

Synthesis and Antibacterial Activity of *N*⁴-Benzoyl-*N*¹-dihydroxybenzoylthiosemicarbazides and Their Cyclic 1,3,4-thiadiazole Derivatives

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Abstract:

Two series of compounds have been synthesized and tested for their antimicrobial activity using the broth macrodilution method. Series I included *N*⁴-benzoyl-*N*¹-dihydroxybenzoylthiosemicarbazides (3a-e) and series II included 2-benzoylamino-5-(dihydroxyphenyl)-1,3,4-thiadiazoles (4a-e) the later of which showed selectivity against *Staphylococcus aureus*. The most potent compound from series I was the parent compound 1 (*N*⁴-benzoyl-*N*¹-2,5-dihydroxybenzoylthiosemicarbazide), while the most potent member in series II was compound 4c (2-benzoylamino-5-(2,6-dihydroxyphenyl)-1,3,4-thiadiazole).

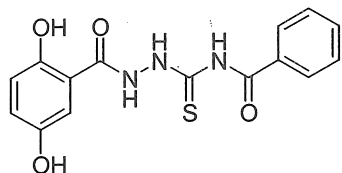
Key words: Antibacterial, Thiosemicarbazide, Thiadiazole, dihydroxybenzoic acid hydrazides

Introduction:

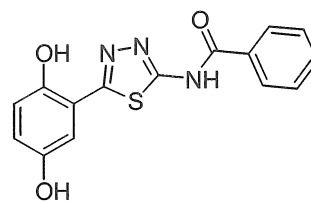
With the rapid emergence of bacterial resistance to antibacterial agents, it is essential to look for novel templates for the design and synthesis of new antibacterial agents to aid in the battle against pathogenic microorganisms. *Staphylococcus aureus* has developed resistance to many known antibacterial agents (Livermore 2003). In the USA alone, the estimated annual

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cost of antimicrobial resistance in hospitals due to *S. aureus* is \$122 million (Cassell and Mekalanos 2001). A recent example of such novel templates was the oxazolidinone antimicrobial agent linezolid which is currently in clinical practice (Barbachyn and Ford 2003). 1,3,4-Thiadiazoles (Desai and Baxi 1992; Khanum *et al.* 2003; Rollas *et al.* 1996; Zamani *et al.* 2004) and their open chain thiosemicarbazide (Durgun *et al.* 1995; Hassan *et al.* 1998) analogs have been incorporated in many antibacterial agents. We have reported previously the synthesis of compound 1 and 2 (Hassan *et al.* 1998).

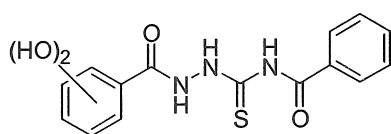


Compound 1



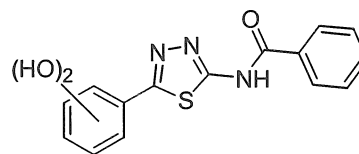
Compound 2

Promising preliminary antibacterial assays data for the above two compounds has prompted us to explore the effect of the dihydroxy-substitution pattern on the phenyl group. Here, we report the synthesis and antibacterial activity of two series of compounds. Series I included *N'*-benzoyl-*N'*-dihydroxybenzoylthiosemicarbazides **3a-e** and series II included 2-benzoylamino-5-(dihydroxyphenyl)-1,3,4-thiadiazoles **4a-e** as potential antibacterial agents.



3a-e

- 3a: 2,3-Dihydroxy**
- 3b: 2,4-Dihydroxy**
- 3c: 2,6-Dihydroxy**
- 3d: 3,4-Dihydroxy**
- 3e: 3,5-Dihydroxy**



4a-e

- 4a: 2,3-Dihydroxy**
- 4b: 2,4-Dihydroxy**
- 4c: 2,6-Dihydroxy**
- 4d: 3,4-Dihydroxy**
- 4e: 3,5-Dihydroxy**

Material and Methods

Melting points were determined using a Stuart Scientific melting point apparatus (Ribby, UK) and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance UltraShield (400 MHz) and the chemical shifts are reported in parts per million. Solvent used for NMR is $\text{DMSO-}d_6$ unless mentioned otherwise. FT-IR spectra were recorded on a Nicolet Avatar (Nicolet, USA) spectrophotometer using the KBr disk technique. Low resolution mass spectra were obtained on a 7070-E VG analytical mass spectrometer using electron impact.

Chemistry:

General procedure (3a-e)

A mixture of dihydroxybenzoic acid hydrazide 6a-e (12.60 g, 75 mmol) and benzoylthiocyanate (12.23 g, 75 mmol) in ethanol (75 mL) were heated under reflux for 0.15-1 h. The reaction mixture was allowed to cool to room temperature during which a precipitate is formed. The precipitate was filtered and the cake was washed with ethanol. The crude products were crystallized from appropriate solvents to afford the pure products

Synthesis of *N*^t-Benzoyl-*N*^t-2,3-dihydroxybenzoylthiosemicarbazide (3a)

The crude product was recrystallized from methanol/dichloromethane to afford the pure product as off-white crystals (21.62 g, 87%). m.p. 233-235 °C. FT-IR: ν (cm^{-1}) = 3226-3047 (OH, NH), 1655, 1648 (C=O). ^1H NMR δ 6.82 (t, J = 8.0 Hz, Ar-H, 1H), 7.04 (dd, J = 1.7, 8.0 Hz, Ar-H, 1H), 7.44 (dd, J = 1.7, 8.0 Hz, Ar-H, 1H), 7.56 (t, J = 7.6 Hz, Ar-H, 2H), 7.66 (t, J = 7.2 Hz, Ar-H, 1H), 8.00 (d, J = 7.6, Ar-H, 2H), 9.91 (bs, OH, 1H), 10.96 (bs, OH, 1H), 11.90 (bs, NH, 2H), 13.48 (bs, NH, 1H). ^{13}C NMR δ 116.30, 119.58, 119.83, 120.14, 128.03, 129.20, 132.24, 133.66, 146.42, 146.56, 162.10, 168.78, 173.12. EI m/z : 331 (M^+)

Synthesis of N^t-Benzoyl-N^t-2,4-dihydroxybenzoylthiosemicarbazide (3b)

The crude product was crystallized from methanol/dichloromethane to afford the pure product as off-white crystals (17.72 g, 71.3%). m.p. 233-235 °C. FT-IR: ν (cm⁻¹) = 3389 (OH), 3227 (NH), 1672, 1655 (C=O). ¹H NMR δ 6.44 (m, Ar-H, 2H), 7.52 (t, J = 7.6 Hz, Ar-H, 2H), 7.60 (t, J = 7.2 Hz, Ar-H, 1H), 7.82 (d, J = 8.0 Hz, Ar-H, 1H), 7.97 (d, J = 7.6 Hz, Ar-H, 2H), 10.33 (s, OH, 1H), 11.72, (bs, OH, 1H), 11.84 (s, NH, 2H), 13.34 (bs, NH, 1H). ¹³C NMR δ 102.93, 107.56, 108.69, 128.13, 128.93, 129.13, 132.40, 133.64, 158.89, 161.20, 162.89, 168.71, 171.30. EI m/z : 329 (M-2H⁺)

Synthesis of N^t-Benzoyl-N^t-2,6-dihydroxybenzoylthiosemicarbazide (3c)

The crude product was crystallized from methanol/dichloromethane to afford the pure product as off-white crystals (18.76 g, 75.5%). m.p. 244-246 °C. FT-IR: ν (cm⁻¹) = 3238 (OH, NH), 1681, 1648 (C=O). ¹H NMR δ 6.45 (d, J = 8.0 Hz, Ar-H, 2H), 7.28 (t, J = 8.0 Hz, Ar-H, 1H), 7.54 (t, J = 7.6 Hz, Ar-H, 2H), 7.67 (t, J = 7.2 Hz, Ar-H, 1H), 8.00 (d, J = 8.6 Hz, Ar-H, 2H), 12.03 (s, OH, 2H), 12.30 (bs, NH, 2H), 13.87 (bs, NH, 1H). ¹³C NMR δ 100.95, 107.87, 128.93, 129.25, 132.11, 133.74, 135.29, 160.50, 164.42, 169.16, 171.68. EI m/z : 329 (M-2H⁺) and 331 (M⁺)

Synthesis of N^t-Benzoyl-N^t-3,4-dihydroxybenzoylthiosemicarbazide (3d)

The crude product was crystallized from ethanol to afford the pure product as off-white crystals (18.02 g, 72.5%). m.p. 248-249 °C. FT-IR: ν (cm⁻¹) = 3489 (OH), 3176 (NH), 1679, 1651 (C=O). ¹H NMR δ 6.85 (d, J = 8.0 Hz, Ar-H, 1 H), 7.32 (d, J = 8.0 Hz, Ar-H, 1 H), 7.37 (s, Ar-H, 1H), 7.54 (t, J = 7.6 Hz, Ar-H, 2 H), 7.66 (t, J = 7.2 Hz, Ar-H, 1 H), 7.98 (d,

$J = 7.6$ Hz, Ar-H, 2H), 9.35 (s, OH, 1H), 9.70 (s, OH, 1H), 10.80 (s, NH, 1H), 11.74 (s, NH, 1H), 12.44 (s, NH, 1H). ^{13}C NMR δ 115.59, 115.75, 120.27, 123.32, 128.95, 129.18, 132.35, 133.64, 145.51, 149.85, 164.76, 168.23, 168.36. EI m/z : 331 (M^+)

Synthesis of N^4 -Benzoyl- N^1 -3,5-dihydroxybenzoylthiosemicarbazide (3e)

The crude product was crystallized from ethanol to afford the pure product as off-white crystals (17.52 g, 70.5%). m.p. > 300 °C. FT-IR: ν (cm^{-1}) =3228-3062 (OH, NH), 1673 (C=O). ^1H NMR δ 6.44 (s, Ar-H, 1H), 6.77 (s, Ar-H, 2H), 7.54 (t, $J = 7.6$ Hz, Ar-H, 2H), 7.60 (t, $J = 7.2$ Hz, Ar-H, 1H), 7.95 (t, $J = 7.6$ Hz, Ar-H, 2H), 9.67 (s, OH, 2H), 10.89 (s, NH, 1H), 10.89 (s, NH, 1H), 12.35 (bs, NH, 1H). ^{13}C NMR δ 106.22, 106.29, 128.14, 128.97, 129.17, 132.27, 133.68, 134.44, 158.80, 165.17, 168.28. EI m/z : 331 (M^+)

General procedure (4a-e)

To a stirred solution of 3a-f (9 g, 27 mmol) in absolute ethanol (200 mL), concentrated sulfuric acid (24 mL) was carefully added over a period of 15 min. The reaction mixture was left to stir at room temperature for 20 h and then was poured onto an equal volume of ice-water. The precipitate formed was filtered and washed extensively with water. The crude product was recrystallized from appropriate solvent to afford pure products.

Synthesis of 2-Benzoylamino-5-(2,3-dihydroxyphenyl)-1,3,4-Thiadiazole (4a)

The crude product was recrystallized from methanol/dichloromethane to afford the pure product as off-white crystals (7.71 g, 91.1%). m.p. dec. FT-IR: ν (cm^{-1}) =3285-3118 (OH, NH), 1647 (C=O). ^1H NMR δ 6.70 (t, $J = 7.6$ Hz, Ar-H, 1H), 6.94 (d, $J = 7.6$ Hz, Ar-H, 1H),

7.57 (t, $J = 7.6$ Hz, Ar-H, 2H), 7.65 (m, Ar-H, 2H), 8.14 (d, $J = 7.6$ Hz, Ar-H, 2H), 10.09 (bs, OH, 2H), 12.98 (bs, NH, 1H). ^{13}C NMR δ 116.98, 117.86, 118.07, 120.15, 128.84, 129.11, 132.15, 133.36, 143.82, 146.36, 159.01, 161.04, 175.52. EI m/z : 313 (M^+)

Synthesis of 2-Benzoylamino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (4b)

The crude product was recrystallized from acetone/water to afford the pure product as off-white crystals (5.90 g, 69.8%). m.p. > 300 °C. FT-IR: ν (cm^{-1}) = 3135-3022 (OH, NH), 1661, 1636 (C=O). ^1H NMR δ 6.45 (m, Ar-H, 2H), 7.54 (t, $J = 7.6$ Hz, Ar-H, 2H), 7.66 (t, $J = 7.2$ Hz, Ar-H, 1H), 7.81 (d, $J = 8.0$ Hz, Ar-H, 1H), 7.99 (d, $J = 7.6$ Hz, Ar-H, 2H), 10.26 (s, OH, 1H), 11.86 (s, OH, 1H), 13.64 (s, NH, H). ^{13}C NMR δ 102.91, 107.56, 108.66, 128.92, 129.18, 132.25, 132.37, 133.62, 158.89, 161.13, 162.96, 168.76, 171.23. EI m/z : 313 (M^+)

Synthesis of 2-Benzoylamino-5-(2,6-dihydroxyphenyl)-1,3,4-thiadiazole (4c)

The crude product was recrystallized from methanol to afford the pure product as off-white crystals (5.88 g, 69.7%). m.p. 247-250 °C. FT-IR: ν (cm^{-1}) = 3239-3201 (OH, NH), 1661, 1636 (C=O). ^1H NMR δ 6.55 (d, $J = 8.0$ Hz, Ar-H, 2H), 7.24 (t, $J = 8.0$ Hz, Ar-H, 1H), 7.58 (t, $J = 7.6$ Hz, Ar-H, 2H), 7.67 (t, $J = 7.2$ Hz, Ar-H, 1H), 8.14 (t, $J = 7.6$ Hz, Ar-H, 2H), 12.27 (bs, OH, 2H), 13.85 (bs, NH, 1H). ^{13}C NMR δ 100.94, 107.20, 128.94, 129.24, 132.70, 133.75, 135.30, 160.38, 164.37, 168.97, 171.70. EI m/z : 313 (M^+)

Synthesis of 2-Benzoylamino-5-(3,4-dihydroxyphenyl)-1,3,4-thiadiazole (4d)

The crude product was recrystallized from ethanol to afford the pure product as off-white crystals (7.16 g, 84.7%). m.p. 247-250 °C. FT-IR: ν (cm^{-1}) = 3555 (OH), 3352 (NH), 1680,

1651 (C=O). ^1H NMR δ 6.87 (d, $J = 8.4$ Hz, Ar-H, 1 H), 7.25 (d, $J = 8.4$ Hz, Ar-H, 1 H), 7.39 (s, Ar-H, 1H), 7.57 (t, $J = 7.6$ Hz, Ar-H, 2 H), 7.66 (t, $J = 7.2$ Hz, Ar-H, 1 H), 8.12 (d, $J = 7.6$ Hz, Ar-H, 2H), 9.55 (bs, OH, 2H), 12.98 (bs, NH, 1H). ^{13}C NMR δ 114.05, 116.63, 119.55, 121.91, 128.84, 129.12, 132.15, 133.41, 146.22, 148.52, 158.88, 162.80, 166.68. EI m/z : 313 (M^+)

Synthesis of 2-Benzoylamino-5-(3,5-dihydroxyphenyl)-1,3,4-thiadiazole (4e)

The crude product was recrystallized from acetone/water to afford the pure product as off-white crystals (8.19 g, 96.8%). m.p. > 300 °C. FT-IR: ν (cm^{-1}) = 3482 (OH), 3191 (NH), 1672, 1648 (C=O). ^1H NMR δ 6.36 (t, $J = 2.4$ Hz, Ar-H, 1H), 6.82 (t, $J = 2.4$ Hz, Ar-H, 2H), 7.57 (t, $J = 7.6$ Hz, Ar-H, 2H), 7.67 (t, $J = 7.2$ Hz, Ar-H, 1H), 8.13 (t, $J = 7.6$ Hz, Ar-H, 2H), 9.12 (s, OH, 2H), 13.15 (bs, NH, 1H). ^{13}C NMR δ 105.20, 105.40, 127.41, 128.88, 129.14, 129.85, 132.03, 133.49, 159.33, 162.72, 165.78. EI m/z : 313 (M^+).

Microbiological assay

Microorganisms used for assay are *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853). MIC of the compounds was determined according to macrodilution broth method (National Committee for Clinical Laboratory Standards 2000) in Mueller-Hinton Broth (MHB, Difco, USA). Nalidixic acid (pharmaceutical grade) was generously provided by Dar Al-Dawa Development and Investment Co. (DAD), Na'ur, Jordan. Trimethoprim was obtained from Aldrich Chemical Company, USA.

Stock solutions of the compounds were prepared in dimethylsulfoxide. The stock solution was then two-fold diluted in MHB to give an initial concentration of 256 µg/mL, further dilution was performed until a final concentration of 0.5 µg/mL was obtained.

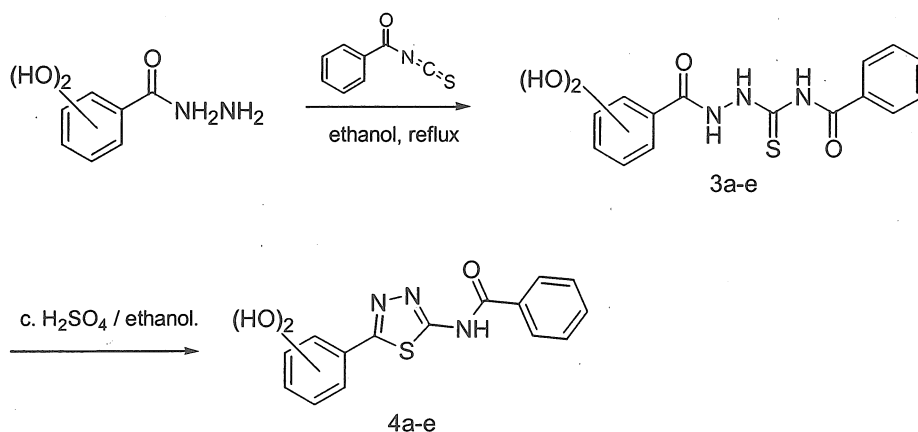
The microorganisms were incubated overnight in MHB at 37 °C. 4-5 colonies of the microorganism were placed in 5 mL MHB so that it will be equal to McFarland No 0.5 (10^8 CFU/mL). After two- fold dilution, the final concentration was 5×10^6 CFU/mL. Then 1 mL of the adjusted inoculum was added to 1 mL of various concentrations of the test compound. This resulted in a 1:2 dilution of both the test compound and inoculum. All test tubes were incubated at 37 °C for 16-18 h. The MIC was recorded as the lowest concentration of the test compound which inhibited the growth of bacteria in the broth.

Results

Chemistry

The target compounds were synthesized according to scheme 1 following previously reported procedure (Hassan *et al.* 1998). The appropriate dihydroxy benzoic acid hydrazides were added to benzoylisothiocyanate under reflux in ethanol to give *N'*-Benzoyl-*N'*-dihydroxybenzoylthiosemicarbasides (**3a-e**) in 70.5-87.6% yield. Cyclodehydration of the thiosemicarbazides with concentrated sulfuric acid in absolute ethanol afforded the desired 1,3,4-thiadiazoles (**4a-e**) in 69.7-96.8% yield.

Scheme 1



Microbiological testing

Antimicrobial activity of all target compounds was evaluated against two Gram-positive bacteria namely *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 and two Gram-negative bacteria namely *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853). MICs of the compounds were determined according to macrodilution broth method (National Committee for Clinical Laboratory Standards 2000).

Results

Compound 1 and compound 2 have demonstrated moderate but selective antibacterial action, with compound 1 showing selectivity to Gram-negative *E. coli* and compound 2 showing selectivity to Gram-positive *S. aureus*.

In this work we report the synthesis and antibacterial evaluation of analogs of the previously mentioned compounds that differ in the pattern of dihydroxylation of the phenyl ring. The synthesized compounds as well as their antibacterial activities reported as MIC values ($\mu\text{g/L}$) are summarized in tables 1 and 2.

Table 1. Antimicrobial activity results of thiosemicarbazides (3a-e) expressed as MICs ($\mu\text{g/mL}$)

Compound	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. Coli</i>	<i>E. faecalis</i>
(1)	64	128	8	64
3a	64	64	32	64
3b	64	64	32	64
3c	64	-	-	-
3d	-	-	-	-
3e	128	32	32	128
Nalidixic acid	-	-	2	-
Trimethoprim	2	128	2	1

Table 2. Antimicrobial activity results of 1,3,4-thiadiazoles (4a-e) expressed as MICs ($\mu\text{g/mL}$).

Compound	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. Coli</i>	<i>E. faecalis</i>
(2)	8	-	-	-
4a	16	128	64	128
4b	-	64	64	64
4c	2	64	128	128
4d	16	-	-	-
4e	8	64	128	64
Nalidixic acid	-	-	2	-
Trimethoprim	2	128	2	1

From the antibacterial assay data presented in these tables, two things can be noticed. First the reported compounds have a broad spectrum of activity with potency comparable or even better than sulfa drugs. Secondly, the synthesized compounds have retained the selectivity trends of the parent compounds 1 and 2. In other words, compounds in series I showed slight

selectivity against Gram negative *E. coli* while compounds in series II have significant selectivity to Gram positive *S. aureus*.

With regard to compounds in series I, generally they showed activities that are less in magnitude than that of the standard compounds. The parent, compound **1**, was most potent against *E. coli*, albeit being 4 folds less potent than nalidixic acid. Compound **3d** showed no antibacterial activity at the MIC range used in this report and compound **3c** showed activity toward *S. aureus* only at the same MIC range.

As for compounds in series II, they showed good potencies and significant selectivity against *S. aureus* with compound **4c** showing equal potency to trimethoprim and the least potent (**4a** and **4d**) being only 8 folds less potent. With regard to selectivity, compounds **2** and **4d** were the most selective showing exclusive activity toward *S. aureus*, and compound **4c** showed 32-64 fold selectivity toward the same bacteria.

The mechanism of action of the reported compounds is not known; hence accurate deduction about the structure-activity relationships is not possible. It is worth mentioning that activity differences between the active compounds within each series are not large. In general, hydroxyl groups in drugs are involved in hydrogen bonding with their target mainly as hydrogen-donors and it is likely that the active compounds are participating in such bonds, but with variable strengths. Catechols (**3a**, **3d**, **4a** and **4d**) were the least potent with compound **3d** being totally inactive and compound **4d** showing activity toward *S. aureus* only. This may be due to the fact that they show intramolecular hydrogen bond between the two adjacent hydroxyl groups. Compound **4b** was not effective against *S. aureus*, in the MIC range used in the assay, which may be due to unfavorable steric interaction at their target site or inability to reach that site.

In conclusion, promising results have been obtained for these two series of compounds. These results clearly indicate that the position of the hydroxyl groups in the phenyl ring is important for the activity of these compounds. Also, cyclization improves activity toward *S. aureus* only. These findings warrant further investigation of the structure-activity relationships through structural modification of these classes of compounds is required, a task that is now underway in our labs.

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