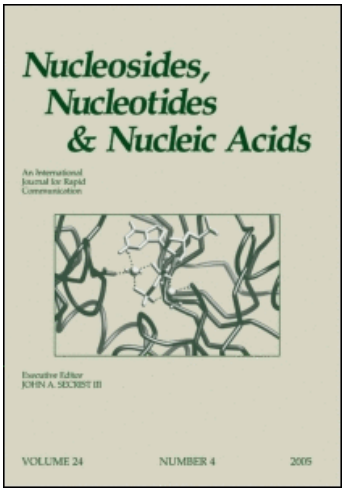

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SYNTHESIS OF 1*H*-INDOLE-2,3-DIONE-3-THIOSEMICARBAZONE RIBONUCLEOSIDES AS ANTIBACTERIAL AGENTS

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□ *A new isatin ribonucleoside (**3**) was synthesized in a good yield by trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed coupling reaction between the silylated nitrogenated base of* 1H*-Indole-2,3-dione (**1**) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribfuranose (**2**). Thiosemicarbazides **4a–e** were utilized by the prepared ribonucleoside (**3**) to give new series of* 1H*-indole-2,3-dione-3-thiosemicarbazone ribonucleosides **5a–e**. All compounds tested as antibacterial agents showed slight inhibitory activity against the selected bacterial strains.*

Keywords Ribonucleosides; thiosemicarbazone ribonucleosides; antibacterial agents

INTRODUCTION

1*H*-Indole-2,3-dione (isatin) is an endogenous compound identified in humans and its effect has been studied in a variety of systems.[1] Biological properties of 1*H*-indole-2,3-dione include a range of actions in the brain and offer protection against certain types of infections.[1] Investigation of the structure-activity relationships in 1*H*-indole-2,3-dione derivatives revealed that *N*-alkylation,[1,2] *N*-Mannich base,[3,4] and 3-thiosemicarbazone formation[4–6] resulted in broad-spectrum chemotherapeutic properties such as antiviral,[5–7] anti-tuberculosis,[3] antifungal, and antibacterial activities.[4] Thus, it will be of interest to investigate the chemotherapeutic activity of unstudied series of new

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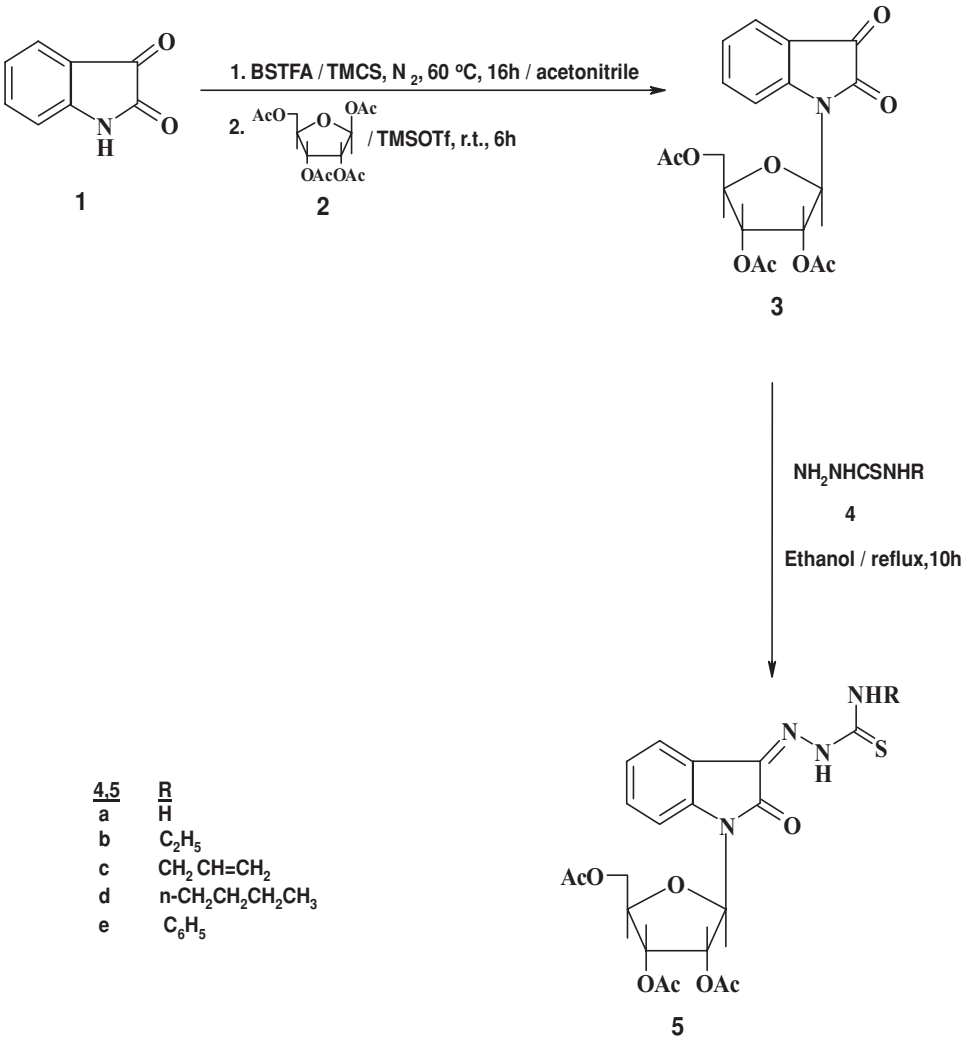
1*H*-indole-2,3-dione-3-thiosemicarbazone ribonucleosides that carry synthetic hybridization of two privileged drug scaffolds,[8,9] that is, those molecular frameworks that have spawned a significant number of drugs and other biologically active agents and can be used to discover molecular master keys.[10] The first is a nucleoside scaffold that has yielded many valuable therapeutic compounds for microbial infections.[11–13] The second scaffold is 1*H*-indole-2,3-dione-3-thiosemicarbazone, which is the basis of various antiviral, antibacterial, and antifungal agents. This is coupled with reporting that 1*H*-indole-2,3-dione-3-thiosemicarbazone derivatives possess significant antibacterial activity against Gram positive and Gram negative bacteria.[4] Because of all the above findings, the antibacterial activity of the target compounds will be tested against *Bacilius subtilis* (Gram positive), *Staphylococcus aureus* (Gram positive), *Pseudomonas aeruginosa* (Gram negative), and *Escherichia coli* (Gram negative) bacterial strains. The reaction sequence for the preparation of new compounds is outlined in Scheme 1.

RESULTS AND DISCUSSION

The method chosen for the synthesis of isatin ribonucleoside **3** was the coupling between a previously silylated nitrogenated base and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2**) using Lewis acid catalysis.[14,15] Heating **1** with bis(trimethylsilyl)trifluoroacetamide (BSTFA)[16] containing 1% trimethylchlorosilane (TMCS), at 60°C, under nitrogen atmosphere for 16 hours, followed by reaction with **2**, in the presence of TMSOTf as catalyst, at room temperature for 6 hours, to give isatin ribonucleoside in 56% total yield (Scheme 1). Microanalytical data of the coupling product **3** was in agreement with the molecular formula of the compound $C_{19}H_{19}NO_9$. The ^{1}H NMR spectrum of **3** confirmed the successful coupling due to presence of a doublet peak at δ 5.86 ppm for the anomeric proton of ribobfuranosyl ring. The other five protons resonated at δ 4.30–5.73 ppm. The three acetyl groups appeared as three singlets at δ 2.04–2.09 ppm. Infrared (IR) spectrum showed a CO band at 1744.30 cm^{-1} assigned to the acetoxy carbonyl protecting groups. Some publications[17,18] provided spectral evidence for the presence of isatin ribofuranosides glycosidic bond in the β-configuration based on having a negative cotton effect in the circular dichroism spectra that is characteristic for β-D- or α-L-nucleosides. Moreover, the β-configuration of the isatin ribofuranoside glycosidic bond was confirmed by reporting the observation of a nuclear Overhauser effect (NOE) for the H4′ signals while the anomeric proton was being irradiated. Hence, the newly synthesized isatin ribonucleoside glycosidic bond was assigned in β-configuration.[19]

In order to prepare the 1*H*-indole-2,3-dione-3-thiosemicarbazone ribonucleosides (**5a–e**), the proper thiosemicarbazides **4**, namely, N_4-ethyl **4b**,



SCHEME 1

*N*4-allyl **4c**, *N*4-n-butyl **4d**, and *N*4-phenyl **4e** were first obtained from the respective isothiocyanate and hydrazine hydrate as previously described,[1] as well as the commercially available thiosemicarbazide **4a**. Refluxing ethanolic solution of **3** with the appropriate thiosemicarbazides **4** for 10 hours, gave the corresponding thiosemicarbazone ribonucleosides **5a–e** in high yields (Scheme 1) (**5a:** 85%; **5b:** 90%; **5c:** 70%; **5d:** 79%; **5e:** 75%). The structures of thiosemicarbazone ribonucleosides **5a–e** were established and confirmed on the basis of their microanalytical and spectral data (IR, ^{1}H NMR). For the whole series, elemental analysis of thiosemicarbazone derivatives went parallel to the molecular formula for each. ^{1}H NMR spectrum of **5b** confirmed the successful process of condensation for thiosemicarbazone

formation that revealed the presence of triplet peak at δ 9.30 ppm assigned for N_4-H and singlet peak at δ 12.25 ppm assigned to N_2-H, both peaks were exchangeable by D_2O and characteristic for thiosemicarbazone residue; CH_2 of N_4-ethyl substituent resonated as quartet peak at δ 3.65 ppm and CH_3 of N_4-ethyl substituent resonated as triplet peak at δ 1.20 ppm. IR spectrum of **5b** was characterized by NH band at 3335.28 cm^{-1}, CO ester band at 1748.16 cm^{-1}, CO lactam band at 1699.94 cm^{-1}, and CS band at 1158.04 cm^{-1}. The point of attachment of the sugar to the base assigned to the nitrogen atom from the isatin nucleus. This was inferred by the IR spectral data that showed the CO band of acetoxy carbonyl protecting groups of ribofuranose in combination with the CO band of the lactam ring of the isatin nucleus in all thiosemicarbazone ribonucleosides. This was consistent with similar reported spectral data for *N*-alkylated 1*H*-indole-2,3-dione-3-thiosemicarbazone in the literature.[1,20,21] Furthermore, de Oliveira et al.[19] introduced an additional proof for formation of *N*-ribonucleoside of 1*H*-indole-2,3-dione when using the adopted technique for ribosylation process by the aid of spectral evidences.

It is known that the β-thiosemicarbazones of isatin can exist in the form of syn (**A**) and anti (**B**) isomers[18] (Figure 1). The β-thiosemicarbazones of isatin and its *N*-alkyl derivatives that contain a hydrogen atom attached to N_2 atom exist in solution and in the crystalline state primarily in the form of syn isomers, which are stabilized by intramolecular hydrogen bonds. The high values of the chemical shifts of 2-H protons ($\delta > 12$ ppm) and their constancy as the concentration is changed (from 20% to 5%) confirmed that the obtained thiosemicarbazones exist primarily in the form of syn isomers.

Since the nucleosides of isatin contain electron-acceptor groups, they are unstable with respect to the action of acidic and alkaline agents.[18,19] This was attributed to the initial fragmentation of the glycosidic bond which leads to nucleoside decomposition products.[19] Consequently, the new *O*-acetyl protected nucleosides **5a–e** were subjected to antibacterial activity

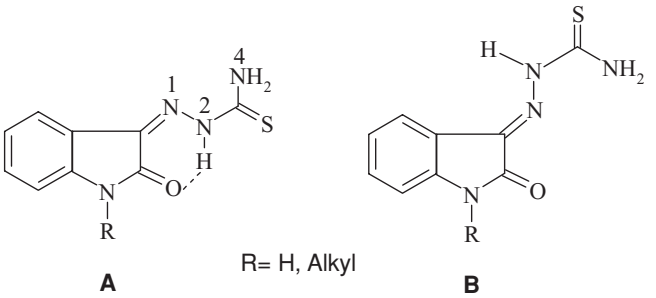


FIGURE 1 syn(**A**) and anti (**B**) isomers of isatin- and *N*-alkylated isatin-β-thiosemicarbazone.

TABLE 1 Antibacterial activity of thiosemicarbazone ribonucleosides **5a–e** compared to streptomycin as standard antibacterial agent

	Inhibition zone diameter (mm)			
Compound	*Bacillus subtilis*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*
5a	12	12	11	11
5b	14	13	12	12
5c	14	14	12	14
5d	13	14	14	13
5e	13	13	12	13
Streptomycin	29	28	32	31

*The sensitivity of the microorganisms toward the tested compounds and streptomycin is identified in the following manner: inhibition zone diameter ≥23 mm (high sensitivity); inhibition zone diameter = 16–22 mm (moderate sensitivity); inhibition zone diameter = 11–15 mm (slight sensitivity).

testing, taking into account the fact that their *O*-deacetylation to give the active metabolite would occur under the influence of bacterial esterases.[22]

All thiosemicarbazone ribonucleosides **5a–e** were evaluated for their antibacterial activity using disc diffusion method against *Bacilius subtilis* (Gram positive), *Staphylococcus aureus* (Gram positive), *Pseudomonas aeruginosa* (Gram negative), and *Escherichia coli* (Gram negative) bacterial strains. The inhibitory activity of the tested compounds against the selected bacterial strains is given in (Table 1). The inhibitory activity of the tested compounds was assessed by measuring the inhibition zones in mm caused by the tested compounds.

All tested ribonucleosides showed slight inhibitory activity against all bacterial strains. The slight inhibitory activity of the tested ribonucleosides may be attributed to the inability of bacterial cell to release the expected active metabolites.

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40°C. All melting points are uncorrected. They were taken in open capillaries on Gallenkamp melting point apparatus. Thin layer chromatography was performed on silica gel GF_{254} (Merck, Darmstadt, Germany) aluminium sheets and glass plates (20 cm × 20 cm). Chromatograms were visualized under ultraviolet (UV) light at 254 nm. Column chromatography was performed on silica gel 60 (Fluka, St. Louis, MO, USA) mesh size 70–230 with the specified column size and solvent system. The infrared (IR) spectra were recorded (KBr disk) on Shimadzu 820 PC FTIR Instrument (Shimadzu Corp. Kyoto, Japan). ^{1}H NMR were recorded at 300MHz with a Vairan Mercury 300 spectrometer (Varian, Palo Alto, CA, USA) for solution in

$(CD_3)_2SO$ with $SiMe_4$ as internal standard. *J* Values were given in Hz. Analytical data were obtained from the Microanalytical Data Center at Cairo University (Cairo, Egypt).

1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione (3)

Procedure

A mixture of isatin **1** (0.29 g, 2 mmol) and BSTFA (2 mL, 7.46 mmol) containing 1% TMCS, in anhydrous acetonitrile (4 mL) was stirred at 60°C, under nitrogen atmosphere for 16 hours. The reaction mixture was allowed to cool to room temperature and a solution of 1,2,3,5-tri-*O*-acetyl-β-D-ribofuranose (0.66 g, 2.1 mmol) in anhydrous acetonitrile (15 mL) was added. This was followed by the dropwise addition of a solution of TMSOTf (0.4 mL, 2.1 mmol) in anhydrous acetonitrile (10 mL). After stirring for 6 hours, the resulting mixture was poured into ice-cold water (20 g). Then, it was neutralized with a saturated solution of sodium bicarbonate and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography using chloroform:ether 9.5:0.5 as eluent, to give the title compound in a pure form.

3: 1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione. Yellow crystals; m.p.: 101–103°C; yield: (56%). IR: ν_{max}/cm^{-1} (KBr) 1744.30 (CO). ^1H NMR(DMSO-d_6, δ = ppm): 2.04–2.09(3s, 9H, 3 × CH_3CO); 4.30(m, 3H, 5′-H, 5″-H, 4′-H); 5.47(t, $J_{3',2'}$ = 6.0 Hz, 1H, 3′-H); 5.73(t, $J_{2',1'}$ = 5.1 Hz, 1H, 2′-H); 5.86(d, $J_{1',2'}$ = 5.4 Hz, 1H, 1′-H); 7.23(t, J = 8.1 Hz, 1H, 5-H); 7.40(d, J = 8.1 Hz 1H, 4-H); 7.62(d, J = 7.5 Hz, 1H, 7-H); 7.68(t, J = 7.8 Hz, 1H, 6-H). Anal. Calcd for $C_{19}H_{19}NO_9$ (405.35): C, 56.30; H, 4.72; N, 3.46. Found: C, 56.55; H, 4.96; N, 3.67.

1*H*-Indole-2,3-dione-3-thiosemicarbazone ribonucleosides 5a-e

General Procedure

A hot solution of the respective thiosemicarbazides **4** (1 mmol) in water (0.5 mL) was added to a solution of **3** (1 mmol) in ethanol (10 mL), and the mixture was heated on boiling water bath for 10 hours. The solvent was evaporated under reduced pressure. The resulting crude residue was purified by preparative thin layer chromatography (TLC) using chloroform:ether 9.5:0.5 as eluent except for **5a** was precipitated upon standing and recrystallized from ethanol to afford the following thiosemicarbazones:

5a: 1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione-3-Thiosemicarbazone. Yellow crystals; m.p.: 210–212°C; yield: (85%). IR: ν_{max}/cm^{-1} (KBr) 3397.96, 3281.29 (NH); 1740(CO ester); 1704(CO lactam); 1158.04(CS). ^1H NMR(DMSO-d_6, δ = ppm): 2.05–2.11(3s, 9H,

3 × CH_3CO); 4.34(m, 3H, 5′-H, 5″-H, 4′-H); 5.49(t, $J_{3',2'} = 5.1$ Hz, 1H, 3′-H); 5.76(t, $J_{2',3'} = 5.1$ Hz, 1H, 2′-H); 5.92(d, $J_{1',2'} = 5.4$ Hz, 1H, 1′-H); 7.22(t, $J =$ 7.5 Hz, 1H, 5-H); 7.37(d, $J = 7.5$ Hz, 1H, 4-H); 7.45(t, $J = 7.8$ Hz,1H, 6-H); 7.79(d, $J = 7.5$ Hz, 1H, 7-H); 8.79(s, 1H, N_4-H, D_2O exchange); 9.13(s, 1H, $N_{4'}$-H, D_2O exchange); 12.20(s, 1H, N_2-H, D_2O exchange). Anal. Calcd for $C_{20}H_{22}N_4SO_8$ (478.47): C, 50.20; H, 4.63; N, 11.71; S, 6.70. Found: C, 49.92; H, 4.34; N, 11.89; S, 6.85.

5b: 1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione-3-(*N*-ethylthiosemicarbazone). Yellow crystals; m.p.: 92°C; yield: (90%). IR: ν_{max}/cm^{-1} (KBr) 3335.28(NH); 1748.16(CO ester); 1699.94(CO lactam); 1158.04(CS). ^{1}H NMR(DMSO-d_6, δ = ppm): 1.20(t, $J = 7.2$ Hz, 3H, ethyl CH_3), 2.04–2.106(3s, 9H, 3 × CH_3CO), 3.65(q, $J = 6.9$ Hz, 2H, ethyl CH_2), 4.30(m, 3H, 5′-H, 5″-H, 4′-H), 5.49(t, $J_{3',2'} = 6.3$ Hz, 1H, 3′-H), 5.76(t, $J_{2',1'} = 4.8$ Hz, 1H, 2′-H), 5.93(d, $J_{1',2'} = 4.8$ Hz, 1H, 1′-H), 7.24(t, $J = 7.5$ Hz,1H, 5-H), 7.38(d, $J = 7.8$ Hz, 1H, 4-H), 7.45(t, $J = 7.8$ Hz, 1H, 6-H), 7.78(d, $J = 7.2$ Hz, 1H, 7-H), 9.38(t, 1H, N_4-H, D_2O exchange), 12.25(s, 1H, N_2-H, D_2O exchange). Anal. Calcd for $C_{22}H_{26}N_4SO_8$ (506.52): C, 52.17; H, 5.17; N, 11.06; S, 6.33. Found: C, 52.46; H, 5.47; N, 11.28; S, 6.22.

5c: 1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione-3-(*N*-allylthiosemicarbazone). Yellow crystals; m.p.: 110–114°C; yield: (70%). IR: ν_{max}/cm^{-1} (KBr) 3327.57(NH); 1749.12(CO ester); 1700.91(CO lactam); 1168.65(CS). ^{1}H NMR(DMSO-d_6, δ = ppm): 2.04–2.13(3s, 9H, 3 × CH_3CO), 4.30(m, 5H, 5′-H, 5″-H, 4′-H, allyl C_1-H_2), 5.18(dd, 2H, allyl C_3-H_2), 5.49(t, $J_{3',2'} = 6.3$ Hz, 1H, 3′-H), 5.77(t, $J_{2',1'} = 4.8$ Hz, 1H, 2′-H), 5.91(m, 2H, 1′-H, allyl C_2-H), 7.24(t, $J = 7.5$ Hz, 1H, 5-H), 7.38(d, $J = 7.8$ Hz, 1H, 4-H), 7.45(t, $J = 7.5$ Hz, 1H, 6-H), 7.79(d, $J = 7.2$ Hz, 1H, 7-H), 9.55(t, 1H, N_4-H, D_2O exchange), 12.33(s, 1H, N_2-H, D_2Oexchange). Anal. Calcd for $C_{23}H_{26}N_4SO_8$ (518.53): C, 53.27; H, 5.05; N, 10.80; S, 6.18. Found: C, 53.59; H, 4.84; N, 11.07; S, 6.35.

5d: 1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione-3-(*N*-n-butylthiosemicarbazone). Yellow crystals; m.p.: 75–77°C; yield: (79%). IR: ν_{max}/cm^{-1} (KBr) 3327.57(NH); 1748.16(CO ester); 1699.94(CO lactam); 1170.58(CS). ^{1}H NMR(DMSO-d_6, δ = ppm): 0.90(t, $J = 7.5$ Hz, 3H, CH_3); 1.34(m, 2H, C_3-H_2); 1.60(p, $J = 7.5$ Hz, 2H, C_2-H_2); 2.04–2.12(3s, 9H, 3 × CH_3CO); 3.62(t, $J = 7.2$ Hz, 2H, C_1-H_2); 4.31(m, 3H, 5′-H, 5″-H, 4′-H); 5.49(t, $J_{3',2'} = 5.1$ Hz, 1H, 3′-H); 5.76(t, $J_{2',3'} = 5.1$ Hz, 1H, 2′-H); 5.92(d, $J_{1',2'} = 4.8$ Hz, 1H, 1′-H); 7.24(t, $J = 7.8$ Hz, 1H, 5-H); 7.37(d, $J = 7.8$ Hz, 1H, 4-H); 7.46(t, $J = 7.8$ Hz, 1H, 6-H); 7.79(d, $J = 7.5$ Hz, 1H, 7-H); 9.36(t, 1H, N_4-H, D_2O exchange); 12.28(s, 1H, N_2-H, D_2O exchange). Anal. Calcd for $C_{24}H_{30}N_4SO_8$ (534.58): C, 53.92; H, 5.66; N, 10.84; S, 6.00 Found: C, 54.23; H, 5.89; N, 10.66; S, 6.15.

5e: 1-[2,3,5-(Tri-*O*-acetyl-β-D-ribofuranosyl)]-1*H*-indole-2,3-dione-3-(*N*-phenylthiosemicarbazone). Yellow crystals; m.p.: 165–167°C; yield:

(75%). IR: ν_{max}/cm^{-1} (KBr) 3424.96, 3289.96(NH); 1749.12(CO ester); 1696.09(CO lactam); 1163.83(CS). ^1H NMR(DMSO-d_6, δ = ppm): 2.06–2.12(3s, 9H, 3 × CH_3CO); 4.31(m, 3H, 5′-H, 5″-H, 4′-H); 5.50(t, $J_{3',2'} = 6.3$ Hz, 1H, 3′-H); 5.78(t, $J_{2',1'} = 5.1$ Hz, 1H, 2′-H); 5.95(d, $J_{1',2'} = 4.8$ Hz, 1H, 1′-H); 7.22–7.92(m, 9H, Ar-H); 10.91(s, 1H, N_4-H, D_2O exchange); 12.51(s, 1H, N_2-H, D_2O exchange). Anal. Calcd for $C_{26}H_{26}N_4SO_8$ (554.57): C, 56.31; H, 4.73; N, 10.10; S, 5.78. Found: C, 56.50; H, 4.89; N, 9.86; S, 5.57.

Antibacterial Activity

All microorganisms used were obtained from the culture collection of the Microanalytical Center, Faculty of Science, Cairo University, Egypt. Media for disc sensitivity test were nutrient broth agar purchased from Defco (Southeast Decatur, AL, USA) for bacterial strains. The disc diameter was 8 mm. Nonsterile powder of the tested compound were dissolved in sterile DMSO to yield 20 mg/ml passed through 0.2 μm membrane filters (Millipore Corp., Bedford, MA, USA). The sterile DMSO solvent had no antimicrobial activity against the tested microorganism.

The antibacterial activity against the selected bacterial strains was assessed by a disc diffusion technique[23] for antibacterial screening. Briefly, 20 ml of Meuller-Hinton agar at 55°C inoculated with 1 mL of the microbial culture (10^6 CFU/mL), was poured in sterile Petri dish and left to solidify. A sterile blank filter paper disc impregnated with solution of the compound under testing (20 mg/mL in DMSO) was placed on the surface of agar, and the plate was incubated 24–48 hours at 37°C. The diameter of the zone of inhibition was measured in millimeters with slipping calipers of the National Committee for Clinical Laboratory Standards (NCCLS). Streptomycin was chosen as the reference standard antibacterial agent.

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