

ORIGINAL ARTICLE

# Design, synthesis, and urease inhibition studies of some 1,3,4-oxadiazoles and 1,2,4-triazoles derived from mandelic acid

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## Abstract

Some new structural type inhibitors of urease, i.e. 2,5-disubstituted-1,3,4-oxadiazoles (**4a–e**) and 4,5-disubstituted-1,2,4-triazole-3-thiones (**5a–e**) were synthesized in two steps from mandelic acid hydrazides (**2a–e**) and aryl isothiocyanates. The hydrazides in turn were synthesized from mandelic acid via esterification. Compounds **4a–e** and **5a–e** were evaluated against jack bean urease. Compounds **4d**, **5b**, and **5d** were found to be more potent, with  $IC_{50}$  values of  $16.1 \pm 0.12 \mu\text{M}$ ,  $18.9 \pm 0.188 \mu\text{M}$ , and  $16.7 \pm 0.178 \mu\text{M}$ , respectively, when compared to the standard (thiourea;  $IC_{50} = 21.0 \pm 0.011 \mu\text{M}$ ). These compounds may be subjected to further investigations for the development of antiulcer drugs.

**Keywords:** Triazoles; oxadiazoles; urease inhibition; mandelic acid; thiosemicarbazides

## Introduction

Heterocycles, especially the bioisosteric 1,3,4-oxadiazoles, 1,2,4-triazoles, and 1,3,4-thiadiazoles, are important molecules known to interact with particular receptors on enzyme active sites. Among these, 1,3,4-oxadiazoles and 1,2,4-triazoles exhibit numerous biological activities such as antimicrobial<sup>1–3</sup>, anticonvulsant<sup>4</sup>, anti-human immunodeficiency virus (HIV)<sup>5</sup>, anticancer<sup>6,7</sup>, and urease inhibition<sup>8,9</sup>. Oxadiazoles and triazoles have been regarded as structural type inhibitors of urease<sup>10</sup>. Serwar *et al.*<sup>8</sup> have attributed the urease inhibition activity of 1,2,4-triazole-3-thiones to the structural similarity of these compounds with the natural substrate of urease, i.e. urea.

As a result of our focus on the synthesis and biological evaluation of five-membered heterocycles<sup>11–13</sup>, in the present study, 2,5-disubstituted-1,3,4-oxadiazoles and 4,5-disubstituted-1,2,4-triazole-3-thiones were synthesized

starting from mandelic acid (Scheme 1) and their urease inhibition evaluated.

## Experimental

### Materials

The synthesized compounds were characterized by their physical constants and spectroanalytical techniques. Thin layer chromatography (TLC) was carried out using precoated silica gel 60 HF<sub>254</sub> aluminum sheets (Merck, Germany). The melting points were determined on a Sanyo Gallenkamp digital melting point apparatus (MPD 350) in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrophotometer (USA) using the ATR (attenuated total reflectance) facility. <sup>1</sup>H- and <sup>13</sup>C-nuclear magnetic

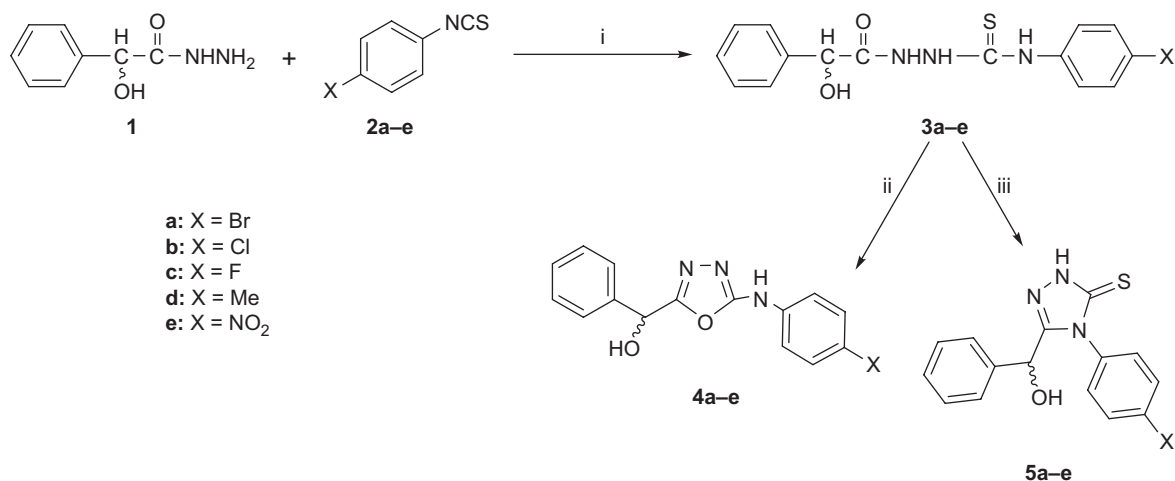
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**Scheme 1.** Synthesis of 1,3,4-oxadiazoles and 1,2,4-triazole-3-thiones. Reagents and conditions: (i) MeOH, reflux; (ii) Hg(OAc)<sub>2</sub>; (iii) 5% NaOH.

resonance (NMR) spectra were recorded on a Bruker Avance 300 MHz spectrometer and calibrated to residual solvent peaks. Mass spectra were recorded on a MAT-112-S spectrometer at 70 eV. Mandelic acid was purchased from Merck Chemicals; all the reagents were of high purity grade and the solvents were distilled before use.

#### General procedure for the synthesis of thiosemicarbazides (3a-e)

To a solution of carboxylic acid hydrazide (5.90 mmol) in absolute MeOH (30 mL) was added the respective isothiocyanate (5.9 mmol) separately dissolved in absolute MeOH (20 mL), with stirring. The reaction mixture was heated under reflux for 2–3 h (TLC). After cooling, the resulting solid was filtered and recrystallized from EtOH/water to give pure thiosemicarbazides (3a-e).

#### 1-[(2-Hydroxy-2-phenyl)acetyl]-4-(4-bromophenyl)thiosemicarbazide (3a)

Yield: 85%; m.p. 56°C; IR (ATR, cm<sup>-1</sup>):  $\nu_{\max}$  3485, 3227, 3119, 2952, 1690, 1642, 1590, 1511, 1484, 1170; <sup>1</sup>H-NMR (300 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  5.12 (1H, s, CHOH), 6.11 (1H, br s, OH), 7.33–7.48 (9H, m, Ar-H), 9.36 (1H, br s, NH), 9.80 (1H, br s, NH), 10.29 (1H, s, NH); EIMS: *m/z* 217, 215, 213, 173, 171, 148, 134, 107, 79, 77.

#### 1-[(2-Hydroxy-2-phenyl)acetyl]-4-(4-chlorophenyl)thiosemicarbazide (3b)

Yield: 81%; m.p. 162–164°C; IR (ATR, cm<sup>-1</sup>):  $\nu_{\max}$  3479, 3227, 3125, 2946, 1689, 1643, 1591, 1510, 1488, 1170; <sup>1</sup>H-NMR (300 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  5.12 (1H, d, *J*=2.4 Hz, CHOH), 6.12 (1H, br s, OH), 7.26–7.50 (9H, m, Ar-H), 9.39 (1H, br s, NH), 9.81 (1H, br s, NH), 10.31 (1H, s, NH); EIMS: *m/z* 208, 171, 170, 169, 148, 111, 107, 91, 79, 77.

#### 1-[(2-Hydroxy-2-phenyl)acetyl]-4-(4-fluorophenyl)thiosemicarbazide (3c)

Yield: 87%; m.p. 178–180°C; IR (ATR, cm<sup>-1</sup>):  $\nu_{\max}$  3424, 3228, 3119, 2952, 1679, 1610, 1548, 1505, 1448, 1414, 1366, 1170;

<sup>1</sup>H-NMR (300 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  5.11 (1H, d, *J*=4.2 Hz, CHOH), 6.10 (1H, br s, OH), 7.16–7.50 (9H, m, Ar-H), 9.37 (1H, br s, NH), 9.73 (1H, br s, NH), 10.29 (1H, s, NH); EIMS: *m/z* 301, 212, 208, 194, 111, 110, 107, 105, 95, 79, 77.

#### 1-[(2-Hydroxy-2-phenyl)acetyl]-4-(4-methylphenyl)thiosemicarbazide (3d)

Yield: 87%; m.p. 109–111°C; IR (ATR, cm<sup>-1</sup>):  $\nu_{\max}$  3479, 3244, 3130, 3033, 2952, 1692, 1644, 1594, 1505, 1449, 1414, 1366, 1170; <sup>1</sup>H-NMR (300 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  5.12 (1H, d, *J*=2.4 Hz, CHOH), 6.12 (1H, br s, OH), 7.15 (2H, d, *J*=8.1 Hz, Ar-H), 7.25–7.37 (5H, m, Ar-H), 7.48 (2H, d, *J*=8.1 Hz, Ar-H), 9.24 (1H, br s, NH), 9.65 (1H, br s, NH), 10.28 (1H, s, NH); EIMS: *m/z* 297, 220, 208, 163, 148, 149, 121, 107, 91, 79, 77, 65.

#### 1-[(2-Hydroxy-2-phenyl)acetyl]-4-(4-nitrophenyl)thiosemicarbazide (3e)

Yield: 79%; m.p. 174–175°C; IR (ATR, cm<sup>-1</sup>):  $\nu_{\max}$  3427, 3217, 3083, 2944, 1678, 1643, 1598, 1552, 1504, 1494, 1172; <sup>1</sup>H-NMR (300 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  5.13 (1H, s, CHOH), 6.18 (1H, br s, OH), 7.27–7.38 (3H, m, Ar-H), 7.49 (2H, d, *J*=7.2 Hz, Ar-H), 7.87 (2H, d, *J*=9.3 Hz, Ar-H), 8.23 (2H, dd, *J*=9.0, 2.4 Hz, Ar-H), 9.69 (1H, br s, NH), 10.08 (1H, br s, NH), 10.38 (1H, s, NH); EIMS: *m/z* 208, 180, 148, 150, 134, 122, 107, 90, 79, 77.

#### General procedure for the synthesis of 1,3,4-oxadiazoles (4a-e)

The respective thiosemicarbazide (1.0 eq) was dissolved in methanol (10 mL) and mercuric acetate (1.1 eq) was added. The reaction mixture was refluxed for 2–3 h while completion of the reaction was monitored by TLC. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The resulting solid was recrystallized from aqueous ethanol.

#### 5-(Hydroxybenzyl)-2-(4-bromophenyl)amino-1,3,4-oxadiazole (4a)

Yield: 79%; m.p. 160–162°C; IR (ATR, cm<sup>-1</sup>):  $\nu_{\max}$  3425, 3061, 2926, 1581, 1493, 1486; <sup>1</sup>H-NMR (300 Hz, CD<sub>3</sub>OD):  $\delta$  4.57 (1H,

s, *CHOH*), 5.90 (1H, s, *CHOH*), 7.51–7.31 (9H, m, *Ar-H*);  $^{13}\text{C-NMR}$  (75 MHz, acetone- $d_6$ ):  $\delta$  67.1, 113.8, 119.0, 126.3, 128.1, 128.4, 131.9, 138.2, 139.2, 160.1, 161.1; EIMS:  $m/z$  345 [ $\text{M}^+$ ], 239, 196, 155, 133, 131, 107, 106, 105, 77.

**5-(Hydroxybenzyl)-2-(4-chlorophenyl)amino-1,3,4-oxadiazole (4b)**

Yield: 76%; m.p. 166–168°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3451, 3069, 3031, 2942, 1608, 1576, 1517, 1488;  $^1\text{H-NMR}$  (300 Hz,  $\text{CD}_3\text{OD}$ ):  $\delta$  4.56 (1H, s, *CHOH*), 5.89 (1H, s, *OH*), 7.51–7.26 (9H, m, *Ar-H*);  $^{13}\text{C-NMR}$  (75 MHz, acetone- $d_6$ ):  $\delta$  67.1, 118.6, 126.3, 128.1, 128.2, 128.4, 128.9, 137.8, 139.5, 160.1, 161.1; EIMS:  $m/z$  301 [ $\text{M}^+$ ], 195, 107, 106, 77, 69.

**5-(Hydroxybenzyl)-2-(4-fluorophenyl)amino-1,3,4-oxadiazole (4c)**

Yield: 79%; m.p. 175–177°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3443, 3063, 3026, 2926, 1603, 1571, 1512, 1486, 1253;  $^1\text{H-NMR}$  (300 Hz,  $\text{DMSO}-d_6$ ):  $\delta$  4.73 (1H, d,  $J=5.3$  Hz, *CHOH*), 5.01 (1H, s, *CHOH*), 7.10–7.49 (9H, m, *Ar-H*), 9.62 (1H, s, *NH*);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  72.8, 115.9 (d,  $J=21.8$  Hz), 120.6 (d,  $J=7.5$  Hz), 127.1, 128.1, 128.6, 132.1, 140.7, 158.1 (d,  $J=237.0$  Hz), 159.3, 161.7; EIMS:  $m/z$  285 [ $\text{M}^+$ ], 272, 224, 194, 175, 149, 148, 136, 110, 105, 77.

**5-(Hydroxybenzyl)-2-(4-methylphenyl)amino-1,3,4-oxadiazole (4d)**

Yield: 81%; m.p. 172–173°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3426, 3081, 3062, 2941, 1606, 1571, 1508, 1489;  $^1\text{H-NMR}$  (300 Hz,  $\text{CD}_3\text{OD}$ ):  $\delta$  2.37 (3H, s, *Ar-Me*), 5.88 (1H, s, *CHOH*), 7.10 (2H, d,  $J=8.3$  Hz, *Ar-H*), 7.31–7.38 (5H, m, *Ar-H*), 7.49 (2H, d,  $J=8.4$  Hz, *Ar-H*);  $^{13}\text{C-NMR}$  (75 MHz, acetone- $d_6$ ):  $\delta$  19.8, 67.1, 117.1, 126.3, 128.3, 128.3, 129.4, 131.3, 136.4, 139.7, 160.5, 160.7; EIMS:  $m/z$  283 [ $\text{M}^+$ ], 281, 176, 148, 133, 132, 107, 106, 105, 91, 65.

**5-(Hydroxybenzyl)-2-(4-nitrophenyl)amino-1,3,4-oxadiazole (4e)**

Yield: 66%; m.p. 179–180°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3260, 3105, 2930, 1627, 1595, 1557, 1515, 1508, 1306;  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  5.96 (1H, d,  $J=4.8$  Hz, *CHOH*), 6.73 (1H, d,  $J=4.8$  Hz, *CHOH*), 7.33–7.50 (5H, m, *Ar-H*), 7.73 (2H, d,  $J=9.0$  Hz, *Ar-H*), 8.26 (2H, d,  $J=9.0$  Hz, *Ar-H*), 11.40 (1H, s, *NH*);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  66.6, 117.2, 126.0, 126.8, 128.6, 128.9, 139.9, 141.6, 145.2, 159.7, 162.1; EIMS:  $m/z$  312 [ $\text{M}^+$ ], 206, 165, 133, 119, 107, 79, 77.

**General procedure for the synthesis of 1,2,4-triazoles (5a–e)**

The respective thiosemicarbazide (**3a–e**; 1.10 mmol) was added portion-wise to a stirred solution of NaOH (5%, 30 mL) and the reaction mixture heated under reflux for 4 h. After cooling, the reaction mixture was filtered and the filtrate acidified with 6 N HCl to pH 2–3. The precipitated solid was filtered, washed thoroughly with water, and recrystallized from EtOH/water.

**5-(Hydroxybenzyl)-4-(4-bromophenyl)-2H-1,2,4-triazole-3-thione (5a)**

Yield: 64%; m.p. 188–190°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3128, 3027, 2937, 1578, 1497, 1488;  $^1\text{H-NMR}$  (300 Hz,  $\text{CD}_3\text{OD}$ ):  $\delta$  5.68 (1H, s, *CHOH*), 6.92 (2H, d,  $J=8.6$  Hz, *Ar-H*), 7.08 (2H, dd,  $J=7.4$ , 5.4 Hz, *Ar-H*), 7.51 (2H, d,  $J=8.6$  Hz, *Ar-H*), 7.27–7.19 (3H, m, *Ar-H*);  $^{13}\text{C-NMR}$  (75 MHz, acetone- $d_6$ ):  $\delta$  67.8, 124.4, 126.5, 128.0, 128.3, 131.2, 133.4, 134.8, 139.2, 155.3, 171.5; EIMS:  $m/z$  359/361 [ $\text{M}^+$ ], 256, 255, 228, 213, 155, 132, 131, 107, 106, 105.

**5-(Hydroxybenzyl)-4-(4-chlorophenyl)-2H-1,2,4-triazole-3-thione (5b)**

Yield: 67%; m.p. 178–180°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3125, 3022, 2934, 1557, 1489, 1485;  $^1\text{H-NMR}$  (300 Hz,  $\text{CD}_3\text{OD}$ ):  $\delta$  5.68 (1H, s, *CHOH*), 6.99 (2H, d,  $J=8.7$  Hz, *Ar-H*), 7.08 (2H, dd,  $J=7.4$ , 5.2 Hz, *Ar-H*), 7.24–7.19 (5H, m, *Ar-H*);  $^{13}\text{C-NMR}$  (75 MHz, acetone- $d_6$ ):  $\delta$  67.5, 126.4, 127.8, 128.0, 128.9, 130.7, 133.1, 134.5, 139.0, 153.5, 170.4; EIMS:  $m/z$  315/317 [ $\text{M}^+$ ], 245, 210, 183, 169, 132, 107, 106, 105, 99.

**5-(Hydroxybenzyl)-4-(4-fluorophenyl)-2H-1,2,4-triazole-3-thione (5c)**

Yield: 63%; m.p. 82–85°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3453, 3069, 3026, 2930, 1599, 1562, 1508, 1487, 1216;  $^1\text{H-NMR}$  (300 Hz,  $\text{DMSO}-d_6$ ):  $\delta$  5.59 (1H, d,  $J=5.4$  Hz, *CHOH*), 6.37 (1H, d,  $J=5.4$  Hz, *CHOH*), 7.13–7.31 (9H, m, *Ar-H*), 13.91 (1H, s, *NH*);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  66.9, 116.3 (d,  $J=23.5$  Hz), 126.8, 128.1, 128.3, 130.4 (d,  $J=3$  Hz), 131.4 (d,  $J=9.8$  Hz), 139.7, 154.0, 162.5 (d,  $J=244.5$  Hz), 169.2; EIMS:  $m/z$  301/303 [ $\text{M}^+$ ], 300, 284, 272, 224, 194, 167, 153, 136, 122, 109, 105, 77.

**5-(Hydroxybenzyl)-4-(4-methylphenyl)-2H-1,2,4-triazole-3-thione (5d)**

Yield: 63%; m.p. 82–85°C; IR (ATR,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3435, 3076, 3034, 2935, 1609, 1567, 1506, 1493, 1223;  $^1\text{H-NMR}$  (300 Hz,  $\text{CD}_3\text{OD}$ ):  $\delta$  2.37 (3H, s, *Ar-Me*), 5.59 (1H, s, *CHOH*), 6.88 (2H, d,  $J=8.3$  Hz, *Ar-H*), 7.07 (2H, dd,  $J=7.6$ , 5.5 Hz), 7.17–7.22 (5H, m, *Ar-H*);  $^{13}\text{C-NMR}$  (75 MHz, acetone- $d_6$ ):  $\delta$  20.3, 67.6, 122.0, 127.8, 128.5, 128.6, 129.4, 131.6, 139.2, 139.3, 153.9, 170.2; EIMS:  $m/z$  297 [ $\text{M}^+$ ], 296, 295, 163, 150, 149, 132, 107, 106, 105, 91, 65.

**5-(Hydroxybenzyl)-4-(4-nitrophenyl)-2H-1,2,4-triazole-3-thione (5e)**

Yield: 64%; m.p. 122–123°C; IR (KBr,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  3429, 3125, 3022, 2934, 1557, 1508, 1489, 1485, 1337;  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  5.93 (1H, d,  $J=4.8$  Hz, *CHOH*), 6.76 (1H, d,  $J=4.8$  Hz, *CHOH*), 7.33–7.50 (5H, m, *Ar-H*), 7.83 (2H, d,  $J=9.0$  Hz, *Ar-H*), 8.32 (2H, d,  $J=9.0$  Hz, *Ar-H*), 12.87 (1H, s, *NH*);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  67.6, 116.4, 126.1, 126.7, 128.9, 129.1, 139.3, 141.9, 146.2, 162.7, 171.1; EIMS:  $m/z$  328 [ $\text{M}^+$ ], 195, 180, 122, 107, 77.

**Results and discussion**

**Synthesis**

Mandelic acid was converted to its hydrazide via esterification. The hydrazide was treated with different

isothiocyanates (**2a-e**) to afford thiosemicarbazides (**3a-e**). The 1,3,4-oxadiazoles (**4a-e**) and 1,2,4-triazoles (**5a-e**) were synthesized from thiosemicarbazides (**3a-e**) using different sets of reaction conditions. The 1,3,4-oxadiazoles were synthesized by cyclization of the thiosemicarbazides (**3a-e**) in the presence of mercuric acetate<sup>14</sup> and 1,2,4-triazoles by cyclodehydration under basic conditions<sup>15</sup>.

The IR spectra of thiosemicarbazides exhibited broad absorptions for NH groups in the region of 3485–3227 cm<sup>-1</sup>. A shift in carbonyl stretching was also observed, when compared to the parent hydrazide, along with the appearance of thiocarbonyl stretchings around 1170 cm<sup>-1</sup>.

In <sup>1</sup>H-NMR spectra, formation of the product was confirmed by the appearance of two new doublets/multiplets in the aromatic region, corresponding to the *para*-disubstituted benzene ring in the molecule. The presence of three broad downfield singlets integrating to one proton each, assigned to the three NH protons, was strong evidence for the formation of thiosemicarbazides.

The syntheses of oxadiazoles (**4a-e**) and triazoles (**5a-e**) were indicated in the IR spectra by the appearance of weak bands in the region of 1620–1580 cm<sup>-1</sup> for C=N stretchings, and also in that the strong carbonyl absorptions, observed for thiosemicarbazides, were absent. The disappearance of broad NH absorption bands, observed in the spectra of thiosemicarbazides in the region of 3480–3260 cm<sup>-1</sup>, also indicated cyclization into the respective nucleus.

In <sup>1</sup>H-NMR spectra, the disappearance of three signals for NH protons confirmed the cyclization of thiosemicarbazides to the respective nucleus. A downfield singlet observed in the range of 5.90–5.59 ppm was assigned to the only CH proton in these compounds (**4a-e**, **5a-e**). The signals for the aromatic protons were observed as three sets. The phenyl ring protons appeared as a multiplet integrating to five protons, and the signals for the *p*-disubstituted benzene ring were observed as two doublets. In <sup>13</sup>C-NMR spectra, the carbon signal observed in the range of 63.6–67.6 ppm was assigned to the carbinol carbon (CHOH). The aromatic carbons were observed between 113 and 126 ppm. In the <sup>13</sup>C-NMR spectra of triazoles (**5a-e**), the carbon signals in the range 169.7–170.4 ppm and 153.5–155.6 ppm were assigned to C-3 (C=S) and C-5 (C=N) of the triazole ring, respectively. The appearance of a carbon signal near 170 ppm for the thiocarbonyl group confirmed the existence of the triazole nucleus in the thione form. In the case of oxadiazoles (**4a-e**), the C-2 and C-5 (C=N) carbons were observed between 160.1 and 161.1 ppm. The mass spectra further confirmed formation of the desired nuclei. Molecular ion peaks were observed for all the compounds. In the case of chloro and bromo substituents, characteristic isotopic patterns were observed. Fragments corresponding to both aromatic rings were also observed along with fragments corresponding to cleavage of the oxadiazole and triazole moieties.

### Urease inhibition studies

The synthesized compounds (**4a-e**, **5a-e**) were tested for their *in vitro* urease inhibition activities at 0.2 mM

concentration against jack bean urease. The urease inhibition activity was determined according to literature protocols<sup>8</sup> using thiourea as the standard inhibitor, having an IC<sub>50</sub> value of 21 ± 0.01 μM. The results are summarized in Table 1.

The tested compounds exhibited weak to moderate and excellent inhibition. The compounds **4d**, **5b**, and **5d** were found to be more potent inhibitors than the standard, with IC<sub>50</sub> = 16.1, 18.9, and 16.7 μM, respectively (compared to thiourea with IC<sub>50</sub> = 21.0 μM). The most active compound was that with a methyl group in the aminophenyl part, in both 1,3,4-oxadiazole (**4d**) and 1,2,4-triazole (**5d**) nuclei. Compound **5b** with a 4-chloro substituent in the aminophenyl part was also a stronger inhibitor than the standard, but its corresponding oxadiazole (**4b**) revealed no inhibition. The compounds with a *p*-fluoro substituent (**4c**, **5c**) exhibited no observable activity.

It may be concluded from these results that triazolothiones (**5a-e**), in general, are more potent than their oxadiazole (**4a-e**) counterparts. This may be attributed to the substrate-like inhibition mechanism<sup>10</sup> where compounds **5a-e** with N2–C(=S)–N4 have a structure similar to the natural substrate of the enzyme, i.e. urea<sup>8</sup>. It is supposed that these compounds (**5a-e**) bind to the enzyme active site. Thus, the enzyme fails to catalyze hydrolysis and the activity of the enzyme is retarded.

It may also be observed that compounds with an electron donating group, i.e. methyl (**4d**, **5d**), are more potent inhibitors of urease, while those with strong electron withdrawing groups such as NO<sub>2</sub> (**4e**, **5e**) and F (**4c**, **5c**) are either less potent or are not active. Compounds with bromo (**5a**) and chloro (**5b**) substituents are also strong inhibitors, while the corresponding fluoro substituted compound (**5c**) is devoid of any activity. The fluorine atom, being most electronegative, is a strong electron withdrawing group, while bromine and chlorine, being relatively less electronegative, may donate electrons mesomerically. This also augments the hypothesis that electron donor groups increase the inhibition activity, in contrast to strong electron withdrawing groups.

**Table 1.** Urease inhibition studies of oxadiazoles (**4a-e**) and triazoles (**5a-e**).

Compound	I <sup>a</sup>	IC <sub>50</sub> ± SEM (μM)
<b>4a</b>	6.7	—
<b>4b</b>	—	—
<b>4c</b>	3.1	—
<b>4d</b>	91.5	16.1 ± 0.12
<b>4e</b>	86.2	80.3 ± 1.97
<b>5a</b>	99.3	32.0 ± 0.0272
<b>5b</b>	98.0	18.9 ± 0.188
<b>5c</b>	2.1	—
<b>5d</b>	99.6	16.7 ± 0.178
<b>5e</b>	61.2	131.7 ± 1.546
Thiourea		21.0 ± 0.011

<sup>a</sup>Percent inhibition was calculated from the formula  $100 - (\text{OD}_{\text{testwell}}/\text{OD}_{\text{control}}) \times 100$ .

## Conclusions

1,3,4-Oxadiazoles and 1,2,4-triazoles were synthesized from a common intermediate, i.e. thiosemicarbazides, and evaluated for urease inhibition. Three of the compounds, **4d**, **5b**, and **5d**, exhibited excellent urease inhibition, with  $IC_{50}$  values lower than that of the standard. These compounds may be subjected to further structural modifications and investigations for the development of antiulcer drugs.

## Declaration of interest

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