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# Synthesis and Antimicrobial Evaluation of 1,3,4-Oxadiazole-2-thione from Some Pyridine Carboxylic Acids

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The 5-(2-pyridyl)-1,3,4-oxadiazole-2-thione (**4a**) and the *bis*-5-(2,6-pyridyl)-1,3,4-oxadiazole-2-thione (**4b**) have been synthesized from the corresponding 2-pyridine carboxylic acid (picolinic acid) (**1a**) and 2,5-pyridine dicarboxylic acid (**1b**) by similar method. The esterification of the acids with ethyl and methyl alcohols gave the corresponding esters **2a** and **2b**. The hydrazides **3a** and **3b** were obtained in good yields. The 1,3,4-oxadiazoles **4a** and **4b** were formed by treatment of the corresponding hydrazides with $CS_2$ and KOH. The intermediates and the final products were characterized with IR, UV, $^1H$ and $^{13}C$ NMR and MS. The hydrazides **3a** and **3b**, the final products and the commercially available 5-(4-pyridyl)-1,3,4-oxadiazole-2-thione (**5**) were tested *in vitro* against the following micro organisms: *Escherichia coli* ATCC 25924, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATTC 29212, *Staphylococcus aureus* ATCC 25923 and *Pseudomonas fluorescens* ATCC 17552 and compared with the known antibiotics Cephalosporin (cefotaxim) and Gentamycin. The results have shown that the synthesized compounds have appreciable effects. The *bis*-5-(2,6-pyridyl)-1,3,4-oxadiazole-2-thione (**4b**) had the highest effect upon all the tested microorganisms in general and on the gram-negative bacteria *Pseudomonas fluorescens* in particular, where its effect exceeded that of the well known Cephalosporin (cefotaxim).

**Key Words: 5-(2-Pyridyl)-1,3,4-oxadiazole-2-thione, *Bis*-5-(2,6-pyridyl)-1,3,4-oxadiazole-2-thione, 5-(4-Pyridyl)-1,3,4-oxadiazole-2-thione, Antibacterial activity.**

## INTRODUCTION

1,3,4-Oxadiazole and 1,3,4-oxadiazole-2-thione nuclei have many pharmacological activities as antibacterial[1], antifungal[2], antiinflammatory[3], CNS depressing[4], anticonvulsant[5], anticancer[5] and antimycobacterium tuberculosis compounds[6]. On the other hand the derivatives of the 1,3,4-oxadiazole and 1,3,4-oxadiazole-2-thione

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from pyridine monocarboxylic acids (picolinic, nicotinic and isonicotinic) as well as the pyridine dicarboxylic acids in the positions (2,3-; 2,4-; 2,5-; 2,6-; 3,4- and 3,5-) have widely industrial applications[7,8].

4-(1,3,4-Oxadiazole-2-thione-5-yl)pyridine (**5**) commercially available[9-13] was used to form some asymmetric polymers[14]. Also the 5-(2-pyridyl)-1,3,4-oxadiazole-2-thione, 2,5-*bis*-(2-pyridyl)-1,3,4-oxadiazole and 2,5-*bis*-(4-pyridyl)-1,3,4-oxadiazole compounds as complexing agents with copper have been discussed[15-19]. While the 2,6-*bis*-(1,3,4-oxadiazole-2-yl)pyridine was synthesized and linked to poly(*p*-phenylene vinylene) was demonstrated to have sensivity towards various metal ions as a fluorescence mode chemosensor[20,21].

Due to the wide applications of pyridine carboxylic acids and their derivatives and the 1,3,4-oxadiazole-5-thione in the field of medicine, agriculture and industry, here we report the synthesis and the antibacterial evaluation of two members of this class of pyridine carboxylic acids namely 5-(2-pyridyl)-1,3,4-oxadiazole-2-thione (**4a**) and the 2,6-*bis*-(1,3,4-oxadiazole-2-thione-5-yl)-pyridine (**4b**) and evaluate their antibacterial activity compared to the commercially available 5-(4-pyridyl)-1,3,4-oxadiazole-2-thione (**5**) using *Escherichia coli* ATCC 25924, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATTC 29212, *Staphylococcus aureus* ATCC 25923 and *Pseudomonas fluorescens* ATCC 17552 and compare these with the known antibiotics Cephalosporin (cefotaxim) and Gentamycin.

## EXPERIMENTAL

All reactions were monitored by TLC analysis (silica gel for TLC supplied by Merck). The melting points were measured with a BUCHI 540 melting point apparatus and are uncorrected. The UV spectra were recorded in methanol on a ZUZI Split-Beam UV-vis 4418PC (4418SPC) spectrophotometer. The IR spectra were recorded using KBr discs in a JASCO V-530 spectrophotometer and the IR spectra solutions were obtained with a GENESIS II FTIR spectrophotometer. The $^{1}H$ and $^{13}C$ NMR (250 MHz) spectra were recorded in DMSO-$d_6$ at the department of chemistry, University of Rennes (France). The MS spectra were recorded in the "Laboratoire de chimie et ingenierie moleculaire d'Angers" (CIMA), Universite des Sciences, Angers, (France) on a MAT 312 mass spectrometer using glycerol as matrix. Micro organisms in this study were supplied by the university hospital of Oran and identified by the laboratory of applied microbiology, University of Oran Es Senia. The Mueller Hinton medium was supplied by Difco.

**General procedure for esterification of carboxylic acids (1a and 1b):** An acid (**1g**) was dissolved in an appropriate alcohol (20 mL of ethanol or methanol) added to it $H_2SO_4$ (4 mL) dropwise. The mixture was heated under reflux at the appropriate temperature for 24 h. The reaction mixture was cooled down to room temperature and neutralized by solid $NaHCO_3$, filtered off and washed with alcohol (2 mL). The filtrate was dried over anhydrous $MgSO_4$, filtered and washed with alcohol (2 mL), the combined filtrates was evaporated to dryness to give the ester.

**Ethyl picolinate (2a):** Colourless syrup (0.37 g, 30 %), (lit., m.p. 2 °C, lit. b.p. 240-241 °C)[11]. UV, $\lambda_{max}$ 235 nm. Lg ε 3.52. Lit $\lambda_{max}$ 237. Lg ε 4. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1719 (CO).

***Bis*-2,6-dimethyl picolinate (2b):** Crystalline solid (0.35 g, 30 %), m.p. 120-125 °C, lit. m.p. 121-125 °C. $\lambda_{max}$ 205 nm. Lg ε 0.7516, 265 nm. Lg ε 0.2101. IR (KBr, $\nu_{max}$, $cm^{-1}$): 1732-br (CO).

**General procedure for preparation of hydrazides (3a and 3b):** The ester (5 g, 0.031 mol) was dissolved in ethanol (8 mL), added to it dropwise a hydrazine hydrate 51 % (2 mL) and the mixture was heated under reflux on a water bath 90 °C for 20 h. The solvents were evaporated under reduced pressure to give white solid which was washed with a small quantity of ether (few mL) to give white crystalline products.

**Picolinic hydrazide (3a):** White crystalline (4.1 g, 90 %), m.p. 142-143 °C (Lit. m.p. 144-145)[28]. UV, $\lambda_{max}$ 218, 260 nm, Lg ε 3.44, 4.05, respectively. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3309 (NH), 1677.8 (N-CO). $^1H$ $NMR_{\delta H}$ 10.6 (m, 3H, $NHNH_2$), 8.45 (d, 1H, H 3), 7.85 (dd, 2H, $H_{4 \text{ and } 5}$), 7.5 (d, 1H, H6). $^{13}C$ NMR 166.3 ppm (C=O), 149.2, 148.6, 138.7, 127.5 and 122.8 ppm (C=C).

***Bis*-2,6-dihydrazide pyridine (3b):** White crystalline (4.5 g, 90 %), m.p. > 260 °C. UV, $\lambda_{max}$ 205 nm, Lg ε 0.7778. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3270 (NH), 1685.5 (N-CO). $^1H$ $NMR_{\delta H}$, 10.7 (m, 6H, $2NHNH_2$), 8.2 (m, 3H, $H_{3, 4 \text{ and } 5}$). $^{13}C$ NMR 159.6 ppm (C=O), 149.5, 145.8, 137.8, 126.5 and 121.6 ppm (C=C).

**General procedure for preparation of 1,3,4-oxadiazole-2-thiones (4a and 4b):** The hydrazides (0.26 g) in an ethanolic solution of KOH 85 % (from KOH, 0.13 g in ethanol 8 mL), added to it dropwise $CS_2$ ( 0.22 mL) and the mixture was heated for 40 °C for 7 h. The bulk of the solvents were removed under vacuum at 50 °C, the remaining solid was washed with iced diluted HCl in the filter paper. The solid was dissolved in a small amount of ethanol and left into the refrigerator to give fine crystalline products.

**5-(2-Pyridyl)-1,3,4-oxadiazole-2-thione (4a):** White crystalline (0.24 g, 70 %), m.p. 205-210 °C. UV, $\lambda_{max}$ 240, 345, 375 nm. Lg ε (6.0, 1.926, 2.772), respectively. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3429 (NH), 3074 (C-H aromatic), 2630 (SH), 1658 (C=N) 1589 and 1565 (C=C and C=N aromatic) and 1465 (C=S). $^1H$ NMR, δ ppm; 10.7 (s, 1H, N-H), 8.0 (m, 3H, C-H aromatic) 3.4 (weak, s, 1H, SH). $^{13}C$ NMR, 181.2 ppm for C=S and at 160.5 ppm (C=N) and at 148.4, 144.2 and 138 ppm (pyridine ring). MS 179 ($C_7H_5N_3OS$).

***bis*-5-(2,6-Pyridyl)-1,3,4-oxadiazole-2-thione (4b):** White crystalline (0.26 g, 68 %), m.p. > 260 °C. UV, $\lambda_{max}$ 200, 385 nm. Lg ε 2.211, 4.4163, respectively. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3409.7, 3300, 3250 (NH free and bonded), 1655.2, 1587.4 (C=C and C=N), 1490.2 (C=S). $^1H$ $NMR_{\delta H}$ 10.7 (s, 1H, NH), 9.7 (s, 1H, NH), 8.19-7.8 (m, 3H, H) , 3.52 (s, 2H, 2SH). $^{13}C$ NMR, 160.5 ppm (C=N), 181.2 ppm (C=S), 148.4, 144.2 and 138 ppm (pyridine ring). MS 280.4 ($C_9H_5N_5O_2S_2$).

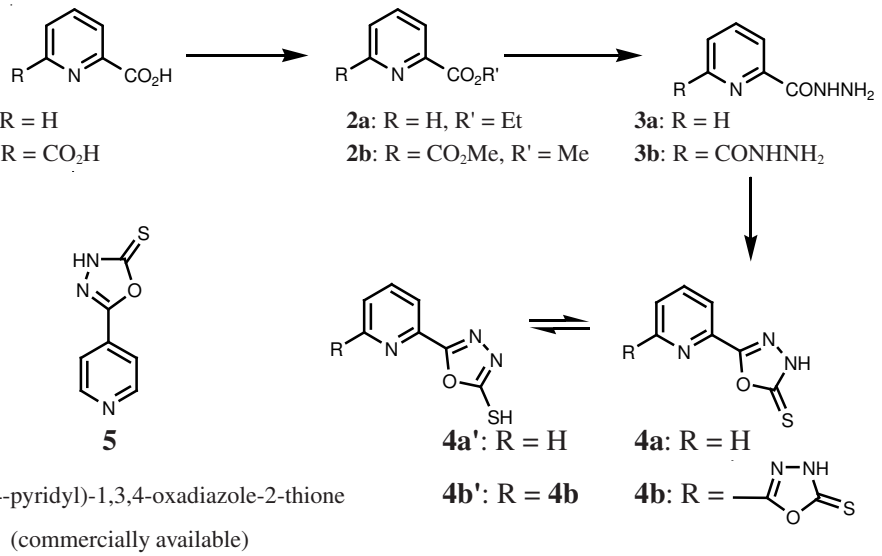
**Antibacterial tests:** The filter paper disc method was performed in duplicate using fresh Mueller Hinton agar medium. This agar medium was inoculated with

0.5 mL of cultures containing about $10^6$ CFU/mL. Filter paper discs (5 mm diameter) saturated with solutions of each compound (concentrations 10 µg $mL^{-1}$ DMSO) was placed on the indicated agar mediums. The incubation time was 24 h at 37 °C. The blank test disc with DMSO was used. Inhibitory activity was evaluated by measuring the diameter of clear zone observed around the disc (in mm).

**Minimum inhibition concentration (MIC) tests:** Each 1 mL of the original concentration [c] (10 µg $mL^{-1}$) in DMSO of the compounds **3a, 3b, 4a, 4b, 5** were diluted with DMSO for five times to 1/2 [c], 1/4[c] , 1/8 [c] ,1/16[c], 1/32[c] and optical density was measured at 0, 18, 24 and 48 h.

## RESULTS AND DISCUSSION

The oxadiazoles **4a,b** have been synthesized according to the following **Scheme-I**:




5-(4-pyridyl)-1,3,4-oxadiazole-2-thione

(commercially available)

**Scheme-I**: General synthetic scheme

**Esterification of the carboxylic acids (1a and 1b):** The ethyl picolinate (**2a**) and the *bis*-2,5-dimethyl picolinate (**2b**) have been prepared in the conventional way by treating the corresponding acids with ethanol or methanol in presence of catalytic amounts of $H_2SO_4$. Infrared spectra of **2a** showed a band at 1719 $cm^{-1}$ for C=O (Lit. 1675 $cm^{-1}$) while the C=O for **2b** was exhibited at 1732 $cm^{-1}$ due to effect of the second methyl carboxylate group which might prevent the coplanerity of the molecule.

**Preparation of the hydrazides (3a and 3b):** The hydrazides **3a** and **3b** were prepared in almost quantitative yields from their corresponding esters and they were highly crystalline. The hydrazides were characterized by IR, $^1H$ and $^{13}C$ NMR. The hydrazide **3a** had exhibited bands at 3309 $cm^{-1}$ for NH and 1677 $cm^{-1}$ for N-CO while **3b** showed a band at 3270 $cm^{-1}$ for NH and 1685 $cm^{-1}$ for N-CO. The NH

signals were shown in $^1$H NMR at 10.6 ppm ($NHNH_2$) for **3a** and 10.7 ppm ($2xNHNH_2$) for **3b**. The $^{13}$C NMR of the hydrazide **3a** showed signals at 166.3 ppm (C=O), 149.2, 148.6, 138.7, 127.5 and 122.8 ppm (C=C in pyridine). While the dihydrazide **3b** showed almost similar $^{13}$C NMR 159.6 ppm (C=O), 149.5, 146.8, 137.8, 126.5 and 121.6 ppm (C=C in pyridine).

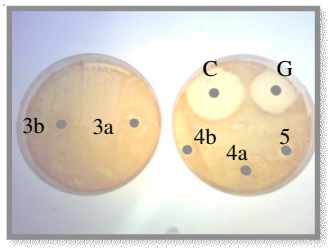
**Preparation of the oxadiazoles (4a and 4b):** The oxadiazoles **4a** and **4b** have been synthesized by treating the corresponding hydrazides **3a** and **3b** with carbon disulphide and potassium hydroxide. The oxadiazoles have been characterized by IR, UV, $^1$H NMR, $^{13}$C NMR and MS. The IR and NMR spectra have shown that the oxadiazoles **4a** and **4b** thiones might existed as tautomers with their corresponding thiols **4a'** and **4b'**[11,22]. The IR spectra showed both the NH and SH bands in the regions 3400 and 2600 $cm^{-1}$, respectively, in addition to the 1610, 1620 $cm^{-1}$ for C=N while the C=S exhibited as a band at the region of 1465 $cm^{-1}$. The symmetrical and the asymmetrical C-O-C group stretching vibrations had shown at 1245-1275 and 1155-1165 $cm^{-1}$, respectively. The $^1$H NMR spectrum of **4a** exhibited signals at 10.6 and 3.4 ppm for the NH and SH, respectively, which indicated the existence of both thione and thiol forms[23]. The $^{13}$C NMR of **4a** exhibited signals at 181.2 ppm for C=S and at 160.5 ppm for C=N in oxadiazole ring[24] and at 148.4, 144.2 and 138 ppm for pyridine ring[25]. The $^1$H NMR of **4b** had shown two signals for NH at 10.7 and 9.7 ppm and a signal at 3.5 ppm for SH. The $^{13}$C NMR of **4b** exhibited signals at 181.2 ppm for C=S and at 161.9 and 160.5 ppm for C=N, for two oxadiazole rings[24] and at 148.4, 144.2 and 138.0 ppm for pyridine ring[25]. The mass spectra of **4a** and **4b** showed the expected molecular ion peaks at m/z 179 and 280.4, respectively.

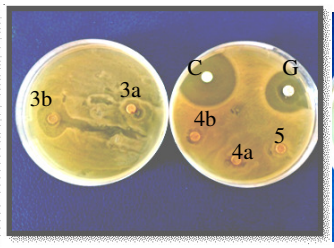
**Antibacterial evaluations:** The filter paper disk method (NCCLS)[26,27] was employed in duplicate for the *in vitro* study of antibacterial effects against two gram-positive bacteria *Staphylococcus aureus* ATCC 25923 and *Enterococcus feacalis* ATTC 29212 and three gram-negative bacteria *Escherichia coli* ATCC 25924, *Pseudomonas aeruginosa* ATCC 27835, *Pseudomonas fluorescens* ATCC 17552 using Gentamycin and Cephalosporin as references. The inhibitory effects of hydrazides **3a** and **3b** and the oxadiazoles **4a**, **4b** and **5** are summarized in Table-1 and are shown in Figs. 1-5.

TABLE-1
INHIBITION ZONES IN (mm)

| Compounds* | *S. aureus* | *E. feacalis* | *E. coli* | *P. aeruginosa* | *P. fluorescens* |
|---|---|---|---|---|---|
| Gentamycin | 27 | 27 | 25 | 20 | 13 |
| Cephalosporin | 35 | 34 | 28 | 22 | 15 |
| **3a** | 6 | 0 | 8 | 15 | 8 |
| **3b** | 0 | 0 | 8 | 12 | 8 |
| **4a** | 10 | 0 | 6 | 6 | 9 |
| **4b** | 9 | 0 | 7 | 7 | 16 |
| **5** | 13 | 0 | 8 | 0 | 12 |

*: Concentration 10 μg $mL^{-1}$.
Highly active = inhibition zone > 12 mm; Moderately active = inhibition zone 9-12 mm; Slightly active = inhibition zone 6-9 mm; Inactive = inhibition zone < 6 mm.



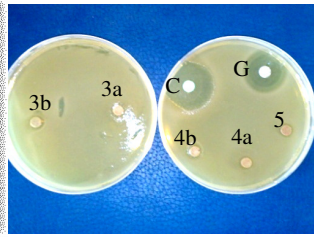




Fig. 1. Antibiogramme of *S. aureus* Fig. 2. Antibiogramme of *E. feacalis* Fig. 3. Antibiogramme of *E. coli*

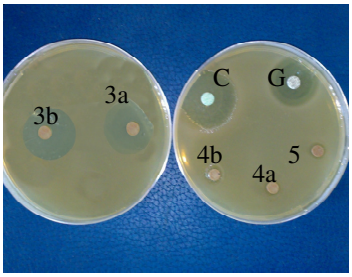




Fig. 4. Antibiogramme of *P. aeruginosa* Fig. 5. Antibiogramme of *P. fluorescens*

The screening results in Table-1 indicates that all compounds under study showed no inhibition effect against the gram-positive bacteria *E. feacalis* but showed variable effect upon the other gram-positive and gram-negative bacteria. The hydrazides **3a** and **3b** exhibited an inhibition effect on all gram-negative bacteria particularly upon *S. aeruginosa*, whereas they showed almost no effect upon gram-positive bacteria. The mono-oxadiazole derivative from picolonic acid **4a** showed a moderate activity against gram-positive *S. aureus*, gram-negative bacteria *P. fluorescens* and weak effect against *E. coli* and *S. aeruginosa*. The modified di-picolinic acid with two oxadiazole residue **4b** showed a weak activity against gram-negative *E. coli* and *P. aeruginosa*. In another hand, **4b** exhibited the highest activity against gram-negative *P. fluorescens* which exceeded the inhibition influence of the known Cephalosporin against the same microorganism (Table-1 and Fig. 5).

In comparison with a previous work[1], the mono-hydrazide **3a** showed relatively more inhibition effect upon *S. aureus* and *P. aeruginosa* than salicylic hydrazide. Whereas oxadiazole derivative **4a** has relatively lower inhibition effect on *S. aureus* and *E. coli* but exhibited more effect on *P. aeruginosa* than 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2-thione. The sensitivity of these compounds on gram-negative bacteria showed their action on the membrane type of these bacteria which are rich in phospholipids. To confirm the above test, the minimum inhibition concentrations (MIC) were determined in DMSO medium for the tested compounds for three times and the averages are shown in Table-2.

TABLE-2
INHIBITION OF MICROORGANISMS BY COMPOUNDS
**3a**, **3b**, **4a**, **4b** AND **5** AT DIFFERENT CONCENTRATIONS

| Compound | Concentration‡ (μg mL$^{-1}$) | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **3a** | | | | **3b** | | | | **4a** | | | | **4b** | | | | **5** | | | |
| | a | b | c | d | a | b | c | d | a | b | c | d | a | b | c | d | a | b | c | d |
| **i**† | + | – | – | – | – | – | – | – | + | + | – | – | + | – | – | – | + | + | – | – |
| **ii** | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| **iii** | + | – | – | – | + | – | – | – | + | – | – | – | + | – | – | – | + | – | – | – |
| **iv** | + | + | + | – | + | + | – | – | + | – | – | – | + | – | – | – | – | – | – | – |
| **v** | + | – | – | – | + | – | – | – | + | – | – | – | + | + | + | – | + | + | – | – |

†Microorganismes: i, *S. aureus*; ii, *E. feacalis*; iii, *E. coli*; iv, *P. aeruginosa*; v, *P. fluorescens*. ‡Concentration (μg mL$^{-1}$): a = 5; b = 2.5; c = 1.25; d = 0.625. Notes: the sign (+) for microorganisms inhibition and (–) for microorganisms unaffected.

Table-2 shows that the hydrazides **3a** and **3b** have shown their minimum inhibition concentration (MIC) at 1.25 and 2.5 μg mL$^{-1}$ on gram-negative *P. aeruginosa*, respectively. The oxadiazole derivatives **4a** and **5** have shown their MIC at 2.5 μg mL$^{-1}$ on gram-positive bacteria *S. aureus* whereas **5** showed similar MIC in gram-negative *P. fluorescens*. The most active compound **4b** has exhibited its MIC at a lower concentration 0.625 μg mL$^{-1}$ in gram-negative *P. fluorescens*.

## Conclusion

The hydrazides and the 1,3,4-oxadiazole residues in the compounds **3a, 3b, 4a, 4b** and **5** have a significant effect on phospholipids which is one of the major composition of the cell wall of the gram-negative bacteria. From the data of the inhibition effect it seems that there is no clear relationship between the number of the active groups and the strength of the inhibition effect.

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