seco-acyclo-N- AND *-S-* NUCLEOSIDE ANALOGUES FROM CINNAMIC ACID: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY

Mostafa Rahmouni[a,b] and Adil A. Othman[a]*

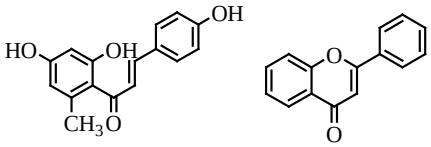
Keywords: 1,3,4-Oxadiazole-5-thione; 1,2,4-triazole-5-thiol; 1,2,4-4*H* aminotriazole-5-thiol; cinnamic acid; synthesis; antibacterial activity, nucleoside analogues

Three seco-acyclo-*N*- and -*S*- nucleosides analogues, namely 2-phenyl-1,3-dioxan-5-yl 5-[(*E*)-2-phenylethenyl]-1,3,4-oxadiazole-2-sulfenate, 4-[(2-phenyl-1,3-dioxan-5-yl)amino]-5-[(*E*)-2-phenylethenyl]-4*H*-1,2,4-triazole-3-thiol and 2-[(2-phenyl-1,3-dioxan-5-yl)sulfanyl]-5-[(*E*)-2-phenylethenyl]-1,3,4-thiadiazole have been synthesized from cinnamic acid via a common synthetic pathway. Treatment of (2*E*)-3-phenylprop-2-enehydrazide with CS_2 under different conditions led to oxadiazole and thiadiazole derivatives on oxadiazole on treatment with hydrazine hydrate gave N-aminotriazole derivative. These diazolethiols gave the nucleoside analogues when treatment with freshly prepared 2-phenyl-1,3-dioxan-5-yl 4-methylbenzenesulfonate. All reaction intermediates and final products where characterized by IR, ^{1}H- and ^{13}C NMR spectroscopy**.** The antibacterial activities assessed against Gram-positive bacteria, *Staphylococcus aureus*, *Bacillus* c*ereus*, and Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*. Some of the synthetic compounds showed promising activity against microorganisms under test in comparison to commercially available antibiotics Gentamycin.

* Corresponding Authors
Fax:
E-Mail: adelaliothman@gmail.com
[a] Laboratoire de Synthèse Organique Bioactive, Département de Chimie Organique Industrielle, Faculté de Chimie, Université des Sciences et de la Technologie d'Oran, Mohamed Boudiaf-USTO-MB, BP. 1505, El-M'naouer, 31003 Oran, Algérie.
[b] Laboratoire des Ressources Naturelles Saharienne, Département des Hydrocarbures et des Énergies Renouvelables, Faculté des sciences et de la Technologie, Université Ahmed Draia, Adrar, Algeria.

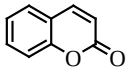
INTRODUCTION

Cis- and trans-cinnamic acid moiety is present in some important phenylpropanoid natural products such as lignins, naringenine chalcone (**A**), flavone (**B**) and coumarine (**C**).[1]



A

B



C

Figure 1. Chemical structures of some phenylpropanoids (cinnamic acid) natural products.

Cinnamic acid derivatives have been utilized in a wide range of biological activities such as anticancer,[2,3] antioxidant,[3,4] anti-inflammatory,[5] antibacterial,[1,4,6] antifungal,[7-9] antiviral,[10] dietary[11] and as a fragrance ingredient in many fragrance formulations.[12]

Cinnamic acid has the tendency to form metallic complexes[13] and various derivatives concerning their phenyl group and side chain moieties, those have shown pharmaceutical activity.[14] The natural piperidine derivative of cinnamic acid showed anticonvulsive effect.[15]

To our knowledge, there are only few cases where carboxylic group have been modified to heterocycles. The synthesis of N-(3-aryl-1,2,4-triazo-5-yl)cinnamide derivative and 2-[(*E*)-2-phenyethenyl]-4,5-dihydro-1,3-oxazole derivatives have been reported.[16,17] In this work we report first, the conversion of some modified cinnamic acid to 1,3,4-oxadiazolethiol, 1,3,4-thiadiazolethiol and N-amino-1,2,4-triazolethiol derivatives. The second stage of work concerns with the synthesis of sugar analogue molecule followed by the third stage to form seco-acyclo nucleoside analogues. All the compounds including starting material, intermediates and final nucleoside analogues were tested for biological activity.

EXPERIMENTAL

All reactions were monitored by TLC analysis (silica gel for TLC supplied by MERCK), iodine was used for visualization. The melting points were measured with a BÜCHI 540 melting point apparatus and are uncorrected. The IR spectra (ν cm^{-1}) were recorded using KBr discs in a JASCO V-530 spectrophotometer and a Bruker-Alpha (Platinium-ATR). The ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AC 300 MHz spectrometer in DMSO-d_6 and expressed as δ (ppm) with reference to TMS.

Microorganisms in this study were supplied by the University Hospital of Oran and identified in our laboratory. The Mueller Hinton medium was supplied by Difco.

Syntheses

Methyl cinnamate (2)

The cinnamic acid **1** (1g, 6.75 mmol) and methanol (30 mL) in presence of concentrated sulfuric acid (1 mL) were refluxed for 6 h at 80 °C. The excess methanol was distilled out and the contents were cooled to a room temperature. The reaction mixture was diluted with 50 mL water and extracted by dichloromethane. The product was isolated in 90 % yield, m.p. 37 °C. The compound **2** was characterized by IR spectrum which showed absorption at 1717.3, 1278.57 and 1574.59 cm^{-1} for (C=O), (C-O) and (C=C) respectively.

(2E)-3-phenylprop-2-ene hydrazide(3)

The methyl cinnamate **2** (1 g, 6.17 mol) is dissolved in 30 mL methanol and hydrazine hydrate 99 % (5 mL) was added to it. The solution was refluxed for 10 h. After evaporating the solvent under reduced pressure, a solid appeared. This was recrystallized form ethanol to afford compound **3**. The product was isolated in 65 % yield, m.p. 98 °C. Its IR spectrum exhibited bands at 3293.82 and 3229.62 cm^{-1} for (NH) and (NH_2) respectively.

5-[(*E*)-2-Phenylethenyl]-1,3,4-oxadiazole-2-thione/thiol (4)

A mixture of compound **3 (**4.9 mmol in 20 mL ethanol) and 17.8 mmol of KOH in 10 mL ethanol was agitated continuously for a period of 30 min. To this, carbon disulfide (3 mL) was added dropwise. The mixture was refluxed for 14 h. The reaction mixture was then acidified with HCl (37 %) to pH 5 to give a yellow precipitate, which was filtered off, washed with ethyl acetate and recrystallized from ethanol. The product was isolated in 57 % yield, m.p. 158 °C. The IR spectrum showed the characteristic bands at 3423.03, 1622.8, 1051.98 and 1402.63 1687.41 cm^{-1} for (NH), (C=N), (C-O-C) and (C=S) respectively. ^{1}H NMR δ = 4.26, 4.97 (s, 2H, HC=CH), 7.45(s, 1H, NH), 8.46, 8.48, 8.52, 8.54, 8.56 (m, 5H, H_{arom}). ^{13}C NMR, δ = 111.4, 164.5 (C=C), 129.1, 129.2, 129.3, 129.5, 129.7, 140 (C_{arom}), 165.7 (N=CO), 179.6 (NC_2=S).

4-Amino-5-[(*E*)-2-phenylethenyl]-4*H*-1,2,4-triazole-3-thiol (5)

To a solution of 3.9 mmol of compound **4** in 20 mL of ethanol, 4 mL of hydrazine hydrate 99 % was added and the reaction mixture was refluxed for 14 h. After cooling, the mixture was filtered and washed by ethyl acetate. The product was isolated in 74 % yield, m.p. 215 °C. The IR spectrum showed absorption at 1637.27, 3242.72 and 3143.4 cm^{-1} for (C=N), (NH_2) and (NH) respectively. ^{1}H NMR δ = 2.98 (s, 2H, NH2), 5.16, 5.32 (s, 2H, HC=CH), 6.83, 6.84, 6.85, 6.87 (m, 5H, H_{arom}), 13.04(s, H, SH). ^{13}C NMR δ = 128.10, 128.31, 128.34, 140.3, (6C_{arom}), 126.16, 125.75 (2C, C=C), 151.4 (C1, N=CN), 165.8 (N=CSH).

5-[(*E*)-2-Phenylethenyl]-1,3,4-thiadiazole-2(3*H*)-thione/thiol (6)

KOH (5.8 mmol) was dissolved in ethanol (5 mL) and carbon disulfide (1.5 mL) was added drop-wise with stirring at 0 °C during 40 min. To this, 3 mmol of compound **3** in 20 mL of ethanol was added. After that, the mixture was refluxed for 10 h. After cooling the reaction mixture was acidified with H_2SO_4 to pH 2 to give a brown precipitate, which was filtered off, washed with ethyl acetate and recrystallized from ethanol. Yield 70 %. The IR spectrum showed the characteristic bands at 1620.88 and 649.89 cm-1 for (C=N) and (C-S-C). ^{1}H NMR δ = 5.91, 5.93 (s, 2H, C=C), 6.51, 6.54, 6.58, 6.73, 6.77 (m, 5H, H_{arom}), 13.66 (s, H, SH). ^{13}C NMR δ = 126.62, 1267.71 (2C, C=C), 128.51, 128.64, 128.76, 128.85, 129.09, 139.66 (6C_{arom}), 163.72 (N=CS), 177.9 (C-SH).

2-Phenyl-1,3-dioxan-5-ol (9)

A mixture of solution of glycerol (97 mmol) in chloroform (15 mL) and a solution of benzaldehyde (2 mol) in chloroform (10 mL) in presence of *p*-toluenesulfonic acid was refluxed for 6 h with magnetic stirring at 50-60 °C. After cooling to room temperature the product was extracted with dichloromethane and washed with $NaHCO_3$, then dried over $MgSO_4$ and filtered. Yield 50 %. The IR spectrum showed the characteristic bands at 3311.18, 2977.55 and 1600 cm^{-1} for (OH), ($CH_{aromatic}$) and (C =C) respectively.

2-Phenyl-1,3-dioxan-5-yl 4-methylbenzenesulfonate (10)

The compound **9** (22 mmol) was added to tosyl chloride (18 mmol) in the presence of pyridine. The mixture was refluxed for 6 h with magnetic stirring at 80 °C. After cooling to room temperature the product was extracted with dichloromethane and washed with $NaHCO_3$, then dried over $MgSO_4$ and filtered. Yield 60 %. The IR spectrum showed absorption at 1654.96 and 1080.62 cm^{-1} for (C=C) and (C-O-C).

Seco-acyclo glycosides and nucleosides

Treatment of compounds **4, 5, 6** with the equivalent amount of compound **10** in DMF (4 mL), in presence of dimethylamine (DEA) (2 mL), under reflux for 48 h and extraction with dichloromethane led to the formation of the desired compounds **11, 12** and **13.**

2-Phenyl-1,3-dioxan-5-yl-5-[(*E*)-2-phenylethenyl]-1,3,4-oxadiazole-2-sulfenate (11)

Yield 35 %. IR (KBr**):** 1656.27 (C=N, Ph), 1062.47 (C-S-C) cm^{-1}. ^{1}H NMR δ = 1.14 (m, H, H-CS), 2.43, 2.7, 3.04, 3.23 (d, 4H, 2CH_2), 3.83(s, H, H-CO_2), 6.44-6.49 (m, 2H, HC=CH), 7.29-8.19 (m, 10H, H_{arom}). ^{13}C NMR δ = 37(C, H-C-S), 41.99 (2C, CH_2), 101(C, Ph-C-H), 125.8-126.1 (2C, C=C); 127-142 (10C, $C_{aromatic}$),165(C, N=C-S), 170(C, N=C-C).

4-[(2-Phenyl-1,3-dioxan-5-yl)amino]-5-[(*E*)-2-phenylethenyl]-4*H*-1,2,4-triazole-3-thiol (12)

Yield 35 %. IR (KBr): 1656,27 (C=N, Ph) cm^{-1}. ^{1}H NMR δ = 2.18 (m, H, H-CNH), 2.86, 2.96 (d, 4H, 2CH_2), 3.4 (s, H, H-CO_2), 3.92 (s, H, H-NC), 5.55, 8.3 (d, 2H, HC=CH), 7.35-7.98 (m, 10H, H_{arom}), 10.55 (s, H, NH). ^{13}C NMR δ = 36.6(C, H-C-NH), 49,9 (2C, CH_2), 101(C, Ph-C-H), 127-

134.4 (10C,$C_{aromatic}$), 126.1, 143.9(2C, C=C); 162.9 (C, N=C-C), 173.7(C, N-C=S).

2-[(2-Phenyl-1,3-dioxan-5-yl)sulfanyl]-5-[(*E*)-2-phenylethenyl]-1,3,4-thiadiazole (13)

Yield 40 %. IR (KBr): 1631.19 (C=N, Ph), 1096.68 (C-S-C) cm^{-1}. ^{1}H NMR δ = 1.21 (m, H, H-CS); 2.93-3.48 (d, 4H, $2CH_2$), 4.40, 4.42 (m, 2H, HC=CH), 5.30 (s, H, H-CO_2), 7.20-8.05 (m, 10H, H_{arom}). ^{13}C NMR δ = 38.2 (C, H-C-S), 43.3-45.5 (2C, CH_2), 106 (C, Ph-C-H); 126.1, 129 (2C, C=C), 126.4-141.4 (10C, $C_{aromatic}$), 155.8(C, N=C-S), 172.3 (C, S-C-S).

Antibacterial evaluation

Antibacterial activity was determined by diffusion method on two strains of bacteria. The tests were carried out on Gram negative bacteria *Escherichia coli (*ATCC- 25924) and *Pseudomonas aeruginosa (*ATCC-27853), and Gram positive bacteria *Staphylococcus aureus (*ATCC-25923) sensitive and *Staphyloccocus aureus* resistant strains.

Table 1. Antibacterial activity of compounds **1-6** and **11-13**.

Comp-ounds	Gram positive, inhibition										GramnNegative, inhibition zone									
	S. aureus					*B. cereus*					*E. coli*					*P. aeruginosa*				
	a	**b**	**c**	**d**	**e**	**a**	**b**	**c**	**d**	**e**	**a**	**b**	**c**	**d**	**e**	**a**	**b**	**c**	**d**	**e**
1	8	7	0	-	-	10	5	0	-	-	0	-	-	-	-	0	-	-	-	-
2	10	7	6	0	-	8	7	6	0	-	0	-	-	-	-	0	-	-	-	-
3	12	7	0	-	-	14	10	0	-	-	0	-	-	-	-	8	0	-	-	-
4	0	-	-	-	-	9	8	0	-	-	0	-	-	-	-	0	-	-	-	-
5	0	-	-	-	-	12	10	8	0	-	0	-	-	-	-	19	7	0	-	-
6	8	7	0	-	-	16	14	13	10	8	0	-	-	-	-	14	7	0	-	-
11	16	12	8	0	-	0	-	-	-	-	0	-	-	-	-	0	-	-	-	-
12	18	7	0	-	-	8	0	-	-	-	0	-	-	-	-	0	-	-	-	-
13	0	-	-	-	-	7	5	0	-	-	0	-	-	-	-	0	-	-	-	-
†	24	-	-	-	-	20	-	-	-	-	20	-	-	-	-	19	-	-	-	-
DMSO	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

a, b, c, d, e: concentrations:(10, 10/2, 10/4, 10/8, 10/16) mg mL^{-1}, respectively; † Gentamycine; Key to the inhibition zones activities: Highly active = Inhibition zone > 15 mm, Moderately active = Inhibition zone 15-10 mm, Slightly active = Inhibition zone 9-6 mm, Inactive = Inhibition zone < 6 mm., O = not active, - = not tested.

The synthesized compounds were dissolved in DMSO to obtain a concentration of 30 mg mL^{-1}. A standard inoculum (10^5-10^7 c.f.u. mL^{-1}, 0.5 McFarland standards) was introduced on to the surface of sterile agar plates and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 5 mm in diameter were prepared and sterilized by dry heat at 140°C for 1 h. The sterile discs previously soaked in known concentrations of the test compounds were placed in Mueller Hinton agar medium. The inhibition zones were measured in mm at the end of an incubation period of 24 h at 37 °C and compared with the positive control (Gentamycin) and negative control DMSO, (Table 1). Compounds that showed good antibacterial activity tested by the diffusion method were further tested by dilution, when different concentrations of the tested compounds were prepared (15, 7.50, 3.75 and 1.80 mg mL^{-1} from 30 mg mL^{-1} in DMSO). After the incubation for 24 h, the last plate with no growth of microorganisms was taken to represent minimum inhibitory concentration (MIC) expressed in mg mL^{-1}. (Table 1).

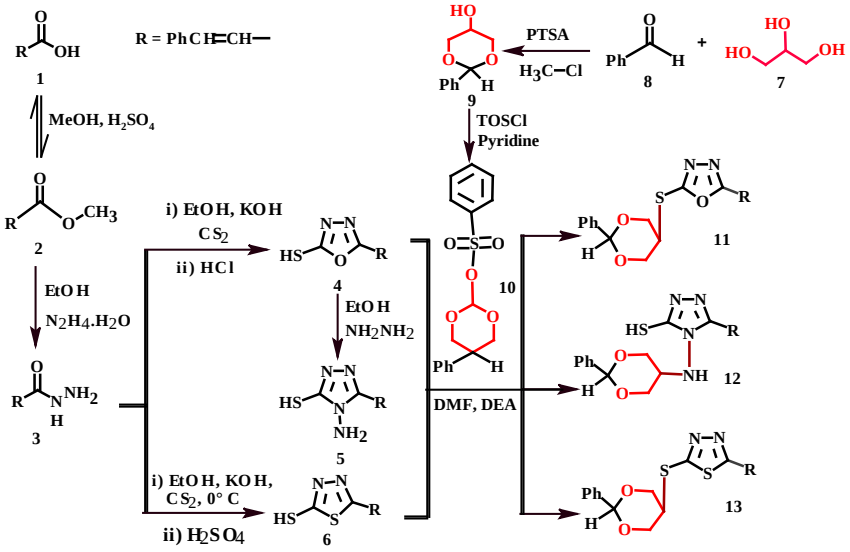
RESULTS AND DISCUSSION

Synthesis of diazole thiols **4-6,** and seco-acyclo N- and S-nucleosides analogues **11-13**, from cinnamic acid has been accompalished by a common synthetic pathway as described in Scheme 1 divided into three stages. All steps were monitored by TLC and products characterized were spectrally by IR, ^{1}H- and ^{13}C-NMR.

The key intermediate hydrazide **3** was obtained by classical procedures.[18,19] When **3** was refluxed with alcoholic solution of KOH and CS_2 for 14 h and finally treated by HCl, it gave the oxadiazole **4,** which on treatment with hydrazine hydrate yielded the N-amino triazole **5**.[20] On the other hand, when **3** was refluxed with alcoholic solution of KOH and CS_2 for 10 h and finally acidified by H_2SO_4 thiadiazole **6** was obtained.[21]

Synthesis of 2-phenyl-1,3-dioxan-5-yl 4-methylbenzenesulfonate **(10)**: Glycerol as a mimic for acyclic sugar molecule may be selectively protected to leave the desired OH group for further reactions. Glycerol was reacted with bezaldehyde to give a moderate yield of 2-phenyl-1,3-dioxan-5-ol **(9)**.[21] Treating **9** with *p*-toluene sulphonyl chloride yielded p-toluenesulphonate **10**. IR spectrum showed a reduction of OH absorption with the appearance of S=O absorption at 1373 cm^{-1}.

Synthesis of seco-acyclo glycosides **11, 12, 13**: Refluxing compounds **4, 5, 6** with an equivalent amount of **10** in DMF, in presence of dimethylamine, for 48 h led to the formation of the desired compounds **11, 12** and **13.**[21]



Scheme 1 : Summary of synthesis; *stage 1(left)* : synthesis of **4,5,6** ; *stage 2(middle)* : synthesis of tosylate **10** and *stage 3(right)* : synthesis of seco-acyclo glycosides **11, 12, 13**.

Antibacterial activity

Starting compound cinnamic acid **1**, synthetic intermediates **2-6** and final compounds **11-13** were assayed in vitro using the paper disk diffusion method for their antibacterial activities against Gram-positive bacteria, *S. aureus*, and *B. cereus*, and Gram-negative bacteria, *E. coli* and *P. aeruginosa*. In primary screening a concentration of 10 μg. mL^{-1} was maintained. Only compounds found active in this primary screening were further tested in a second set of concentration 5 μg mL^{-1} and lower against susceptible microorganisms as shown in Table 1.

Data in Table 1 showed that compounds under consideration (**1-6** and **11-13**) exhibited their effect mostly against Gram-positive bacteria *S. aureus*, *B. cereus*, and to less extent against Gram-negative *P. aeruginosa*, but non against *E. coli*. Gram-positive *S. aureus* is affected by compounds **1, 2, 3, 6, 11, 12** and **13**. The significant effect was exerted by seco-acyclo oxadiazole **11** and seco-acyclo amino triazole **12** and to less extent by **2** and **3**, whereas *B. cereus* was mostly affected by **6** and to a less extent by **1, 3** and **5.** Gram negative *E. coli* was affected by none of the compounds under consideration**.** *P. aeruginosa* was highly affected by heterocyclic clycon amino triazole **5** and to a lesser extent by **6**.

CONCLUSION

The three nucleobases: 5-[(*E*)-2-phenylethenyl]-1,3,4-oxadiazole-2-thione/thiol (**4**), 4-amino-5-[(*E*)-2-phenylethenyl]-4H-1,2,4-triazole-3-thiol (**5**) and 5-[(*E*)-2-phenylethenyl]-1,3,4-thiadiazole-2(3H)-thione/thiol (**6**) were successfully prepared from cinnamic acid and structures were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The seco-acyclo nucleoside analogues **11**, **12** and **13** were synthesized by two steps. First step concerned with the synthesis of 2-phenyl-1,3-dioxan-5-yl-4-methylbenzene-sulfonate **(10).** The second step including treatment of the latter with the nucleobases **4**, **5** and **6**. The substitution reactions were monitored by TLC and structure of the products were determined spectrally.

Biological evaluation between nucleobases **4**, **5** and **6** themselves and with their corresponding seco-acyclo nucleoside analogues revealed the following:

The 1,3,4-oxadiazole **4** exerted less biological effect upon both G(+) and G(-) bacteria under consideration. When 4-amino-1,2,4-triazole showed more antibacterial effect upon G(+) *b.cereus* and G(-) *p. aeruginosa***.** While the thiadiazole **6** showed a wider spectrum effect upon G(+) *S. aureus*, *B. cereus* and G(-) *P. aeruginosa.*

The nucleobases **4**, **5** and **6**, generally showed an more appreciable effect than their corresponding nucleosides analogues **11**, **12** and **13** did. Relatively, nucleosides **11** and **12** showed better biological effect than **13** as shown on G(+) *S. aureus* while **13** showed no antibacterial effect upon all bacteria under consideration.

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