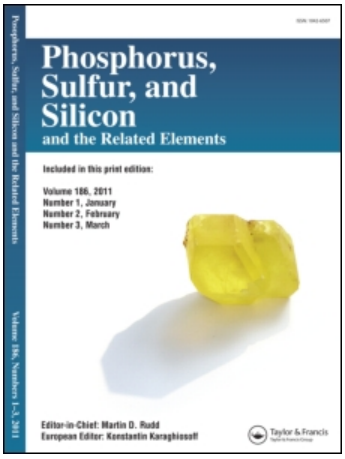


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# A Novel Synthesis of Some New Imidazothiazole and Glycocyamidine Derivatives and Studies on Their Antimicrobial Activities

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# A Novel Synthesis of Some New Imidazothiazole and Glycocyamidine Derivatives and Studies on Their Antimicrobial Activities

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*5,5-diphenyl-2-thioxoimidazolidin-4-one (**1**) reacted with chloroacetic acid **2a** and ethyl chloroacetate **2b** in an alkaline medium to afford 2-(4,5-dihydro-5-oxo-4,4-diphenyl-1*H*-imidazol-2 ylthio)acetic acid (**3a**) and ethyl 2-(4,5-dihydro-5-oxo-4,4-diphenyl-1*H*-imidazol-2 ylthio)acetate (**3b**), respectively. Compounds **3a**,**b** were converted to 5,5-diphenylimidazolidine-2,4-dione (**4**) by boiling in ethanolic hydrochloric acid. When compounds **3a**,**b** were treated with polyphosphoric acid, cyclization occurred, and 6,6-diphenylimidazo[2,1-b]thiazole 3,5(2*H*,6*H*)-dione (5) was obtained.*

*2-(methylthio)-1*H*-imidazol-5(4*H*)-one derivatives (**a**,**b** reacted with hydrazine hydrate to give the corresponding hydrazones **7a**,**b**. The reaction of **6a**,**b** with hydrazine hydrate afforded 3-amino-2-phenylimino imidazolidin-4-one derivatives **10a,b**. The antimicrobial activities of compounds **1**. **3a**,**b**, **5**, **7a**,**b**, and **10a**,**b** were studied.*

**Keywords** 5,5-diphenyl-2-thioxoimidazolidin-4-one; antimicrobial activity; imidazole; Imidazolidin-4-one; thiazole

## INTRODUCTION

2-thiohydantoin derivatives possess anticonvulsant activity[1,2] and antiasthmatic activity.[3] Thiazole derivatives have considerable fungicidal action,[4] antibacterial activity,[5–7] and anticonvulsant activity.[8–10] Thiazine derivatives have been recommended as antihypertensive agents,[1]

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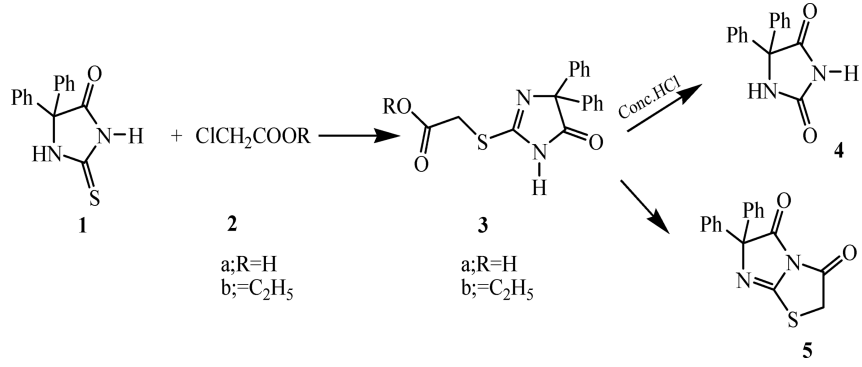
and antibiotics[12] and have a hypnotic effect.[13] In addition, they are used in the synthesis of dyes for plastics and hydrophobic fibers,[14] acetate, nylon, and polyester fibers.[15,16]

The previously mentioned biological and medicinal activities together with the industrial importance of these compounds stimulated interest for the synthesis of several new condensed heterocyclic compounds containing a thiohydantoin moiety condensed with thiazines and thiazoles. The new condensed heterocyclic derivatives possess latent functional substituents and thus appear promising to fulfill the objectives of biological activity studies and further chemical transformations. Compounds **1** and **6a,b** seemed to be excellent candidates for this synthesis.

## RESULTS AND DISCUSSION

5,5-diphenyl-2-thioxoimidazolidin-4-one (**1**) reacted with **2a** and **2b** in an alkaline medium to afford 2-(4,5-dihydro-5-oxo-4,4-(diphenyl-1*H*-imidazol-2-ylthio)acetic acid (**3a**) and ethyl 2-(4,5-dihydro-5-oxo-4,4-diphenyl-1*H*-imidazol-2-ylthio)acetate (**3b**), respectively. The structures of **3a** and **3b** were elucidated via elemental analysis and spectral data (see Experimental section).

Moreover, compounds **3a**,**b** were converted to 5,5-diphenylimidazolidine-2,4-dione (**4**) on boiling with ethanolic hydrochloric acid for 2 h (Scheme 1). When compounds **3a**,**b** were treated with polyphosphoric acid, cyclization occurred, and only one product was obtained (by melting point and mixed melting point determinations). The reaction product was formulated as 6,6-diphenylimidazo[2,1-*b*]thiazole-3,5(2*H*,6*H*)-dione (**5**) based on elemental analysis and




**SCHEME 1**

spectral data (see Experimental Section). Product **5** was formed via elimination of one molecule of water or one molecule of ethanol from **3a, b**, respectively (Scheme 1).

Work was further extended to investigate the behavior of 5-furfurylidene- and 5-thienylidene-2-methylmercaptohydantion derivatives[17] **6a–d** toward the action of hydrazine hydrate for the synthesis of some new glycocyamidines containing 2-furyl and 2-thienyl moieties required for biological activity studies.

2-(methylthio)-1*H*-imidazol-5(4*H*)-one derivatives **6a**,**b** reacted with hydrazine hydrate to give 2-hydrazone derivatives **7a**,**b**. 3-phenyl derivatives **6c**,**d** reacted with hydrazine hydrate; the products from this reaction were established to be 5-ylidene-3-amino-$N^2$-phenylglycocyamidines **10a,b** instead of the expected 2-hydrazone-3-phenyl derivatives **8a**,**b**. Scheme 2 illustrates the possible mechanism for this rearrangement in this class of compounds. The formation of hydrazones **8a**,**b** is probably the first step followed by a nucleophilic attack of a second hydrazine molecule on C-4 to give intermediates **9a**,**b**.

Apparently, the increased electrophilicity of this carbon atom is due to the presence of the 3-phenyl group[18] (in cases where there are no such 3-aryl substituents, no such rearrangements have been reported)[19,20] Intermediates **9a**,**b** may undergo ring closure according to two possible pathways, A and B (Scheme 2).

Structures of the newly synthesized derivatives were established on the basis of elemental analysis, IR, and $^1$H NMR spectral data together with alternative synthetic pathways whenever possible.

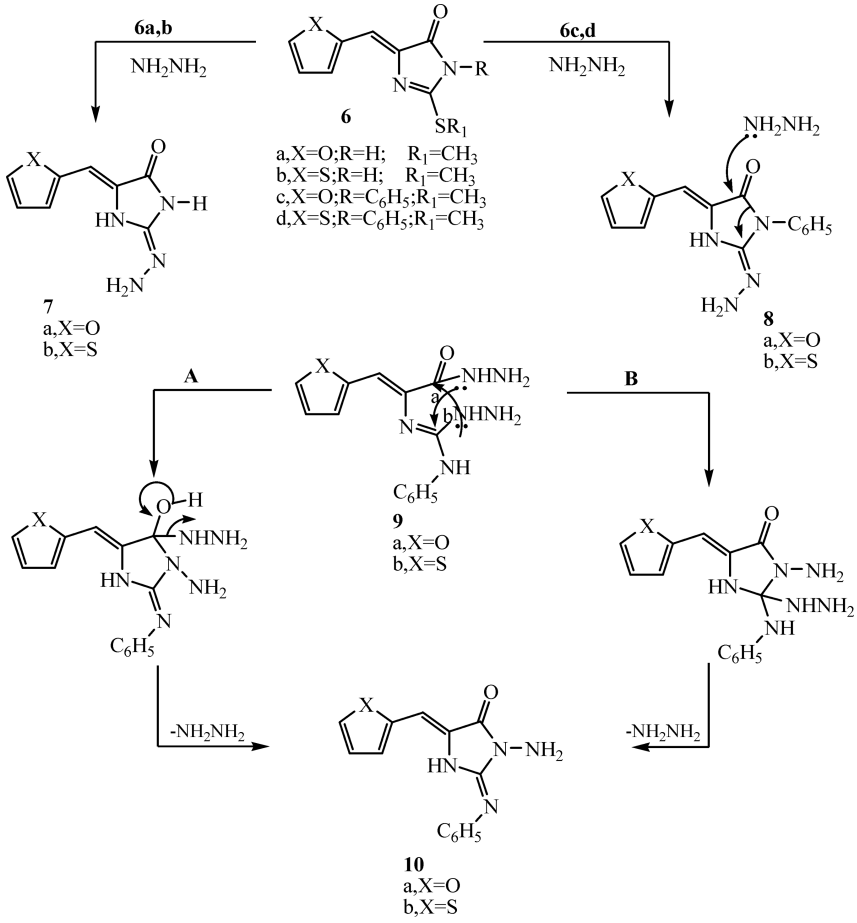


## ANTIMICROBIAL ACTIVITY

Table I shows the effect of compounds **1**, **3a**,**b**, **5**, **7a**,**b**, and **10a**,**b** on the microorganisms tested. It is of interest to note that the most active compound is **5** followed by the other compounds, which are slightly less active. The activity increased after cyclization of **3a**,**b**, to **5**, Indicating that the combined imidazothiazole ring is totally responsible for the activity.

## EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer using KBr oiscs. $^1$H NMR spectra were recorded on a Varian EM 390 90 MHz spectrometer using DMSO-$d_6$ as a solvent and TMS as the internal standard. Chemical shifts are expressed as $\delta$ ppm units. Microanalytical data were carried




**SCHEME 2**

out in the Microanalytical Centre, Faculty of Science, Cairo University, Cairo, Egypt.

## Preparation of 2-(4,5-Dihydro-5-oxo-4,4-diphenyl-1*H*-imidazol-2-ylthio) Acetic Acid (3a)

To a solution of 5,5-diphenylimidazolidine-2,4-dione (**1**) (2.52 g, 0.01 mole) in a mixture of 2% potassium hydroxide (1.12 g, 56 mL) and ethanol (40 mL) was added chloroacetic acid (0.95 g, 0.01 mole). The reaction mixture was refluxed on a steam bath for 3 h and then left to cool at r.t. It was acidified with diluted hydrochloric acid, and the

**TABLE I Antimicrobial Activity of Compounds 1, 3a,b, 5, 7a,b, and 10a,b**

| Compound no. | *Bacillus subtilis* | *Candida utilis* | *Micrococcus* | *Staphylococcus* | *Pseudomonas* |
|---|---|---|---|---|---|
| **1** | + | + | ++ | + | — |
| **3a** | + | + | ++ | ++ | — |
| **3b** | ++ | ++ | +++ | +++ | — |
| **5** | +++ | ++ | +++ | ++++ | — |
| **7a** | ++ | ++ | +++ | +++ | — |
| **7b** | +++ | +++ | +++ | +++ | — |
| **10a** | ++ | ++ | +++ | ++ | — |
| **10b** | ++ | ++ | +++ | +++ | — |

(−) no inhibition zone; (+) slightly inhibition zone; (++) moderate inhibition zone; (+++) extensive inhibition zone; (++++) highly extensive inhibition zone.



precipitated solid was collected by filtration and crystallized from ethyl alcohol as yellow crystals of **3a**.

**3a**, m.p. 285°C, yield 70%, elemental analysis for $C_{17}H_{14}N_2O_3S$ (326.37): calcd: C, 62.56; H, 4.32; N, 8.58; S, 9.82; found: C, 62.40; H, 4.15; N, 8.90; S, 10.13; IR ($cm^{-1}$): 3400–2500 (broad, OH, NH), 1725, 1720 (2 C=O) and 1645 (C=N) and $^1$H-NMR ($\delta$ ppm): 3.7 (s, 2H, $CH_2$), 7.2–7.5 (m, 10H, Ar-H), 9.6, 11.5 (2s, 2H, NH, COOH, exchangeable with $D_2O$).

## Preparation of Ethyl 2-(4, 5-Dihydro-5-oxo-4, 4-diphenyl-1*H*-imidazol-2-ylthio) Acetate (3b)

A mixture of **1** (2.52 g, 0.01 mole), sodium ethoxide (0.25 g), and cthyl chloroacetate (0.01 mole) in ethanol (40 mL) was stirred at r.t. for 4 h. The solid obtained was collected and crystallized from ethanol as yellow crystals of **3b**.

**3b**, m.p. 135°C, yield 75%, elemental analysis for $C_{19}H_{18}N_2O_3S$ (354.42): calcd: C, 64.39; H, 5.12; N, 7.90; S, 9.05; found: C, 64.24; H, 4.85; N, 8.21; S, 8.96; IR ($cm^{-1}$): 3280 (NH), 1735, 1720 (2 C=O) and 1645 (C=N) and $^1$H NMR ($\delta$ ppm): 1.8 (t, 3H, $CH_2C\underline{H}_3$), 3.8 (s, 2H, $CH_2$), 4.1 (q, 2H, $C\underline{H}_2CH_3$), 7.3–7.5 (m, 10H, Ar-H) and 11.4 (s, 1H, NH, exchangeable with $D_2O$).

## Hydrolysis of 3a,b with Hydrochloric Acid

A mixture of **3a** (1 g, 0.003 mole) or **3b** (1 g, 0.0028 mole), ethanol (20 mL), and conc. hydrochloric acid (8 mL) was refluxed for 2 h.

The solid product obtained on cooling was filtered off and erystallized from ethanol to give 5,5-diphenylimidazolidine-2,4-dione (**4**), m.p. 291–294°C, yield 65%; it showed no depression in melting point when mixed with an authentic sample.[21]

## Preparation of 6,6-Diphenylimidazo[2,1-b]thiazole-3,5-(2H,6H) dione(5)

A mixture of (1 g, 0.003 mole) or **3b** (1 g, 0.0028 mole) and polyphosphoric acid (prepared from 4 g of phosphorus pentaoxide and 4 mL 85% phosphoric acid) was heated on a water bath for 1 h and then in an oil bath (125–130°C) for 30 min. The reaction mixture was poured into ice-cold water and neutralized with potassium carbonate solution. The solid thus obtained as yellow crystals was crystallized from ethanol and identified as one product, **5**, by melting point and mixed melting point determinations.

**5**, m.p. 220°C, yield 65%, elemental analysis for $C_{17}H_{12}N_2O_2S$ (308.35): calcd: C, 66.22; H, 3.92; N, 9.08; S, 10.40; found: C, 66.52; H, 3.65; N, 9.31; S, 10.14; IR ($cm^{-1}$): 1725, 1710 (2 C=O) and 1645 (C=N) and $^1H$ NMR ($\delta$ ppm): 3.9 (s, 2H, $CH_2$) and 7.3–7.5 (m, 10H, Ar-H).

## Action of Hydrazine Hydrate on (4Z)-4-((Furan-2-yl)-methylene)-2-(methylthio)-1H-imidazol-5(4H)-one (6a) and (4Z)-2-(methylthio)-4-((thiophen-2-yl)methylene)-1H-imidazol-5(4H)-one (6b)

A mixture of **6a** (2.08 g, 0.01 mole) or **6b** (2.24 g, 0.01 mole) with hydrazine hydrate (0.11 mole) was refluxed in ethanol (30 mL) for 1 h. The solid products that were obtained by cooling were filtered off, dried, and crystallized from ethanol as yellow crystals of (2*E*,5*Z*)-5-((furan-2-yl)methylene)-2-hydrazonoeimidazolidin-4-one (**7a**) and (2*E*,5*Z*)-2-hydrazonoe-5-((thiophen-2-yl)methylene)imidazolidin-4-one (**7b**).

**7a**, m.p. 202°C, yield 70%, elemental analysis for $C_8H_8N_4O_2$ (192.17): calcd.: C, 50.00; H, 4.20; N, 29.15; found: C, 49.86; H, 4.03; N, 29.30; IR ($cm^{-1}$): 3400–3260 ($NH_2$, 2NH), 1720 (C=O) and 1635 (O=N) and $^1H$ NMR ($\delta$ ppm): 6.2 (s, 1H, CH=C), 6.6–6.9 (m, 3H, furan H-3, H-4 and H-5), 8.9 (s, br., 2H, $NH_2$) and 9.7–10.1 (2s, 2H, 2NH).

**7b**, m.p. 226°C, yield 72%, elemental analysis for $C_8H_8N_4OS$ (208.24): calcd.: C, 46.14; H, 3.87; N, 26.90; S, 15.40; found: C, 46.31; H, 4.10; N, 26.85; S, 15.52; IR ($cm^{-1}$): 3380–3220 ($NH_2$, 2NH), 1720 (C=O) and 1645 (C=N).

### Preparation of (2E,5Z)-5-((Furan-2-yl)methylene)-3-amino-2-(phenylimino)imidazolidin-4-one (10a) and (2E,5Z)-3-amino-2-(phenylimino)-5-((thiophen-2-yl)methylene)imidazolidin-4-one (10b)

A mixture of each 5-ylidene-2-methylmercaptohydantoin derivatives **6c** (2.07 g, 0.01 mole) or **6d** (2.23 g, 0.01 mole) and hydrazine hydrate (0.11 mole) was refluxed in ethanol (30 mL) for 1 h. The solid products that were obtained by cooling were filtered off, dried, and crystallized from ethanol as yellow crystals of **10a**,**b**.

**10a**, m.p. 220°C, yeild 79%, elemental analysis for $C_{14}H_{12}N_4O_2$ (268.27): calcd: C, 62.68; H, 4.51; N, 20.88; found: C, 62.52; H, 4.60; N, 21.11; IR ($cm^{-1}$): 3370, 3260, 3170 ($NH_2$, NH), 1720 (C=O) and 1640 (C=N).

**10b**, m.p. 231°C, yield 76%, elemental analysis for $C_{14}H_{12}N_4OS$ (284.34): calcd.: C, 59.14; H, 4.25; N, 19.70; S, 11.28; found: C, 59.30; H, 4.36; N, 19.56; S, 11.00; IR ($cm^{-1}$): 3350, 3280, 3150 ($NH_2$, NH), 17–5 (C=O) and 1645 (C=N); and $^1$H NMR ($\delta$ ppm): 6.2 (s, 1H, CH=C), 6.7–7.0 (m, 3H, thiophen H-3, H-4 and H-5), 7.2–7.5 (m, 5H, Ar-H), 8.6 (s, br., 2H, $NH_2$) and 9.7 (s, 1H, NH).

## ANTIMICROBIAL ACTIVITY

The following microbial strains were used as target organisms. *Bacillus subtilis* (gram positive bacteria), *Pseudomonas aureginosa* (gram negative bacteria), *Micrococcus tetragena, Candida utilis* (yeast), and *Staphylococcus aureus.* The compounds under investigation were insoluble in water; therefore, they were dissolved in ethyl alcohol at a concentration of 10 mg/mL and filtered through a bacterial membranes filter (0.45 $\mu$m).

The antimicrobial effects of the compounds were tested by the whole-plate method.[22] Spores or cells of the tested organisms were mixed with the media before solidification (at about 45°C), and the whole mixture was poured into a sterile plate for solidification (pH 7) 1 miligram of each compound dissolved in 0.1 mL of ethyl alcohol; incubation temperature was 35–37°C for bacteria and 27–30°C for yeast. The toxicity was measured after 24 and 48 h for bacteria and 5–7 days for yeast. The previously discussed estimation was based on the diameter of the inhibition zones formed. A control experiment with ethyl alcohol was also carried out.

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