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ORIGINAL PAPER

Addition–cyclization reactions of furan-2-carbonyl isothiocyanate with nitrogen nucleophiles as a synthetic route to novel azines and azoles of potential biological activity

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Abstract
Heterocyclization of furan-2-carbonyl isothiocyanate **1** with a variety of aliphatic and aromatic nitrogen nucleophiles resulted in the formation of a new series of heterocycles including triazines, pyrimidines, oxadiazines, imidazolidines, thiadiazoles and their condensed candidates. The antibacterial screening for a group of the newly synthesized compounds showed that they possess moderate antibacterial activities against examples of Gram-positive and Gram-negative bacteria.

Keywords Anomeric-based oxidation · Oxadiazine · Quinazoline · Thiadiazole · Triazine

Introduction

Acyl isothiocyanates are bifunctional compounds containing an acyl group and a thiocyanate group. They are more reactive than alkyl isothiocyanates obviously due to the presence of electron-withdrawing acyl group which reinforces the reactivity of the isothiocyanate group and enhances nucleophilic addition at this site. The reactivity of acyl isothiocyanates is, thus, determined by four active centers: the nucleophilic nitrogen and sulfur atoms, and the electrophilic carbon atoms of the carbonyl and thiocarbonyl groups (Fig. 1), which make them able to participate in diverse types of reactions, especially multicomponent reactions which become increasingly widespread as extremely ideal and eco-friendly tools for the rapid synthesis of many heterocyclic compounds [1–3].

Thus, the chemistry of acyl isothiocyanates is very rich and diverse and has been employed in the synthesis of a number of biologically active heterocycles such as thiazoles, thiadiazoles, triazoles, benzimidazoles, dithiolane, oxazolines, triazines and oxazines [4–11].

Furan-containing compounds were reported to exhibit a wide diversity of pharmacological activities including antimicrobial, antitumor, analgesic, antihypertensive and anti-inflammatory activity [12–18] (Fig. 2). These reports stimulated my efforts to utilize furan-2-carbonyl isothiocyanate as a precursor to construct and evaluate the biological activity of a new series of heterocycles containing furan moiety.

Results and discussion

In continuation of our efforts aiming to synthesize and evaluate the biological activity of novel heterocycles [19–21], I report in this work on the utilization of furan-2-carbonyl isothiocyanate **1** as a versatile precursor for the building of some novel heterocycles of expected biological activity. Thus, refluxing of compound **1** with urea in dry acetone afforded the thiourea derivative **2**. The ^{1}H NMR spectrum of **2** clarified three singlets at $\delta = 10.93$, 11.19 and 13.68 ppm for NH_2 and two NH, respectively. Also, the ^{13}C spectrum of **2** showed the expected sp^2 carbon signals for its structure; and its IR spectrum showed absorption bands at 1686, 1678 and 1265 cm^{-1} for two C=O and C=S functions, respectively. The intramolecular cyclization of compound **2** under diverse conditions resulted in the formation of different heterocycles. Thus, oxidative cyclization of **2** using bromine gave thiadiazole derivative **3**, whereas the base-catalyzed cyclization of **2** in sodium ethoxide solution at room temperature afforded triazine derivative **4**. These cyclizations were supported by ^{1}H NMR spectra which showed disappearance

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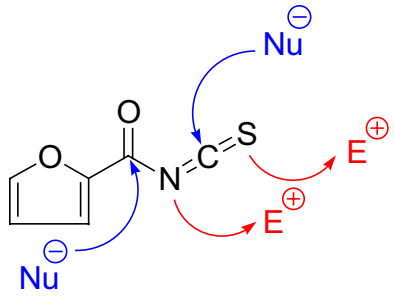


Fig. 1 Reactive sites of furan-2-carbonyl isothiocyanate

of NH_2 signals, in addition to ^{13}C NMR spectra of **3** and **4** which agreed with their structures (see the "Experimental" part). Further heterocyclization of triazine **4** with 1,2-dichloroethane in the presence of K_2CO_3 tolerated the dihydrothiazolotriazine **5** whose ^1H NMR spectrum clarified two triplet signals at $\delta = 3.49$ and 4.12 ppm for the two adjacent CH_2; and its ^{13}C NMR displayed two sp^3 carbon signals at $\delta = 34.47$ and 55.36 ppm for the two CH_2 (Scheme 1).

In a similar manner, benzaldehyde semicarbazone could be reacted with **1** to give thiourea derivative **6**. Treatment of the latter compound with sodium ethoxide at room temperature did not result in any cyclization and compound **6** was recovered unchanged, but refluxing of compound **6** in sodium ethoxide solution resulted in the desired intramolecular cyclization affording triazolylfuropyrrol-6-one **8** not the expected triazine **7**. This result was established based on the following facts:

1. Lassaigne's test for the product revealed the absence of sulfur.
2. IR spectrum of the product clarified two C=O absorption bands which means that no C=O function was involved in the cyclization.
3. ^1H NMR of the product displayed one NH signal.
4. Also, ^{13}C NMR of the product agreed with the proposed structure **8**.

Compound **8** may be formed by the intramolecular cycloaddition of amidic NH to the electrophilic carbon of azamethine group to give intermediate **A** which was converted to the desired triazole derivative **B** via anomeric-based oxidation upon releasing of molecular hydrogen (H_2) [22–24]. It has been suggested that the latter stage is supported by the driving force of aromatization and anomeric effect [25]. The latter compound underwent another cyclization via loss of H_2S upon attack of furan ring on the electrophilic carbon of N=C-SH of intermediate **C** to furnish the final product **8** (Scheme 2).

The oxadiazine derivative **9** was obtained directly from acyl isothiocyanate **1** in a one-step addition–cyclization reaction via refluxing of **1** with biuret in dioxane. ^1H NMR spectrum of **9** displayed two singlets at $\delta = 9.66$ and 11.16 ppm for NH_2 and NH, respectively. ^{13}C NMR of compound **9** clarified three sp^2 signals at 157.65, 166.02 and 181.99 ppm for oxadiazine ring. Also, its IR spectrum showed the presence of one C=O absorption band at 1670 cm^{-1}, in addition to C=S band at 1265 cm^{-1} (Scheme 1).

The three-component reaction of furan-2-carbonylisothiocyanate **1**, hippuric acid and *p*-chlorobenzaldehyde in dry pyridine gave imidazolidin-4-one **10** in moderate yield. The structure of **10** was confirmed by its ^1H NMR, ^{13}C NMR and IR spectral data. ^1H NMR of **10** showed multiplet signals in the region 7.38–8.35 ppm for aromatic-H and exocyclic vinylic-H. IR spectrum of **10** displayed three absorption bands for C=O and C=S functions. Also, its ^{13}C NMR showed the expected sp^2 signals. Anthranilic acid was reacted with compound **1** in refluxing acetone affording the acid derivative **11** which underwent cyclocondensation upon refluxing in acetic anhydride yielding quinazoline **12**. The structures of compounds **11** and **12** were confirmed by their spectral data. ^1H NMR of **11** displayed three singlets at $\delta = 11.75$, 12.17 and 12.97 ppm for two NH and carboxylic-H, respectively. Also, its IR spectrum showed three absorption bands at 1685, 1663 and 1269 cm^{-1} for two C=O and C=S functions, whereas ^1H NMR spectrum of **12** showed disappearance of one NH and carboxylic-H.

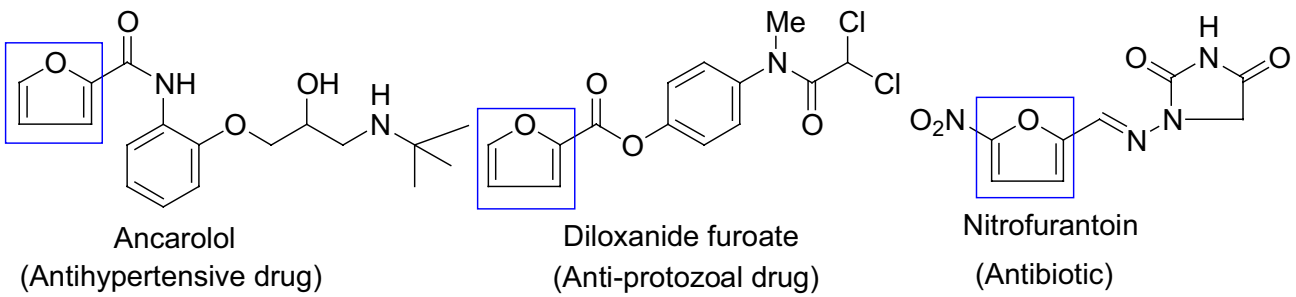
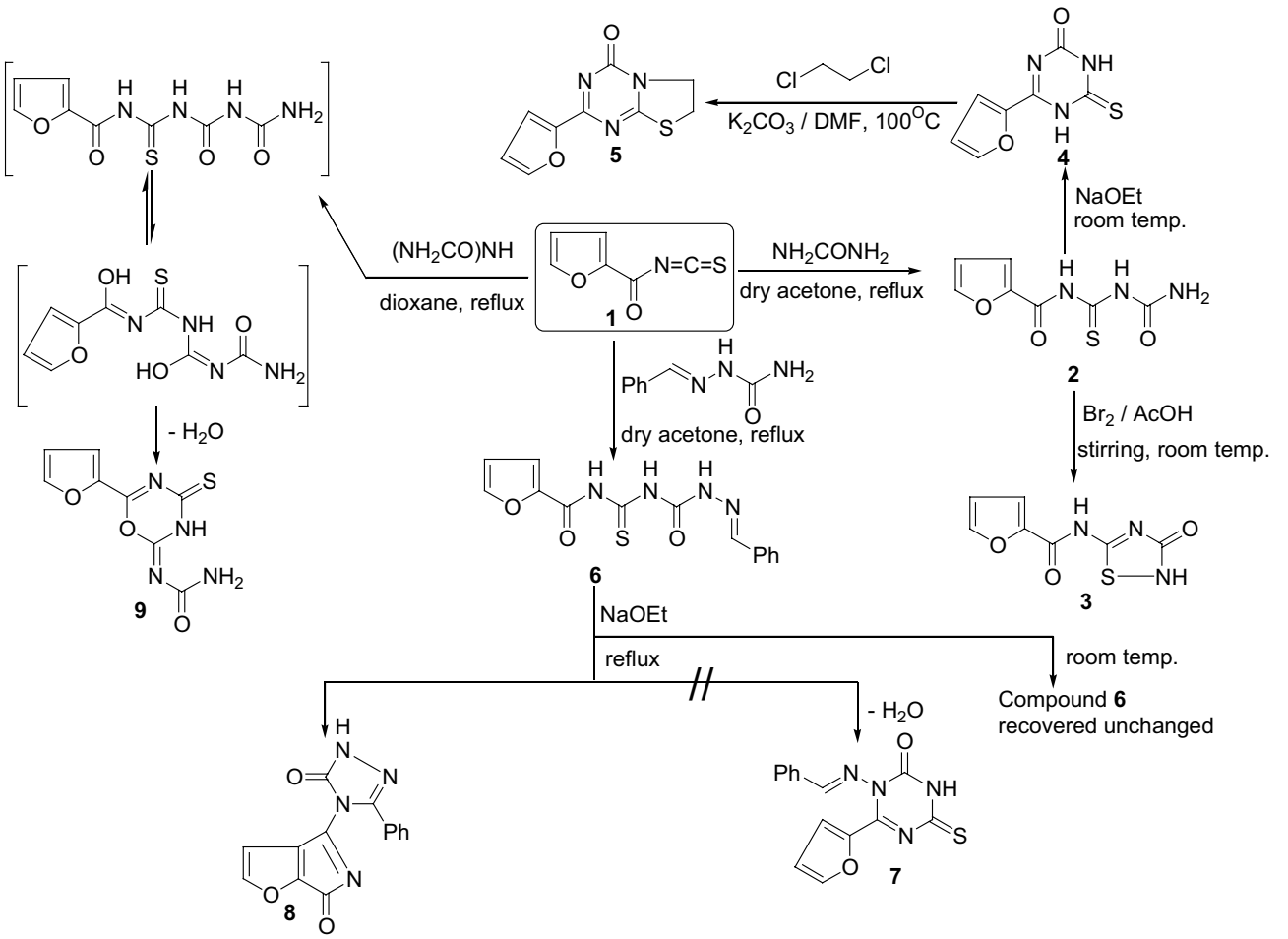
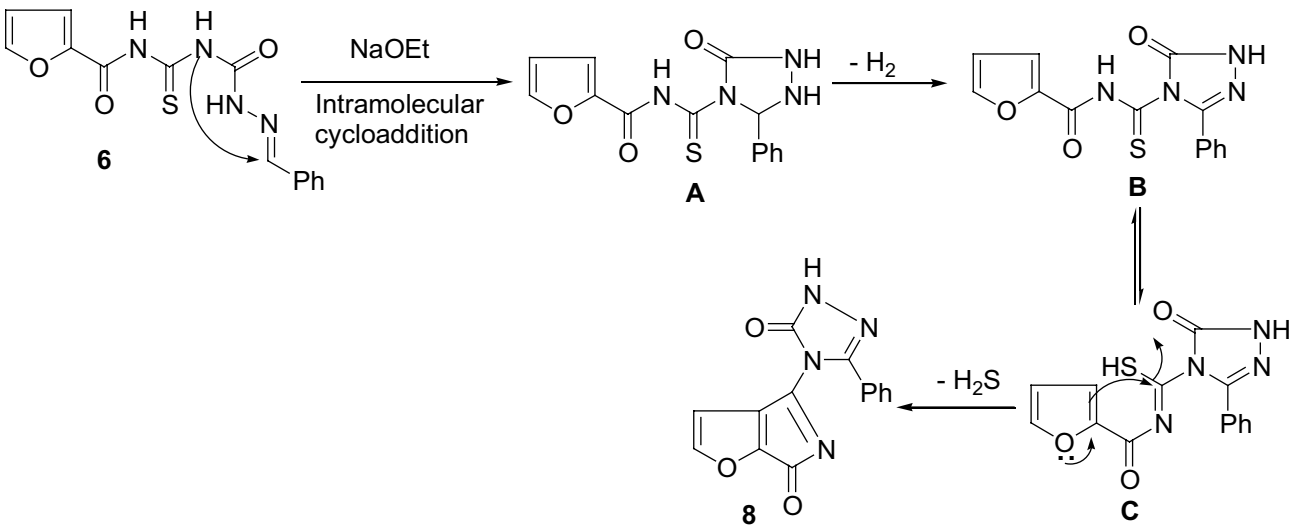


Fig. 2 Examples of furan drugs



Scheme 1 Heterocyclization of furan-2-carbonylisothiocyanate 1 with different amides

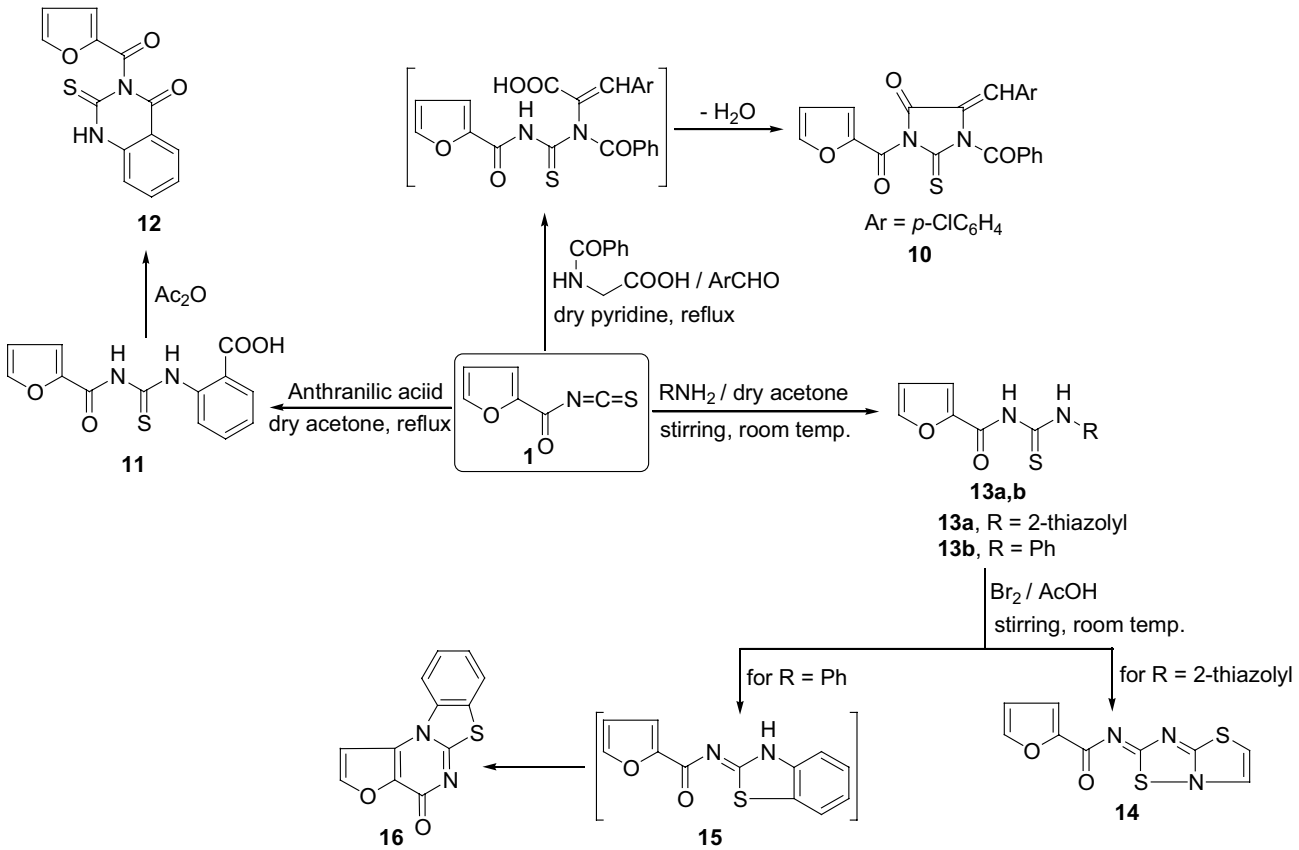


Scheme 2 Mechanistic route of formation of triazolylfuropyrrol-6-one 8

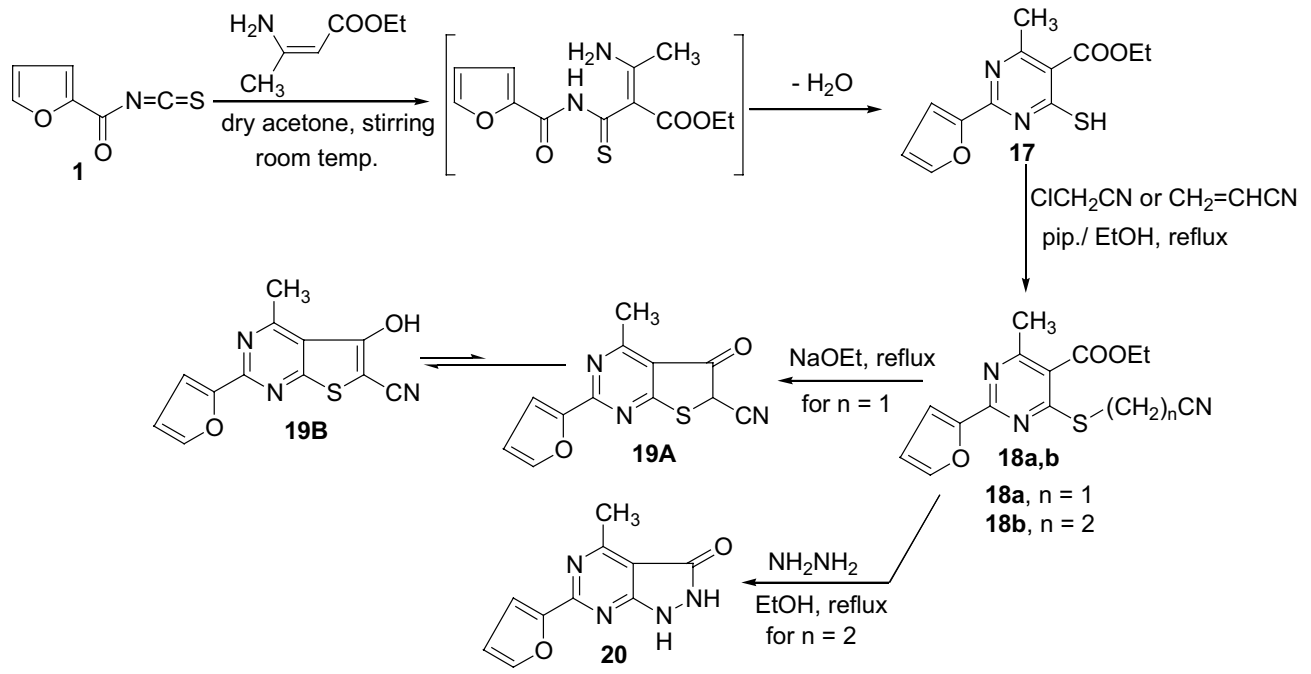
The nucleophilic addition of aromatic amines, namely 2-aminothiazole and aniline to compound **1**, yielded thiazolyl thiourea **13a** and phenyl thiourea **13b** derivatives, respectively. ^{1}H NMR of these compounds showed two singlets for two NH; also their IR spectra displayed absorption bands for C=O and C=S functions. Oxidative cyclization of **13a** and **13b** with bromine in acetic acid at room temperature afforded thiazolo[3,2-*b*][1,2,4] thiadiazole **14** and 3-oxa-6-thia-5,10b-diazacyclopenta[*c*]fluoren-4-one **16** which may be formed from **13b** via two successive oxidation steps. These cyclizations were supported by disappearance of the two NH signals from ^{1}H NMR spectra of **14** and **16**, in addition to ^{13}C NMR spectra which displayed the carbon signals expected for their structures (Scheme 3).

Stirring of compound **1** with ethyl 3-aminocrotonate in dry acetone furnished pyrimidine thiol **17**. The ^{1}H NMR of the latter compound displayed two singlets at $\delta = 2.68$ and 14.23 ppm for pyrimidine-CH_3 and SH, respectively, in addition to a triplet at $\delta = 1.28$ and a quartet at $\delta = 4.27$ ppm for the ester ethyl group. Also, its IR spectrum showed absorption bands at 2573 and 1716 cm^{-1} for SH and ester C=O functions, respectively.

The structure of pyrimidine thiol **17** received another support upon its alkylation with chloroacetonitrile and acrylonitrile in the presence of piperidine as a catalyst to afford *S*-cyanomethyl **18a** and *S*-cyanoethyl **18b** derivatives, respectively. ^{1}H NMR spectra of the *S*-alkylated products showed a singlet at $\delta = 4.27$ for SCH_2 (in case of **18a**) and two triplets at $\delta = 3.00$ and 3.47 ppm for SCH_2CH_2 (in case of **18b**). Their IR displayed absorption bands at 2245 and 2229 cm^{-1} for C≡N functions. Also, their ^{13}C NMR displayed the expected SP^3 carbon signals for the *S*-alkyl groups. Compounds **18a** and **18b** seemed to be suitable for further heterocyclizations; thus, refluxing of **18a** in sodium ethoxide solution afforded thienopyrimidine **19** which is present mainly in the more thermodynamically stable form **19B**. Also, hydrazinolysis of **18b** resulted in the formation of pyrazolopyrimidine **20**. The structures of compounds **19** and **20** were established depending on their spectral data. ^{1}H NMR spectra of the latter compounds showed disappearance of the ester ethyl group and appearance of a singlet at $\delta = 13.05$ ppm for OH (in case of **19**) and two singlets at $\delta = 11.46$ and 12.44 ppm for two NH (in case of **20**). Also, their IR spectra showed disappearance of C=O band (in case of **19**) and C≡N band (in case of **20**) (Scheme 4).



Scheme 3 Heterocyclization of compound **1** with different nitrogen nucleophiles



Scheme 4 Reaction of compound **1** with enamine as a synthetic entry to compounds **17**–**20**

Antibacterial activity

Compounds **2**, **3**, **9**, **11**, **13a**, **18b** and **19** were tested in vitro for their antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus* and *Streptococcus faecalis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*) using disk diffusion method [26] at 1 mg/ml disk concentration. Ampicillin was used as antibacterial agent standard. DMSO was used as solvent. The zone of inhibition of bacterial growth was observed.

The results given in Table 1 indicated that:

1. Compounds **2**, **3**, **11**, **13a** and **19** have moderate antibacterial activity against the tested microorganisms.
2. Compound **9** has weak antibacterial activity against the tested microorganisms.
3. Compound **18b** does not have antibacterial activity against the tested microorganisms.

Table 1 In vitro antibacterial activity for a group of the synthesized compounds

Sample	Inhibition zone diameter (mm/mg sample)					
	Bacterial species					
	G+			G+		
	Bacillus subtilis	*Staphylococcus aureus*	*Streptococcus faecalis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Neisseria gonorrhoeae*
Control: DMSO	0.0	0.0	0.0	0.0	0.0	0.0
Standard ampicillin	26	21	27	25	26	28
2	15	14	11	13	15	10
3	13	14	12	15	14	11
9	9	9	9	8	9	8
11	15	15	11	14	14	11
13a	13	11	10	12	12	10
18b	0.0	0.0	0.0	0.0	0.0	0.0
19	18	17	13	16	17	14

Experimental

All melting points are uncorrected. IR spectra (KBr) were run on a Unicam SP 1200G infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra (DMSO-d6) were run on a Bruker spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) with a TMS as internal standard and were carried out at Microanalytical Unit, Faculty of Pharmacy, Cairo University. Elemental analyses and antibacterial evaluation were carried out at Microanalytical Center, Cairo University. Compound **1** was prepared as described in the literature [27].

N-(Carbamoylcarbamothioyl)furan-2-carboxamide (2)

A mixture of compound **1** (0.01 mol) and urea (0.01 mol) in dry acetone (50 ml) was heated under reflux for 6 h. The reaction mixture was then concentrated, cooled and then poured into cold water, and the precipitate formed was filtered off, dried and recrystallized from water to give **2** as pale yellow crystals.

m.p. 162–164 °C, Yield: 71%. IR (KBr, cm^{-1}) υ_{max}: 3336, 3228, 3167 (NH, NH_2), 1686, 1678 (C=O), 1265 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.77–8.09 (m, 3H, furan-H), 10.93 (s, 2H, NH_2), 11.19 (s, 1H, NH), 13.68 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.07, 119.19, 145.21, 148.57, 172.27, 179.03, 181.98. Anal. Calc. for $C_7H_7N_3O_3S$ (213.22): C, 39.43; H, 3.31; N, 19.71; Found: C, 39.54; H, 3.22; N, 19.63.

N-(3-Oxo-2,3-dihydro-1,2,4-thiadiazol-5-yl) furan-2-carboxamide (3)

Bromine (0.01 mol) was added dropwise with stirring to a solution of compound **2** (0.01 mol) in acetic acid (20 ml) at room temperature. The reaction mixture was further stirred for 3 h, and the solid precipitated was filtered off, dried and recrystallized from acetic acid to give **3** as brown crystals.

m.p. 278–280 °C, Yield: 63%. IR (KBr, cm^{-1}) υ_{max}: 3371, 3128 (NH), 1708, 1670 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.75–8.04 (m, 3H, furan-H), 11.94 (s, 1H, NH), 12.08 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.09, 118.53, 146.72, 148.40, 161.54, 162.59, 173.23. Anal. Calc. for $C_7H_5N_3O_3S$ (211.20): C, 39.81; H, 2.39; N, 19.90; Found: C, 39.72; H, 2.27; N, 19.81.

4-(Furan-2-yl)-6-sulfanylidene-5,6-dihydro-1,3,5-triazin-2(1*H*)-one (4)

Compound **2** (0.01 mol) was dissolved in sodium ethoxide solution (prepared by dissolving Na (0.01 mol) in absolute ethanol (50 ml)). The reaction mixture was then kept overnight at room temperature, then poured into cold water and neutralized with dil HCl. The precipitate obtained was filtered off, dried and recrystallized from ethanol to give **4** as yellow crystals.

m.p. 242–244 °C, Yield: 79%. IR (KBr, cm^{-1}) υ_{max}: 3128, 3151 (NH), 1685 (C=O), 1246 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.82–8.16 (m, 3H, furan-H), 11.18 (s, H, NH), 12.63 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.24, 119.17, 145.32, 148.86, 158.24, 172.30, 180.88. Anal. Calc. for $C_7H_5N_3O_2S$ (195.20): C, 43.07; H, 2.58; N, 21.53; Found: C, 43.17; H, 2.49; N, 21.65.

2-(Furan-2-yl)-6,7-dihydro-4*H*- [1, 3] thiazolo[3,2-a] [1, 3, 5] triazin-4-one (5)

A mixture of compound **4** (0.01 mol), 1,2-dichloroethane (0.01 mol) and K_2CO_3 (0.02 mol) in DMF (25 ml) was heated under reflux on a water bath for 6 h. The reaction mixture was then cooled and poured into cold water, and the separated solid was filtered off, dried and recrystallized from ethanol to give **5** as pale brown crystals.

m.p. 158–160 °C, Yield: 60%. IR (KBr, cm^{-1}) υ_{max}: 1670 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 3.49 (t, 2H, ^{3}J = 8.04 Hz, CH_2), 4.12 (t, 2H, ^{3}J = 8.04 Hz, CH_2), 6.71–8.03 (m, 3H, furan-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 34.47, 55.36, 113.60, 119.79, 145.95, 148.51, 151.48, 159.57, 171.11. Anal. Calc. for $C_9H_7N_3O_2S$ (221.24): C, 48.86; H, 3.19; N, 18.99; Found: C, 48.95; H, 3.27; N, 18.86.

2-Benzylidene-*N*-[(furan-2-carbonyl)carbamothioyl] hydrazine-1-carboxamide (6)

A mixture of compound **1** (0.01 mol) and benzaldehyde semicarbazone (0.01 mol) in dry acetone (50 ml) was heated under reflux for 4 h. The reaction mixture was then cooled and poured into cold water, and the separated solid was filtered off, dried and recrystallized from water to give **6** as yellow crystals.

m.p. 166–168 °C, Yield: 65%. IR (KBr, cm^{-1}) υ_{max}: 3140, 3329, 3460 (NH), 1685, 1651 (C=O), 1253 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.48–8.02 (m, 9H, furan-H + phenyl-H + N = CH), 9.67 (s, 1H, NH), 10.24 (s, 1H, NH), 10.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.05, 118.85, 126.97, 129.01, 129.56, 135.04, 145.22, 148.47, 157.61, 166.50, 172.30, 181.95. Anal. Calc. for $C_{14}H_{12}N_4O_3S$ (316.34): C, 53.16; H, 3.82; N, 17.71; Found: C, 53.25; H, 3.92; N, 17.63.

4-(5-Oxo-3-phenyl-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)-6*H*-furo[2,3-*c*]pyrrol-6-one (8)

Compound **6** (0.01 mol) was heated under reflux in sodium ethoxide solution (prepared by dissolving Na (0.01 mol) in

absolute ethanol (50 ml)) for 3 h. The reaction mixture was then cooled, poured into cold water and neutralized with dil HCl. The separated solid was then filtered off, dried and recrystallized from ethanol to give **8** as pale yellow crystals.

m.p. 220–222 °C, Yield: 72%. IR (KBr, cm^{-1}) υ_{max}: 3286 (NH), 1689, 1651 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.51–7.85 (m, 7H, furan-H + phenyl-H), 10.27 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 112.77, 118.56, 127.00, 129.03, 129.47, 135.24, 145.09, 148.80, 151.75, 157.27, 168.47, 176.35. Anal. Calc. for $C_{14}H_8N_4O_3$ (280.24): C, 60.00; H, 2.88; N, 19.99; Found: C, 60.11; H, 2.79; N, 19.86.

N-[6-(furan-2-yl)-4-sulfanylidene-3,4-dihydro-2*H*-1,3,5-oxadiazin-2-ylidene]urea (9)

A mixture of compound **1** (0.01 mol) and biuret (0.01 mol) in dioxane (50 ml) was heated under reflux for 8 h. The reaction mixture was concentrated then cooled and poured into cold water, and the precipitate formed was filtered off, dried and recrystallized from ethanol to give **8** as brown crystals.

m.p. 182–184 °C, Yield: 83%. IR (KBr, cm^{-1}) υ_{max}: 3336, 3209 (NH, NH_2), 1670 (C=O), 1265 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.72–8.02 (m, 3H, furan-H), 9.66 (s, 2H, NH_2), 11.16 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.07, 118.84, 145.21, 148.59, 157.65, 166.02, 170.45, 181.99. Anal. Calc. for $C_8H_6N_4O_3S$ (238.23): C, 40.34; H, 2.54; N, 23.52; Found: C, 40.41; H, 2.44; N, 23.63.

1-Benzoyl-5-[(4-chlorophenyl)methylidene]-3-(furan-2-carbonyl)-2-sulfanylideneimidazolidin-4-one (10)

A mixture of compound **1** (0.01 mol), hippuric acid (0.01 mol) and *p*-chlorobenzaldehyde (0.01 mol) in dry pyridine (15 ml) was heated under reflux for 5 h. The reaction mixture was then cooled, poured into cold water and neutralized with dil HCl. The solid obtained was filtered off, dried and recrystallized from ethanol to give **10** as yellow crystals.

m.p. 190–192 °C, Yield: 69%. IR (KBr, cm^{-1}) υ_{max}: 1697, 1654 (C=O), 1234 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 7.38–8.35 (m, 13H, furan-H + phenyl-H + Aryl-H + exocyclic vinylic-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.62, 115.21, 118.42, 125.36, 127.04, 128.53, 129.59, 129.81, 132.53, 133.00, 133.98, 134.24, 134.33, 136.35, 145.25, 148.46, 163.70, 165.39, 167.20, 180.83. Anal. Calc. for $C_{22}H_{13}ClN_2O_4S$ (436.88): C, 60.49; H, 3.00; N, 6.41; Found: C, 60.56; H, 3.09; N, 6.35.

2-{[(Furan-2-carbonyl)carbamothioyl]amino}benzoic acid (11)

A mixture of compound **1** (0.01 mol) and anthranilic acid (0.01 mol) in dry acetone (50 ml) was heated under reflux for 6 h. The reaction mixture was then cooled and poured into cold water, and the solid obtained was filtered off, dried and recrystallized from ethanol to give **11** as pale yellow crystals.

m.p. 184–186 °C, Yield: 88%. IR (KBr, cm^{-1}) υ_{max}: 3275, 3124 (NH), 1685, 1663 (C=O), 1269 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 7.16–8.03 (m, 7H, furan-H + Aryl-H), 11.75 (s, 1H, NH), 12.17 (s, 1H, NH), 12.97 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.19, 118.00, 125.12, 126.77, 127.86, 130.93, 133.78, 138.52, 145.10, 148.87, 167.58, 168.40, 179.78. Anal. Calc. for $C_{13}H_{10}N_2O_4S$ (290.30): C, 53.79; H, 3.47; N, 9.65; Found: C, 53.87; H, 3.58; N, 9.55.

3-(Furan-2-carbonyl)-2-sulfanylidene-2,3-dihydroquinazolin-4(1*H*)-one (12)

A mixture of compound **11** (0.01 mol) and Ac_2O (20 ml) was heated under reflux for 4 h. The reaction mixture was then cooled, and the solid obtained was filtered off, dried and recrystallized from ethanol to give **12** as white crystals.

m.p. 264–266 °C, Yield: 81%. IR (KBr, cm^{-1}) υ_{max}: 3209 (NH), 1658 (C=O), 1273 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 7.50–8.05 (m, 7H, furan-H + quinazoline-H), 11.90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 112.45, 119.82, 124.74, 127.44, 129.33, 132.24, 136.75, 145.07, 148.02, 153.35, 169.28, 171.32, 185.02. Anal. Calc. for $C_{13}H_8N_2O_3S$ (272.28): C, 57.35; H, 2.96; N, 10.29; Found: C, 57.44; H, 2.87; N, 10.35.

N-[(1,3-thiazol-2-yl)carbamothioyl]furan-2-carboxamide (13a) and *N*-(phenylcarbamothioyl) furan-2-carboxamide (13b)

General method

A mixture of compound **1** (0.01 mol) and 2-aminothiazole or aniline (0.01 mol) in dry acetone (50 ml) was stirred at room temperature for 3 h. The reaction mixture was then poured into cold water, and the separated precipitate was filtered off, dried and recrystallized from the proper solvent to give **13a** and **13b**, respectively.

Compound 13a

From water as yellow crystals, m.p. 120–122 °C, Yield: 85%. IR (KBr, cm^{-1}) υ_{max}: 3336, 3113 (NH), 1666 (C=O), 1253 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.73–8.11 (m, 5H, furan-H + thiazole-H), 10.94 (s, 1H, NH), 12.61 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 112.73, 114.30, 118.76, 137.92, 145.29, 148.67, 169.21, 177.84, 182.07. Anal. Calc. for $C_9H_7N_3O_2S_2$ (253.30): C, 42.68; H, 2.79; N, 16.59; Found: C, 42.75; H, 2.68; N, 16.46.

Compound 13b

From water as pale brown crystals, m.p. 114–116 °C, Yield: 87%. IR (KBr, cm^{-1}) υ_{max}: 3294, 3190 (NH), 1670 (C=O), 1276 (C=S) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.77–8.08 (m, 8H, furan-H + phenyl-H), 11.28 (s, 1H, NH), 12.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.15, 119.15, 126.82, 128.86, 129.40, 138.43, 145.16, 148.93, 176.94, 179.19. Anal. Calc. for $C_{12}H_{10}N_2O_2S$ (246.29): C, 58.52; H, 4.09; N, 11.37; Found: C, 58.63; H, 4.17; N, 11.29.

N-(2*H*-[1,3]thiazolo[3,2-*b*][1,2,4]thiadiazol-2-ylidene)furan-2-carboxamide (14) and 3-Oxa-6-thia-5,10*b*-diazacyclopenta[*c*]fluoren-4-one (16)

General method

Bromine (0.01 mol) was added dropwise to a stirred solution of compound **13a** or **13b** (0.01 mol) in acetic acid (30 ml). The reaction mixture was then stirred at room temperature overnight and then poured into cold water. The separated solid was filtered off, dried and recrystallized from the proper solvent to give **14** and **16**, respectively.

Compound (14)

From ethanol as pale brown crystals, m.p. 202–204 °C, Yield: 66%. IR (KBr, cm^{-1}) υ_{max}: 1627 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.73–8.26 (m, 5H, furan-H + thiazole-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.08, 116.70, 118.85, 145.25, 147.78, 148.64, 168.88, 170.20, 181.17. Anal. Calc. for $C_9H_5N_3O_2S_2$ (251.29): C, 43.02; H, 2.01; N, 16.72; Found: C, 43.13; H, 2.11; N, 16.65.

Compound (16)

From ethanol as white crystals, m.p. 252–254 °C, Yield: 60%. IR (KBr, cm^{-1}) υ_{max}: 1674 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.70–8.02 (m, 6H, furan-H + Ar–H). ^{13}C NMR (DMSO-d_6) δ (ppm): 113.52, 116.07, 120.47, 125.97, 128.78, 129.53, 130.05, 147.88, 149.26, 150.44, 162.56, 171.55. Anal. Calc. for $C_{12}H_6N_2O_2S$ (242.26): C, 59.50; H, 2.50; N, 11.56; Found: C, 59.41; H, 2.39; N, 11.64.

Ethyl 2-(furan-2-yl)-4-methyl-6-sulfanylpyrimidine-5-carboxylate (17)

A mixture of compound **1** (0.01 mol), ethyl 3-aminocrotonate (0.01 mol) in dry acetone (50 ml) was stirred at room temperature for 6 h. The reaction mixture was then poured into cold water, and the separated solid was filtered off, dried and recrystallized from ethanol to give 1**7** as yellow crystals. m.p. 84–86 °C, Yield: 67%. IR (KBr, cm^{-1}) υ_{max}: 2573 (SH), 1716 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.28 (t, 3H, ^3J = 7.08 Hz, $OCH_2\underline{CH_3}$), 2.68 (s, 3H, pyrimidine-CH_3), 4.27 (q, 2H, ^3J = 7.08 Hz, $O\underline{CH_2}CH_3$), 6.79–8.07 (m, 3H, furan-H), 14.23 (s, 1H, SH). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.30, 21.97, 61.76, 113.25, 114.88, 117.93, 144.99, 148.42, 155.30, 165.63, 167.73, 180.39. Anal. Calc. for $C_{12}H_{12}N_2O_3S$ (264.31): C, 54.53; H, 4.58; N, 10.60; Found: C, 54.61; H, 4.49; N, 10.47.

Ethyl 4-[(cyanomethyl) sulfanyl]-2-(furan-2-yl)-6-methylpyrimidine-5-carboxylate (18a) and Ethyl 4-[(2-cyanoethyl) sulfanyl]-2-(furan-2-yl)-6-methylpyrimidine-5-carboxylate (18b)

General method

A mixture of compound **17** (0.01 mol), chloroacetonitrile or acrylonitrile (0.01 mol) and catalytic amount of piperidine in absolute ethanol (30 ml) was heated under reflux for 3 h. The reaction mixture was then cooled and poured into cold water, and the solid obtained was filtered off, dried and recrystallized from the proper solvent to give **18a** and **18b**, respectively.

Compound 18a

From ethanol as brown crystals, m.p. 174–176 °C, Yield: 83%. IR (KBr, cm^{-1}) υ_{max}: 2245 (C≡N), 1685 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.34 (t, 3H, ^3J = 7.08 Hz, $OCH_2\underline{CH_3}$), 2.66 (s, 3H, pyrimidine-CH_3), 4.27 (s, 2H, SCH_2), 4.36 (q, 2H, ^3J = 7.08 Hz, $O\underline{CH_2}CH_3$), 6.78–8.04 (m, 3H, furan-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.38, 16.65, 24.91, 62.54, 113.48, 117.29, 118.36, 119.18, 147.84, 150.95, 155.29, 165.32, 167.87, 168.11. Anal. Calc. for $C_{14}H_{13}N_3O_3S$ (303.34): C, 55.43; H, 4.32; N, 13.85; Found: C, 55.50; H, 4.41; N, 13.78.

Compound 18b

From ethanol as white crystals, m.p. 126–128 °C, Yield: 81%. IR (KBr, cm^{-1}) υ_{max}: 2229 (C≡N), 1701 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.33 (t, 3H, ^3J = 7.08 Hz, $OCH_2\underline{CH_3}$), 2.54 (s, 3H, pyrimidine-CH_3), 3.00 (t, 2H, ^3J = 6.68 Hz, CH_2), 3.47 (t, 2H, ^3J = 6.68 Hz, CH_2), 4.35 (q, 2H, ^3J = 7.08 Hz, $O\underline{CH_2}CH_3$), 6.74–7.98 (m, 3H, furan-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.37, 17.78, 24.06, 25.87, 62.27, 113.25, 116.17, 119.78, 120.50, 147.39, 151.22, 155.39, 165.49, 165.96, 168.24. Anal. Calc. for $C_{15}H_{15}N_3O_3S$ (317.37): C, 56.77; H, 4.76; N, 13.24; Found: C, 56.84; H, 4.66; N, 13.35.

2-(Furan-2-yl)-5-hydroxy-4-methylthieno[2,3-*d*] pyrimidine-6-carbonitrile (19)

Compound **18a** (0.01 mol) was heated under reflux in sodium ethoxide solution (prepared by dissolving Na (0.01 mol) in absolute ethanol (50 ml)) for 3 h. The reaction mixture was then cooled, poured into cold water and neutralized with dil HCl. The solid obtained was filtered off, dried and recrystallized from ethanol to give **19** as pale brown crystals.

m.p. 252–254 °C, Yield: 69%. IR (KBr, cm^{-1}) υ_{max}: 3421 (OH), 2218 (C≡N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.84 (s, 3H, pyrimidine-CH_3), 6.74–7.98 (m, 3H, furan-H), 13.05 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ (ppm): 18.93, 113.34, 114.27, 115.76, 119.19, 134.13, 147.15, 151.35, 154.92, 158.73, 165.85, 166.34. Anal. Calc. for $C_{12}H_7N_3O_2S$ (257.27): C, 56.02; H, 2.74; N, 16.33; Found: C, 56.11; H, 2.67; N, 16.24.

6-(Furan-2-yl)-4-methyl-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (20)

A mixture of compound **18b** (0.01 mol) and hydrazine hydrate (1 ml) in ethanol (30 ml) was heated under reflux on water bath for 5 h. The solid formed on hot was filtered off, dried and recrystallized from n-butanol to give **20** as white crystals.

m.p. > 300 °C, Yield: 64%. IR (KBr, cm^{-1}) υ_{max}: 3367, 3136 (NH), 1670 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.69 (s, 3H, pyrimidine-CH_3), 6.69–7.90 (m, 3H, furan-H), 11.46 (s, 1H, NH), 12.44 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 19.07, 112.87, 114.07, 146.02, 152.54, 155.27, 156.00, 164.08, 167.11, 171.40. Anal. Calc. for $C_{10}H_8N_4O_2$ (216.20): C, 55.56; H, 3.73; N, 25.91; Found: C, 55.67; H, 3.65; N, 25.80.

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