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Heterocyclization of Cyanoacetamide Derivatives: Synthesis and Biological Activity of Novel Azoles and Azines

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Abstract—The intermolecular cyclization of *N*-benzyl-2-cyanoacetamide with carbon disulfide followed by intramolecular cyclization gave thioxothiazinone **3**. This compound was used to synthesize a series of novel fused furopyrrole, pyridine, pyrimidine and other azine and azole derivatives. The Michael-type reaction of compound **3** with maleic anhydride followed by pyrrole and furan cyclizations and aromatization yielded polycyclic compound **7**. The [3+3]-cycloaddition of benzylidene malononitrile and its derivative to compound **3** gave pyridothiazines **10–12**. The ring opening in compound **3** under the action of urea or thiourea followed by pyrimidine cyclization and subsequent air oxidation resulted in the synthesis of oxa- and thiadiazolopyrimidinones **15** and **16**, respectively. The reaction of compound **3** with H_2O_2 in a basic medium provided pyrimidine derivative **17**. The oxidation of compound **3** with Br_2 in an acid medium led to bromo derivative **19**. The synthesized novel compounds were characterized by elemental analysis and IR and ^1H and ^{13}C NMR spectroscopy and tested antibacterial and anticancer activities.

Keywords: pyridinone, pyrimidine, thiazine, chromene, anticancer activity

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INTRODUCTION

Cyanoacetamides are highly reactive compounds. They are extensively utilized as reactants or reaction intermediates, since the carbonyl and cyano functions in these compounds are suitably arranged to enable reactions with common bidentate reagents to form a variety of heterocyclic compounds [1–8]. Moreover, the active hydrogen on C^2 in these compounds can take part in a variety of condensation and substitution reactions. In addition, many cyanoacetamide derivatives have been reported to exhibit antibacterial [9], anticoagulant [10], antifungal [11], antihistaminic [12], antileishhumanial [13], antimicrobial [14], and herbicidal properties [15]. The literature covering the chemistry of cyanoacetamide derivatives is limited. In particular, the review of the chemistry and reactions of cyanothioacetamides (in Russian) was published as far back as 1999 [16]. The main objective of the present work was to provide a comprehensive account of the synthetic utility of *N*-aryl- and/or *N*-heterylcyanoacetamides in constructing various organic heterocycles and to highlight their potential in developing better chemotherapeutic agents.

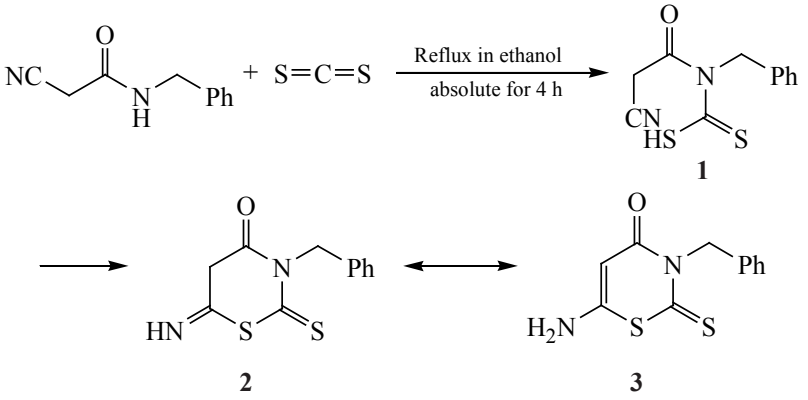
RESULTS AND DISCUSSION

The cyclocondensation of *N*-benzyl-2-cyanoacetamide with carbon disulfide provides thiazinone **3**. The reaction presumably involves the formation of a non-isolable aza adduct **1** and its intramolecular cyclization via addition of the mercapto function to cyano group followed by a [1,3]-sigmatropic shift (Scheme 1).

The ^1H NMR spectrum of compound **3** displays a downfield signal at 8.21 ppm from the NH_2 protons, a multiplet of aromatic protons at 7.25–7.33 ppm, an ethylene proton singlet at 5.86 ppm, and a doublet of the CH_2N protons at 4.33 and 4.55 ppm. The ^{13}C NMR spectrum shows C=S and C=O carbon signals at 167.69 and 161.02 ppm and a CH_2 carbon at 85 ppm. The IR spectrum contains a C=O stretching band at 1650 cm^{-1} (the frequency is decreased by the +*M* effects of S and NH_2).

Due to the presence of a cyclic enamine system, compound **3** can undergo heterocyclization to form interesting condensed polycyclic compounds. Thus, the cyclocondensation of compound **3** with maleic anhyd-

Scheme 1.

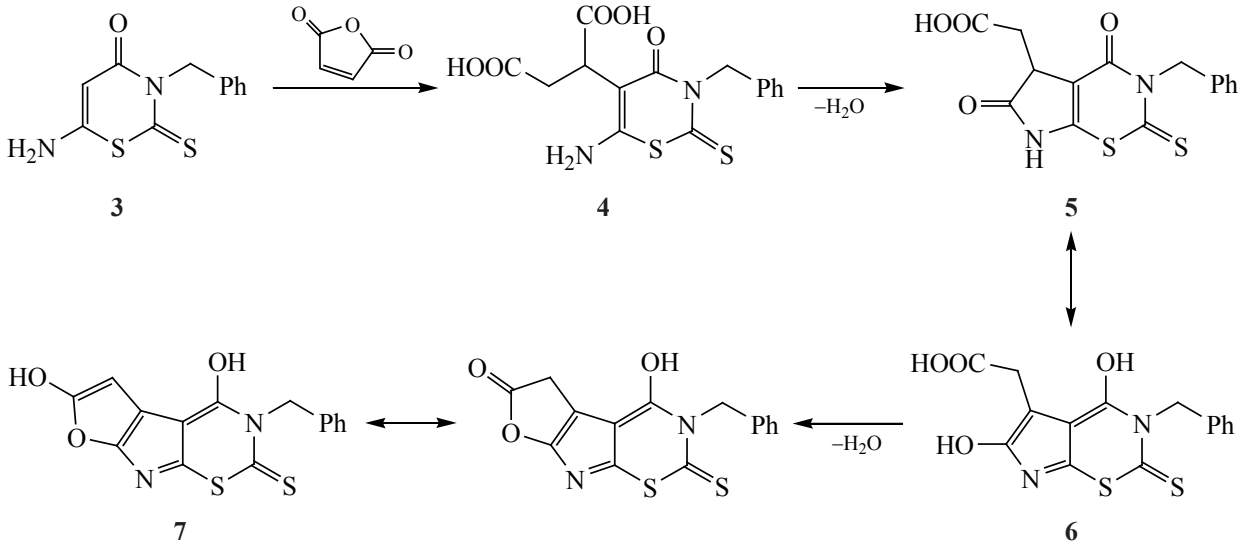


ride affords furopyrrole thiazine derivative **7** through the formation Michael adduct **4** and its cyclization via the condensation of the enamine nitrogen with the carboxyl group (with elimination of a water molecule) and subsequent intramolecular cycloaddition (Scheme 2).

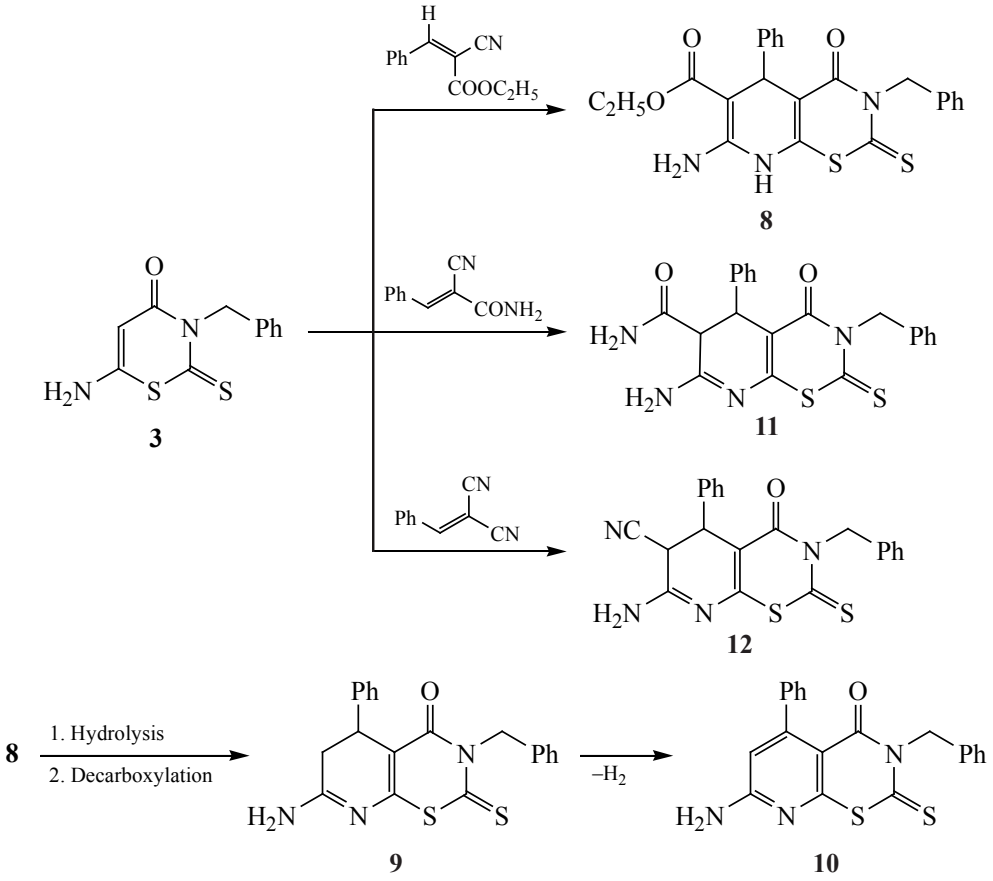
Compound **3** undergoes [3+3]-cycloaddition reaction with ethyl benzylidenecyanoacetate followed by hydrolysis, decarboxylation, and aromatization to furnish pyridothiazine derivative **10** (Scheme 3). The ^{1}H NMR spectrum of compound **10** displays aromatic proton signals signal at 7.25–7.30 ppm and a benzylic signal at 5.16–5.25 ppm. The IR spectrum of **10** shows bands at 3330 and 1663 cm^{-1} due to NH_2 and C=O stretching vibrations, respectively.

Amidopyrrolothiazine **11** was obtained as a result of the cycloaddition reaction between compound **3** and benzylidene cyanoacetamide (Scheme 3). The ^{1}H NMR spectrum of compound **11** displays a downfield broad signal of the NH_2 protons at 10.31 ppm, as well as amide and benzylic proton signals at 5.12 and 4.16–4.20 ppm, respectively. The IR spectrum contains bands at 3300, 1650, and 1250 cm^{-1} from the NH_2, C=O, and C=S groups, respectively. As shown in Scheme 3, compound **12** forms as a result of the attack of the enamine carbon in **3** to the polarized double bond in benzylidene malonitrile, after which the exocyclic amino group adds to the cyano function. The spectral characteristics of compound **12** are consistent with the proposed structure. The ^{1}H NMR spectrum of compound **12** displays a downfield broad singlet for NH_2 at 11.6 ppm, a signal of $PhCH_2$ methylene protons at 5.26–5.27 ppm, as well as PhCH and CHCN methine proton signals at 5.10–5.12 and 4.36–4.37 ppm, respectively. The IR spectrum

Scheme 2.



Scheme 3.



displays bands at 3300, 2198, 1650, 1547, and 1220 cm^{-1} assignable to the NH_2, CN, C=O, C=C, and C=S groups, respectively.

Compound **3** undergoes ring opening under the action of urea or thiourea followed by cyclization to form pyrimidine derivative **14**, whose air oxidation of leads to oxadiazolopyrimidine **15** or thiadiazolopyrimidine **16**, respectively (Scheme 4). The ^1H NMR of compound **16** shows a downfield signal for NH at 10.54 ppm, as well as aromatic and CH_2N methylene proton signals at 7.26–7.32 and 3.98 ppm, respectively. The IR spectrum displays bands at 3300 (OH), 3170 (NH), and 1225 (C=S) cm^{-1}.

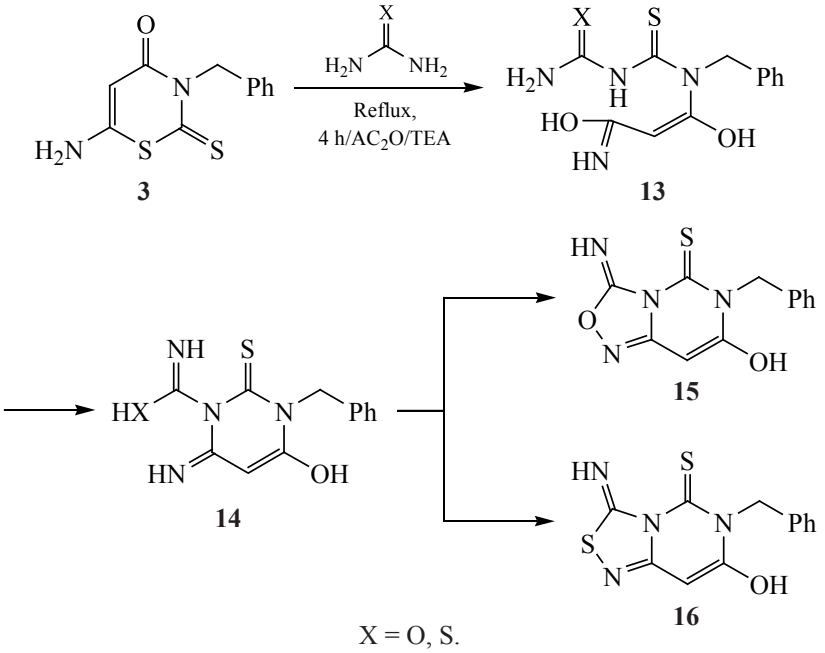
Treatment of thiazinthione derivative **3** with a mixture of NaOH and H_2O_2 leads to ring transformation to form mercaptopyrimidine **17** presumably via Dimorth rearrangement. At the same time, no disulfide **18** was detected (Scheme 5). The ^1H NMR spectrum of compound **17** displays downfield singlets at 8.22, 8.20, and 8.19 ppm from the OH, NH, and SH protons, respectively.

The ring transformation in compound **3** under the action of Br_2 in acetic acid under reflux followed by benzylic bromination produces derivative **19** and no expected desulfurized product **20** (Scheme 6). The ^1H NMR spectrum of compound **19** shows downfield signals of the NH, SH, and benzylic PhCHBr protons at 10.72, 9.63, and 4.98 ppm, respectively.

Antimicrobial and antifungal activity testing. Compounds **7**, **15**, **16**, and **19** were tested for in vitro antimicrobial activity against Gram-positive (*S. aureus*, *S. faecalis*, and *B. subtilis*) and Gram-negative bacteria (*E. coli*, *N. gonorrhoeae*, and *P. aeruginosa*). The antifungal activity of the compounds was tested against two fungi *C. albicans* and *A. flavus*. According to the resulting data (Table 1), compounds **15** and **19** showed inhibitory activity against *S. aureus*, *E. coli*, *S. faecalis*, *B. subtilis*, *N. gonorrhoeae*, *P. aeruginosa*, *A. flavus*, and *C. albicans* strains.

The biological activity of the test compounds was determined by a modified Kirby–Bauer disc diffusion method [17]. Briefly, 100 μl of a 100 mL of a solution

Scheme 4.

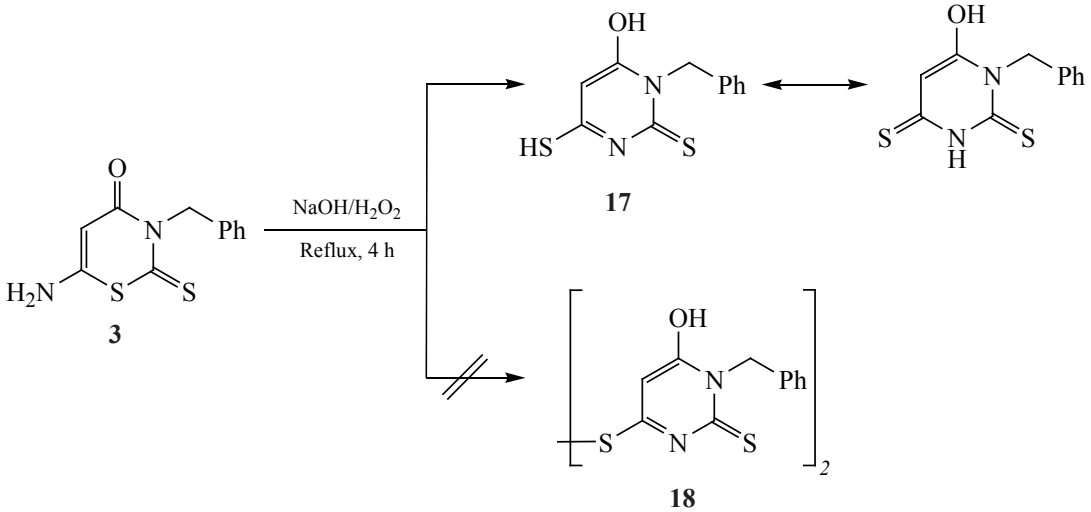


X = O, S.

of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 108 cells/mL for bacteria and 105 cells/mL for fungi [18].

Anticancer activity testing. Compounds **7**, **15**, **16**, and **19** were tested against HepG-2 (human hepatocellular cancer cell line) and HCT-116 cells (human colon cancer cell line) obtained from VACSERA Tissue

Scheme 5.



Scheme 6.

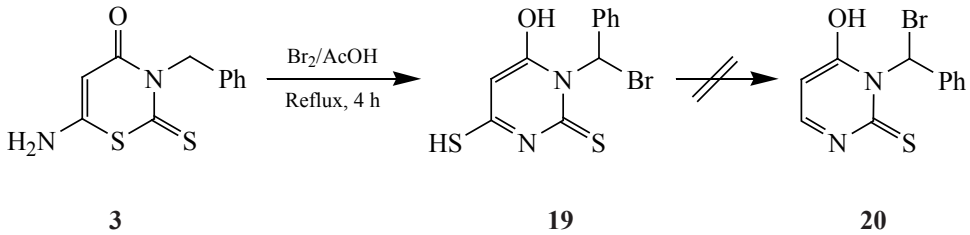


Table 1. Antibacterial and antifungal activity testing of the synthesized compounds, control: DMSO

Compound no.		Inhibition zone diameter, mm/mg sample							
		bacterial species						fungi	
		G+			G–				
		B. subtilis	*S. aureus*	*S. faecalis*	*E. coli*	*N. gonorrhoeae*	*P. aeruginosa*	*A. flavus*	*C. albicans*
Standard	Ampicillin (antibacterial)	26	21	27	25	28	26	–	–
	Amphotericin B (antifungal)	–	–	–	–	–	–	17	21
	17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	15	12	9	0.0	9	0.0	9	0.0	0.0
	16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	19	12	14	14	12	13	12	0.0	0.0

Culture Unit (Cairo, Egypt). The procedures of testing are described in detail in [19–21].

The results of the testing of the effect of compounds **7**, **15**, **16,** and **19** on the in vitro growth of HepG-2 cells after continuous exposure for 48 h are presented in Table 2.

All the test compounds were able to inhibit the growth of the test HepG-2 cells in a dose-dependent manner. As seen from Table 2, compound **15** showed the highest growth inhibitory activity, while not as high as the reference Doxorubicin. Compounds **7** and **19** exhibited a moderate growth inhibitory effect against HepG-2 cells, and compound **16** was the least active.

The cytotoxic activity of compounds **7**, **15**, **16** and **19** against HepG-2 cells was evaluated using solutions of different concentrations (0, 3.9, 7.8, 15.6, 31.25, 62.5, 125, 250, and 500 μg/mL). The resulting cell viabities (%) and IC_{50} values (mg/mL) are listed in Table 3.

As seen from Table 3, compounds **15** and **19** showed a high cytotoxic activity against HepG-2 cancer cell line, whereas compounds **7** and **16** were moderately active.

The results of the testing of the effect of compounds **7**, **15**, **16**, and **19** on the in vitro growth of HCT-116 cells after continuous exposure for 48 h are presented in Table 4.

All the test compounds were able to inhibit the growth of HCT-116 cells in a dose-dependent manner. As seen from Table 4, compound **15** showed a strong inhibitory effect against HCT-116 cells line, but not as strong as the reference drug Doxorubicin. Compound **16** proved the least active, while compounds **7**, **19** exhibited a moderate growth inhibitory effect. For the cytotoxicity testing of compounds **7**, **15**, **16** and **19** against the HCT-116 cell line, solutions of the same concentrations as in the cytotoxicity testing against the HepG-2 cell line. The resulting cell viabities (%) and IC_{50} values (mg/mL) are listed in Table 5.

As seen from Table 5, compounds **15** and **19** showed a high cytotoxic activity against the HCT-116 cancer cell line, and compounds **7** and **16** were moderately active.

Table 2. Effect of the synthesized compounds on HepG-2 cell growth

Compound no.	GI_{50}, μmol L^{-1}
Doxorubicin	0.36
7	89.20
15	9.86
16	248
19	40.9

Table 3. Cytotoxicity testing of the synthesized compounds against the HepG-2 cell line

Compound no.	Viability rate, %									IC_{50}, mg/mL
	0	3.9	7.8	15.6	31.25	62.5	125	250	500	
	μg/mL									
Doxorubicin	100	25.59	20.81	18.13	13.05	6.13	4.22	2.70	1.72	0.36
7	100	100	96.18	86.59	72.60	56.34	41.52	29.78	12.46	89.2
15	100	67.31	52.95	41.76	32.47	20.89	12.52	6.98	3.74	9.86
16	100	100	100	98.74	93.21	86.45	72.64	49.72	32.19	248
19	100	96.21	82.63	70.94	53.60	41.89	34.56	15.27	6.48	40.9

Table 4. Effect of the synthesized compounds on HCT-116 cell growth

Compound no.	GI_{50}, μmol L^{-1}
Doxorubicin	0.49
7	61.6
15	14.4
16	383
19	30.9

EXPERIMENTAL

The melting points were measured using an Electro thermal IA 9100 apparatus in open capillary tubes and are uncorrected. All experiments were carried out using dry solvents. Thin-layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates with detection in UV light. The products were purified by crystallization. The IR spectra were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 spectrophotometer in KBr discs. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury VX-300 spectrometer at 300 and 75.4 MHz, respectively, in DMSO-d_6. All chemical shifts were expressed in ppm on the δ scale using TMS as internal reference. The elemental analysis and in vitro antimicrobial activity testing were performed at the Microanalysis Center, Cairo University, Giza, Egypt.

6-Amino-3-benzyl-2-thioxo-2*H*-1,3-thiazin-4(3*H*)-one (3). A solution of carbon disulfide (0.01 mol), compound **1** (0.01 mol), and potassium hydroxide (0.01 mol) in absolute ethanol (20 mL) was refluxed for 6 h and then poured into glacial acetic acid. The precipitate that formed was filtered off, washed with

Table 5. Cytotoxicity testing of the synthesized compounds against the HCT-116 cell line

Compound no.	Viability rate, %									IC_{50}, mg/mL
	0	3.9	7.8	15.6	31.25	62.5	125	250	500	
	μg/mL									
Doxorubicin	100	28.86	24.82	19.38	11.04	6.51	4.86	3.36	2.08	0.49
7	100	99.72	95.23	86.39	73.46	49.28	36.45	23.16	8.91	61.6
15	100	75.82	61.34	47.86	39.15	24.96	15.73	7.87	4.12	14.4
16	100	100	100	100	99.58	92.76	79.83	64.49	37.25	383
19	100	88.42	79.17	64.39	49.72	38.68	27.14	18.62	8.71	30.9

water, dried, and crystallized from ethanol. Yield 90%, white crystals, mp 138–142°C. IR spectrum, ν, cm^{-1}: 3212 (NH_2), 1650 (C=O), 1492 (C=N), 1295 (C=S). ^1H NMR spectrum, δ, ppm: 4.44 d (2H, CH_2N, *J* 7.0 Hz), 5.86 s (1H, CH olefinic), 7.25–7.33 m ($5H_{arom}$), 8.21 s (2H, NH_2). ^{13}C NMR spectrum, δ, ppm: 43.37 (CH_2), 85.87 (=CH), 126.98 (phenyl carbons), 127.93, 128.70, 137.70, 140.12, 153.13, 156.06 (=C–NH_2), 161.02 (C=O), 167.69 (C=S). Found, %: C 52.50; H 3.95; N 11.00; O 6.20; S 26.40. $C_{11}H_{10}N_2OS_2$. Calculated, %: C 52.77; H 4.03; N 11.19; O 6.39; S 26.62. *M* 250.33.

3-Benzyl-4-hydroxy-6-hydroxyfuro[3',2':4,5]-pyrrolo[3,2-*e*][1,3]thiazine-2(3*H*)-thione (7) A solution of maleic anhydride (0.01 mol), compound **3** (0.01 mol), and sodium acetate (0.01 mol) in acetic acid (20 mL) was refluxed for 6 h and then poured into ice water. The precipitate that formed was filtered off, washed with water, dried and crystallized from acetic acid. Yield 94%, yellow powder, mp 78–82°C. IR spectrum, ν, cm^{-1}: 3250 (OH), 3174 (NH), 1650 (C=O), 1575 (C=C), 1326 (C=S). ^1H NMR spectrum, δ, ppm: 4.55 d (2H, CH_2Ph, *J* 5.5 Hz), 5.00 d.d (2H, CH_2, *J* 31.0 Hz), 5.43 d (1H, CH, *J* 35.5 Hz), 7.26–7.32 m ($5H_{arom}$), 10.45 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 42.22 (CH_2), 127.45 (phenyl carbons), 127.69, 127.76, 128.32, 128.53, 128.59, 139.16 (=C–OH), 164.48 (imine carbon), 184.31 (=C–OH), 201.63 (C=S). Found, %: C 54.33; H 2.99; N 8.60; O 14.33; S 19.39. $C_{15}H_{10}N_2O_3S_2$. Calculated, %: C 54.53; H 3.05; N 8.84; O 14.53; S 19.41. *M* 330.01.

7-Amino-3-benzyl-5-phenyl-2-thioxo-2*H*-pyrido[3,2-*e*][1,3]thiazin-4(3*H*)-one (10). A solution compound **3** (0.01 mol), (*Z*)-2-benzylidene-3-oxopentanenitrile (0.01 mol), and 3 drops of trimethylamine in DMF (20 mL) was refluxed for 6 h and then pour in several portions into HCl diluted with ice water. The precipitate that formed was filtered off, washed in water, dried, and crystallized from DMF. Yield 93%, yellow powder, mp 148–152°C. IR spectrum, ν, cm^{-1}: 3330 (NH_2), 1663 (C=O), 1563 (C=C), 1220 (C=S). ^1H NMR spectrum, δ, ppm: 5.21 d (2H, CH_2Ph, *J* 34.4 Hz), 7.25–7.30 m (13H, H_{arom} and NH_2). Found, %: C 64.00; H 4.00; N 11.00; O 4.19; S 16.97. $C_{20}H_{15}N_3OS_2$. Calculated, %: C 63.63; H 4.00; N 11.13; O 4.24; S 17.00. *M* 377.48.

7-Amino-3-benzyl-4-oxo-5-phenyl-2-thioxo-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*e*][1,3]thiazine-6-carboxamide (11). A solution of (*Z*)-2-cyano-3-phenylacrylamide (0.01 mol), compound **3** (0.01 mol), and 3 drops of TEA in DMF (20 mL) was refluxed for 6 h the solution was poured into dilute HCl. The precipitate that formed was filtered off, washed in water, dried, and crystallized from DMF. Yield 95%, brown powder, mp 118–122°C. IR spectrum, ν, cm^{-1}: 3300 (NH_2), 1650 (C=O), 1575 (C=C), 1250 (C=S). ^1H NMR spectrum, δ, ppm: 4.18 d (2H, CH_2Ph, *J* 8.0 Hz), 4.46–4.70 m (2H, CH–CH), 5.12 s (2H, NH_2C=O), 7.30–7.32 m ($10H_{arom}$), 10.32 d (2H, NH_2, *J* 5.0 Hz). Found, %: C 59.00; H 3.20; N 13.11; O 3.98; S 15.00. $C_{21}H_{18}N_4O_2S_2$. Calculated, %: C 59.70; H 3.82; N 13.26; O 4.00; S 15.20. *M* 422.52.

7-Amino-3-benzyl-4-oxo-5-phenyl-2-thioxo-3,4,5,6-tetrahydro-2*H*-pyrido[3,2-*e*][1,3]thiazine-6-carbonitrile (12). A mixture of 2-benzylidenemalononitrile (0.01 mol), compound **3** (0.01 mol), and 3 drops of TEA was refluxed in DMF (20 mL) for 6 h and then poured in several portions into dilute HCl. The precipitate that formed was filtered off, washed with water, dried, and crystallized from DMF. Yield 96%, beige powder, mp 128–132°C. IR spectrum, ν, cm^{-1}: 3330 (NH_2), 2198 (CN), 1650 (C=O), 1547 (C=C), 1220 (C=S). ^1H NMR spectrum, δ, ppm: 11.6 s (2H, NH_2), 7.31–7.35 m ($10H_{arom}$), 5.27 d (2H, CH_2Ph, *J* 8.5 Hz), 5.11 d (1H, PhCH, *J* 9.0 Hz), 4.37 d (1H, NC–CH, *J* 6.5 Hz). Found, %: C 60.00; H 3.60; N 13.70; O 3.55; S 15.66. $C_{21}H_{16}N_4OS_2$. Calculated, %: C 62.35; H 3.99; N 13.85; O 3.96; S 15.86. *M* 404.51.

6-Benzyl-7-hydroxy-3-imino-3*H*-[1,2,4]oxadiazolo[4,3-*c*]pyrimidine-5(6*H*)-thione (15). A mixture of urea (0.01 mol), compound **3** (0.01 mol), and sodium acetate (0.01 mol) was refluxed for 6 h in acetic acid (20 mL) and then poured into KOH solution. Then precipitate that formed was filtered off and crystallized from acetic acid. Yield 88%, orange powder, mp 83–87°C. IR spectrum, ν, cm^{-1}: 3167 (OH), 2922 (NH), 1538 (C=C), 1328 (C=S). ^1H NMR spectrum, δ, ppm: 4.55 d (2H, CH_2Ph, *J* 5.6 Hz), 5.33 s (1H, NH), 7.25–7.33 m ($6H_{arom}$), 10.42 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 42.22 (CH_2), 128.32 (phenyl carbons), 128.53, 128.59, 128.74, 128.89, 128.92, 164.43 (imine carbons), 172.67, 184.31 (=C–OH), 201.63 (C=S). Found, %: C 52.00; H 3.60; N 20.33; O 11.60; S 11.66. $C_{12}H_{10}N_4O_2S$. Calculated, %: C 52.54; H 3.67; N 20.43; O 11.67; S 11.69. *M* 274.30.

6-Benzyl-7-hydroxy-3-imino-3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidine-5(6*H*)-thione (16). A solution of thiourea (0.01 mol), compound **3** (0.01 mol), and sodium acetate (0.01 mol) was refluxed in acetic acid (20 mL) for 6 h and then poured into KOH solution and stirred until a precipitate formed. The precipitate was filtered off and crystallized from acetic acid. Yield 95%, orange powder, mp 158–162°C. IR spectrum, ν, cm^{-1}: 3300 (OH), 3170 (NH), 1650 (C=O), 1530 (C=C), 1225 (C=S). ^{1}H NMR spectrum, δ, ppm: 3.98 d (2H, CH_2N, *J* 18.0 Hz), 4.54 d (2H, CH_2Ph, *J* 6.0 Hz), 7.26–7.32 m ($6H_{arom}$), 10.54 s (1H, NH). Found, %: C 49.00; H 3.40; N 19.00; O 5.30; S 22.00. $C_{12}H_{10}N_4OS_2$. Calculated, %: C 49.63; H 3.47; N 19.03; O 5.51; S 22.09. *M* 290.36.

1-Benzyl-6-hydroxy-4-sulfanylpyrimidine-2(1*H*)-thione (17). A mixture of compound **3** (0.01 mol), sodium hydroxide (0.01 mol) and 20 mL of hydrogen peroxide was refluxed for 4 h then pour in to ice water, precipitate was filtered off, washed in water, dried, and crystallized. Yield 97%, beige powder, mp 133–137°C. IR spectrum, ν, cm^{-1}: 3350 (OH), 3215 (NH), 3100 (SH), 1744 (C=O), 1493 (C=C), 1394 (C=S). ^{1}H NMR spectrum, δ, ppm: 4.36 d (2H, CH_2Ph, *J* 7.0 Hz), 6.95–7.31 m ($6H_{arom}$), 8.19 s (1H, SH), 8.20 s (1H, NH), 8.22 s (1H, OH). Found, %: C 50.00; H 4.00; N 11.00; O 6.30; S 25.00. $C_{11}H_9N_2OS_2$. Calculated, %: C 52.78; H 4.03; N 11.19; O 6.39; S 25.2. *M* 249.02.

1-[Bromo(phenyl)methyl]-6-hydroxy-4-mercaptopyrimidine-2(1*H*)-thione (19). A solution of compound **3** (0.01 mol) and brome (0.01 mol) and in 20 mL acetic acid was refluxed for 4 h then pour in potassium hydroxide solution, obtainable precipitate was filtered off, washed in water, dried and crystallized form acetic acid. Yield (95%), beige powder, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3273 (OH), 3100 (NH), 3012 (SH), 1645 (C=C), 1594 (C=S). ^{1}H NMR spectrum, δ, ppm: 4.98 s (1H, PhCHBr), 7.31–7.65 m ($5H_{arom}$), 9.63 s (1H, SH), 10.72 s (1H, NH). Found, %: C 40.00; H 2.66; N 8.44; O 4.80; S 19.40. $C_{11}H_8BrN_2OS$. Calculated, %: C 40.13; H 2.76; Br 24.27; N 8.51; O 4.86; S 19.48. *M* 296.17.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020110159 and are accessible for authorized users.

REFERENCES

1. Bondock, S., El-Tarhoni, A.E.G., and Fadda, A.A., *Arkivoc*, 2006, vol. 9, p. 113. https://doi.org/10.3998/ark.5550190.0007.905
2. Majumdar, P., Pati, A., Patra, M., Behera, R. K., and Behera, A.K., *Chem. Rev*., 2014, vol. 114, p. 2942. https://doi.org/10.1021/cr300122t
3. Shams, H.Z., Mohareb, R.M., Helal, M.H., and Mahmoud, A.E., *Phosphorus Sulfur Silicon Relat. Elem*., 2007, vol. 182, p. 237. https://doi.org/10.1080/10426500600892776
4. Eldin, S.M., El-Din, A.A.M., and Basyouni, W.M., *Arch. Pharm. Res*., 1993, vol. 16, p. 318. https://doi.org/10.1007/BF02977523
5. Baskar, B., Dakas, P.Y., and Kumar, K., *Org. Lett*., 2011, vol. 13, p. 1988. https://doi.org/10.1021/ol200389p
6. He, J., Zheng, J., Liu, J., She, X., and Pan, X., *Org. Lett*., 2006, vol. 20, p. 4637. https://doi.org/10.1021/ol061924f
7. Hohmann, C., Schneider, K., Bruntner, C. Brown, R., Jones, A.L., Goodfellow, M., Krämer, M., Imhoff, J.F., Nicholson, G., Fiedler, H-P., and Süssmuth, R.D., *J. Antibiot*., 2009, vol. 62, p. 75. https://doi.org/10.1038/ja.2008.15
8. Jain, A.C. and Gupta, P.K., *Tetrahedron*, 1975, vol. 31, p. 1695. https://doi.org/10.1016/0040-4020(75)85089-7
9. DeMarinis, R.M., Hoover, J.R.E., Dunn, G.L., Actor, P., Uri, J.V., and Weisbach, J.A., *J. Antibiot*., 1975, vol. 28, p. 463. https://doi.org/10.7164/antibiotics.28.463
10. Verhoef, T.I., Redekop, W.K., Daly, A.K., and De Boer, A., *Br. J. Clin. Pharmacol*., 2014, vol. 77, p. 626.
11. Lv, Z., Sheng, C., Zhang, Y., Wang, T., Feng, J., Sun, H., Zhong, H., Zhang, M., Chen, H., and Li, K., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 7106. https://doi.org/10.1016/j.bmcl.2010.09.072
12. Farag, N.A., Mohamed, S.R., and Soliman, G.A.H., *Bioorg. Med. Chem*., 2008, vol. 16, p. 9009. https://doi.org/10.1016/j.bmc.2008.08.039
13. Fan, X., Feng, D., Qu, Y., Zhang, X., Wang, J., Loiseau, P.M., Andrei, G., Snoeck, R., and De Clercq, E., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 809. https://doi.org/10.1016/j.bmcl.2009.12.102

14. Sakhuja, R., Panda, S.S., Khanna, L., Khurana, S., and Jain, S.C., *Bioorg. Med. Chem. Lett*., 2011, vol. 21, p. 5465. https://doi.org/10.1016/j.bmcl.2011.06.121

15. Poulomi, M., Anita, P., Manabendra, P., Rajani, K.B., and Ajaya, K.B., *Chem. Rev*., 2014, vol. 114, p. 2942. https://doi.org/10.1021/cr300122t

16. Litvinov, V.P., *Russ. Chem. Rev*., 1999, vol. 68, p. 737. https://doi.org/10.1070/RC1999v068n09ABEH000533

17. Bauer, A.W., Kirby, W.M., Sherris, C., and Turck, M., *Am. J. Clin. Pathol*., 1966, vol. 45, p. 493. https://doi.org/10.1093/ajcp/45.4_ts.493

18. Pfaller, M.A., Burmeister, L., Bartlett, M.A., and Rinaldi, M.G., *J. Clin. Microbiol*., 1988, vol. 26, p. 1437.

19. Mosmann, T., *J. Immunol. Methods*, 1983, vol. 65, p. 55. https://doi.org/10.1016/0022-1759(83)90303-4

20. Gomha, S.M., Riyadh, S.M., Mahmoud, E.A., and Elaasser, M.M., *Heterocycles*, 2015, vol. 91, p. 1227. https://doi.org/10.3987/COM-15-13209

21. Eman, O.H., Mohamed, G.A., Adel, M.S., and Rawda, E.S., *J. Heterocycl. Chem*., 2020, vol. 57, p. 1672. https://doi.org/10.1002/jhet.3892