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Author: Adel A.-H. Abdel-Rahman

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Synthesis and Antimicrobial Activity of Modified 1,3,4-Oxadiazoles and Their Sugar Derivatives

Adel A.-H. Abdel-Rahman

Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt

Correspondence
Email: adelnassar63@gmail.com

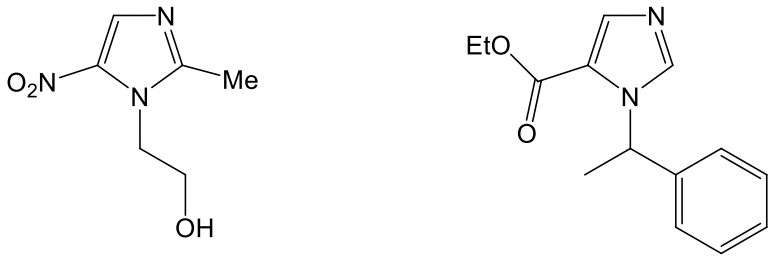
Abstract: A number of new substituted [(nitro-1H-imidazol-1-yl)methyl]-1,3,4-oxadiazoles, their derived sugar hydrazones as well as their N- and S-substituted derivatives were synthesized and tested for their antimicrobial activity against Bscillus subtilis (Gram-positive), Pseudomonas aeruginosa (Gram-negative), and Streptomyces species (Actinomycetes). The synthesized compounds displayed different degrees of antimicrobial activities or inhibitory actions.

Keywords: Modified 1,3,4-Oxadiazoles, Synthesis and Antimicrobial Activity , Sugar Derivatives

1. Introduction

Imidazoles are common scaffolds in highly significant biomolecules, including biotin, the essential amino acid histidine, histamine, the pilocarpine alkaloids (Grimmett, 1996) and other alkaloids, which have been shown to exhibit interesting biological activities such as antimicrobial, anticryptococcal, inhibition of nitric oxide synthase, and cytotoxic activities (De Luca, 2006). Imidazole derivatives have also been found to possess many pharmacological properties and are widely implicated in biochemical processes. Members of this class of diazoles are known to possess NO synthase inhibition (Sennequier *et al.*, 1999), antibiotic (Brogden *et al.*, 1978),

antifungal (Niwano *et al.*, 1994; Di Santo *et al.,* 2005; Botta *et al.,* 2000; Saha *et al.*, 2000) and neuropeptide Y antagonistic activities (Blum *et al.*, 2004). In addition, these heterocycles include several inhibitors of p38 MAP kinases (Jackson and Bullington*,* 2002; Wilson *et al*., 1997; Bolos, 2005; Diller *et al.,* 2005) which are thought to be involved in a variety of inflammatory and immunological disorders, and some derivatives such as mitronidazole (**I**), etomidate (**II**) (Fig. 1), and ketoconazole which have found application in drug therapy (Coura and de Castro, 2002).



I **II**

Fig. 1. Structure of Metronidazole and Etomidate

Recently certain imidazole based compounds were reported to possess antimicrobial activities (Banfi *et al.,* 2006). Further recent literature revealed that N^1-substitution of imidazoles improves the antibacterial activity (Khbnadideh *et al*., 2003). Among the five-membered nitrogen heterocycles, the 1,3,4-oxadiazoles are associated with broad spectrum of biological activities (Zareen *et al.,* 2004; El-Azzouny *at al.,* 2003; Loetchutinat *et al.,* 2003). Their derivatives have been known to possess antibacterial (Ates *et al.,* 1997), antimicrobial (Rahman and Farghaly 2004), insecticidal (Li *et al.,* 2003), herbicidal, fungicidal (Zou *et al.,* 2002), anti-inflammatory (Palaska *et al.,* 2002), hypoglycaemic (Mhasalkar *et al.,* 1971) characteristics, antiviral (El-Emam *et al.,* 2004), and anti-tumour activities (Liszkiewicz *et al.,* 2003). On the other hand, the acyclic *C*-nucleoside analogues possess a wide range of biological properties, including antibiotic,

antiviral, and anti-tumour activities (Holy, 1987; Remy and Secrist, 1985; Larson *et al.,* 1983; El Ashry and El Kilany, 1996; 1997; 1998; Chu and Cutler, 1986; Markar and Keseru, 1997; Franchetti *et al.,* 1997; Hammerschmidt *et al.,* 1997). Consequently, newly synthesized compounds containing imidazole and 1,3,4-oxadiazole moieties as well as their substituted sugar derivatives will be expected of enhanced biological activities. Owing to the above facts and our interest in the attachment of carbohydrate residues to newly synthesized heterocycles (El-Sayed *et al.*, 2008; 2009; Ali *et al.*, 2007) searching for potent leads as antimicrobial agents, our aim is the synthesis and antimicrobial evaluation of new (imidazol-1-yl)methyl[1,3,4]oxadiazoles and their sugar derivatives.

2. Experimental

General

Melting points were determined using a Büchi apparatus. IR spectra (KBr) were recorded with a Bruker-Vector22 instrument (Bruker, Bremen, Germany). ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 300 MHz and 200 MHz with TMS as internal standard. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard, and the coupling constants (*J* values) are given in Hz. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. EI-mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard, Palo Alto, CA, USA).

The synthesized compounds were tested for their antimicrobial activity against three microorganisms and the minimal inhibitory concentrations (MICs) of the tested compounds were determined by the dilution method.

Sample preparation

Each of the test compounds and standards were dissolved in 12.5% DMSO, at concentrations of 500 µg/mL. Further dilutions of the compounds and standards in the test medium were prepared at the required quantities.

Culture of microorganisms

Bacteria strains were supplied from Botany Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt, namely *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa* (ATCC 27853) (Gram-negative) and *Streptomyces* species (Actinomycetes). The bacterial strains were maintained on MHA (Mueller – Hinton agar) medium (Oxoid, Chemical Co., UK) for 24 h at 37 °C. The medium was molten on a water bath, inoculated with 0.5 mL of the culture of the specific microorganism and poured into sterile Petri dishes to form a layer of about 3-4 mm thickness. The layer was allowed to cool and harden. With the aid of cork-borer, cups of about 10 mm diameter were produced (Jorgensen *et al.*, 1999).

Agar diffusion technique

The antibacterial activities of the synthesized compounds were tested against *Bacillus subtilis* (Gram-positive), *Pseudomonas aeruginosa* (Gram-negative) and *Streptomyces* species (Actinomycetes) using MH medium (17.5 g casein hydrolysate, 1.5 g soluble starch, 1000 mL beef extract). A stock solution of each synthesized compound (500 µg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. Different concentrations of the test compounds in DMF were placed separately in cups in the agar medium. All plates were incubated at 37 ºC overnight. The inhibition zones were

measured after 24 h. The minimum inhibitory concentration (MIC) was defined as the intercept of the grave of logarithm concentrations versus diameter of the inhibition zones (Janssen *et al.*, 1987; Greenwood, 2000).

3. Results and Discussion

Chemistry

The starting acid hydrazide **1** was synthesized following the reported procedure (Palaska *et al.*, 2002) by refluxing its corresponding ethyl ester and hydrazine hydrate in ethanol. When the hydrazide **1** was reacted with carbon disulphide in alkaline medium it afforded 5-[(5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (**2**) in 80% yield. The ^{1}H NMR spectrum **2** showed a signal corresponding to the CH_2 group as a siglet at δ 5.58 ppm, H-2 and H-4 signals as singlets at δ 7.98 and 8.48 ppm in ddition to the NH signal at δ 14.2 ppm. Alkylation of the 1,3,4-oxadiazole thione **2** with methyl or ethyl iodide in alkaline medium afforded the corresponding *S*-methyl or *S*-ethyl derivatives **3a, b** in 78% and 80% yields respectively. Hydrazinolysis of **3a** and **3b** gave 2-hydrazinyl-5-[(5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazole (**4**) in 84% yield. The ^{1}H NMR spectra of **3a, b** showed the signals of the methyl group in **3a** as a singlet and the ethyl group in **3b** as triplet and quartet which disappeared in the ^{1}H NMR spectrum of **4** in which the NH_2 signal appeared at δ 5.80 ppm.

When the hydrazine derivative **4** was allowed to react with D-galactose and D-xylose in an aqueous ethanolic solution and a catalytic amount of acetic acid, the corresponding sugar (*E*)-5-{[(5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazoleacetohydrazone**s** (**5a, b**) were obtained in 75 – 80% yields. The IR spectra of **5a, b** showed the presence of characteristic absorption bands corresponding to the hydroxyl groups in the region 3378 – 3460 cm^{-1}. The ^{1}H NMR spectra showed

the signals of the sugar chain protons at δ 3.39 – 5.45 ppm, the C–1 methine proton as a doublet in the range δ 7.11 – 7.59 ppm in addition to H-2 and H-4 signals as singlets at δ 7.92 and 8.47 ppm.

The reaction of sugar arylhydrazones with acetic anhydride is well known to give either the corresponding per-*O,N*-acetyl derivatives or cyclization derivatives could be afforded (Abdel-Aal *et al.*, 2006; 2008; Somogyi, 1977; 1978). However, reaction of the sugar hydrazones **5a, b** with acetic anhydride in pyridine at room temperature gave the corresponding per-*O*-acetyl derivatives **6a, b** in 77 – 81% yields. Whereas, carrying out the reaction using acetic anhydride only at 100 °C afforded the corresponding sugar substituted [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazol derivatives **7a, b**. The IR spectra of **6a, b** showed characteristic absorption bands at 1740 – 1747 cm^{-1} corresponding to the carbonyl ester groups. The ^1H NMR spectra of **6a, b** showed the signals of the *O*-acetyl-methyl protons as singlets in the range δ 1.88-2.07 ppm, the rest of the sugar chain protons appeared in the range δ 3.94 – 5.49 ppm and the C-1 signal at δ 7.54. On the other hand The IR spectra of **7a, b** showed characteristic absorption bands at 1664 – 1672 cm^{-1} and 1742 – 1745 cm^{-1} corresponding to the carbonyl amide and the carbonyl ester groups, respectively indicating the presence of *N*-acetyl group in addition to the *O*-acetyl groups. The structures of **7a, b** were proved by analytical and spectral data which agreed with the assigned structures. The ^1H NMR spectra of **7a, b** showed the signals of the *O*-acetyl-methyl protons as singlets in the range δ 1.85-2.06 ppm and the *N*-acetyl-methyl protons in the range δ 2.19 – 2.22 ppm. The rest of the sugar chain protons appeared in the range δ 3.94 – 5.70 ppm in addition to H-2 and H-4 signals as singlets at δ 7.95 and 8.48 ppm. The disappearance of the C-1 signal at higher chemical shift (δ 7.54 ppm) and the presence of a doublet signal at δ 5.70 ppm corresponding to H-3 in the triazole ring indicated that cyclization has taken place (Fig. 2).

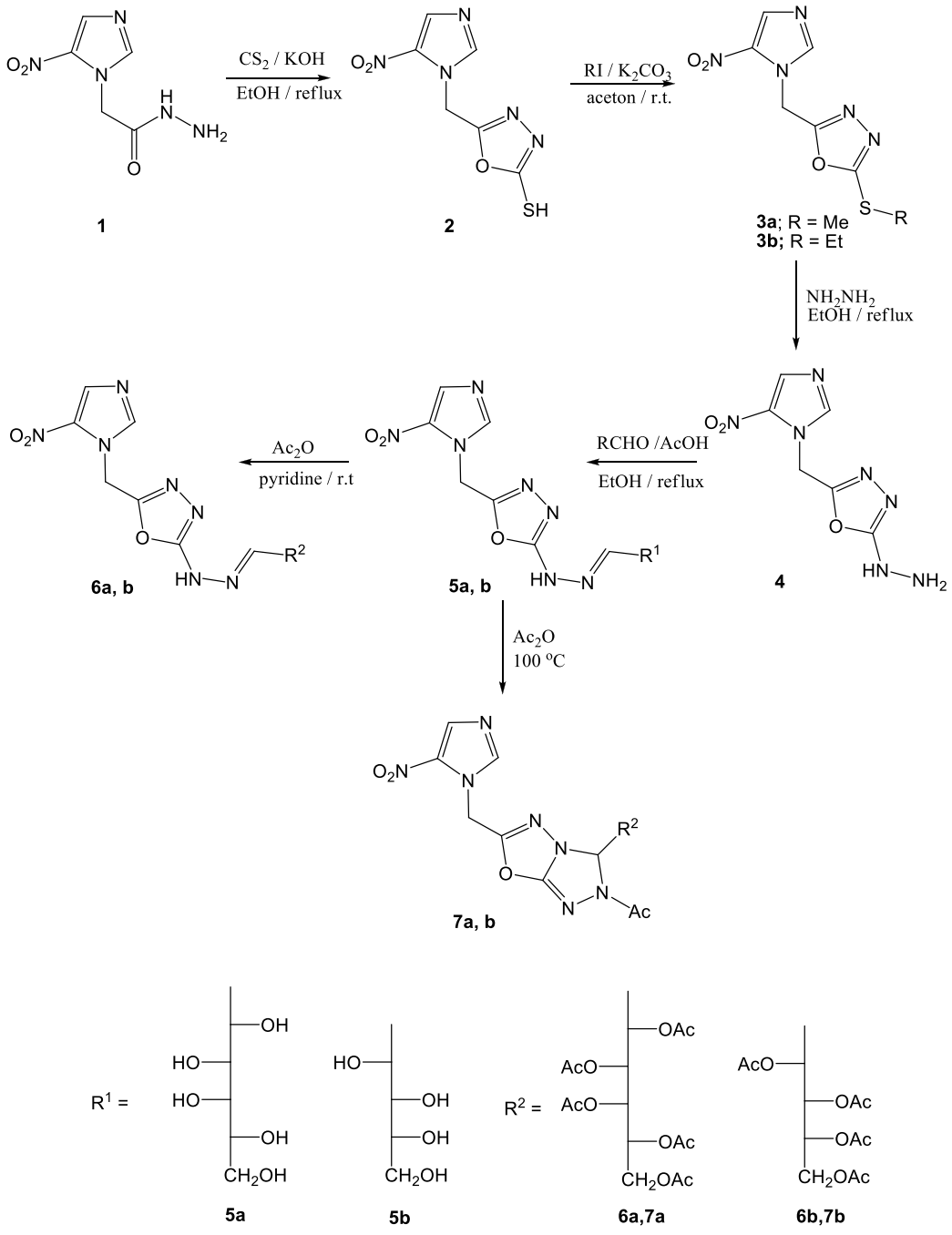


Fig.2. Synthesis of [imidazolyl]methyl[1,3,4]oxadiazole sugar derivatives

When the oxadiazole thione **2** was reacted with acrylonitrile the corresponding *N*-substituted alkyl nitrile derivative **8** was obtained in 75% yield. Its IR spectrum showed a

characteristic peak at 2210 cm^{-1} for the CN group and its ^1H NMR spectrum showed the signal for the two CH_2 groups each as a triplet at δ 3.91 and 4.17 ppm, while the remaining CH_2 as a singlet at δ 5.51 ppm. Treatment of **8** with hydrazine hydrate in ethanol at the reflux temperature afforded 3-{5-[(5-nitro-1*H*-imidazol-1-yl)methyl]-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl}propanimidhydrazide (**9**) in 74% yield. Its structure was proved by means of IR, ^1H NMR and mass spectra which all agreed with the assigned structure. Reaction of **2** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**10**) in acetone at room temperature afforded the thioglycoside derivative **11** in 79% yield. Its ^1H NMR spectrum revealed the presence of the *O*-acetyl-methyl groups at δ 1.84 – 2.05 ppm, the signals of the sugar protons at δ 3.86 – 5.28 ppm and the anomeric proton as a doublet at δ 5.71 ppm with coupling constant 10.2 Hz indicating the β-configuration of the thioglycosidic bond. Deacetylation of **11** by methanolic ammonia solution at room temperature afforded the deprotected thioglycoside **12**. Its IR spectrum showed the characteristic absorption bands at 3477 – 3462 cm^{-1} corresponding to the hydroxyl groups. The ^1H NMR spectrum of **8** revealed the absence of the acetyl-methyl signals and instead signals corresponding to the sugar hydroxyl groups appeared at δ 4.14 – 5.68 ppm. Reaction of **2** with chloroethylmethyl ether or 2-(2-chloroethoxy)ethanol gave the corresponding *S*-substituted derivatives **13** and **14**, respectively. The ^1H NMR spectrum of **14** showed the five CH_2 groups at δ 1.35, 2.49, 3.63, 4.31, and 5.45 ppm in addition to H-2 and H-4 at δ 7.49 and 7.84 (Fig. 3).

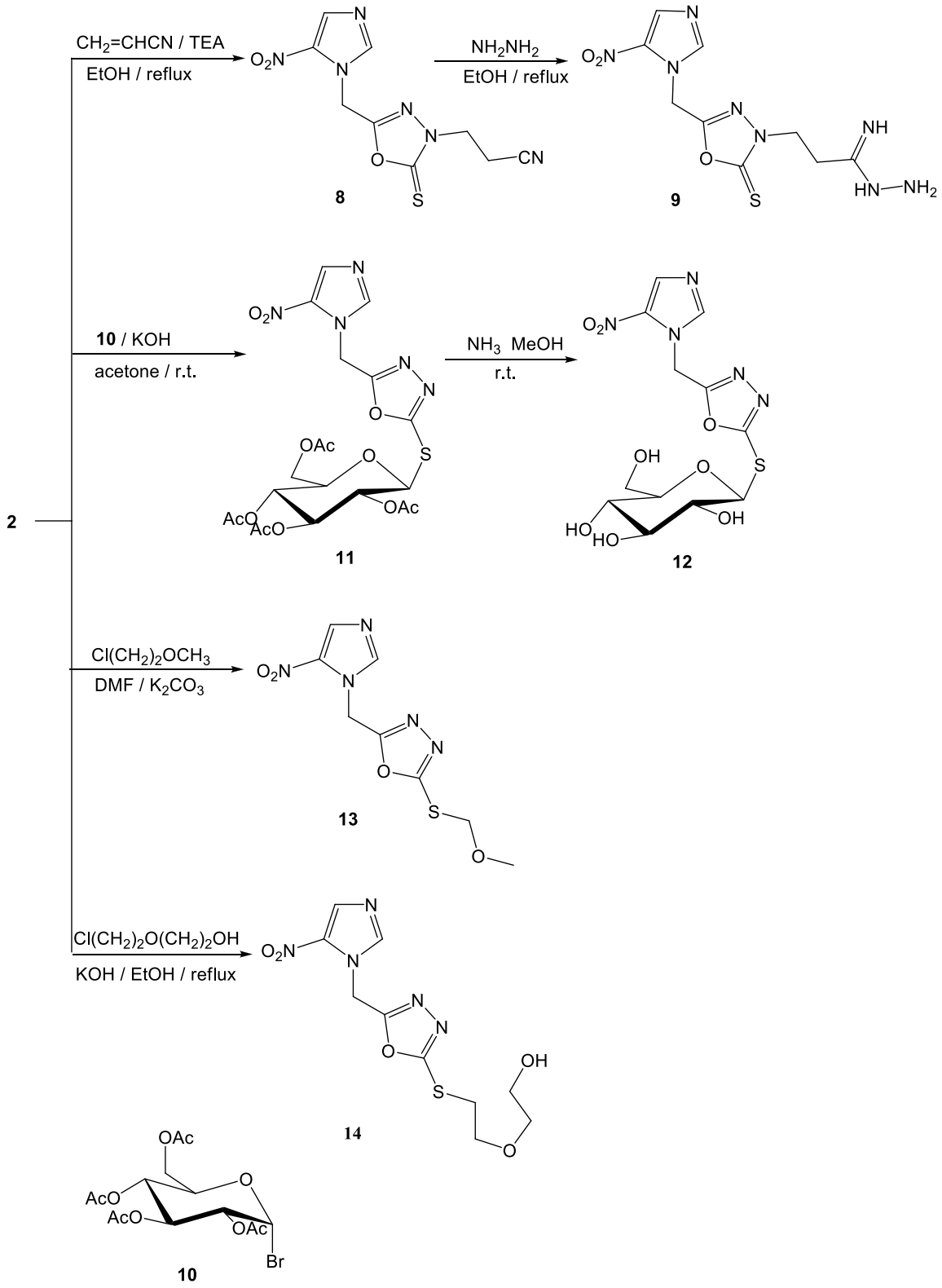


Fig. 3. Snthesis of *N*- and *S*-[imidazolyl]methy[1,3,4]oxadiazole derivatives

When the hydrazine derivative **4** was reacted with carbon disulphide in the presence of KOH, it afforded the [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole derivatives **15**. Its ^{1}H NMR spectrum showed a signal characteristic for CH_2 at δ 5.56 ppm, H-2 and H-4 signals at δ 7.89 and 8.25 ppm in addition to the NH signal at δ 12.88 ppm. Condensation of **6** with 3,4,5-trimethoxybenzaldehyde, *p*-chlorobenzaldehyde or *p*-bromobenzaldehyde afforded the corresponding arylidinehydrazinyl derivatives **16a-c** in 78 – 82% yields. The ^{1}H NMR spectra showed signals corresponding to the CH_2, H-2, H-4 and the aromatic protons. In addition, the mass spectra of **16a-c** revealed the presence of the characteristic signals corresponding to their molecular formulas (Fig. 4).

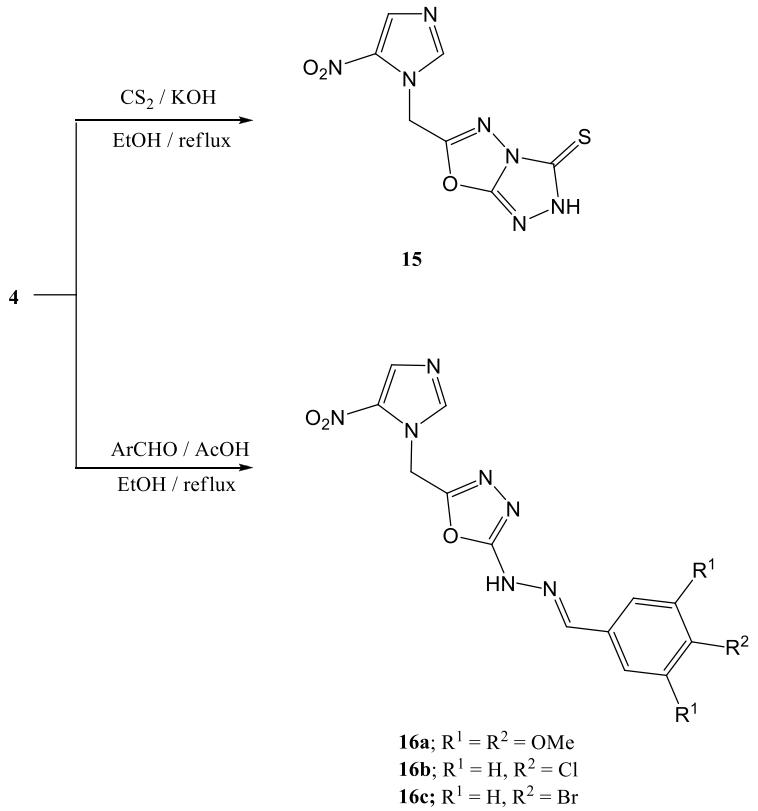


Fig. 4. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole and arylidinehydrazinyl derivatives

Antimicrobial activity

The antimicrobial activity of the synthesized compounds was evaluated against three microorganisms; *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa* (ATCC 27853) (Gram-negative) and *Streptomyces* species (Actinomycetes). The values of minimal inhibitory concentrations (MICs) of the tested compounds are presented in Table I. The results of the antimicrobial activity test revealed that **2**, **5b**, **9** and **15** showed the highest activity against *B. subtilis* with MIC values of 75 µg/mL followed by compounds **7b**, **12, 13** and **16b**. Compounds **2**, **14** and **16b** showed the highest inhibition activity against *P′ aeruginosa*, whereas **7b, 14** and **15** were the most active among the series of tested compounds against *Streptomyces species* with MIC values of 75 µg/mL. The results also revealed that some compounds showed little or no activity against the microorganisms (Table I).

Structure-activity relationship indicated that [(nitroimidazol-1-yl)methyl]-1,3,4-oxadiazole moiety with a free thiol-thione group showed the highest activity against both *B. subtilis* and *Streptomyces* species. The imidrazone derivative **9** revealed higher activity than the corresponding hydrazine analogue. Furthermore, the sugar hydrazones with free hydroxyl groups showed higher activity than the corresponding acetylated analogous. Moreover, the bicyclic analogous **7b** and **15** showed higher activity against *Streptomyces* species and *B. subtilis*. It is also clear that the sugar hydrazone carrying five carbon sugar moiety showed higher activity against *Streptomyces* species and *B. subtilis* than the corresponding hexose sugar. In addition, the *S*-substituted acyclic nucleoside analogue **14** exhibited higher activity against *Pseudomonas aeruginosa* and *Streptomyces* species.

Table I. Minimum inhibitory concentrations (MIC in µg/mL) of the title compounds. The negative control DMSO showed no activity

Compound	Gram-positive	Gram-negative	Actinomycetes
	Bacillus subtilis	*Pseudomonas aeruginosa*	*Streptomyces* specie
2	75	75	125
3a	250	-[a]	500
3b	125	100	100
4	125	500	-
5a	250	100	125
5b	75	125	100
6a	-	250	125
6b	500	500	100
7a	125	100	250
7b	100	-	75
8	-	250	-
9	75	100	125
11	250	500	100
12	100	125	125
13	100	125	-
14	125	75	75
15	75	100	75
16a	250	-	500
16b	100	75	125
16c	125	100	125
Penicillin	31	46	33

[a] Totally inactive (MIC > 500 µg/mL).

4. Conclusion

New [(nitroimidazol-1-yl)methyl]-1,3,4-oxadiazole, their sugar hydrazones and *N*- and *S*-substitued derivatives were synthesized and some of them showed moderate to high antimicrobial activity against *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Streptomyces* species (Actinomycetes). The bicyclic analogoues, sugar hydrazones with free hydroxyl pentose sugar and imidrazone derivatives showed higher activities. Substitution of the thiol with acyclic oxegenated hydroxyl alkyl chain enhances the antimicrobial activity.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

All data supporting this work are original and is included within the manuscript. The corresponding author is responsible for supplying any additional data.

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