Synthesis and Bioassay of a New Class of Furanyl-1,3,4-Oxadiazole Derivatives

Mohamed M. El Sadek 1,*, Seham Y. Hassan 1, Huda E. Abdelwahab 1 and Galila A. Yacout 2

1 Chemistry Department, Faculty of Science, Alexandria University, Alexandria 21231, Egypt; E-Mails: sehamyassen@yahoo.com (S.Y.H.); huda_eid@yahoo.com (H.E.A.)
2 Biochemistry Department, Faculty of Science, Alexandria University, Alexandria 21231, Egypt; E-Mail: galila_69@yahoo.com

* Author to whom correspondence should be addressed; E-Mail: mohamed.elsadik@alexu.edu.eg; Tel.: +2-001-006-544-617; Fax: +2-035-932-488.

Received: 22 May 2013; in revised form: 19 June 2013 / Accepted: 20 June 2013 / Published: 19 July 2013

Abstract: Tyrosinase enzyme is a monophenol monoxygenase enzyme, which plays an important role in human as a rate limiting step enzyme for different specific metabolic pathways, as well as its useful application in industry and agriculture. So this study was carried out to test the effect of newly prepared compounds containing 1,3,4-oxadiazoles with different substituted groups on tyrosinase enzyme activity, hoping to use them in the treatment of some diseases arising from tyrosinase activity disorders such as Parkinson’s disease, schizophrenia, autism, attention deficit, hyperactivity disorder, and cancer.

Keywords: carbohydrazide; oxadiazole; triazole; tyrosinase

1. Introduction

1,3,4-Oxadiazoles are of great practical significance [1] which is primarily due to their large number of uses, in the most diverse areas, for example in drug synthesis, as scintillation materials, in the production of polymers and dyes, and uses in photography as light screening agents. 1,3,4-Oxadiazole (OXD) derivatives are useful targets in the search for antivirals as they have been associated with many types of biological properties such as anti-inflammatory [2,3], antibacterial, antifungal activities [4,5] and HIV replication inhibition [6]. Oxadiazoles have often been described as bio-isosteres for amides and esters [7]. As a consequence of these characteristics, oxadiazoles have
impacted drug discovery programs in numerous areas including muscarinic agonists [8,9], benzodiazepine receptor partial agonists [10,11], dopamine transporters [12], anti-rhinovirals [13], growth hormone secretagogues [14], 5-HT agonists[15], antipsasmodics [16], nematocidal, fungicidal and microbicides [17], analgesics [18], anti-inflammatory agents [19,20], Fab I inhibitors as antibacterial agents [21], immunosuppressants [22], and also antiplatelet and antithrombotic agents [23], 5-HT antagonists [24], human NK1 antagonists [25], They have been used as peptide mimetics due to their particular geometric and electrostatic properties [26,27]. Accordingly, in continuation of our work [28–34], a variety of heterocyclic derivatives involving some new oxadiazoles have been prepared from saccharide derivatives, and their chemistry and the effect of these derivatives on tyrosinase enzyme [35–38], which is the rate limiting step in melanine biosynthesis [39] as well as different biological actions were studied [40].

2. Results and Discussion

2.1. Chemistry

Ethyl 5-(1,2,3,4-tetrahydroxybutyl)-2-methylfuran-3-carboxylate (1) [41] was oxidized to the corresponding formyl derivative 2 [42,43], which was condensed with a number of aroylhydrazines to afford hydrazones 3a–c [44]. Oxidative cyclization of compounds 3a–c with iodine, yellow mercuric oxide, and magnesium oxide in dry ether [44] (yields 41%–47%) or by an improved procedure through refluxing with chloramine-T in ethanol [32] (which gave higher yields: 78%–91%) afforded the corresponding 1,3,4-oxadiazole derivatives 4a–c. Furthermore, boiling 1,3,4-oxadiazole derivatives 4a–c with hydrazine hydrate afforded the corresponding hydrazide derivatives, the 2-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)furans 5a–c (Scheme 1).

The 1H-NMR spectra of compounds 5a–c showed the disappearance of both the CH3 and CH2 protons of the ethyl ester group. Instead, they displayed two signals for the NH protons in the δ 4.59–1.64 range, and the NH proton of the hydrazide group at 9.82–9.00 ppm, respectively (for other protons see Experimental). The mass spectra of compounds 5a and 5c showed the molecular ion peaks at m/z 284 and 318, respectively. The base peaks of compound 5a and 5c appeared at m/z 171 and 105, respectively.

On the other hand, condensation of the hydrazide derivative 5a with a number of aldehydes afforded the corresponding hydrazone derivatives 6a–h (Scheme 1). The 1H-NMR spectra of compounds 6a–h showed the disappearance of the NH2 protons and instead, displayed a singlet signal for the CH=N protons in the δ 10.2–8.30 range, while the NH protons appeared as a singlet at δ 8.85, 9.98, 7.85, 8.80, 9.52, and 9.38, respectively (see Experimental). The mass spectra of the compounds 6d, 6e, 6f and 6h showed the molecular ion peaks at m/z 417, 393,440 and 447, respectively; while the base peaks appeared at m/z 176, 115, 77 and 358, respectively (see Experimental).

Cyclization of the hydrazones 6a, 6e, and 6f with acetic anhydride under reflux, afforded the oxadiazoline derivatives 7a–e (Scheme 1). The mechanism of their formation probably proceeded through the highly stable enolized form.
Scheme 1. Synthesis of 1,3,4-oxadiazole derivatives.

The $^1$H-NMR spectra of compounds 7a–c showed the disappearance of both the NH and CH=N protons. Instead, their $^1$H-NMR showed the methyl protons of the N-COCH$_3$ group as a singlet in the $\delta$ 1.24–1.22 ppm range (see Experimental). In addition, the proton at position-5 in the triazole ring (Compound 7c) resonates at lower field than the proton of the oxadiazolyl ring due to the strong electron attracting property of the triazole moiety. On the other hand, oxidative cyclization
of the hydrazone compounds \(6b\) and \(6d\) with chloramine-T afforded the corresponding 1,3,4-oxadiazolderivatives \(8a\) and \(8b\) in high yield (Scheme 1). The \(^1\text{H-NMR}\) spectra of compounds \(8a\) and \(8b\) showed the disappearance of both the NH and (CH=N) protons (see Experimental). The mass spectrum of compound \(8b\) showed the expected molecular ion peak at \(m/z\) 415, while the base peak appeared at \(m/z\) 91.

2.2. Biological Activity Assays

2.2.1. Enzyme Activity Assay

Tyrosinase enzyme was prepared from mushrooms in a phosphate buffer (50 mM, pH 6.0) according to the method of Yang and Robb [45]. The activity of the prepared enzyme solution was determined by following spectrophotometrically the formation of dopachrome at 30 °C. After addition of enzyme preparation (50 \(\mu\)L) to a cuvette containing phosphate buffer (1.2 mL, 50 mM, pH 6.0) and 10 mM L-dopa (0.8 mL), the solution was immediately mixed and the increase in absorbance at 475 nm (indicating the formation of dopachrome) was recorded with a UV-20100 spectrophotometer. A blank experiment was carried out as mentioned above using buffer (50 \(\mu\)L) instead of enzyme preparation [46].

2.2.2. Enzyme Activity Assay in the Presence of the Tested Compounds

Activity of the enzyme in the presence of the examined compounds was determined by following the above steps for the formation of dopachrome and each examined compound (0.8 mL, 10 mmol) separately, and the increase in absorbance at 475 nm was recorded, separately, as shown in Tables 1 and 2 and Figures 1 and 2. All tests carried out in triplicate.

Table 1. Effect of time (s) the absorbance of on tyrosinase-catalyzed reaction in presence of the examined compounds \(6a, 6b, 6d\) and \(6g\) compared to control enzyme.

| Time (s) | Control enzyme | Absorbance (\(\lambda\)) |
|---------|----------------|-------------------------|
|         | 0.0670         | 0.1870 0.1810 0.1520 0.4115 |
|         | 0.1010         | 0.5340 0.2710 0.1670 0.4185 |
|         | 0.1425         | 1.0050 0.3490 0.2700 0.4345 |
|         | 0.1845         | 1.2650 0.3810 0.2800 0.4470 |
|         | 0.2250         | 1.7130 0.4000 0.3000 0.4935 |
|         | 0.2650         | 2.0790 0.5830 0.3120 0.6620 |
|         | 0.3035         | 2.1790 0.6500 0.3210 0.8810 |

Table 2. Effect of time (s) on the absorbance of tyrosinase-catalyzed reaction in presence of the examined compounds \(5a, 5c, 6f, 7a, 7c, 8a, 8b\) compared to control enzyme.

| Time (s) | Control enzyme | Absorbance (\(\lambda\)) |
|---------|----------------|-------------------------|
|         | 0.0670         | 0.0365 0.0405 0.0645 0.0570 0.0780 0.0580 0.0785 |
|         | 0.1010         | 0.0510 0.0555 0.0720 0.0890 0.0765 0.0795 0.0885 |
|         | 0.1425         | 0.0645 0.0785 0.0895 0.1300 0.0760 0.0870 0.1230 |
Table 2. Cont.

| Time (s) | Control enzyme | 5a   | 5c   | 6f   | 7a   | 7c   | 8a   | 8b   |
|----------|----------------|------|------|------|------|------|------|------|
| 90       | 0.1845         | 0.0765 | 0.0995 | 0.1085 | 0.1790 | 0.0605 | 0.0895 | 0.1480 |
| 120      | 0.2250         | 0.0865 | 0.1170 | 0.1334 | 0.2060 | 0.0560 | 0.0950 | 0.1760 |
| 150      | 0.2650         | 0.0965 | 0.1330 | 0.1465 | 0.2455 | 0.0515 | 0.1025 | 0.2000 |
| 180      | 0.3035         | 0.1060 | 0.1480 | 0.1580 | 0.2785 | 0.0450 | 0.1070 | 0.2100 |

Figure 1. Effect of time (s) on the absorbance of tyrosinase-catalyzed reaction in presence of the examined compounds 6a, 6b, 6d and 6g compared to control enzyme.

Figure 2. Effect of time (s) on the absorbance of tyrosinase-catalyzed reaction in presence of the examined compounds 5a, 5c, 6f, 7a, 7c, 8a, 8b compared to control enzyme.
2.3. Results

Our obtained data revealed that the examined compounds showed different effects [47] on the tyrosinase enzyme activity between inhibition and activation in which compounds containing one 1,3,4-oxadiazole ring in addition to the furan ring (compounds 6a, 6b, 6d, 6g) have an activating effect on the enzyme tyrosinase with different values (Table 1 and Figure 1). Compound 6a in which there is no substituent on the phenyl group, which probably makes it easier to bind with the active sites of the enzyme, showed the highest activation effect. The presences of substituents on the phenyl group such as halogens, or a nitro group (compounds 6b, 6d) decrease the activation ability of the compound, while compounds containing a CONHNH₂ group have inhibitory effects (5a, 5c).

On the other hand compounds containing two 1,3,4-oxadiazole rings or one oxadiazole ring and one 1,2,3-triazole ring have inhibitory effects on tyrosinase enzyme (compounds 6f, 7a, 8a and 8b). In addition compound 7c which contains two 1,3,4-oxadiazoles and one 1,2,3-triazole ring has the highest inhibition effect (Table 2 and Figure 2). The increasing number of heterocyclic rings containing nitrogen such as 1,3,4-oxadiazole and 1,2,3-triazole rings has a noticeable inhibitory effect on tyrosinase enzyme.

3. Experimental

3.1. General Methods

Melting points were determined on a Köfler block and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 spectrometer. ¹H-NMR was recorded on a JEOL JNM ECA 500 MHz instrument using tetramethylsilane as an internal standard. Mass spectra were recorded on a GC-MS solution DI Analysis Shimadzu Qp-2010 unit. Elemental analysis was determined at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Thin layer chromatography (TLC) was carried out on silica gel plates. Solutions were evaporated under diminished pressure unless otherwise stated. The ChemDrew-Ultra-8.0 software was used for naming the prepared compounds.

3.2. Reactions of Compounds 4a–c with Hydrazine Hydrate

A mixture of ethyl-5-(5-(4-substituted phenyl)-1,3,4-oxadiazole-2-yl)-2-methylfuran-3-carboxylates 4a–c (1 g, 3.4 mmol), and hydrazine hydrate (5 mL, 103 mmol) was refluxed for one hour. The resulting solution was left at R.T. for one hour, and the product that separated out was filtered off, washed with a little ethanol, recrystallized from ethanol and dried.

2-Methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl) furan-3-carbohydrazide (5a). Yield: 682 mg (79%). White crystals; m.p. 103–104 °C; Rf: 0.72 (n-hexane/ETOAc, 3:1, V/V); IR (KBr): 1,621 (C=N), 1,643 (C=O amide), 3,142 (NH), 3,321 cm⁻¹ (NH₂); ¹H-NMR (CDCl₃) δ: 1.64 (bs, 2H, NH₂; exchangeable with D₂O), 2.73 (s, 3H, CH₃), 7.45 (s, 1H, H-furan), phenyl protons: 7.50–7.56 (m, 3H, m-H, p-H), 8.10–8.13 (dd, 2H, o-H; J₁,₂ = 2.3 Hz, J₁,₃ = 6.9 Hz), 9.00 (s, 1H, NH; exchangeable with D₂O); MS: m/z (%), 51 (10.85), 63 (13.22), 64 (7.87), 65 (46.02), 77 (17.44), 79 (5.49), 80 (4.51), 89 (13.57), 90 (7.27), 91 (80.36), 92 (12.96), 93 (80.36), 105 (14.12), 106 (16.08), 107 (51.20), 108 (30.53), 155
Molecules 2013, 18 8556

(70.23), 156 (6.30), 167 (0.17), 171 (100), 172 (9.42), 284 (5.47, M⁺); Anal. Calcd for C₁₄H₁₂N₄O₃ (284.27): C, 59.15; H, 4.25; N, 19.71; Found: C, 58.94; H, 4.09; N, 19.59.

5-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-methylfuran-3-carbohydrazide (5b). Yield: 620 mg (65%). White crystals; m.p. 121–122 °C; Rf: 0.86 (CHCl₃/MeOH, 25:1, V/V); IR (KBr): 1,599 (C=N), 1,656 (C=O amide), 3,261 (NH), 3,360 cm⁻¹ (NH₂); ¹H-NMR (DMSO-d₆): δ: 2.24 (s, 3H, CH₃-furan), 3.88 (s, 3H, OCH₃), 4.59 (bs, 2H, NH₂; exchangeable with D₂O), 7.23 (s, 1H, H-furan), 7.47 (d, 2H, o-OCH₃; J = 8.4 Hz), 7.80 (d, 2H, m-OCH₃; J = 8.4 Hz), 9.82 (bs, 1H, NH; exchangeable with D₂O); MS: m/z (%), 50 (15.66), 51 (16.66), 55 (24.81), 56 (13.73), 57 (24.81), 60 (15.93), 65 (15.33), 69 (18.74), 71 (15.62), 75 (14.92), 77 (45.62), 83 (15.33), 91 (35.71), 97 (12.70), 105 (100), 106 (13.09), 107 (11.69), 111 (51.13), 113 (10.93), 138 (11.03), 139 (33.40), 141 (11.32), 155 (10.76), 171 (12.76), 309 (11.93), 318 (11.93, M⁺); Anal. Calcd for C₁₅H₁₄N₄O₄ (314.3): C, 57.32; H, 4.49; N, 17.83; Found: C, 57.16; H, 4.37; N, 17.78.

5-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylfuran-3-carbohydrazide (5c). Yield: 810 mg (84%). White crystals; m.p. 153–154 °C; Rf: 0.77 (CHCl₃/MeOH, 25:1, V/V); IR (KBr): 1,618 (C=N), 1,661 (C=O amide), 3,224, 3,310 cm⁻¹ (NH, NH₂); ¹H-NMR (DMSO-d₆): δ: 2.24 (s, 3H, CH₃-furan), 4.59 (bs, 2H, NH₂; exchangeable with D₂O), 7.23 (s, 1H, H-furan), 7.48 (d, 2H, o-Cl; J = 8.4 Hz), 7.79 (d, 2H, m-Cl; J = 8.4 Hz), 9.82 (bs, 1H, NH; exchangeable with D₂O); MS: m/z (%), 50 (15.66), 51 (16.66), 55 (24.81), 56 (13.73), 57 (24.81), 60 (15.93), 65 (15.33), 69 (18.74), 71 (15.62), 75 (14.92), 77 (45.62), 83 (15.33), 91 (35.71), 97 (12.70), 105 (100), 106 (13.09), 107 (11.69), 111 (51.13), 113 (10.93), 138 (11.03), 139 (33.40), 141 (11.32), 155 (10.76), 171 (12.76), 309 (11.93), 318 (11.93, M⁺); Anal. Calcd for C₁₄H₁₁ClN₄O₃ (318.72): C, 52.76; H, 3.48; N, 17.58; Found: C, 52.89; H, 3.51; N, 17.43.

3.3. Reactions of Carbohydrazide 5a with Aldehydes

A solution of 2-methyl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)furan-3-carbohydrazide (5a, 500 mg, 1.8 mmol) in ethanol (15 mL, 257 mmol) containing acetic acid (0.1 mL, 1.75 mmol) was treated with aldehyde (1.8 mmol) in ethanol (10 mL, 171 mmol). The mixture was refluxed on a water bath for 10 min, and after cooling, the product that separated out was filtered off, washed with little ethanol, recrystallized from ethanol and dried.

N-Benzylidene-2-methyl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)furan-3-carbohydrazide (6a). Yield: 317 mg (81%). Pale yellow crystals; m.p. 73–74 °C; Rf: 0.42 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1,559 (C=N), 1,641 (C=O amide), 3,224, 3,310 cm⁻¹ (NH, NH₂); ¹H-NMR (CDCl₃): δ: 2.76 (s, 3H, CH₃-furan), 7.43 (s, 1H, H-furan), 7.53–7.57 (m, 4H, Ar-H), 7.62–7.66 (m, 1H, Ar-H), 7.89 (d, 2H, Ar-H; J = 6.9 Hz), 8.11–8.14 (m, 3H, Ar-H), 8.85 (s, 1H, NH; exchangeable with D₂O); Anal. Calcd for C₂₁H₁₆N₄O₃ (372.38): C, 67.73; H, 4.38; N, 15.05; Found: C, 67.64; H, 4.32; N, 14.93.

N-(4-Chlorobenzyldiene)-2-methyl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)furan-3-carbohydrazide (6b). Yield: 760 mg (98%). Faint golden crystals; m.p. 198–199 °C; Rf: 0.91 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1,623 (C=N), 1,655 (C=O amide), 3,241 cm⁻¹ (NH); ¹H-NMR (CDCl₃): δ: 2.21 (s, 3H, CH₂-furan), 7.26 (s, 1H, H-furan), 7.34–7.38 (m, 2H, Ar-H), 7.44 (d, 2H, o-Cl; J = 8.4 Hz), 7.51–7.53 (m, 2H, Ar-H), 7.81 (d, 2H, m-Cl; J = 8.4 Hz), 8.04 (d, 1H, Ar-H; J = 8.4 Hz), 8.67 (s, 1H, CH=N), 9.98 (s, 1H, NH; exchangeable with D₂O); Anal. Calcd for C₂₁H₁₅ClN₄O₃ (406.82): C, 62.00; H, 3.72; N, 13.77; Found: C, 61.89; H, 3.58; N, 13.73.
**N'-(4-Methoxybenzylidene)-2-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)furan-3-carbohydrazide** (6c). Yield: 580 mg (41%). Yellow crystals; m.p. 166–167 °C; Rf: 0.41 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1,602 (C=N), 1,642 (C=O amide), 3,176 cm⁻¹ (NH); Anal. Calcd for C₂₂H₁₈N₄O₄ (402.4): C, 65.66; H, 4.51; N, 13.92; Found: C, 65.44; H, 4.34; N, 14.00.

**N-(4-Nitrobenzylidene)-2-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)furan-3-carbohydrazide** (6d). Yield: 640 mg (88%). Golden crystals; m.p. 295–296°C; Rf: 0.56 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1,596 (C=N), 1,652 (C=O amide), 3,431 cm⁻¹ (NH), 1H-NMR (CDCl₃) δ: 2.16 (s, 3H, CH₃-furan), 6.75 (s, 1H, H-furan), 7.54–7.57 (m, 1H, Ar-H), 7.85 (bs, 1H, NH; exchangeable with D₂O), 8.02–8.14 (m, 4H, Ar-H), 8.27–8.40 (m, 4H, Ar-H), 8.71 (s, 1H, CH=N); MS: m/z (%), 50 (37.75), 51 (21.53), 63 (28.45), 64 (9.55), 76 (66.32), 77 (25.51), 89 (17.28), 91 (6.32), 92 (6.75), 102 (8.13), 103 (39.92), 104 (13.76), 118 (6.65), 130 (41.48), 149 (9.77), 150 (7.10), 151 (8.98), 152 (5.50), 156 (20.45), 157 (12.07), 183 (7.91), 206 (2.88), 217 (4.28), 232 (76.86), 233 (58.29), 234 (9.82), 259 (64.74), 260 (55.93), 261 (11.03), 395 (2.13,M⁺-3); Anal. Calcd for C₂₁H₁₅N₅O₅ (417.37): 417.37; C, 60.43; H, 3.62; N, 16.78; Found: C, 60.34; H, 3.57; N, 16.67.

**2-Methyl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)-N-(3-phenylallylidene)furan-3-carbohydrazide** (6e). Yield: 513 mg (91%). Yellow crystals; m.p. 158–159 °C; Rf: 0.61 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1559 (C=N), 1,641 (C=O amide), 3,301 cm⁻¹ (NH), 1H-NMR (CDCl₃) δ: 2.72 (s, 3H, CH₃-furan), 7.13–7.21 (m, 1H, Ph-CH), 7.19 (s, 1H, H-furan), 7.35–7.57 (m, 10H, Ar-H), 8.03–8.15 (m, 1H, CH=), 8.46 (d, 1H, CH=N; J = 8.4 Hz), 8.80 (bs, 1H, NH; exchangeable with D₂O); MS: m/z (%), 50 (5.66), 51 (19.21), 52 (4.67), 65 (5.70), 77 (50.41), 78 (10.66), 89 (11.09), 91 (69.20), 102 (16.88), 103 (42.06), 104 (16.28), 115 (100), 116 (17.95), 117 (8.46), 129 (40.84), 130 (95.23), 131 (11.37), 142 (2.91), 156 (20.45), 157 (12.07), 183 (7.91), 206 (2.88), 217 (4.28), 232 (76.86), 233 (58.29), 234 (9.82), 259 (64.74), 260 (55.93), 261 (11.03), 395 (2.13,M⁺-3); Anal. Calcd for C₂₃H₁₈N₄O₃ (398.41): C, 69.34; H, 4.55; N, 14.06; Found: C, 69.11; H, 4.52; N, 14.10.

**2-Methyl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)-N-(3-phenylallylidene)furn-3-carboxylate** (6g). Yield: 658 mg (43%). Pale green crystals; m.p. 185–186 °C; Rf: 0.43 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1,591 (C=N), 1,643 (C=O amide), 3,137 cm⁻¹ (NH); 1H-NMR (DMSO-d₆) δ: 1.35 (t, 3H, CH₃-ester; J = 6.9Hz), 2.70 (s, 6H, 2CH₃-furan), 3,137 cm⁻¹ (NH), 1H-NMR (DMSO-d₆) δ: 1.35 (t, 3H, CH₃-ester; J = 6.9Hz), 2.70 (s, 6H, 2CH₃-furan),
4.31 (q, 2H, CH$_2$-ester; $J = 6.9$ Hz), 7.26 (s, 1H, H-furan$_1$), 7.45 (s, 1H, H-furan$_2$), 7.50–7.56 (m, 3H, Ar-H), 8.12 (dd, 2H, Ar-H; $J_{1,2} = 2.3$ Hz, $J_{1,3} = 6.9$ Hz), 8.48 (s, 1H, CH=N), 9.52 (s, 1H, NH; exchangeable with D$_2$O). Anal. Calcd for C$_{23}$H$_{20}$N$_4$O$_6$ (448.43): C, 61.60; H, 4.50; N, 12.49; Found: C, 61.49; H, 4.44; N, 12.34.

Ethyl-5-((2-methyl-5-(5-phenyl-1,3,4-oxadiazole-2-yl)furan-3-carboylimino)methyl)-2-methyl-1H-pyrrole-3-carboxylate (6h). Yield: 140 mg (58%). Yellow crystals; m.p. 262–263 °C; R$_f$: 0.5 (n-hexane/EtOAc, 7:1, V/V); IR (KBr): 1,598 (C=N), 1,656 (C=O amide), 1,675 (CO ester), 2,976 (NH$_{-1}$), 3,314 cm$^{-1}$ (NH-pyrrole); 1H-NMR (DMSO-d$_6$) $\delta$: 1.22 (t, 3H, CH$_3$-ester; $J = 6.9$ Hz), 2.42 (s, 3H, CH$_3$-pyrrol), 2.46 (s, 3H, CH$_3$-furan), 4.13 (q, 2H, CH$_2$-ester; $J = 6.9$ Hz), 6.76 (s, 1H, H-furan), 6.91 (d, 1H, Ar-H; $J = 2.3$ Hz), 7.27 (s, 1H, H-pyrrole), 7.60–7.62 (m, 2H, Ar-H), 8.02–8.07 (m, 2H, Ar-H), 8.30 (s, 1H, CH=N), 9.38 (s, 1H, NHCO; exchangeable with D$_2$O), 12.08 (s, 1H, NH-pyrrole; exchangeable with D$_2$O); MS: m/z (%), 66 (3.78), 78 (4.11), 106 (4.95), 107 (12.50), 120 (2.26), 124 (1.77), 134 (21.63), 135 (22.36), 136 (4.07), 151 (39.81), 152 (15.73), 165 (5.69), 180 (24.27), 184 (2.00), 228 (2.82), 256 (2.24), 283 (2.13), 313 (14.14), 358 (100), 359 (22.22), 447 (4.95, M$^+$. Anal. Calcd for C$_{23}$H$_{21}$N$_5$O$_5$ (447.44): C, 61.74; H, 4.73; N, 15.65; Found: C, 61.69; H, 4.70; N, 15.76.

3.4. Reaction of Compounds 6a, 6e, 6f with Acetic Anhydride

A mixture of 6a, 6e or 6f (100 mg, 27 mmol) and acetic anhydride (1 mL, 10.6 mmol) was refluxed for 15 min on gentle heating. The hot solution was poured onto ice water (10 mL) and the product which separated was filtered off, washed several times with water, recrystallized from ethanol and dried.

1-(5-(2-Methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)furan-3-yl)-2-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone (7a). Yield: 92 mg (84%). White powder; m.p. 97–98 °C; R$_f$: 0.5 (n-hexane/EtOAc, 5:1, V/V); IR (KBr): 1,584 (C=N), 1,671 cm$^{-1}$ (C=O acetyl); 1H-NMR (CDCl$_3$) $\delta$: 1.24 (s, 3H, CH$_3$CO), 2.85 (s, 3H, CH$_3$-furan), 7.18 (s, 1H, H-furan), 7.23 (s, 1H, H-oxadiazoline), 7.36–7.57 (m, 10H, 2Ph). Anal. Calcd for C$_{23}$H$_{18}$N$_4$O$_4$ (414.41): C, 66.66; H, 4.38; N, 13.52; Found: C, 66.90; H, 4.28; N, 13.55.

1-(5-(2-Methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)furan-3-yl)-2-styryl-1,3,4-oxadiazol-3(2H)-yl)ethanone (7b). Yield: 102 mg (98%). Yellow powder; m.p. 150–151 °C; R$_f$: 0.7 (n-hexane/EtOAc, 6:1, V/V); IR (KBr): 1,584 (C=N), 1,669 cm$^{-1}$ (C=O acetyl); 1H-NMR (CDCl$_3$) $\delta$: 1.24 (s, 3H, CH$_3$CO), 2.73 (s, 3H, CH$_3$-furan), 6.34 (s, 1H, H-furan), 7.12 (s, 1H, H-oxadiazoline), 7.08–7.15 (m, 1H, PhCH=), 7.33–7.42 (m, 6H, Ar-H), 7.49 (d, 4H, Ar-H; $J = 6.1$ Hz), 8.40 (dd, 1H, CH=; $J_{1,2} = 1.6$ Hz, $J_{1,3} = 6.9$ Hz); MS: m/z (%), 50 (6.82), 51 (22.37), 63 (14.07), 77 (53.47), 91 (49.70), 103 (41.24), 115 (57.27), 128 (10.49), 129 (13.26), 130 (100), 142 (2.54), 156 (36.13), 183 (6.91), 205 (1.96), 217 (2.68), 233 (44.00), 259 (45.70), 260 (90.95), 286 (2.31), 390 (0.02), 397 (0.03), 399 (0.12), 414 (0.12), 434 (0.05), 440 (14.07, M$^+$); Anal. Calcd for C$_{25}$H$_{20}$N$_4$O$_4$ (440.45): C, 68.17; H, 4.58; N, 12.72; Found: C, 68.39; H, 4.44; N, 12.66.
1.22 (s, 3H, CH3CO), 1.25 (s, 3H, CH3-furan), 7.33–7.46 (m, 10H, Ar-H), 8.23 (s, 1H, H-furan), 8.24 (s, 1H, H-oxadiazoline), 9.12 (s, 1H, H-triazole); MS: m/z (%), 50 (3.35), 51 (23.27), 64 (25.65), 77 (100), 91 (83.64), 104 (30.74), 105 (14.66), 118 (18.87), 128 (2.50), 145 (6.44), 157 (2.35), 170 (17.37), 171 (16.02), 172 (15.57), 184 (7.88), 209 (4.49), 229 (2.02), 247 (0.93), 287 (4.10), 299 (0.28), 311 (0.49), 313 (14.20), 342 (58.26), 428 (13.25), 481 (13.26, M+). Anal. Calcd for C25H19N7O4 (481.46): C, 62.37; H, 3.98; N, 20.36; Found: C, 62.28; H, 4.20; N, 20.29.

3.5. Reaction of Compounds 8a, 8b with Chloramine-T

A mixture of 8a or 8b (1.28 g, 3.2 mmol) and chloramine-T (710 mg, 3.2 mol) in isopropyl alcohol (50 mL, 654 mmol) was refluxed for 4 hours, then it was concentrated, and after cooling, the product which separated out was filtered off, washed with a little ethanol, recrystallized from ethanol and dried.

2-(4-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-5-methylfuran-2-yl)-5-phenyl-1,3,4-oxadiazole (8a). Yield: 830 mg (65%). Brown crystals; m.p. 178–179 °C, Rf: 0.12 (n-hexane/EtOAc, 5:1, V/V); IR (KBr): 1,593 cm\(^{-1}\) (C=N); \(^1\)H-NMR (DMSO-d\(_6\)) \(\delta\): 2.32 (s, 3H, CH\(_3\)-furan), 6.87 (s, 1H, H-furan), 7.42–7.44 (m, 5H, Ar-H), 7.91–7.97 (m, 4H, Ar-H). Anal. Calcd for C\(_{21}\)H\(_{13}\)ClN\(_4\)O\(_3\) (404.81): C, 62.31; H, 3.24; N, 13.84; Found: C, 62.11; H, 3.08; N, 13.62.

2-(5-Methyl-4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)furan-2-yl)-5-phenyl-1,3,4-oxadiazole (8b). Yield: 590 mg (81%). It was recrystallized from ethanol as deep yellow crystals; m.p. 97–98 °C; Rf: 0.13 (n-hexane/EtOAc, 5:1, V/V); IR (KBr): 1,597 cm\(^{-1}\) (C=N); \(^1\)H-NMR (DMSO-d\(_6\)) \(\delta\): 2.34 (s, 3H, CH\(_3\)-furan), 7.38 (s, 1H, H-furan), 7.43–7.44 (m, 5H, Ar-H), 7.92–7.94 (m, 4H, Ar-H); MS: m/z (%), 57 (5.50), 65 (17.99), 68 (1.60), 69 (5.37), 77 (7.26), 91 (100), 92 (10.33), 93 (3.44), 105 (5.03), 107 (24.57), 108 (18.05), 109 (2.98), 115 (3.92), 121 (2.74), 129 (5.44), 130 (5.60), 149 (25.33), 155 (36.75), 171 (52.53), 183 (2.31), 206 (2.18), 236 (2.61), 252 (1.69), 273 (1.77), 281 (2.21), 319 (1.87), 362 (1.84), 415 (1.82, M\(^+\)). Anal. Calcd for C\(_{21}\)H\(_{13}\)N\(_5\)O\(_5\) (415.36): C, 60.72; H, 3.15; N, 16.86; Found: C, 60.59; H, 2.99; N, 16.69.

4. Conclusions

Some new oxadiazole derivatives have been prepared from carbohydrate precursors. Their physical and chemical properties were studied, as well as their effect on the enzyme tyrosinase.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Hetzheim, A.; Möckel, K. Recent advances in 1, 3, 4-oxadiazole chemistry. Adv. Heterocycl. Chem. 1967, 7, 183–224.
2. Arrington, J.P.; Wade, L.L. Method for the control of manure-breeding insects. U.S. Patent 4,215,129, 1980.
1. Tan, T.M.C.; Chen, Y.; Kong, K.H.; Li, Y.; Lim, S.G.; Ang, T.H. Synthesis and the biological evaluation of 2-benzensulfonylalkyl-5-substituted-sulfanyl-[1,3,4]-oxadiazoles as potential anti-hepatitis B virus agents. *Antiviral Res.* 2006, 71, 7–14.

2. Holla, B.S.; Gonsalves, R.; Shenoy, S. Synthesis and antibacterial studies of a new series of 1,2-bis(1,3,4-oxadiazol-2-yl)ethanes and 1,2-bis(4-amino-1,2,4-triazol-3-yl)ethanes. *Eur. J. Med. Chem.* 2000, 35, 267–271.

3. El-Emam, A.A.; Al-Deeb, O.A.; Al-Omar, M.; Lehmann, J. Synthesis, antimicrobial, and anti-HIV-1 activity of certain 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones. *Bioorg. Med. Chem.* 2004, 12, 5107–5113.

4. Sahin, G.; Palaska, E.; Ekizoglu, M.; Ozalp, M. Synthesis and antimicrobial activity of some 1,3,4-oxadiazole derivatives. *Farmaco* 2002, 57, 539–542.

5. Jonathan, R.Y.; Robert, J.D. Novel synthesis of oxadiazoles via palladium catalysis. *Tetrahedron Lett.* 1998, 39, 3931–3934.

6. Orlek, B.S.; Balney, F.E. Comparison of azabicyclic esters and oxadiazoles as ligands for the muscarinic receptor. *J. Med. Chem.* 1991, 34, 2726–2735.

7. Saunders, J.; Cassidy, M.; Freedman, S.B.; Harley, E.A.; Iversen, L.L.; Kneen, C.; Macleod, A.M.; Merchant, K.J.; Snow, R.J.; Baker, R. Novel quinuclidine-based ligands for the muscarinic cholinergic receptor. *J. Med. Chem.* 1990, 33, 1128–1138.

8. Watjen, F.; Baker, R. Novel benzodiazepine receptor partial agonists: Oxadiazolylimidazobenzodiazepines. *J. Med. Chem.* 1989, 32, 2282–2291.

9. Tully, W.R.; Gardner, C.R.; Gillespie, R.J.; Westwood, R. 2-(Oxadiazolyl)- and 2-(thiazolyl)imidazo[1,2-a]pyrimidines as agonists and inverse agonists at benzodiazepine receptors. *J. Med. Chem.* 1990, 33, 1128–1138.

10. Ankersen, M.; Peschke, B. Investigation of biososters of the growth hormone secretagogue L-692,429. *Bioorg. Med. Chem. Lett.* 1997, 7, 1293–1298.

11. Chen, C.; Senanyake, C.H.; Bill, T.J.; Larsen, R.D.; Veshoeven, T.R.; Reider, P.J. Improved Fischer Indole Reaction for the Preparation of N,N-Dimethyltryptamines: Synthesis of L-695,894, a Potent 5-HT1D Receptor Agonist. *J. Org. Chem.* 1994, 59, 3738–3744.

12. Sousa, A.A.; Chitwood, H.C.; Durden, J.A. Method of ombating nematodes. *Chem. Abstr.* 1965, 62, 5282–2589.

13. Ulrich, H.; Wilfried, H.G. *Ger Offen.* DE 3,805, 698, 1989.

14. Afiafatpour, P.; Srivastava, R.M. Analgesic and anti-inflammatory effects of 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid. *Braz. J. Med. Biol. Res.* 1994, 27, 1403–1406.

15. Dahlgren, S.E.; Dalham, T. The anti-inflammatory action of phenyl-methyl-oxadiazole (PMO): An experimental study on guinea-pig trachea. *Acta Pharmacol. Toxicol.* 1972, 31, 193–202.
20. Omar, F.A.; Mahfouz, N.M.; Rahman, M.A. Design, synthesis and anti-inflammatory activity of some 1,3,4-oxadiazole derivatives. *Eur. J. Med. Chem.* **1996**, *31*, 819–825.

21. Dirk, A.; Heerding, G.C. 1,4-Disubstituted imidazoles are potential antibacterial agents functioning as inhibitors of enoyl acyl carrier protein reductase (FabI). *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2061–2065.

22. Vu, C.B.; Corpuz, E.G. Discovery of potent and selective SH2 inhibitors of the tyrosine kinase ZAP-70. *J. Med. Chem.* **1999**, *42*, 4088–4093.

23. Bethge, K.; Pertz, H.H. New oxadiazole derivatives showing partly antiplatelet, antithrombotic and serotonin antagonistic properties. *Arch. Pharm.* **2005**, *338*, 78–86.

24. Swain, C.J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E.M.; Stevenson, G.; Beer, M.; Stanton, J.; Walting, K. Novel 5-HT3 antagonists. Indole oxadiazoles. *J. Med. Chem.* **1991**, *34*, 140–151.

25. Ladduwahetty, T.; Baker, R.; Cascieri, M.A.; Chambers, M.S.; Haworth, K.; Keown, L.E.; MacIntyre, D.E.; Metzer, J.M.; Owen, S.; Rycroft, W.; *et al.* N-Heteroaryl-2-phenyl-3-(benzyloxy)piperidines: A novel class of potent orally active human NK1 antagonists. *J. Med. Chem.* **1996**, *39*, 2907–2914.

26. Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Scoregh, I.; Hesselink, W.; Hacksell, U. Synthesis of 1,2,4-Oxadiazole-, 1,3,4-Oxadiazole-, and 1,2,4-Triazole-Derived Dipeptidomimetics. *J. Org. Chem.* **1995**, *60*, 3112–3120.

27. Borg, S.; Vollinga, R.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. Design, synthesis, and evaluation of Phe-Gly mimetics: heterocyclic building blocks for pseudo peptides. *J. Med. Chem.* **1999**, *42*, 4331–4342.

28. Padmavathi, V.; Nagendra Mohan, A.V.; Thiveni, P.; Shazia, A. Synthesis and bioassay of a new class of heterocycles pyrrolyl oxadiazoles/thiadiazoles/triazoles. *Eur. J. Med. Chem.* **2009**, *44*, 2313–2321.

29. Warmus, J.S.; Flamme, C.; Zhang, L.Y.; Barrett, S.; Bridges, A.; Chen, H.; Gowan, R.; Kaufman, M.; Sebolt-Leopold, J.; Leopold, W.; *et al.* 2-Alkylamino- and alkoxy-substituted 2-amino-1,3,4-oxadiazoles—O-Alkyl benzhydroxamate esters replacements retain the desired inhibition and selectivity against MEK (MAP ERK kinase). *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6171–6174.

30. Padmavathi, V.; Sudhakar Reddy, G.; Padmaja, A.; Kondaia, P.; Ali-Shazia. Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. *Eur. J. Med. Chem.* **2009**, *44*, 2106–2112.

31. Dornow, A.; Brunchen, K. Notiz über die darstellung von 1.3.4-oxdiazo lon-(5) und seinen c2-alkylierten derivaten. *Chem. Ber.* **1949**, *82*, 121–123.
34. El-Sadek, M.M.; Hassan, S.Y.; Abd El-Dayem, N.S.; Yacout, G.A. 5-(5-Aryl-1,3,4-oxadiazole-2-carbonyl)furan-3-carboxylate and New Cyclic C-Glycoside Analogues from Carbohydrate Precursors with MAO-B, Antimicrobial and Antifungal Activities. *Molecules* 2012, 17, 7010–7027.

35. Hayes, F.N.; Rogers, B.S.; Ott, D.G. The parent 2-phenyl-5-(2-thienyl)-1,3,4-oxadiazoles are known. *J. Am. Chem. Soc.* 1955, 77, 1850–1852.

36. Stolle, R.; Laux, J. Über eine neue Art der Darstellung von Azoverbindungen. *Ber. Dtsch. Chem. Ges.* 1911, 44, 1127–1134.

37. Bogert, M.T.; Tuttle, J.R. The synthesis of p-cymene 2-monocarboxylic acid and of p-cymene 3-monocarboxylic acid, together with certain of their derivatives. *J. Am. Chem. Soc.* 1916, 38, 1349–1368.

38. Ainsworth, C. The condensation of carboxylic acid hydrazides with carbon disulfide. *J. Am. Chem. Soc.* 1956, 78, 4475–4478.

39. Ainsworth, C.; Hackler, R.E. Alkyl-1,3,4-oxadiazoles. *J. Org. Chem.* 1966, 31, 3442–3444.

40. Rufenachat, V.K. Arbeiten über Phosphorsäure- und Thiophosphorsäureester mit einem heterocyclischen Substituenten. 5. Mitteilung. 2-Alkoxy- und 2-Alkylthio-5-chlormethyl-1,3,4-thiadiazole, 2-Alkyl-5-chlormethyl-1,3,4-oxadiazole und daraus hergestellte Thiound Dithiophosphorsäure-O, O-dialkyl-S-[(2-alkoxy- und 2-alkylthio-1,3,4-thiadiazol-5-yl)-methyl]-bzw. -S-[(2-alkyl-1,3,4-oxadiazol-5-yl)-methyl-ester. *Helvet. Chem. Acta* 1972, 55, 1979–1986.

41. Gonzalez, G. Reactions of monosaccharides with beta-ketonic esters and related substances. *Adv. Carbohydr. Chem.* 1956, 11, 97–143.

42. Muller, A.; Varaga, I. Die oxydative Spaltung der Polyoxy-Seitenketten in den Zucker-Kondensationsprodukten des Acetessigesters und des o-Phenylendiamins. *Chem. Ber.* 1939, 72, 1993–1999.

43. Jones, J.K.N. The condensation of glucose and β-diketones. *J. Chem. Soc.* 1945, 116–119.

44. El Sadek, M.M.; Khald, F.G.A.; Abd El Baky, S.A. Reactions of periodate oxidized methyl-4,6-O-benzylidene-α-D-glucopyranoside with hydrazines. 3rd Bratislava symposium on saccharides (17). Presented at the *Bratislava Symposium on Saccharides*, Bratislava, Czechoslovakia, 8–12 September 1986.

45. Yang, Z.; Robb, D.A. Tyrosinase activity in reversed micelles. *Biocatal. Biotransform.* 2005, 23, 423–430.

46. Yang, Z.; Wu, F. Catalytic properties of tyrosinase from potato and edible fungi. *Biotechnology* 2006, 5, 344–348.

47. Ramsdena, C.A.; Rileyb, P.A. Mechanistic studies of tyrosinase suicide in activation. *ARKIVOC* 2010, i, 260–274.

*Sample Availability*: Samples of the compounds (1–8) are available from the authors.

© 2013 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).