: C, 42.54; H, 4.05; N, 23.15. Found: C, 42.63; H, 4.07; N, 23.09.

#### 3.9.2. 5-[1-(4-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-oxadiazol-2-amine (8b)

White solid, yield 71%, mp 188–191 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 1.54–3.52 (m, 3H, O–H); 2.50 (s, 3H, $CH_3$), 3.85 (t, $J$ = 11.1 Hz, 1H, C4–H), 4.04–4.08 (m, 1H, C5–Ha), 4.55–4.57 (m, 2H, C5–Hb, C2–H), 4.59–4.62 (m, 1H, C3–H), 4.81–4.83 (m, 1H, C1–H), 4.96 (s, 2H, $CH_2$), 7.48–7.63 (m, 4H, ArH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 160.23, 155.73, 154.29 (C=N), 145.58, 130.26, 125.17, 114.38 (phenyl-C), 82.67 (C1), 71.46 (C3), 65.31 (C5), 63.22 (C4), 58.23 (C2), 49.89 ($SCH_2$); IR (KBr) $\nu$: 3300 (O–H, N–H), 1556, 1507, 1434 (C=N, Aryl), 1246 (N–N=C), 1060 (C–O–C), 901 (C1–H) cm$^{-1}$; ESIMS: $m/z$ (%) 460 (59, [M+23]$^+$), 438 (47, [M+H]$^+$); Anal. Calcd for $C_{16}H_{19}N_7O_4S_2$: C, 43.93; H, 4.38; N, 22.41. Found: C, 44.01; H, 4.36; N, 22.37.

#### 3.9.3. 5-[1-(4-Chlorophenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-oxadiazol-2-amine (8c)

White solid, yield 74%, mp 219–220 °C; $^1$H NMR ($CD_3OD$, 400 MHz): 3.17 (t, $J$ = 11.0 Hz, 1H, C4–H), 3.67–3.71 (m, 1H, C5–Ha), 4.13–4.16 (m, 1H, C5–Hb), 4.52–4.55 (m, 1H, C2–H), 4.59–4.63 (m, 1H, C3–H), 4.70 (d, $J$ = 8.4 Hz, 1H, C1–H), 4.85 (s, 2H, $CH_2$), 7.63 (d, $J$ = 8.8 Hz, 2H, ArH), 7.70 (d, $J$ = 8.8 Hz, 2H, ArH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 163.52, 160.25, 154.71 (C=N), 142.18, 131.57, 125.61, 120.07 (phenyl-C), 85.21 (C1), 74.58 (C3), 71.46 (C5), 63.24 (C4), 58.27 (C2), 50.43 ($SCH_2$); IR (KBr) $\nu$: 3254 (O–H, N–H), 1551, 1507, 1431 (C=N, Aryl), 1245 (N–N=C), 1058 (C–O–C), 899 (C1–H) cm$^{-1}$; ESIMS: $m/z$ (%) 480 (20, [M+23]$^+$), 458 (58, [M+H]$^+$); Anal. Calcd for $C_{15}H_{16}ClN_7O_4S_2$: C, 39.34; H, 3.52; N, 21.41. Found: C, 39.27; H, 3.50; N, 21.46.

#### 3.9.4. 5-[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-oxadiazol-2-amine (8d)

White solid, yield 63%, mp 139–142 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 3.43 (s, 3H, $OCH_3$), 3.59 (t, $J$ = 10.8 Hz, 1H, C4–H), 4.18–4.21 (m, 1H, C5–Ha), 4.88 (s, 2H, $SCH_2$), 4.99–5.03 (m, 2H, C5–Hb, C2–H), 5.05–5.08 (m, 1H, C3–H), 5.31(m, 1H, C1–H), 5.82 (br, 1H, NH), 7.24–7.47 (m, 4H, ArH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 160.46, 160.09, 156.42 (C=N), 155.17, 143.15, 126.42, 119.12 (phenyl-C), 80.05 (C1), 71.63 (C3), 67.53 (C5), 61.38 (C4), 59.21 (C2), 49.65 ($SCH_2$); IR (KBr) $\nu$: 3351 (N–H, O–H), 2927 (C–H), 1534, 1497, 1429 (C=N, Aryl), 1237 (N–N=C), 1058 (C–O–C) cm$^{-1}$; ESIMS: $m/z$ (%) 476 (25, [M+23]$^+$), 454 (34, [M+H]$^+$); Anal. Calcd for $C_{16}H_{19}N_7O_5S_2$: C, 42.38; H, 4.22; N, 21.62. Found: C, 42.29; H, 4.24; N, 21.67.

#### 3.9.5. 5-[1-(2-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-oxadiazol-2-amine (8e)

White solid, yield 71%, mp 116–118 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 2.35 (s, 3H, $CH_3$), 3.78 (t, $J$ = 10.8 Hz, 1H, C4–H), 4.20–4.24 (m, 1H, C5–Ha), 4.92 (s, 2H, $SCH_2$), 5.03–5.06 (m, 2H, C5–Hb, C2–H), 5.13–5.17 (m, 1H, C3–H), 5.38–5.43 (m, 1H, C1–H), 7.02–7.47 (m, 4H, ArH), 8.76 (br, 1H, NH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 161.58, 158.47, 154.86 (C=N), 150.32, 130.25, 124.90, 120.18 (phenyl-C), 83.46 (C1), 73.46 (C3), 70.55 (C5), 69.92 (C4), 68.39 (C2), 55.16 ($SCH_2$); IR (KBr) $\nu$: 3272 (O–H, N–H), 1550, 1502, 1461 (C=N, Aryl), 1245 (N–N=C), 1051 (C–O–C), 895 (C1–H) cm$^{-1}$; ESIMS: $m/z$ (%) 438 (42, [M+H]$^+$), 460 (35, [M+23]$^+$); Anal. Calcd for $C_{16}H_{19}N_7O_4S_2$: C, 43.93; H, 4.38; N, 22.41. Found: C, 43.82; H, 4.40; N, 22.46.

#### 3.9.6. 5-(1-Phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)-*N*-xylopyranosyl-1,3,4-thiadiazole-2-amine (9a)

White solid, yield 75%, mp 109–111 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 3.36 (t, $J$ = 11 Hz, 1H, C4–H), 4.15–4.19 (m, 1H, C5–Ha), 4.78 (s, 2H, $SCH_2$), 4.99–5.05 (m, 2H, C5–Hb, C2–H), 5.14–5.21 (m, 1H, C3–H), 5.40–5.43 (m, 1H, C1–H), 6.67 (br 1H, NH),

7.58 (s, 5H, ArH); $^{13}$C NMR (DMSO-$d_6$, 150 MHz): $\delta$ 153.67, 150.45 (C=N), 137.12, 130.87, 131.06, 125.35 (phenyl-C), 72.14 (C3), 70.37 (C5), 66.75 (C4), 50.43 (C2), 49.17 ($SCH_2$); IR (KBr) $v$: 3256 (O–H, N–H), 1640, 1499 (C=N, Aryl), 1240 (N–N=C), 1044 (C–O–C) $cm^{-1}$; ESIMS: $m/z$ (%) 430 (55, $[M+23]^+$), 408 (37, $[M+H]^+$); Anal. Calcd for $C_{15}H_{17}N_7O_5S$: C, 44.22; H, 4.21; N, 24.07. Found: C, 44.15; H, 4.23; N, 24.13.

### 3.9.7. 5-[1-(4-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-thiadiazole-2-amine (9b)

White solid, yield 73%, mp 132–133 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 2.48 (s, 3H, $CH_3$), 3.44 (t, $J$ = 10.8 Hz, 1H, C4–H), 4.15–4.20 (m, 1H, C5–Ha), 4.83 (s, 2H, $SCH_2$), 5.05–5.09 (m, 2H, C5–Hb, C2–H), 5.21–5.24 (m, 1H, C3–H), 5.44–5.47 (m, 1H, C1–H), 5.79 (br 1H, NH), 7.27–7.41 (m, 4H, ArH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 163.08, 154.27, 150.38 (C=N), 147.59, 144.25, 137.46, 118.65 (phenyl-C), 83.47 (C1), 72.09 (C3), 69.18 (C5), 63.42 (C4), 60.79 (C2), 51.16 ($SCH_2$); IR (KBr) $v$: 3327 (N–H, O–H), 1530, 1421 (C=N, Aryl), 1231 (N–N=C), 1076 (C–O–C) $cm^{-1}$; ESIMS: $m/z$ (%) 444 (57, $[M+23]^+$), 422 (48, $[M+H]^+$); Anal. Calcd for $C_{16}H_{19}N_7O_5S$: C, 45.60; H, 4.54; N, 23.27. Found: C, 45.69; H, 4.52; N, 23.21.

### 3.9.8. 5-[1-(4-Chlorophenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-thiadiazole-2-amine (9c)

White solid, yield 68%, mp 113–115 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 0.93–2.20 (m, 3H, O–H), 3.50 (t, $J$ = 11.0 Hz, 1H, C4–H), 4.05–4.09 (m, 1H, C5–Ha), 4.46–4.49 (m, 2H, C5–Hb, C2–H), 4.52–4.55 (m, 1H, C3–H), 5.62–5.64 (m, 1H, C1–H), 4.73 (s, 2H, $CH_2$), 7.65–7.72 (m, 4H, ArH), 7.94 (br, 1H, NH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 160.32, 158.73, 150.45 (C=N), 137.28, 129.67, 123.51, 117.61 (phenyl-C), 80.24 (C1), 71.22 (C3), 70.96 (C5), 65.34 (C4), 60.13 (C2), 51.73 ($SCH_2$); IR (KBr) $v$: 3373 (O–H, N–H), 1639, 1584, 1495 (C=N, Aryl), 1243 (N–N=C), 1053 (C–O–C) $cm^{-1}$; ESIMS: $m/z$ (%) 464 (95, $[M+23]^+$), 442 (46, $[M+H]^+$); Anal. Calcd for $C_{15}H_{16}ClN_7O_5S$: C, 40.77; H, 3.65; N, 22.19. Found: C, 40.70; H, 3.66; N, 22.24.

### 3.9.9. 5-[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-thiadiazole-2-amine (9d)

White solid, yield 76%, mp 128–130 °C; $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 0.90–3.52 (m, 3H, O–H), 3.64 (t, $J$ = 10.8 Hz, 1H, C4–H), 3.88 (s, 3H, $OCH_3$), 4.05–4.19 (m, 1H, C5–Ha), 4.34 (br, 1H, NH); 4.69 (s, 2H, $SCH_2$), 4.85–4.89 (m, 2H, C5–Hb, C2-H), 4.91–4.95 (m, 1H, C3–H), 5.13 (d, $J$ = 8.8 Hz, 1H, C1–H), 7.18–7.56 (m, 4H, ArH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 163.89, 161.47, 156.81 (C=N), 152.92, 125.96, 125.82, 114.72 (phenyl-C), 84.76 (C1), 72.52 (C3), 69.62 (C5), 67.11 (C4), 54.86 (C2), 48.01 ($SCH_2$); IR (KBr) $v$: 3385 (N–H, O–H), 1564, 1520, 1433 (C=N, Aryl), 1228 (N–N=C), 1065 (C–O–C) $cm^{-1}$; ESIMS: $m/z$ (%) 460 (15, $[M+23]^+$), 438 (25, $[M+H]^+$); Anal. Calcd for $C_{16}H_{19}N_7O_6S$: C, 43.93; H, 4.38; N, 22.41. Found: C, 43.82; H, 4.36; N, 22.46.

### 3.9.10. 5-[1-(2-Methylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]-*N*-xylopyranosyl-1,3,4-thiadiazole-2-amine (9e)

White solid, yield 61%, mp 120–122 °C; $^1$H NMR ($CD_3OD$, 600 MHz): $\delta$ 2.88–3.52 (m, 3H, O–H), 2.45 (s, 3H, $CH_3$), 3.29 (t, $J$ = 11.0 Hz, 1H, C4–H), 3.89–3.94 (m, 1H, C5–Ha), 4.90 (s, 2H, $SCH_2$), 4.65–4.77 (m, 2H, C5–Hb, C2–H), 5.10–5.14 (m, 1H, C3–H), 5.83–5.90 (m, 1H, C1–H), 7.18–7.59 (m, 4H, ArH); $^{13}$C NMR ($CD_3OD$, 150 MHz): $\delta$ 163.88, 160.29, 158.42 (C=N), 151.36, 130.15, 115.07 (phenyl-C), 82.19 (C1), 73.14 (C3), 71.25 (C5), 66.73 (C4), 50.41 (C2), 47.65 ($SCH_2$); IR (KBr) $v$: 3252 (O–H, N–H), 1639, 1499, 1259 (N–N=C), 1395 (C=N, Aryl), 1038 (C–O–C) $cm^{-1}$; ESIMS: $m/z$ (%) 444 (28, $[M+23]^+$), 422 (12, $[M+H]^+$); Anal. Calcd for $C_{16}H_{19}N_7O_5S$: C, 45.60; H, 4.54; N, 23.27. Found: C, 45.51; H, 4.56; N, 23.31.

### 3.10. Biological activity

#### 3.10.1. Antibacterial activity assays

Strains: *S. aureus*, *Escherichia coli* and *C. albicans*.

Method: All used bacteria inoculated into liquid medium. (The *C. albicans* were inoculated into Sandburg culture media), cultured on 37 °C to $OD_{600}$ value 0.6–0.8. Bacterial suspension 400 μL and solid medium (containing 1.5% agar) 100 mL were mixed on 55 °C, paved at the plate, was reserved it on 4 °C awaiting congealing. The 20 μL (100 mmol/L) of sample was dripted to the 2 mm diameter holes of plate, cultured 18–24 h on 37 °C (*C. albicans* cultured 48 h), the size of inhibition zone was measured.

#### 3.10.2. PTP1B enzyme inhibition assay

PTP1B reaction system contained 5 mM pNPP, 0.09 μM his-$PTP1B_{1-321}$ and buffer containing 20 mM HEPES, 150 mM NaCl, and 1 mM EDTA (pH 7.0). After incubation of extracts for 10 min, the reaction was initiated by addition of pNPP. The amount of produced pNP was measured by detecting absorbance at 405 nm using microplate spectrophotometer (SpectraMax M5/M5e). $IC_{50}$ value was calculated by fitting data with Origin software.

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## Supplementary data

Complete crystallographic data for the structural analysis of compounds **2e**, **3e**, **5a**, and **5c** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers **2e**: 689056, **3e**: 689055, **5a**: 688446, **5c**: 689054. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Tel.: +44 01223 762910, fax: +44 01223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.01.010.

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