Synthesis of new 2-amino-1,3,4-oxadiazole derivatives with anti-salmonella typhi activity evaluation

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Abstract
Reaction of phenyl acetic acid derivatives with thiosemicarbazide in the presence of POCl3 afforded 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine 1 and 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-amine 2. Acylation of the amino group of oxadiazoles 1 and 2 with some acid chlorides such as methyl 4-(chlorocarbonyl) benzoate, 3-nitrobenzoyl chloride, 4-methoxy-benzoyl chloride, 4-isobutylbenzoyl chloride and chloroacetyl chloride yielded the acylated compounds 3–8. Cyclization of acetamides 7 and 8 by reaction with ammonium thiocyanate gave the thiazolidinones 9 and 10. Coupling of chloroacetamide 7 with two mercaptothiazoles gave coupled heterocyclic derivatives 11 and 12. Coupling of amino-oxadiazole 1 with N-Boc-glycine and N-Boc-phenylalanine lead to the formation of 16 and 17 respectively. All compounds were screened for their antibacterial activity against Salmonella typhi where compounds 3, 4, 10, 11 and 15 showed significant activity. Structures of the new synthesized compounds were confirmed using the spectral analysis such as IR, 1H NMR and 13C NMR and mass spectrometry.

Keywords: Oxadiazole, Acid chloride, Aromatic thiol, Amino acid, Anti-salmonella typhi

Introduction
Oxadiazole derivatives represent an important class of heterocyclic compounds with broad spectrum of biological activity. Oxadiazoles have been reported to possess anti-inflammatory [1, 2], anti-HIV [3], antibacterial [4, 5], anticonvulsant activities [6], antimalarial [7], herbicidal [8], antianxiety [9], insecticidal [10], antitubercular [11], antiviral [12], antifungal [13, 14], anti-HBV [15], antineoplastic [16], analgesic [17].

Typhoid is actually an infection as a result of Salmonella typhi which causes symptoms [18]. Symptoms can vary from gentle to extreme and in most cases, start 6 to 30 days soon after exposure. Frequently there is a progressive beginning of a very high fever more than several days. Weaknesses, abdominal pain, constipation, and migraines also commonly happen [19]. Diarrhea is uncommon, and vomiting is not usually severe. Some people develop a skin rash with rose-colored spots [20, 21].

Salmonella enterica subsp. enterica is a subspecies of Salmonella enterica, the rod-shaped, flagellated, aerobic, Gram-negative bacterium. Many of the pathogenic serovars of the S. enterica species are in this subspecies, including that responsible for typhoid [22].

Herein, we synthesized about seventeen new oxadiazole derivatives and screen them against Salmonella typhi to find new leads.

Results and discussion
4-Bromophenylacetic acid and 3-nitrobenzoic acid was allowed to react with semicarbazide in presence of phosphorus oxychloride followed by basification of product with potassium hydroxide to give 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine 1 and 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-amine (2).
Oxadiazole 1 or 2 were acylated by methyl-4-(chlorocarbonyl)-benzoate, 3-nitrobenzoyl chloride, 4-methoxybenzoyl chloride or 4-tert-butylbenzoyl chloride in presence of triethylamine to give N-acetyl derivatives 3–6 (Scheme 1).

Oxadiazole 1 and 2 were reacted with chloroacetyl chloride in presence potassium carbonate to give N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-chloroacetamide 7 and N-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-chloroacetamide 8 respectively. Refluxing 7 and 8 with ammonium thiocyanate in ethanol gave 2-[(5-(4-bromobenzyl)-[1, 3, 4] oxadiazol -2-yl}-imino]-1,3-Thiazolidin-4-one 9 and 2-[(5-(3-nitrophenyl)-[1, 3, 4]-oxadiazol-2-yl]-imino]-1,3-thiazolidin-4-one 10. Acyl chloride 7 reacted with benzo[d]thiazole-2-thiol and 4,5-dihydro-thiazole-2-thiol to give compounds 11–12 (Scheme 2).

Oxadiazole 1 was refluxed with 3-chlorophenyl isocyanate in ethanol to afford 1-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-3-(3-chlorophenyl)urea 13.

Coupling of oxadiazole 1 with N-protected amino acids such as N-Boc glycine and N-Boc phenylalanine gave tert-butyl-(-5-(4-bromobenzyl)-1,3,4-oxadiazole-2-ylcarbamoyl)-methyl-carbamate 14 and tert-butyl-1-(5-(4-bromobenzyl)-1,3,4-oxadiazol-2-ylcarbamoyl)-2-phenylethyl-carbamate 15 respectively. Deprotection of 14 and 15 was carried out by reaction with trifluoroacetic acid in presence of anisol to give N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-amino acetamide 16 and N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-amino-3-phenyl propanamide 17 as salts (Scheme 3).

Structure confirmation

Structure 1 has confirmed by infrared spectra which showed well defined bands attributable for νC=Н at 1610 cm⁻¹ and νNH₂ at 3310–3400 cm⁻¹. The 4-bromophenyl ring revealed two doublets at δ 7.215 and 7.497 ppm. Characteristic singlet of methylene group appeared at 4.097 ppm and the amino group was found as singlet at 7.006 ppm. ¹³C-NMR of 1 revealed the presence two carbon of oxadiazole ring around 169.0 and 157.3 ppm, carbons of 4-bromophenyl appeared around 137.9 and 120.5 ppm whereas, the methylene carbon appeared at 35.2 ppm. The ¹H-NMR of 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-amine 2 amino group at 7.622 ppm. ¹³C NMR spectrum revealed the two oxadiazole carbons at 169.0 and 164.7 ppm. ¹H-NMR spectrum for compounds 3–6 showed NH signal appeared around 12.00 ppm. Infrared spectra showed well-defined bands attributed to νNH at 3200–3400 cm⁻¹. ¹H NMR of 7 and 8 showed new signal for CH₂ around 4.00 ppm. ¹³C NMR of 9 and 10 spectrum showed signal for Carbon of methylene group at signal at 35.4 ppm.
Structure of compound 13 was assigned from the characteristic two singlet's for two NH groups at 9.52 and 12.23 ppm. The methylene protons found at 4.26 ppm. Infrared spectra showed well-defined bands attributable for $\nu_{\text{C=O}}$ at 1653.80 cm$^{-1}$ and $\nu_{\text{NH}}$ at 3369.59 cm$^{-1}$. Structure of compound 14 and 15 confirmed from $^1$H NMR which revealed the nine protons of tert-butyl group at 1.34 ppm, two methylene groups at 3.81 and 4.31 ppm, two NH groups at 7.16 and 12.80 ppm. $^1$H NMR of 16 and 17 proved the removal N-Boc group and formation of 16 and 17 moreover, $^{19}$F NMR showed signal around 73.84 ppm indicating the presence of fluoride.

**Antibacterial activity**

The novel seventeen compounds were screened for their antibacterial activity against gram negative bacteria *Salmonella typhi* at three concentrations i.e. 1000, 100 and 10 ppm using ditch dilution method. The test organism was a 2-h culture of *Salmonella typhi* incubated and grown in peptone-water medium (temperature 37 °C). DMF was used as solvent control which did not show any zone of inhibition. Muller-Hilton agar medium was used as culture medium. The culture plates were incubated at 37 °C for 24 h. Antibacterial activity was determined by measuring the diameter of the inhibition zone. The results are given in Table 1. Compounds 3, 4, 10, 11 and 15 displayed greater antibacterial activity against *Salmonella typhi*. Especially Compounds 10 and 11 exhibited the broadest spectrum activity in this series due to the heterocyclic ring of the imine and sulfide. Whereas, compounds 2, 5, 6, 8, 9, 12 and 16 showed moderately activity. Resistance of bacteria to these synthesized compounds could be associated to alteration of the bacterial protein targeted by compounds, enzymatic degradation of the synthesized compounds, or change in the membrane permeability to them.
Experimental

All melting points were uncorrected, performed on a MEL-TEMP II. Melting point apparatus. Microanalysis was performed by micro analytical laboratory, Cairo University, Egypt. Infrared spectra were recorded (ν in cm⁻¹) with pye Unicam SP 1200 spectrophotometer and using KBr Wafer technique. Mass spectra were measured with a Thermo Scientific LTQ Linear Ion Trap. Nuclear magnetic resonance spectra (¹H NMR, ¹³C NMR) were recorded (δ in ppm) on Bruker (300 MHz) spectrometer. The purity of the synthesized compounds was checked by TLC on glass coated plates in the laboratory with silica gel GF 254 type, 60 mesh, size 50–250.

Synthesis of 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine (1) and 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-amine (2)

The mixture of 4-bromophenyl acetic acid and/or 3-nitrobenzoic acid (1 mol) and semicarbazide (0.455 g, 1 mol) were dissolved in 3 mL of phosphorus oxychloride and refluxed for 45 min. The reaction was cooled to room temperature then 3 mL of water was added carefully. The mixture was refluxed for 4 h, filtered on hot and the solid washed by warm water and the filtrate was basified with saturated potassium hydroxide. The precipitate was filtered off and recrystallised from ethanol.

5-(4-Bromobenzyl)-1,3,4-oxadiazole-2-amine 1

Yield 65%; mp: 200–202 °C; IR (KBr) cm⁻¹: 3310–3400 (NH₂), 1610 (C=O), 1570, 1370, 1320, 1205, 1150, 1090; ¹H NMR (DMSO-d₆, δ ppm): 4.097 (s, 2H, –CH₂–), 7.006 (s, 2H, –NH₂), 7.215 (d, 2H, J = 8.18 Hz), 7.4971 (d, 2H, J = 8.079 Hz); ¹³C NMR (DMSO-d₆, δ ppm): (169.0, 157.3, 137.9, 132.0, 131.4, 120.5, 115.0); ESI–MS: 252 (100%), 254 (98%). Anal. Calcd. For C₉H₇BrN₃O (252.99): C, 42.54; H, 3.17; N, 16.54. Found C, 42.51; H, 3.12; N, 16.50.

Table 1 The activity of the tested compounds against Salmonella typhi

| Compound | S. typhi | Compound | S. typhi |
|----------|---------|----------|---------|
| 1        | +       | 10       | +++     |
| 2        | ++      | 11       | +++     |
| 3        | +++     | 12       | +       |
| 4        | +++     | 13       | +       |
| 5        | ++      | 14       | +       |
| 6        | ++      | 15       | +++     |
| 7        | –       | 16       | ++      |
| 8        | ++      | 17       | +       |
| 9        | ++      |          |         |

+++ strongly active, ++ moderately active, + weakly active range, – inactive

Scheme 3 Reaction of oxadiazole 1 with chlorophenyl isocyanate, glycine and phenylalanine
5-(3-Nitrophenyl)-1,3,4-oxadiazole-2-amine 2
Yield 60%, mp: 236–238 °C; IR (KBr) cm⁻¹: 3330–3410 (NH), 1610 (C= N); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 7.71–8.45 (m, 4H, ArH), 7.622 (s, 2H, –NH₂); ¹³C NMR (DMSO-d₆, δ ppm): (169.0, 164.7, 148.5, 133.7, 130.6, 127.4, 122.4, 121.6); ESI–MS: 206 (100%). Anal. Calcd. For (C₆H₄NO₂)₂: C, 51.94; H, 3.36; N, 10.07. Found: C, 46.57; H, 2.89; N, 27.14.

Reaction of oxadiazoles 1 and 2 with acid chlorides derivatives
To a solution of 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine 1 and/or 5-(3-nitrophenyl)-1,3,4-oxadiazole-2-amine 2 (0.5 mol) in methylene chloride (20 mL) containing triethylamine (0.069 mL, 0.5 mol), methyl-(chlorocarbonyl)-benzoate, 3-nitro-benzoyl chloride, 4-methoxybenzoyl chloride and/or 4-tert-butylbenzoyl chloride (0.5 mol) were added. The reaction mixture was stirred continuously at room temperature for overnight. The solvent was evaporated under vaccum and the residue was extracted with EtOAc and washed with NH₄Cl, dil HCl(1 N)/water and brain (NaCl). The product formed after evaporation was recrystallized from ethanol.

Methyl-4-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-ylcarbamoyl)benzoate 3
Yield 70%, mp: 281–283 °C; IR (KBr) cm⁻¹: 3430 (NH), 3057 (aromatic C=H), 1683 (C=O), 1605, 1551, 1440 (C= N and C= C). ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 3.8622 (s, 3H, –OCH₃), 4.3417 (s, 2H, –CH₂), 7.2866 (d, J = 8.19 Hz, 2H), 7.5122 (d, J = 8.202 Hz, 2H), 8.0324 (d, J = 8.3310 Hz, 2H), 8.1431 (d, J = 8.253 Hz, 2H), 12.6132 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (166.1, 165.6, 163.6, 161.4, 137.7, 137.1, 133.2, 132.1, 131.6, 129.7, 129.2, 120.6, 53.0, 34.8); ESI–MS: 326 (100%), 324 (89%). Anal. Calcd. For C₁₅H₁₃BrN₂O₄ (415.02): C, 52.60; H, 3.63; N, 10.82. Found: C, 52.57; H, 3.59; N, 10.78.

4-tert-Butyl-N-(5-(3-nitrophenyl)-1,3,4-oxadiazole-2-yl) benzamide 6
Yield 65%, mp: 290–291 °C; IR (KBr) cm⁻¹: 3320 (NH), 1640 (C= N), 1674 (C= O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 1.29 (s, 9H, –(CH₃)₃), 7.55–8.69 (m, 8H, ArH), 11.53 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (165.6, 160.8, 160.4, 156.8, 148.8, 133.8, 132.2, 131.7, 128.9, 126.0, 125.3, 121.3, 35.4, 31.3); ESI–MS: 366 (100%). Anal. Calcd. For C₁₅H₁₃BrN₂O₃ (387.02): C, 62.29; H, 4.95; N, 15.29. Found: C, 62.24; H, 4.90; N, 15.24.

Reaction of oxadiazole-2-amine 1 and 2 with chloroacetyl chloride
To a solution of 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine 1 and/or 5-(3-nitro-phenyl)-1,3,4-oxadiazole-2-amine 2 (1 mol) and potassium carbonate (0.69 g, mmole) in Dimethylformamide (11 mL), chloroacetyl chloride (0.75 mL, 1 mol) was added dropwise. The mixture was stirred well at room temperature for 4 h. Left to cool then pour the reaction mixture carefully onto crushed ice/water. The solid product that formed was filtered, washed with water three times, dried and recrystallised from ethanol.

N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-chloroacetamide 7
Yield 80%, mp: 233–234 °C; IR (KBr) cm⁻¹: 3419 (NH), 1653 (C=O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 4.2554 (s, 2H, –CH₂), 4.3675 (s, 2H, –CH₂), 7.2493 (d, J = 8.31 Hz, 2H), 7.4971 (d, J = 8.34 Hz, 2H), 12.8013 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (165.8, 163.9, 159.1, 137.5, 132.1, 131.6, 120.7, 42.8, 34.6); ESI–MS: 328 (77), 330 (100). Anal. Calcd. For C₁₆H₁₄BrCIN₂O₂ (328.96): C, 39.97; H, 2.74; N, 12.71. Found: C, 39.92; H, 2.70; N, 12.67.
N-(5-(3-nitrophenyl)-1,3,4-oxadiazole-2-yl)-2-chloroacetamide 8
Yield 65%, mp: 168–170 °C; IR (KBr) cm⁻¹: 3419 (NH), 1653 (C=N); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 4.45 (s, 2H, –CH₂), 7.73–8.61 (m, 4H, ArH), 12.91 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (166.0, 160.4, 159.4, 148.6, 133.7, 131.5, 131.2, 125.3, 120.4, 42.7); ESI–MS: 282 (100%). Anal. Calcd. For C₁₈H₁₃BrN₄O₂S₂ (411.97): C, 40.68; H, 3.17; N, 13.56. Found: C, 40.76; H, 2.52; N, 15.81.

Synthesis of thiazolidin-4-ones 9 and 10
Compound 7 and/or 8 (7 mmol) and ammonium thiocyanate (15 mmol) in ethanol 35 mL were refluxed for 3 h, the reaction mixture was left overnight. The obtained precipitate was filtered off, dried and recrystallised from ethanol–water to yield compounds 9 and 10.

2-(5-(4-bromobenzyl)-1,3,4-oxadiazol-2-ylmino)thiazolidin-4-one 9
Yield 75%, mp: 261–263 °C; IR (KBr) cm⁻¹: 3215 (NH), 1641 (C=N), 1672 (C=O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 4.3292 (s, 2H, –CH₂), 4.0470 (s, 2H, –CH₂), 7.2614 (d, J = 8.31 Hz, 2H), 7.5054 (d, J = 8.31 Hz, 2H), 12.2460 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (174.4, 170.9, 166.09, 166.05, 137.3, 132.0, 131.5, 120.7, 36.0, 35.4); ESI–MS: 351 (100), 353 (98). Anal. Calcd. For C₁₄H₁₂BrN₄O₂S (351.96): C, 40.81; H, 2.57; N, 15.86. Found: C, 40.76; H, 2.52; N, 15.81.

2-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-ylmino)1,3-thiazolidin-4-one 10
Yield 60%, mp: 107–110 °C; IR (KBr) cm⁻¹: 3230 (NH), 1645 (C=N), 1674 (C=O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 4.10 (s, 2H, –CH₂), 7.77–8.62 (m, 4H, ArH), 12.4 (bs, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (173.6, 171.2, 164.1, 163.4, 148.3, 133.3, 130.1, 127.6, 123.5, 122.7, 32.4); ESI–MS: 305 (100%). Anal. Calcd. For C₁₄H₁₂N₂O₄S (305.02): C, 43.28; H, 2.31; N, 22.94. Found: C, 43.24; H, 2.27; N, 22.89.

Reaction of 7 with aromatic thiols
To a solution of N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-chloroacetamide 7 (0.314 g, 1 mol) in dimethylformamide (20 mL), containing diisopropylethylamine (0.17 mL, 1 mol) under nitrogen, benzo[d]thiazole-2-thiol and/or 4,5-Dihydrothiazole-2-thiol (1 mol) was added. The reaction mixture was stirred well at room temperature for 4 h. Then the reaction mixture was poured into crushed ice/water, the formed solid was filtered, washed by water and recrystallised from chloroform.

N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-(benzo[d]thiazol-2-ythio)-acetamide 11
Yield 60%, mp: 240–242 °C; IR (KBr) cm⁻¹: 3310 (NH), 1640 (C=N), 1680 (C=O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 4.42 (s, 2H, –CH₂CO), 4.22 (s, 2H, –CH₂), 7.22–7.97 (m, 8H, ArH), 11.86 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (170.2, 168.6, 166.3, 166.8, 154.1, 135.7, 133.7, 132.9, 131.2, 125.1, 124.6, 122.3, 121.5, 120.4, 39.2, 32.1); ESI–MS: 461 (100%), 459 (98%). Anal. Calcd. For C₁₈H₁₃BrN₂O₂S₂ (459.97): C, 46.86; H, 2.84; N, 12.14. Found: C, 46.81; H, 2.80; N, 12.11.

2-(4,5-dihydrothiazol-2-ythio)-N-(5-(4-bromo-1,3,4-oxadiazole-2-yl)-acetamide 12
Yield 60%, mp: 259–260 °C; IR (KBr) cm⁻¹: 3290 (NH), 1644 (C=N), 1685 (C=O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 3.4321 (t, 2H, –CH₂), 4.0512 (t, 2H, –CH₂), 4.0783 (s, 2H, –CH₂), 4.3213 (s, 2H, –CH₂), 7.2637 (d, J = 8.33 Hz, 2H), 7.5053 (d, J = 8.35 Hz, 2H), 12.4894 (s, H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (171.1, 167.9, 165.8, 163.1, 133.1, 132.4, 131.6, 121.3, 68.1, 35.2, 31.4, 30.1). ESI–MS: 413 (100%), 411 (96%). Anal. Calcd. For C₁₄H₁₃BrN₂O₂S₂ (411.97): C, 40.68; H, 3.17; N, 13.56. Found: C, 40.62; H, 3.13; N, 13.52.

Synthesis of 1-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-3-(3-chloro-phenyl)urea 13
To a solution of 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine 1 (0.15 g, 0.5 mol) in ethanol (15 mL), 3-chlorophenyl isocyanate was added, the reaction mixture was refluxed for 6 h. The precipitate was filtered off and recrystallized from ethanol.

1-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-3-(3-chloro-phenyl)urea 13
Yield 60%, mp: 178–180 °C; IR (KBr) cm⁻¹: 3369.59 (NH), 1653.80 C=O (amide); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 4.26 (s, 2H, –CH₂), 7.02–7.68 (8H Ar), 9.52 (s, 1H, –NH), 12.23 (s, H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (161.9, 153.5, 140.9, 137.5, 133.7, 132.1, 131.6, 130.9, 122.8, 120.7, 118.5, 117.6, 34.9); ESI–MS: 405 (78%), 407 (100%). Anal. Calcd. For C₁₆H₁₃BrCIN₂O₂ (405.98): C, 47.14; H, 2.97; N, 13.74. Found: C, 47.11; H, 2.92; N, 13.70.

Reaction oxadiazole-2-amine 1 with amino acid
To a solution of 5-(4-bromobenzyl)-1,3,4-oxadiazole-2-amine 1 in methylene chloride (20 mL), (0.268 g, 1 mol) and/or N-(tert-butoxycarbonyl)glycine, N-(tert-butoxycarbonyl)phenylalanine was added followed by addition
of dimethyl-aminopyridine (DMAP) (0.0122 g, 0.1 mol). N,N′-dicyclohexyl-carbodiimide (0.206 g, 1.1 mol) was added to the reaction mixture. The mixture was stirred at 0 °C for 1 h and it continued overnight at room temperature. The reaction mixture filtered off and washed with methylene chloride. The filtrate evaporated under vacuum and the residue was purified by column chromatography (EtOAc: Hexane, 1:1). The solid formed after evaporation was recrystallised from ethanol.

tert-Butyl-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-ylcarbamoyl)methyl-carbamate 14
Yield 60%, mp: 188–190 °C; IR (KBr) cm⁻¹: 3425.8 (NH), 1667.3, 1700.5 (2C=O); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 1.3390 (s, 9H), 3.8112 (d, J = 5.8 Hz, 2H, –CH₂), 4.3102 (s, 2H, –CH₂), 7.1556 (s, 1H, –NH), 7.2489 (d, J = 8.106 Hz, 2H), 7.4843 (d, J = 8.127 Hz, 2H), 12.8013 (s, 1H, –NH). ¹³C NMR (DMSO-d₆, δ ppm): (169.4, 163.3, 159.3, 156.3, 137.6, 132.1, 131.5, 120.7, 78.7, 43.6, 34.6, 28.6); ESI–MS: 410 (57.7), 412 (56.9), 354 (98), 356 (100), 310 (50.7), 352 (50), 208 (59.2). Anal. Calcd. For C₁₆H₁₉BrN₄O₄ (410.06): C, 46.73; H, 4.66; N, 13.62. Found: C, 46.69; H, 4.61; N, 13.57.

tert-Butyl-1-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-ylcarbamoyl)-2-phenyl-ethylcarbamate 15
Yield 60%, mp: 177–180 °C; IR (KBr) cm⁻¹: 3250–3440 (NH), 1675, 1755 (2C=O); ¹H NMR (300 MHz, CDCl₃, δ ppm): 1.2341 (s, 9H), 3.8124 (d, J = 5.8 Hz, 2H, –CH₂), 4.2974 (s, 2H, –CH₂), 7.1556 (s, 1H, –NH), 7.2637 (d, J = 6.39 Hz, 2H), 7.5034 (d, J = 6.813 Hz, 2H), 9.34179 (s, 3H, –NH₂), 12.5478 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): (166.2, 163.8, 158.7, 137.5, 132.1, 131.6, 120.7, 41.3, 34.6); F¹¹NMR (DMSO-d₆, δ ppm): –73.838 (F); ESI–MS: 510 (100), 312 (97.8). Anal. Calcd. For C₁₁H₁₉BrN₄O₄ (410.01): C, 42.46; H, 3.56; N, 18.01. Found: C, 42.41; H, 3.52; N, 17.96.

N-(5-(4-bromobenzyl)-1,3,4-oxadiazole-2-yl)-2-amino-3-phenylpropanamide 17
Yield 75%, mp: 263–265 °C; IR (KBr) cm⁻¹: 3270 (NH), 1672 (C=O) 2970 (NH salt); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 3.7516 (s, 2H, –CH₂), 4.1342 (s, 2H, –CH₂), 4.8951 (t, 1H, CH), 6.5679 (s, 3H, –NH₂), 7.1203–7.8542 (m, 9H), 12.8013 (s, 1H, –NH); ¹³C NMR (DMSO-d₆, δ ppm): –73.934 (F); ESI–MS: 400 (95.4), 402 (100). Anal. Calcd. For C₁₅H₁₇BrN₄O₂ (400.05): C, 53.88; H, 4.27; N, 13.96. Found: C, 53.82; H, 4.21; N, 13.90.

Conclusion
Seventeen new functionalized oxadiazole hits were synthesized and characterized. The new hits were evaluated for their biological activity against gram-negative bacteria Salmonella typhi, among synthesized 3, 4, 10, 11 and 15 demonstrated strong activities which recommends them for further studies to be future leads.

Acknowledgements
This work was supported by Dr. Ahmed Yousef Ali Desoky, University of waterloo, Canada.

Authors’ contributions
The author read and approved the final manuscript.

Funding
This work only funded by me.

Availability of data and materials
All data and material analyzed or generated during this investigation are included in this manuscript. The raw data can be requested from email of Eid: eidsalama2000@gmail.com.

Competing interests
The author declares no competing interests.

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Received: 24 November 2019   Accepted: 7 April 2020
Published online: 20 April 2020

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