Synthesis, characterization and bioactivities of the new 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines

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Abstract. A series of heterocyclic compounds 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines (2a–2g) were prepared with hydrazones and acetic anhydride. The products were characterized by ¹H-NMR, ¹³C-NMR, IR and elemental analysis. Furthermore, these compounds were tested for their bioactivities of anti-Staphylococcus aureus, HIV-1 RT (Human Immunodeficiency Virus Type 1 Reverse Transcriptase) and proliferative. However, there were no compounds showed promising activities with S. aureus, HIV-1 RT, HT-29 cells and HT-1080 cells.

1. Introduction

Heterocyclic compounds 1,3,4-Oxadiazolines are always used as synthesized intermediate [1-3] and have a wide range of pharmaceutical and biological activities [4-18]. For example, oxadiazolines were reported to possess antitumor [4-6], anti-HIV [7], antibacterial [8-12], anti-inflammatory [13, 14] and anti-convulsant [15] properties. In recent years, many of their synthesis and transformations have been widely discussed. Taking the advantage of their pharmaceutical and biological activities, further research in this area appears promising and necessary.

A survey of the literature revealed that only a few methods to synthesize 2,5-disubstituted-1,3,4-oxadiazolines via oxidation of acylhydrazones have been reported. Such compounds were generally obtained through the following four methods. Lee, et al [19] reported that the hydrazones were oxidized with lead tetraacetate (LTA) in CH₂Cl₂, which led to imino-oxadiazoline. LTA is frequently used as oxidant in the oxidation of acyl hydrazone to oxadiazoline, but it is not friendly to the environment. Yang and Dai [20] have found that the 2,5-disubstituted-1,3,4-oxadiazoline was obtained through the oxidation of ketone N-acylhydrazone with phenyliodine (III) diacetate (PIDA) in alcohol with excellent yields. And the oxidative cyclization of aldehyde N-acylhydrazone by PIDA in methanolic sodium acetate also gave 2,5-disubstituted-1,3,4-oxadiazole in good yields. Chiba and Okimoto [21] reported the electrolytic oxidation of ketone N-acylhydrazones in methanolic sodium acetate, which induced intra-molecular cyclization to corresponding 2-methoxy-1,3,4-oxadiazoline and 2,5-disubstituted-1,3,4-oxadiazole. Yale [22] have treated the acylhydrazones with the acid anhydride, which gave 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines with moderate yield. The acetic anhydride is frequently used as
dehydrazin in these kinds of reactions in many literatures. The method of Yale was chosen for this project because of the easy accessibility to starting materials and the convenience of synthesis. According to Yale’s method, acylhydrazones could be cyclized to 3-acetyl-2,5-disubstituted-1,3,4-oxadiazoline IV by the reflux in acetic anhydride (Scheme 1). Yale [22] have depicted the mechanism of the cyclization of acylhydrazones to oxadiazolines, which were through intermediate II and III. In order to verdict this mechanism, acetic anhydride were added into benzal anil [23] and then R1R2C(OCOCH3)N(COCH3)R were obtained. Walker and Moore have also added acetic anhydride into aniles, which further supported this mechanism [24]. As a result, whether the starting materials were aldehydes N-acylhydrazones or ketones N-acylhydrazones, the products were obtained as oxadiazolines.

Based on the above observation, we synthesized a series of new 1,3,4-Oxadiazolines with hydrazones. The products were fully characterized by elemental analyses, 1H NMR, 13C NMR spectra and Elemental analyses

2. Results and discussion

2.1. Synthesis

![Synthetic route of the title products.](image)

Fig. 1 Synthetic route of the title products.

The 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines (2a-2g) were prepared as shown in Scheme 1. The hydrazones (1a-1g) containing 3,6-dichloro-pyridinyl group [25] were converted into their corresponding 2,5-disubstituted-1,3,4-oxadiazoline by refluxing in acetic anhydride. Some black byproducts were observed when the reaction time more than 3 hours. Therefore, the best reflux time was 1-3 hours, which gave good yield. The pure oxadiazolines could be obtained with recrystallization from ethyl acetate. All the 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines were colorless solid, stable in air and soluble in ordinary organic solvent such as methanol, ethanol, acetone and ethyl acetate, etc.

2.2. Characterization

The structure of oxadiazolines was detected by IR, 1H NMR, 13C NMR spectra and Elemental analyses (Table 1).

The IR spectra of 2a-2g showed a very strong bands in the 1665-1672 cm⁻¹ region which were attributed to the C=O stretching vibration of acetyl groups. The stretching vibration of N-N=C and C-O-C appeared in the region of 1229-1273 cm⁻¹ and 1029-1021cm⁻¹, respectively, which indicated that
the existence of oxadiazolines ring [26,27]. And 2d and 2f was detected to present a band at 1766 cm\(^{-1}\) and 1773 cm\(^{-1}\), respectively, which was attributed to the C=O stretching vibration of the ester’s group.

The \(^1\)H NMR spectra of 2a, 2b, 2d, 2e and 2f showed the O-C=H-N resonance on the 2 position of the oxadiazolines ring in the δ = 7.08-7.14 in accordance with literatures [28, 29]. The proton of N-CO-CH\(_3\) appeared in the region of δ = 2.31-2.41.

The structures of the oxadiazolines (2a-2g) were further confirmed by the \(^13\)C NMR. The carbon atom of the N=CH group in the oxadiazolines were observed at δ = 150.1–156.2 in their \(^13\)C NMR spectra; the C\(_2\) of oxadiazolines ring was observed at δ = 90.2–101.3 [28, 30]. The carbonyl signals of ester groups of 2d and 2f were also observed at δ = 168.8 and δ = 168.7, respectively.

2.3 Bioactivities

The series of 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines were tested for anti-staphylococcus aureus activities. The products showed the minimal inhibitory concentration (MIC) >50μg/ml and the minimal bactericidal concentration (MBC) >50μg/ml (Table 1). These results indicated that these compounds have no promising potential utility as new antibacterial agents.

| compound | Staphylococcus aureus |
|----------|-----------------------|
|          | MIC(μg/ml) | MBC(μg/ml) |
| 2a       | >50        | >50        |
| 2b       | >50        | >50        |
| 2c       | >50        | >50        |
| 2d       | >50        | >50        |
| 2e       | >50        | >50        |
| 2f       | >50        | >50        |
| 2g       | >50        | >50        |
| contrast Mag | 25 | 25        |

Moreover, the products were tested for anti-HIV RT activity. In vitro bioassay screening, the results depicted that there were no activities with these oxadiazolines in inhibiting HIV-1 RT at 200 μg/ml (Table 2).

| compound | initial concentration | IC\(_{50}\) |
|----------|-----------------------|-----------|
| 2a       | 200μg/ml              | -         |
| 2b       | 200μg/ml              | -         |
| 2c       | 200μg/ml              | -         |
| 2d       | 200μg/ml              | -         |
| 2e       | 200μg/ml              | -         |
| 2f       | 200μg/ml              | -         |
| 2g       | 200μg/ml              | -         |
| NVP      | 10μg/ml               | 0.18μg/ml |

Furthermore, all the products were tested on the growth assays for anti-proliferative activities (HeLa cells, HT-29 and HT-1080 cells) at concentrations≤10μM (down to 5nM). However, only compound 2d showed weak anti-proliferative activity at 10μM. Then, 2d and gambogic acid (GA) were tested for apoptotic activity on SK-OV-3 cells (nuclear fragmentation and mitochondrial membrane potential dissipation). 2d was observed to have not any activity at the concentration of ≤10μM, whereas gambogic acid showed activity in assays with an IC\(_{50}\)= 500-600 nM. Lastly, both of the compounds 2d and GA have been tested again in a proliferation assay against 3 additional cell lines with a modified
concentration range for IC50 determination. GA has confirmed its activity with an IC50 = 250-350 nM against all cell lines whereas 2d only showed weak activity with IC50 = 10μM against one cell line.

2.4. Experimental

Materials and Methods: Melting points were determined by X-4 Digital Display Binocular Microscope instrument. Spectroscopic data were detected by the following instruments: IR on a Bruker Vector-22 spectrometer as KBr pellets; 1H NMR and 13C NMR on a Mercury Plus 400 MHz NMR spectrometer in CDCl3 with TMS as an internal reference. Elemental analyses were performed by Carlo Erba 1106. All of the chemicals which were detected were analysis purity. Nevirapine (masculine comparison medicine) was produced by Ze Zhong Yi Hua Information Research Center, Nanjing. The other reagents were prepared by The National Center of Drug Screening. N-acylhydrazones (1a-1e) were synthesized according to the literature [25].

Against S. aureus ATCC 25923: All of the synthesized compounds were screened in vitro for antimicrobial activity by microdilution susceptibility method. S. aureus ATCC 25923 was used as the reference strains and Mueller–Hinton Broth (pH 7.3) was used as the medium in the determination of antibacterial activities. All of the compounds of 2a-2g were dissolved in DMSO at suitable concentration. Mag was treated as comparative antibacterial agents. Each test was performed twice and the average of the results was calculated [31].

Against HIV-1 RT in vitro: The seven samples were dissolved in DMSO with suitable concentration and were diluted with 5 times by double distillation water in buffer. Biotin-d UTP and genetic engineering target enzyme were added into the buffer under the best responsible condition of fosters. It was colored by streptavidin-tagged horseradish peroxidase (SA-HRPO). The optical density at 450 nm (OD450) was measured on a microplate ELISA reader (Boehringer Mannheim, Germany) according to the instructions of the manufacturer.

General procedure for 2a-2g: A solution of 1e (0.5 g, 1.38 mmol) in 10 mL of acetic anhydride was refluxed for 1.5 hours, then, the acetic anhydride was distilled off in vacuum. The residue was recrystallized from ethyl acetate (15 mL). A colorless crystal of 2e (0.37 g, 66.0 %, m.p. 203-204°C) were obtained by slow evaporation of 2e solution in ethyl acetate after 2 days at room temperature. Rf=0.65(petrol ether: ethyl ester=3:1). 1H NMR (400 MHz, CDCl3): δ =7.80(d, 1H, J=8.4 Hz, pyridine-H), 7.53 (dd, 1H, J=7.8 Hz,1.4 Hz, benzene-H), 7.41(s, 1H, oxadiazoline- H), 7.39(d, 1H, J=8.4 Hz, pyridine-H), 7.34(dd, 1H, J=8.0 Hz,1.6 Hz, benzene-H), 7.26(t, 1H, J=7.8 Hz, benzene-H) and 2.41(s, 3H, COCH3) ppm. 13C NMR (400 MHz, CDCl3): δ =168.2, 151.7, 149.2, 141.5, 141.0, 136.7, 134.4, 130.7, 130.1, 128.7, 92.8 and 21.3 ppm. IR (KBr): ν =3068, 3061s, 1665vs, 1273w, 1030s, 2926m and 836s cm

1/1. C13H10ClN2O2 (326.17): calced. C, 53.59; H, 3.30; N, 12.50; found: C, 53.02; H, 3.49; N, 12.94.

2a. Colorless crystal, yield: 63%, m.p. 224-225°C, Rf=0.62(petrol ether: ethyl ester=3:1). 1H NMR (400 MHz, CDCl3): δ =7.81(d, 1H, J=8.4 Hz, pyridine-H), 7.50-7.53(m, 2H, benzene-H), 7.38-7.42 (m, 4H, pyridine-H and benzene-H), 7.14 (s, 1H, oxadiazoline-H) and 2.39 (s, 3H, COCH3) ppm. 13C NMR (400 MHz, CDCl3): δ =168.2, 151.7, 149.2, 141.5, 141.2, 136.7, 134.4, 130.7, 130.1, 128.7, 126.7, 92.8 and 21.5 ppm. IR (KBr): ν =3068, 1665vs, 1273s, 1030s, 2926m and 836s cm

1/1. C13H10ClN2O2 (326.17): calced. C, 53.59; H, 3.30; N, 12.50; found: C, 53.02; H, 3.49; N, 12.94.

2b. Colorless crystal, yield: 54%, m.p. 138-140°C, Rf=0.63(petrol ether: ethyl ester=3:1). 1H NMR (400 MHz, CDCl3): δ =7.82 (d, 1H, J=8.4 Hz, pyridine-H), 7.46 (d, 2H, J=8.8 Hz, benzene-H), 7.41 (d, 1H, J=8.0 Hz, pyridine-H), 7.39 (d, 2H, J=8.8 Hz, benzene-H), 7.10 (s, 1H, oxadiazoline-H) and 2.38 (s, 3H, COCH3) ppm. 13C NMR (400 MHz, CDCl3): δ =168.3, 151.6, 149.2, 141.5, 141.2, 136.7, 134.4, 130.7, 128.7, 126.7, 92.8 and 21.5 ppm. IR (KBr): ν =3061m, 1665vs, 1272w, 1030s, 2925m and 828s cm

1/1. C13H10ClN2O2 (368.98): calced. C, 48.61; H, 2.72; N, 11.34; found: C, 48.77; H, 2.52; N, 11.48.

2c. Colorless crystal, yield: 61%, m.p. 230-231°C, Rf=0.55(petrol ether: ethyl ester=3:1). 1H NMR (400 MHz, CDCl3): δ =7.68(d, 1H, J=8.8 Hz, pyridine-H), 7.57(d, 2H, J=8.8 Hz, benzene-H), 7.52(d, 2H, J=8.4 Hz, benzene-H), 7.32(d, 1H, J=8.4 Hz, pyridine-H), 7.23(s, 3H, COCH3) and 2.01 (s, 3H,
\[ \text{CH}_3 \text{ppm.} \] 1\textsuperscript{3}C NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 159.7, 156.2, 152.2, 149.1, 139.6, 137.4, 131.7, 127.5, 127.3, 125.7, 123.7, 100.1, 23.0 \text{ and } 11.4 \text{ ppm.} \] IR (KBr): \( \nu = 3077 \text{m, 1669\text{vs, 1258\text{vs, 1038\text{vs, 2997s and 824s cm}}}}^{-1}. \]

\[ \text{C}_{16}\text{H}_{12}\text{BrCl}_{2}\text{N}_{3} \text{O}_2 \text{(429.10): calcd. C, 44.79; H, 2.82; N, 9.79; found: C, 44.76; H, 3.00; N, 10.02.} \]

2d. Colorless crystal, yield: 71\%, m.p. 173\^\circ\text{C}, R\text{f} = 0.58(\text{petrol ether: ethyl ester=3:1}). 1\textsuperscript{H} NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 7.80(\text{d, 1H, } J=8.4 \text{ Hz, pyridine-H}), 7.48(\text{dd, 1H, } J=7.8 \text{ Hz, benzene-H}), 7.39(\text{d, 1H, } J=8.4 \text{ Hz, pyridine-H}), 7.29(\text{dd, 1H, } J=7.8, 0.6, \text{ benzene-H}), 7.23(\text{s, 1H, oxadiazoline-H}), 7.18(\text{dd, 1H, } J=8.4, 0.8, \text{ benzene-H}), \text{ 2.35(s, 3H, OCOCH}_3\text{) and 2.31(s, 3H, NCOCH}_3\text{) ppm.} \]

1\textsuperscript{3}C NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 168.8, 168.0, 152.0, 149.2, 141.5, 141.4, 141.0, 131.1, 130.5, 132.0, 129.1, 127.1, 126.8, 126.0, 90.2, 21.2 \text{ and } 21.0 \text{ ppm.} \) IR (KBr): \( \nu = 3064\text{s, 1766\text{vs, 1672\text{vs, 1270m, 1030\text{vs, 2990w and 843s cm}}}}^{-1}. \]

\[ \text{C}_{17}\text{H}_{13}\text{Cl}_{2}\text{N}_{3} \text{O}_4 \text{(394.21): calcd. C, 51.80; H, 3.32; N, 10.66; found: C, 51.43; H, 3.01; N, 10.45.} \]

2f. Colorless crystal, yield: 62\%, m.p. 204-205\^\circ\text{C}, R\text{f} = 0.53(\text{petrol ether: ethyl ester=3:1}). 1\textsuperscript{H} NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 7.83(\text{d, 1H, } J=8.4 \text{ Hz, pyridine-H}), 7.72(\text{s, 2H, benzene-H}), 7.42(\text{d, 1H, } J=8.4 \text{ Hz, pyridine-H}), 7.07(\text{s, 1H, oxadiazoline-H}), 2.40(\text{s, 3H, OCOCH}_3\text{) and 2.39(\text{s, 3H, NCOCH}_3\text{) ppm.} \]

1\textsuperscript{3}C NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 168.7, 166.8, 151.5, 149.3, 147.5, 141.6, 140.7, 136.1, 130.8, 130.7, 127.1, 118.2, 90.0, 21.4 \text{ and } 20.4 \text{ ppm.} \) IR (KBr): \( \nu = 3062\text{s, 1773\text{vs, 1666\text{vs, 1266s, 1035s, 2936m and 845s cm}}}}^{-1}. \]

\[ \text{C}_{17}\text{H}_{11}\text{Br}_{2}\text{Cl}_{2}\text{N}_{3} \text{O}_4 \text{(552.00): calcd. C, 36.99; H, 2.01; N, 7.61; found: C, 36.79; H, 2.31; N, 7.42.} \]

2g. Colorless crystal, yield: 71\%, m.p. 160\^\circ\text{C}, R\text{f} = 0.59(\text{petrol ether: ethyl ester=3:1}). 1\textsuperscript{H} NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 7.78(\text{d, 1H, } J=8.4 \text{ Hz, pyridine-H}), 7.37(\text{d, 1H, } J=8.4 \text{ Hz, pyridine-H}), 2.33(\text{s, 3H, COCH}_3\text{) and 1.92(\text{s, 6H, CH}_3\text{) ppm.} \]

1\textsuperscript{3}C NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 167.6, 150.1, 149.1, 141.8, 141.3, 130.5, 126.5, 101.3, 24.7 \text{ and 22.3 ppm.} \) IR (KBr): \( \nu = 3074\text{m, 1666\text{vs, 1229s, 1029\text{vs, 2943m and 839s cm}}}}^{-1}. \]

\[ \text{C}_{11}\text{H}_{11}\text{Cl}_{2}\text{N}_{3} \text{O}_2 \text{(288.13): calcd. C, 45.85; H, 3.85; N, 14.58; found: C, 45.34; H, 3.44; N, 14.71.} \]

3. Conclusion
In conclusion, we have synthesized novel 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines derived from acylhydrazones. The bioactivities test results of these compounds showed there are not any promising activities with S. aureus, HIV-1 RT, HT-29 cells and HT-1080 cells. Thus, further optimization is required to get good activity.

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References
[1] Q.L. Zhao, L.N. Ren, J. Hou, W.Q. Yu, J.B. Chang, Annulation reactions of in-situ-generated n-(het)aryldiazenes with isothiocyanates leading to 2-imino-1,3,4-oxadiazolines, Org. Lett. 21(2019) 210-213.
[2] Z.P. Che, Y.E. Tian, S.M. Liu, J. Jiang, M. Hu, G.Q. Chen, Microwave-assisted expeditious synthesis of 2-alkyl-2-(n-aryl)sulfonylindol-3-yl)-3-n-acyl-5-aryl-1,3,4-oxadiazolines catalyzed by hgCl2 under solvent-free conditions as potential anti-hiv-1 agents, Molecules 23(2018) 2936.
[3] C. Araniciu, O. Oniga, G. Marc, M.D. Palage, L. Marutescu, M.C. Chifiriuc, C.I. Stoica, I. Ionut, S.D. Oniga, Anti-biofilm activity evaluation and molecular docking study of some 2(3-pyridyl)-thiazolyl-1,3,4-oxadiazolines, Farmaco 66(2018) 627-634.
[4] A. Chimirri, S. Grasso, A.M. Monforte, A. Rao, M. Zappala, Synthesis and antitumor activity evaluation of delta2-1,2,4-oxadiazolone derivatives, Farmaco 51(1996) 125-129.
[5] Y. Hu, X. Lu, K. Chen, R. Yan, Q. S. Li, H. L. Zhu, Design, synthesis, biological evaluation and molecular modeling of 1,3,4-oxadiazoline analogs of combretastatin-A4 as novel antitubulin agents, Biorg. Med. Chem. 20(2012) 903-909.

[6] H.M. Coley, J. Sarju, G. Wagner, Synthesis and characterization of platinum(II) oxadiazoline complexes and their in vitro antitumor activity in platinum-sensitive and -resistant cancer cell lines, J. Med. Chem. 51(2008) 135-141.

[7] A. Chimirri, S. Grasso, A.M. Monforte, P. Monforte, M. Zappala, A. Carotti, Synthesis and in vitro anti-HIV activity of novel delta 2,1,2,4-oxadiazoline derivatives, Farmaco. 49(1994) 509-511.

[8] C.P. Singh, H. Hasan, Synthesis and fungitoxicity of 1,2,4-oxadiazolines derived from 2-hydroxybenzaldehydes, J. Ind. Counc. Chem. 19(2002) 46-49.

[9] D.J. Li, F.J. Dan, H.Q. Fu, Synthesis and antibacterial activities of 1,3-bis[3-n-acetyl-2-aryl-1,3,4-oxadiazoline-5-yl]benzenes. Heterocycl. Commun.14(2008) 101-105.

[10] D.J. Li, F.J. Dan, H.Q. Fu, Synthesis and antibacterial activities of bis-1,3,4-oxadiazoline derivatives, Heterocycl. Commun. 14(2008) 465-468.

[11] J. F. Yang, H. Cao, H. Liu, B. Q. Li, Y. M. Ma, Synthesis and bioactivity of novel bis-heterocyclic compounds containing pyrazole and oxadiazoline, J. Chin. Chem. Soc. 58(2011) 369-375.

[12] O.M. Ali, H.H. Amer, A.A. H. Abdel-Rahman, Synthesis and antiviral evaluation of sugar uracil-1-ylmethylhydrazones and their oxadiazoline derivatives, Synthesis (2007) 2823-2828.

[13] B. Tinperciuc, A. Parvu, M. Palage, O. Oniga, D. Ghiran, Heterocycles.82. The synthesis and the study of the anti-inflammatory activity of some 3-N-acetyl-2-R-5-[2'-aryl-4'-methylthiazole-5'-yl]Δ2-1,3,4-oxadiazoline, Farmacia 47(1999) 77-84.

[14] H. Rajak, R. Veerasamy, M. Kharya, P. Mishra, Design, synthesis, and pharmacological evaluation of novel oxadiazole and oxadiazoline analogs as anti-inflammatory agents, J. Enzym. Inhib. Med. Chem. 25(2010) 492-501.

[15] H.N. Dogan, A. Duran, S. Rollas, G. Sener, Y. Armutak, M. Keyer-Uysal, Synthesis and structure elucidation of some new hydrazones and oxadiazolines: anticonvulsant activities of 2-(3-acetyloxy-2-naphthyl)-4-acetyl-5-substituted-1,3,4-oxadiazolines, Med. Sci. Res. 26(1998) 755-758.

[16] G. Wagner, A. Marchant, J. Sayer, Design, synthesis, characterisation and chemical reactivity of mixed-ligand platinum(II) oxadiazoline complexes with potential cytotoxic properties, Dalton Trans. 39(2010) 7747-7759.

[17] L. Lee, L.M. Robb, M. Lee, R. Davis, H. Mackay, S. Chavda, B. Babu, E.L. O'Brien, A.L. Risinger, S. L. Mooberry, M. Lee, Design, synthesis, and biological evaluations of 2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoline analogs of combretastatin-a4, J. Med. Chem. 53(2010) 325-334.

[18] S. Ke; F.Y. Liu, N. Wang, Q. Yang, X.H. Qian, 1,3,4-Oxadiazoline derivatives as novel potential inhibitors targeting chitin biosynthesis: design, synthesis and biological evaluation. Bioorg, Med. Chem. Lett.19(2009) 332-335.

[19] S.L. Lee, A.M. Cameron, J. Warkentin, Thermolysis of delta3-1,3,4-oxadiazolin-2-ones, Can. J. Chem. 50(1972) 2326-2331.

[20] R.Y. Yang, L.X. Dai, Hypervalent iodine oxidation of N-acetylhydrazones and N-phenylsemicarbazone-an efficient method for the synthesis of derivatives of 1,3,4-oxadiazoles and delta(3)-1,3,4-oxadiazolines, J. Org. Chem. 58(1993) 3381-3383.

[21] T. Chiba, M.Okimoto, Electrooxidative cyclization of N-acylhydrazones of aldehydes and ketones to Δ3-1,3,4-oxadiazolines and 1,3,4-oxadiazoles, J. Org. Chem. 57(1992) 1375-1379.

[22] H.L. Yale, K. Losee, J. Martine, M. Holsing, F.M. Perry, Bernstein J. Chemotherapy of Experimental Tuberculosis. VIII. The synthesis of acid hydrazides, their derivatives and related compounds, J. Am. Chem. Soc. 75(1953) 1933-1942.

[23] J.B. Ekely, M.C. Swisher, C.C. Johnson, Action of acetic anhydride on benzalaniline, Gazz. Chim. Intal., 62(1932) 81-84.
[24] G.N. Walker, M.A. Moore, 3-Aminomethylindoles and 2-(3-indolyl)oxazolidines from indole-3-
aldimines. Some observations on the acetylation of Schiff bases, J. Org. Chem. 26(1961) 432-
439.

[25] J. Zhang; T.H. Shen; L.J. Xu; F.F. Shen; Q. Qin; C.A. Ma, Q.B. Song, Synthesis and bioactivities
of clopyralid hydrazide-hydrazone, Synth. Commun. 40(2010) 814-820.

[26] F.M. Liu, Y.Z. Chen, S.X. Kong, Synthesis and spectroscopic properties of some 1,3,4-
oxadiazoline derivatives. Hua Xue Tong Bao, 1(2000) 38-41.

[27] Z.H. Ge, X.G. Du, D.J. Li, Synthesis and characterization of 3-N-acetyl-2-aryl-5-phenyl-1,3,4-
oxadiazoline, He Cheng Hua Xue, 13(2005) 49-52.

[28] B. Durgun, G.C. Çapan, N. Ergenç, S. Rollas, Synthesis, characterization and biological
evaluation of new benzylidenebenzohydrazides and 2,5-disubstituted 2,3-dihydro-1,3,4-
oxadiazoles, Pharmazie 48(1993) 942-943.

[29] F.M. Liu, Y.T. Liu, S.X. Kong, Y.Z. Chen, Synthesis of chromones and 1,3,4 -oxadiazolines
containing benzotriazole, Chin. J. Org. Chem. 20(2000) 499-504.

[30] L. Somogyi, Notes on the reactions of ketone acylhydrazones under acylation conditions,
Tetrahedron 41(1985) 5187-5190.

[31] National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial
Susceptibility Tests for Bacteria that grow aerobically, 5th ed. (Approved Standard); NCCLS
Document M7-A5; NCCLS: Wayne, PA, 2000.