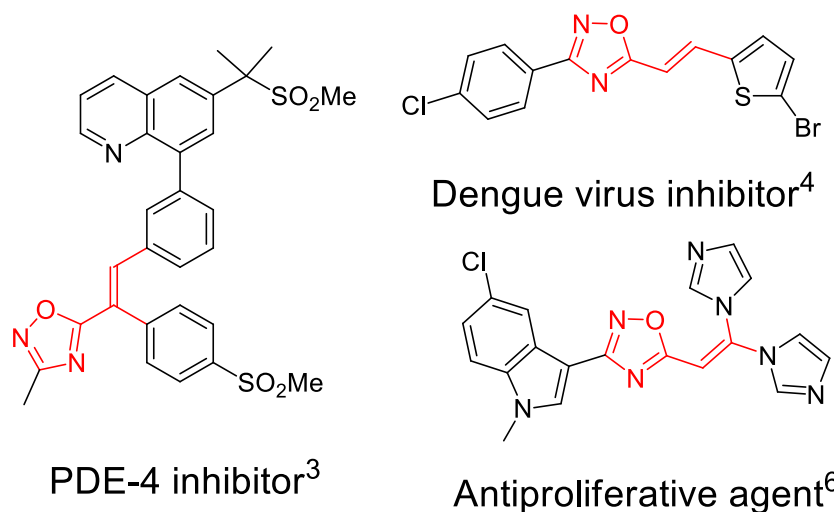




## Introduction

3,5-Disubstituted-1,2,4-oxadiazoles are widely used both in pharmaceutical research and for the development of new materials.<sup>1-4</sup> In particular, compounds bearing a carbon-carbon double bond in the 5-position of the heterocyclic ring are agonists of the central nicotinic acetylcholine receptors<sup>5</sup>, PDE-4 inhibitors<sup>6-8</sup>, non-nucleoside antivirals<sup>9</sup>, antiparasitics<sup>10</sup> and antiproliferative agents (Fig. 1).<sup>11</sup> Moreover, 5-alkenyl- and 5-styryl-1,2,4-oxadiazoles are actively employed in organic synthesis, including Michael addition reactions<sup>12-14</sup>, 1,3-dipolar cycloadditions<sup>15, 16</sup>, Rh-catalyzed<sup>17, 18</sup> or metal-free arylations.<sup>19</sup>



**Figure 1.** Examples of biologically active 5-alkenyl- and 5-styryl-1,2,4-oxadiazoles.

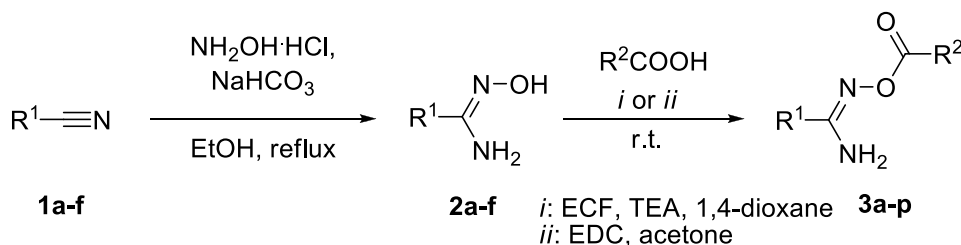
Most of the traditional methods for the preparation of 1,2,4-oxadiazole, such as condensation of amidoximes with carboxylic acids and their derivatives or 1,3-dipolar cycloadditions of nitrile oxides to nitriles,<sup>20-23</sup> require harsh conditions (high temperature, microwave irradiation or high pressure).<sup>24, 25</sup> These conditions pose a serious limitation for labile organic compounds, especially those containing C=C double bonds and typically yield multiple side-products along with low yields of target compounds.<sup>26-30</sup> For this reason, novel synthetic approaches to 1,2,4-oxadiazoles, operating under mild conditions, have been actively developing in recent years.<sup>31-33</sup>

Previously, we have reported that the MOH/DMSO (M = Li, Na, K) system is an efficient medium for the synthesis of 1,2,4-oxadiazoles at ambient temperature.<sup>34-37</sup> While many substrates with aliphatic, aromatic and heterocyclic substituents have been studied, those with alkenyl and styryl groups were not. Herein, we describe an efficient and practical cyclodehydration of *O*-acylamidoximes with alkenyl- and styryl- moieties that occurs in KOH/DMSO medium.

## Results and Discussion

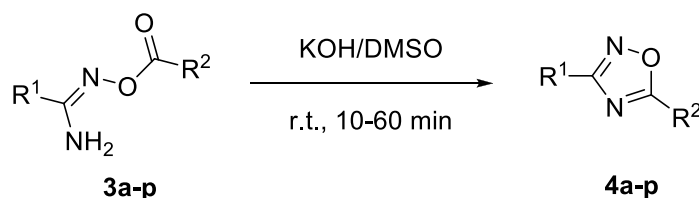
### Synthesis of 5-alkenyl- and 5-styryl-1,2,4-oxadiazoles (4)

The starting *O*-acylamidoximes (**3a-p**) were synthesized from commercial nitriles in two steps (Scheme 1).



**Scheme 1:** Synthetic scheme for generation of the *O*-acylamidoximines (**3a-p**)

The *O*-acylamidoximes **3a-p** were then converted to the corresponding substituted 1,2,4-oxadiazoles in generally good yields under mild conditions (**Scheme 2** and **Table 1**).



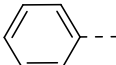


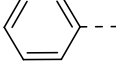


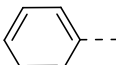


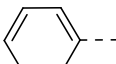


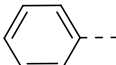

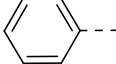

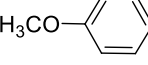

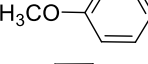

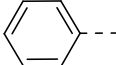

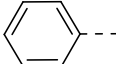

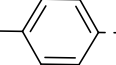


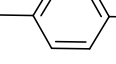


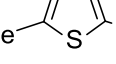


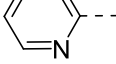

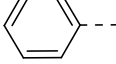

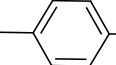

**Scheme 2:** Synthetic scheme for generation of the corresponding substituted-1,2,4-oxadiazoles from the corresponding *O*-acylamidoximines (**3a-p**)

At the onset of our study, we investigated the cyclodehydration of the acrylic acid derivative **3a** (Table 1, entries 1 and 2). Initially, an equimolar ratio of the *O*-acylamidoxime and  $KOH$  was used<sup>38</sup>, and the reaction was carried out for 10 minutes. The targeted 5-vinyl-1,2,4-oxadiazole is a colorless liquid.<sup>26-30</sup> The isolated white powder contained no carbon-carbon double bond according to the IR spectrum. Moreover, the molecular weight of this solid is ~450 kDa (by GPC), suggesting that the material formed is a product of the base-initiated anionic polymerization (anionic polymerization of Michael acceptors in  $DMSO$  is known)<sup>39, 40</sup>

Reducing the amount of  $KOH$  to 0.1 equiv. decreases the reaction rate and allows isolation of the desired **4a** after column chromatography, albeit in low (11%) yield (Table 1, entry 2). Similar results were obtained for the methacrylic derivative **3b** (Table 1, entries 3 and 4). On the contrary, crotonic and methacrotonic derivatives **4c** and **4d** were obtained in good yields (79 and 80%, respectively) with 0.1 equiv. of  $KOH$  (Table 1, entries 6 and 8). The cyclodehydration of *O*-acylamidoximes **3e-n** was successful with 1 equiv. of  $KOH$  (with the single exception of **3k**), furnishing good to excellent yields of desired 1,2,4-oxadiazoles (Table 1, entries 9-21). Our results demonstrate that the presence of alkyl, aryl or heteroaryl substituents at the terminal carbon atom of the double bond reduces the polymerization tendency of 1,2,4-oxadiazoles.

Furthermore, we applied our protocol for the preparation of 5-(4-vinylphenyl)-1,2,4-oxadiazoles. These compounds are only poorly studied, presumably because their synthesis is rather tedious and given that the vinyl group is unstable under thermal cyclodehydration conditions.<sup>41</sup> For this reason, alternative approaches such as the Wittig and Stille reactions or the reduction of the appropriate alkyne<sup>41,42</sup> were utilized for the synthesis of 1,2,4-oxadiazoles with vinylphenyl moiety. Noteworthy, compounds **4o** and **4p** were prepared in good yields according to our method (Table 1, entries 22 and 23).

**Table 1.** Results of cyclodehydration of *O*-acylamidoximes (**3a-p**) to the corresponding oxadiazoles (**4a-p**).

Entry	<i>O</i> -acylamidoxime	R <sub>1</sub>	R <sub>2</sub>	Amount of KOH	Reaction time, min	Product	Yield, %
1	3a			1.0	10	<b>4a</b>	-
2				0.1	30		11
3	3b			1.0	10	<b>4b</b>	-
4				0.1	30		15
5	3c			1.0	10	<b>4c</b>	-
6				0.1	30		79
7	3d			1.0	10	<b>4d</b>	-
8				0.1	30		80
9	3e			1.0	10	<b>4e</b>	87
10	3f			1.0	10	<b>4f</b>	88
11	3g			1.0	10	<b>4g</b>	80
12	3h			1.0	10	<b>4h</b>	82
13	3i			1.0	10	<b>4i</b>	80
14	3j			1.0	10	<b>4j</b>	79
15	3k			1.0	10	<b>4k</b>	35
16				0.1	60	<b>4k</b>	85
17	3l			1.0	10	<b>4l</b>	78
18				0.1	60	<b>4l</b>	78
19	3m			1.0	20	<b>4m</b>	86
20				0.1	60	<b>4m</b>	95
21	3n			1.0	10	<b>4n</b>	74
22	3o			1.0	10	<b>4o</b>	88
23	3p			1.0	10	<b>4p</b>	85

A broad spectrum of compounds based on the 1,2,4-oxadiazole scaffold are well known as potent antimicrobial agents.<sup>43</sup> No antibacterial studies of 1,2,4-oxadiazoles containing a C=C double bond, however, have, hitherto, been conducted. Motivated by this, we assessed the antibacterial and antifungal activities of synthesized heterocycles against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* by the broth double microdilution method.<sup>44,45</sup>

## Biological activity

The antimicrobial activity was determined *in vitro* by broad-dilution method against strains of *S. aureus* (ATCC-25923), *E. coli* (C 600) and *C. albicans* (SC5314)<sup>46</sup>.

The experimental data revealed that all of the tested 1,2,4-oxadiazoles exhibited low to medium activity against both Gram-positive and Gram-negative bacterial strains (Table 2).

**Table 2.** MIC values in µg/mL µmol/mL for compounds **4d-g** and **4j-p** against various bacterial strains and fungi.

Entry	Compound	Gram-negative		Gram-positive		Fungi	
		<i>E. coli</i>		<i>S. aureus</i>		<i>C. albicans</i>	
		MIC, µg/mL	MIC, mM	MIC, µg/mL	MIC, mM	MIC, µg/mL	MIC, mM
1	<b>4d</b>	215	1,07	215	1,07	146	0,73
2	<b>4e</b>	267	1,07	213	0,86	>181	>0,73
3	<b>4f</b>	304	1,07	304	1,07	>207	>0,73
4	<b>4g</b>	299	1,07	299	1,07	>203	>0,73
5	<b>4i</b>	331	1,07	331	1,07	>225	>0,73
6	<b>4j</b>	331	1,07	331	1,07	225	0,73
7	<b>4k</b>	288	1,07	288	1,07	>196	>0,73
8	<b>4l</b>	>584	>2,14	>584	>2,14	>199	>0,73
9	<b>4m</b>	288	1,07	288	1,07	>196	>0,73
10	<b>4n</b>	>533	>2,14	>533	>2,14	>182	>0,73
11	<b>4o</b>	267	1,07	267	1,07	>181	>0,73
12	<b>4p</b>	304	1,07	304	1,07	>207	>0,73
13	Pefloxacin	0,1 <sup>47</sup>	0,0003	1 <sup>48</sup>	0,003	-	-
14	Fluconazole	-	-	-	-	1 <sup>49</sup>	0,0032

The screening set included twelve compounds (**4d-g** and **4i-p**). Three synthesized 1,2,4-oxadiazoles (**4a-4c**) were too unstable at assay conditions, while **4h** was insoluble in the assay medium. Therefore these compounds were excluded from the study. Pefloxacin and Fluconazole were used as reference standards for the comparison of antimicrobial activity. The minimum inhibitory concentration (MIC) for all compounds was determined. The experimental data (Table 2) revealed that all tested 1,2,4-oxadiazoles exhibit low to medium activity against both Gram-positive and Gram-negative bacterial strains.

The most active 1,2,4-oxadiazole **4e** showed bacteriostatic effect with MIC 0.86 mM (213 µg/ml) against *Staphylococcus aureus* (ATCC-25923) and bacteriostatic effect with MIC 1.07 mM (267 µg/ml) against *Escherichia coli* (C-600). Other 1,2,4-oxadiazoles showed moderate to weak MIC against all tested bacteria. While compound **4l** bearing a furan ring displayed no antimicrobial activity in all tests, thiophene derivative **4k** demonstrated moderate activity. Two 1,2,4-oxadiazoles (**4d** and **4i**) showed medium fungistatic effect inhibiting the growth of *Candida albicans* (NCTC 885-653) with MIC 0.73 mM (146-225 µg/ml respectively), which is, however, less potent than the standard drug Fluconazole (1 µg/ml against *Candida albicans*)<sup>50</sup>.

Overnight cultures were grown at 37 °C in Lysogeny broth (LB) and diluted to obtain an opacity equivalent to 0.5 on the McFarland scale. The compounds are weighed and dissolved in DMSO to give concentrations equal to 20.7 µmol/mL. The pefloxacin and miconazole were used to antimicrobial standard. The

concentration of 2.07  $\mu\text{mol/mL}$  was used as the starting one, providing a final concentration equal to 0.03  $\mu\text{mol/mL}$ . The tubes were incubated for 12 h at 37 °C. Growth inhibition detection was considered as positive results. It was verified that DMSO as completely inactive against the tested microorganisms in the less than 10 % concentrations. A series of tubes is prepared by mixing one part of each dilution of the compound with some parts of the LB, previously inoculated and incubated for 24 h at 37 °C. All experiments were carried out in triplicate. The MIC was considered the lowest drug concentration for which there is no microbial growth.

The most active 1,2,4-oxadiazole (**4e**) showed bacteriostatic effect with MIC 0.86 mM (213  $\mu\text{g/mL}$ ) against *Staphylococcus aureus* (ATCC-25923), and bacteriostatic effect with MIC 1.07 mM (267  $\mu\text{g/mL}$ ) against *Escherichia coli* (C-600). Other 1,2,4-oxadiazoles showed moderate to weak MIC against all tested bacteria. While compound **4l** bearing a furan ring displayed no antimicrobial activity in all tests, thiophene derivative **4k** demonstrated moderate activity. Two 1,2,4-oxadiazoles (**4d** and **4i**) showed medium fungistatic effect inhibiting the growth of *Candida albicans* (NCTC 885-653) with MIC 0.73 mM (146-225  $\mu\text{g/mL}$ , respectively), which is, however, less potent than the standard drug Fluconazole (1  $\mu\text{g/mL}$  against *Candida albicans*).<sup>50</sup>

## Conclusions

We have developed a simple, speedy and efficient method for the synthesis of 5-alkenyl- and 5-styryl-1,2,4-oxadiazoles. A series of 16 compounds was obtained, 10 of which have not been previously reported in the literature. The novel synthetic protocol offers several advantages, including short reaction times, high yields of products, and simple work-up procedure. In addition, the twelve 1,2,4-oxadiazoles synthesized were evaluated against both Gram-positive and Gram-negative bacteria strains as well as one fungi strain, and displayed moderate antimicrobial activity.

## Experimental Section

**General.** Starting *O*-acylamidoximes (**3a-p**) were synthesized from commercial nitriles in two steps (for more details see Supplemental Materials). All other reagents and solvents, including DMSO, were purchased and used without further purification. All reactions were conducted in an open flask.. Reactions were monitored by analytical thin layer chromatography (TLC) Macherey-Nagel, TLC plates Silufol UV-254 using UV light for detection. Column chromatography was carried out with silica gel grade 60 (0.040-0.063 mm) 230-400 mesh with a hexane/ethyl acetate mixture as eluent (4/1). NMR spectra were recorded on Bruker Avance DPX 400 (400.13 MHz and 100.61 MHz for  $^1\text{H}$  and  $^{13}\text{C}$ , respectively) or on Bruker Avance III 500 MHz (500.03 MHz for  $^1\text{H}$  and 125.73 MHz for  $^{13}\text{C}$ ) in DMSO- $d_6$  or in  $\text{CDCl}_3$ . Chemical shifts are reported as parts per million ( $\delta$ , ppm). The solvent peaks were used as internal standards: 2.50 ppm for residual  $^1\text{H}$ , 39.50 ppm for  $^{13}\text{C}$  in DMSO- $d_6$ ; 7.26 ppm for residual  $^1\text{H}$ , 77.16 ppm for  $^{13}\text{C}$  in  $\text{CDCl}_3$ . Multiplicities are abbreviated as follows: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br* = broad and coupling constants, *J*, are reported in Hertz (Hz). The signals of second-order proton systems AA'XX' of the para-substituted and AA'XX'Y of the monosubstituted phenyl rings are not seen clearly in the  $^1\text{H}$  NMR spectra, therefore, "apparent" coupling constants for observed "doublets" and "triplets" of appropriate aromatic protons are provided. Melting points were determined in open capillary tubes on Electrothermal IA 9300 series Digital Melting Point Apparatus. High-resolution mass spectra (HRMS) were measured on Bruker Maxis HRMS-ESI-qTOF (ESI Ionization). IR spectra were measured with an IRF Perkin Elmer Spectrum RX1 spectrometer using suspension in Nujol or as

in thin films (microlayer) between KBr discs. Gel permeation chromatography was performed on DIONEX UltiMate–3000 (column:  $l = 15$  cm,  $d = 2$  mm). A mixture of acetonitrile and water (1:4) was used as eluent. “Th” is the abbreviation for the thiophen ring.

**Synthesis and characterization of 1,2,4-oxadiazoles (4a-p).** The corresponding *O*-acylamidoxime (**3a-p**) (1.5 mmol) was added to a suspension of powdered KOH (1.5 or 0.15 mmol, see Table 1) in DMSO (2 mL). The reaction mixture was stirred at room temperature for a specified time (see Table 1). The reaction mixture was diluted with cold water (20 mL), and resulted precipitate was filtered off, washed with cold water (25 mL) and dried in air at room temperature.

**3-Phenyl-5-vinyl-1,2,4-oxadiazole (4a).**<sup>13</sup> The compound was synthesized using 0.1 equiv of KOH for 0.5 h. Yield after purification by column chromatography (ethyl acetate : hexane 1 : 4) was 11% (28 mg) of yellow oil. IR (microlayer,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1215 (C-O), 1593 (C=N), 1647 (CH=CH<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  6.08 (1H, d,  $J$  11 Hz, *cis*-HC=CH<sub>2</sub>), 6.53 (1H, d,  $J$  18 Hz, *tr*-HC=CH<sub>2</sub>), 6.88 (1H, dd,  $J$  18 Hz, 11 Hz, HC=C), 7.48-7.55 (3H, m, *m,p*-H), 7.97-8.04 (2H, m, *o*-H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  120.7 (=CH<sub>2</sub>), 126.6 (*i*-C), 127.4 (*m*-C), 129.5 (*o*-C), 130.2 (-CH=), 131.9 (*p*-C), 168.4 (C-3), 174.9 (C-5). HRMS (ESI),  $m/z$ : calcd for C<sub>10</sub>H<sub>9</sub>N<sub>2</sub>O[M+H]<sup>+</sup> 173.0709, found 173.0701.

**3-Phenyl-5-(prop-1-en-2-yl)-1,2,4-oxadiazole (4b).** The compound was synthesized using 0.1 equiv of KOH for 0.5 h. Total yield after purification by column chromatography (ethyl acetate : hexane 1 : 4) was 15% (41 mg) of yellow oil. IR (microlayer,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1158 (C-O), 1578 (C=N), 1643 (CH<sub>2</sub>=C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  2.22 (3H, s, Me), 5.88 (1H, s, =CH<sub>2</sub>), 6.28 (1H, s, =CH<sub>2</sub>), 7.55-7.61 (3H, m, *m,p*-H), 8.03 (2H, d,  $J$  7.9 Hz, *o*-H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  18.9 (Me), 125.2 (CH<sub>2</sub>=), 125.9 (C=), 126.7 (*i*-C), 127.4 (*m*-C), 129.5 (*o*-C), 131.9 (*p*-C), 168.5 (C-3), 176.5 (C-5). HRMS (ESI),  $m/z$ : calcd for C<sub>11</sub>H<sub>11</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 187.0866, found 187.0860.

**(E)-3-Phenyl-5-(prop-1-en-1-yl)-1,2,4-oxadiazole (4c).**<sup>17</sup> The compound was synthesized using 0.1 equiv of KOH for 0.5 h. Yield 79% (220 mg); yellow oil. IR (microlayer,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1120 (C-O), 1562 (C=N), 1665 (CH=CH). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  2.05 (3H, dd,  $J$  7.0, 2, Me), 6.50 (1H, dq,  $J$  16.2, 2 Hz, Het-CH=), 7.18 (1H, dq,  $J$  16.2, 7.0 Hz, Me-CH=), 7.49-7.52 (3H, m, *m,p*-H), 8.11 (2H, d,  $J$  8.2 Hz, *o*-H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  18.8 (Me), 115.0 (Het-CH=), 127.0 (*i*-C), 127.4 (*m*-C), 128.8 (*o*-C), 131.0 (*p*-C), 142.8 (Ph-CH=), 168.4 (C-3), 174.7 (C-5). HRMS (ESI),  $m/z$ : calcd for C<sub>11</sub>H<sub>11</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 187.0866, found 187.0853.

**5-(2-Methylprop-1-enyl)-3-phenyl-1,2,4-oxadiazole (4d).** The compound was synthesized using 0.1 equiv of KOH for 0.5 h. Yield 80% (240 mg); beige powder, mp 44-46 °C. IR,  $\nu$ ,  $\text{cm}^{-1}$ : 841 (C=CH), 1152 (C-O), 1592 (C=N), 1656 (C=CH). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  2.09 (d,  $J$  1.0 Hz, Me, 3H), 2.38 (d,  $J$  1.0 Hz, Me, 3H), 6.33 (sept,  $J$  1.2 Hz, C=CH, 1H), 7.49-7.52 (m, *m,p*-H, 3H), 8.14 (m, *o*-H, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  21.1 (Me), 27.6 (Me), 108.9 (C=CH), 127.3 (*i*-C), 127.4 (*m*-C), 128.8 (*o*-C), 130.9 (*p*-C), 154.3 (C=CH), 168.1 (C-3), 175.1 (C-5). HRMS (ESI),  $m/z$ : calcd for C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 201.1022, found 201.1020.

**(E)-3-Phenyl-5-(2-phenylethenyl)-1,2,4-oxadiazole (4e).**<sup>19</sup> Yield 87% (324 mg), white powder, mp 95-97 °C (Lit. mp 95-97 °C). IR,  $\nu$ ,  $\text{cm}^{-1}$ : 971 (*tr*-CH=CH), 1175 (C-O), 1593 (C=N), 1644 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  7.45 (1H, d,  $J$  16.4 Hz, Het-CH=), 7.43-7.49 (3H, m, *m,p*-H), 7.56-7.63 (3H, m, *m,p*-H), 7.85 (2H, m, *o*-H), 7.95 (1H, d,  $J$  16.4 Hz, Ph-CH=), 8.05-8.09 (2H, m, *o*-H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  110.7 (Het-CH=), 126.8 (*i*-C, 3-Ph), 127.5 (*o*-C, 5-Ph), 128.9 (*m*-C, 3-Ph), 129.5 (*p*-C, 5-Ph), 129.7 (*m*-C, 5-Ph), 131.1 (*o*-C, 3-Ph), 132.0 (*p*-C, 3-Ph), 134.7 (*i*-C, 5-Ph), 143.3 (Ph-CH=), 168.5 (C-3), 175.9 (C-5). HRMS (ESI),  $m/z$ : calcd for C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 249.1022, found 249.1014.

**5-[(E)-2-(4-Chlorophenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (4f).**<sup>19</sup> Yield 88% (373 mg), white powder, mp 158-160 °C (Lit. mp 154-156 °C). IR,  $\nu$ ,  $\text{cm}^{-1}$ : 975 (*tr*-CH=CH), 1174 (C-O), 1573 (C=N), 1648 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  7.50 (1H, d,  $J$  16.5, Het-CH=), 7.55 (2H, d,  $J$  8.5 Hz, *m*-H), 7.58-7.63 (3H, m, *m,p*-H),

7.90 (2H, d, *J* 8.5 Hz, *o*-H), 7.96 (1H, d, *J* 16.5 Hz, Ph-CH=), 8.05-8.08 (2H, m, *o*-H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 111.5 (Het-CH=), 126.7 (*i*-C, 3-Ph), 127.5 (*m*-C, 3-Ph), 129.5 (*o*-C, 3-Ph), 129.7 (*m*-C, 5-Ph), 130.6 (*o*-C, 5-Ph), 132.1 (*p*-C, 3-Ph), 133.7 (*i*-C, 5-Ph), 135.7 (*p*-C, 5-Ph), 141.9 (Ph-CH=), 168.5 (C-3), 175.7 (C-5). HRMS (ESI), *m/z*: calcd for C<sub>16</sub>H<sub>12</sub>ClN<sub>2</sub>O [M+H]<sup>+</sup> 283.0633, found 283.0632.

**3-(4-Methoxyphenyl)-5-[(*E*)-2-phenylethenyl]-1,2,4-oxadiazole (4g).**<sup>19</sup> Yield 80% (333 mg), white powder, mp 122-123 °C (Lit. mp 130-132 °C). IR, ν, cm<sup>-1</sup>: 975 (*tr*-CH=CH), 1177, 1255 (C–O), 1556 (C=N), 1637 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 3.85 (3H, s, OMe), 7.14 (2H, d, *J* 8.9 Hz, *m*-H), 7.43 (1H, d, *J* 16.5 Hz, Het-CH=), 7.46-7.50 (3H, m, *m,p*-H), 7.85-7.87 (2H, m, *o*-H), 7.94 (1H, d, *J* 16.5 Hz, Ph-CH=), 8.00 (2H, d, *J* 8.8 Hz, *o*-H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 55.9 (OMe), 110.8 (Het-CH=), 115.1 (*m*-C, 3-Ph), 119.1 (*i*-C, 3-Ph), 128.8 (*o*-C, 5-Ph), 129.2 (*o*-C, 3-Ph), 129.5 (*m*-C, 5-Ph), 131.1 (*p*-C, 5-Ph), 134.8 (*i*-C, 5-Ph), 143.1 (Ph-CH=), 162.2 (*p*-C, 3-Ph), 168.2 (C-3), 175.6 (C-5). HRMS (ESI), *m/z*: calcd for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 279.1128, found 279.1133.

**3-(4-Methoxyphenyl)-5-[(*E*)-2-(4-methoxyphenyl)ethenyl]-1,2,4-oxadiazole (4h).**<sup>19</sup> Yield 82% (379 mg), white powder, mp 112-114 °C (Lit. mp 123-125 °C). IR, ν, cm<sup>-1</sup>: 970 (*tr*-CH=CH), 1030, 1172, 1252 (C–O), 1598 (C=N), 1642 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 3.83 (6H, d, *J* 8.2 Hz, OMe), 7.03 (2H, d, *J* 8.5 Hz, *m*-H, 5-Ph), 7.12 (2H, d, *J* 8.9 Hz, *m*-H, 3-Ph), 7.24 (1H, d, *J* 16.4 Hz, Het-CH=), 7.80 (2H, d, *J* 8.8 Hz, *o*-H, 5-Ph), 7.86 (1H, d, *J* 16.4 Hz, Ph-CH=), 7.98 (2H, d, *J* 8.8 Hz, *o*-H, 3-Ph). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 55.9 (2 OMe), 108.1 (Het-CH=), 115.0 (*m*-C, 3-Ph), 115.1 (*m*-C, 5-Ph), 119.2 (*i*-C, 3-Ph), 127.4 (*i*-C, 5-Ph), 129.1 (*o*-C, 3-Ph), 130.6 (*o*-C, 5-Ph), 142.9 (Ph-CH=), 161.8 (*p*-C, 5-Ph), 162.1 (*p*-C, 3-Ph), 168.1 (C-3), 175.9 (C-5). HRMS (ESI), *m/z*: calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 309.1234, found 309.1231.

**5-[(*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (4i).** Yield 80% (369 mg), white powder, mp 118-119 °C. IR, ν, cm<sup>-1</sup>: 966 (*tr*-CH=CH), 1039, 1266 (C–O), 1582 (C=N), 1646 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 7.03 (1H, d, *J* 8.2 Hz, H-6, 5-Ph), 7.35 (1H, d, *J* 8.2 Hz, H-5, 5-Ph), 7.36 (1H, d, *J* 16.5 Hz, Ar-CH=), 7.51 (1H, s, H-2, 5-Ph), 7.60 (3H, m, *m,p*-H, Ph), 7.87 (1H, d, *J* 16.5 Hz, Ph-CH=), 8.06 (2H, m, *o*-H, Ph). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 56.1 (OMe), 56.2 (OMe), 108.2 (Het-CH=), 110.8 (CH, Ar), 112.1 (CH, Ar), 123.7 (CH, Ar), 126.9 (*i*-C, Ph), 127.5 (*m*-C, Ph), 127.6 (*i*-C, Ar), 129.7 (*o*-C, Ph), 131.9 (*p*-C, Ph), 143.5 (Ar-CH=), 149.6 (C, Ar), 151.7 (C, Ar), 168.4 (C-3), 176.3 (C-5). HRMS (ESI) calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 309.1234, found 309.1238.

**5-[(*E*)-2-(2,3-Dimethoxyphenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (4j).** Yield 79% (365 mg), white powder, mp 106-108 °C. IR, ν, cm<sup>-1</sup>: 975 (*tr*-CH=CH), 1071, 1269 (C–O), 1557 (C=N), 1630 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 3.85 (6H, s, 2Me), 7.17 (2H, m, H-4,6, Ar), 7.41 (1H, d, *J* 16.5 Hz, Het-CH=), 7.51 (1H, m, H-5, Ar), 7.55-7.63 (3H, m, *m,p*-H), 8.05-8.10 (3H, m, *o*-H, Ph-CH=). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 56.3 (OMe), 61.4 (OMe), 111.7 (Het-CH=), 115.6 (CH, Ar), 119.5 (CH, Ar), 124.9 (CH, Ar), 126.8 (*i*-C, Ph), 127.5 (*m*-C, Ph), 128.1 (*i*-C, Ar), 129.7 (*o*-C, Ph), 132.0 (*p*-C, Ph), 137.4 (Ar-CH=), 148.3 (C, Ar), 153.2 (C, Ar), 168.5 (C-3), 176.0 (C-5). HRMS (ESI), *m/z*: calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+K]<sup>+</sup> 347.0793, found 347.0794.

**3-(4-Methylphenyl)-5-[(*E*)-2-(thiophen-2-yl)ethenyl]-1,2,4-oxadiazole (4k).** Yield 85% (342 mg), white powder, mp 102-104 °C. IR, ν, cm<sup>-1</sup>: 954 (*tr*-CH=CH), 1160 (C–O), 1550 (C=N), 1629 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 2.35 (3H, s, Me), 6.98 (1H, d, *J* 15.8 Hz, Het-CH=), 7.17 (1H, dd, *J* 5.0, 3.3 Hz, Th, H-4), 7.33 (2H, d, *J* 7.9 Hz, *m*-H), 7.63 (1H, d, *J* 3.3 Hz, Th, H-3), 7.77 (1H, d, *J* 5.0 Hz, Th, H-5), 7.90 (2H, d, *J* 7.9 Hz, *o*-H), 8.04 (1H, d, *J* 16.2 Hz, Th-CH=). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ<sub>c</sub> 21.5 (Me), 108.7 (Het-CH=), 124.0 (Th, C-4), 127.4 (*o*-C), 129.1 (Th, C-3), 130.1 (*m*-C), 130.8 (*i*-C, Ph), 132.5 (Th, C-5), 135.8 (Th, C-2), 139.5 (*p*-C), 141.8 (Het-CH=), 168.4 (C-3), 175.3 (C-5). HRMS (ESI), *m/z*: calcd for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>OS [M+H]<sup>+</sup> 269.0743, found 269.0751.

**3-(4-Chlorophenyl)-5-[(*E*)-2-(furan-2-yl)ethenyl]-1,2,4-oxadiazole (4l).** Yield 78% (319 mg), white powder, mp 115-116 °C. IR, ν, cm<sup>-1</sup>: 964 (*tr*-CH=CH), 1091, 1272 (C–O), 1528 (C=N), 1653 (CH=CH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 6.71 (1H, dd, *J* 3.4, 1.8 Hz, Fur, H-4), 6.97 (1H, d, *J* 15.9 Hz, Het-CH=), 7.09 (1H, d, *J* 3.4 Hz, Fur, H-



3), 7.66 (2H, d,  $J$  8.5 Hz,  $m$ -H), 7.79 (1H, d,  $J$  16.2 Hz, Fur-CH=), 7.95 (1H, m, Fur, H-5), 8.05 (5H, d,  $J$  8.5 Hz,  $o$ -H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  107.0 (Het-CH=), 113.6 (Fur, C-3), 117.2 (Fur, C-4), 125.6 ( $i$ -C, Ph), 129.3 ( $m$ -C), 129.9 ( $o$ -C), 130.1 (Fur-CH=), 136.8 ( $p$ -C), 147.0 (Fur, C-5), 150.7 (Fur, C-2), 167.7 (C-3), 175.9 (C-5). HRMS (ESI),  $m/z$ : calcd for  $\text{C}_{14}\text{H}_{10}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  273.0425, found 273.0427.

**3-(5-Methylthiophen-2-yl)-5-[(*E*)-2-phenylethenyl]-1,2,4-oxadiazole (4m).** Yield 95% (382 mg), white powder, mp 113-115 °C. IR,  $\nu$ ,  $\text{cm}^{-1}$ : 974 ( $tr$ -CH=CH), 1098 (C–O), 1572 (C=N), 1643 (CH=CH).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  2.53 (3H, s, Me), 6.98 (1H, d,  $J$  3 Hz, H-4, Th), 7.41 (1H, d,  $J$  16.4 Hz, Het-HC=), 7.45-7.50 (3H, m,  $m,p$ -H), 7.64 (1H, d,  $J$  3.4 Hz, H-3, Th), 7.84-7.87 (2H, m,  $o$ -H), 7.91 (1H, d,  $J$  16.4 Hz, Ph-HC=).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  15.6 (Me), 110.5 (Het-CH=), 125.5 (Th, C-5), 127.5 ( $p$ -C), 128.9 ( $m$ -C), 129.5 ( $o$ -C), 130.5 (Th, C-3), 131.1 (Th, C-4), 134.7 ( $i$ -C), 143.4 (Ph-CH=), 145.0 (Th, C-2), 164.5 (C-3), 175.6 (C-5). HRMS (ESI),  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_2\text{OS}$   $[\text{M}+\text{H}]^+$  269.0743, found 269.0748.

**2-{5-[(*E*)-2-Phenylethenyl]-1,2,4-oxadiazol-3-yl}pyridine (4n).** Yield 74% (276 mg), white powder, mp 114-116 °C. IR,  $\nu$ ,  $\text{cm}^{-1}$ : 980 ( $tr$ -CH=CH), 1071 (C–O), 1572 (C=N), 1644 (CH=CH).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  7.46-7.50 (4H, m,  $m,p$ -H, Ph, Het-CH=), 7.63 (1H, ddd,  $J$  7.6, 4.9, 1.2 Hz, H-5, Py), 7.86-7.88 (2H, m,  $o$ -H, Ph), 7.99 (1H, d,  $J$  16.5 Hz, Ph-CH=), 8.05 (1H, td,  $J$  7.7, 1.7 Hz, H-4, Py), 8.13 (1H, d,  $J$  7.9 Hz, H-3, Py), 8.78 (1H, d,  $J$  4.5 Hz, H-6, Py).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  110.7 (Het-CH=), 123.8 (Py, C-3), 126.6 (Py, C-5), 128.9 ( $o$ -C), 129.5 ( $m$ -C), 131.3 ( $p$ -C), 134.7 ( $i$ -C, Ph), 138.2 (Ph-CH=), 143.6 (Py, C-4), 146.3 (Py, C-2), 150.8 (Py, C-6), 168.6 (C-3), 176.2 (C-5). HRMS (ESI),  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$  250.0974, found 250.0979.

**3-Phenyl-5-(4-vinylphenyl)-1,2,4-oxadiazole (4o).** Yield 88% (327 g), white powder, mp 75-77 °C. IR,  $\nu$ ,  $\text{cm}^{-1}$ : 991 (CH=CH<sub>2</sub>), 1276 (C–O), 1594 (C=N), 1627 (CH=CH).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  5.47 (1H, d,  $J$  10.9 Hz,  $cis$ -CH=CH<sub>2</sub>), 6.05 (1H, d,  $J$  17.5 Hz,  $tr$ -CH=CH<sub>2</sub>), 6.86 (1H, dd,  $J$  17.5, 10.9 Hz, CH=CH<sub>2</sub>), 7.60 (3H, m,  $m,p$ -H, Ph), 7.74 (2H, d,  $J$  7.9 Hz, Ar), 8.08-8.15 (4H, m,  $o$ -H, Ph, Ar).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  118.1 (=CH<sub>2</sub>), 122.9 ( $i$ -C), 126.7 ( $p$ -C), 127.6 ( $o$ -C), 128.7 ( $m$ -C), 129.7 ( $m$ -C), 132.1 ( $i$ -C), 136.1 (-CH=), 142.2 ( $p$ -C), 168.7 (C-3), 175.6 (C-5). HRMS (ESI),  $m/z$ : calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$  249.1022, found 249.1018.

**3-(4-Chlorophenyl)-5-(4-ethenylphenyl)-1,2,4-oxadiazole (4p).** Yield 85% (360 mg), white powder, mp 110-112 °C. IR,  $\nu$ ,  $\text{cm}^{-1}$ : 992 (CH=CH<sub>2</sub>), 1278 (C–O), 1589 (C=N), 1629 (CH=CH).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  5.46 (1H, d,  $J$  10.9 Hz,  $cis$ -CH=CH<sub>2</sub>), 6.00 (1H, d,  $J$  17.5 Hz,  $tr$ -CH=CH<sub>2</sub>), 6.86 (1H, dd,  $J$  17.5, 10.9 Hz, CH=CH<sub>2</sub>), 7.58-7.72 (4H, m), 8.01-8.14 (4H, m).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  117.9 (=CH<sub>2</sub>), 126.2 ( $i$ -C), 127.2 ( $p$ -C), 127.5 ( $o$ -C), 128.7 ( $m$ -C), 131.5 ( $m$ -C), 131.8 ( $i$ -C), 134.5 (-CH=), 136.2 ( $p$ -C), 142.5 ( $p$ -C), 167.8 (C-3), 176.0 (C-5). HRMS (ESI),  $m/z$ : calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}_2\text{O}$   $[\text{M}+\text{H}]^+$  283.0633, found 283.0622.

### Antimicrobial assay

Overnight cultures were grown at 37 °C in Lysogeny broth (LB) and diluted to obtain an opacity equivalent to 0.5 on the McFarland scale. The compounds are weighed and dissolved in DMSO to give concentrations equal to 21.4  $\mu\text{mol/mL}$ . The pefloxacin and fluconazole were used as antimicrobial drug standards. The concentration of 2.14  $\mu\text{mol/mL}$  was used as the starting one, providing a final concentration equal to 0.03  $\mu\text{mol/mL}$ . The tubes were incubated for 12 h at 37 °C. Growth inhibition detection was considered as positive results. It was verified that DMSO is completely inactive against the tested microorganisms in the less than 0.5 % concentrations. A series of tubes is prepared by mixing one part of each dilution of the compound with some parts of the LB, previously inoculated and incubated for 24 h at 37 °C. All experiments were carried out in triplicate. Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent which will inhibit the visible growth of a micro-organism after overnight incubation.

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## Supplementary Material

Supplementary material, including physical constants and spectral data for known compounds (**4a**, **4c**, **4e**, **4f-h**), and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for new compounds **4b**, **4d**, **4i-p** can be accessed using the link "Supplementary Material" in the journal issue contents page.

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