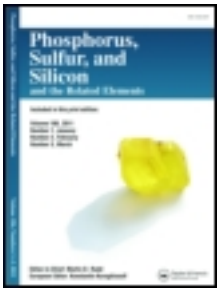


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Some Reactions of 2-Cyanomethyl-1,3-benzothiazole with Expected Biological Activity

A. Y. Hassan [a]

[a] Chemistry Department, Faculty of Science (Girls), Al-Azhar University, Nasr City, Cairo, Egypt

Version of record first published: 03 Nov 2009

To cite this article: A. Y. Hassan (2009): Some Reactions of 2-Cyanomethyl-1,3-benzothiazole with Expected Biological Activity, Phosphorus, Sulfur, and Silicon and the Related Elements, 184:11, 2856-2869

To link to this article: http://dx.doi.org/10.1080/10426500802590244

Phosphorus, Sulfur, and Silicon, 184:2856–2869, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802590244

Taylor & Francis
Taylor & Francis Group

Some Reactions of 2-Cyanomethyl-1,3-benzothiazole with Expected Biological Activity

A. Y. Hassan
Chemistry Department, Faculty of Science (Girls), Al-Azhar University, Nasr City, Cairo, Egypt

*New pyrido[2,1-*b*]benzothiazoles **2a,b**, **3**, 2-aminoquinoline **4**, coumarin **5**, cyclohexane **6a,b**, and 2-(1,3-benzothiazol-2-yl) methylidene **7** derivatives have been prepared via the reaction of 2-cyanomethyl-1,3-benzothiazole **1** with α,β-unsaturated nitriles, α-chloro ethyl acetoacetate, 2-amino benzaldehyde, 5-chlorosalicylaldehyde, α,β-unsaturated ketone, and 2-aminobenzothiol hydrochloride. 2-Thiazole derivatives **9a,b** were prepared from compound **1**, which was converted to thioamide derivative **8** by reaction with HCl and thioacetamide, and cyclization of this thioamide with α-halogenated ketone gave **9a,b**. Reaction of compound **1** and ethylacetate to afford ketonitrile **10**. Treatment of **10** with hydrazine hydrate afforded aminopyrazole derivative **11**. Substituted 4-aminothiophene **13** has been synthesized by reaction of compound **1** with* p*-chlorophenyl isothiocyanate. The resulting product **12** was then alkylated with phenacylbromide. Phenyl-2-ylcarbonylhydroximoyl-chloride **15** was prepared by treatment of the corresponding sulfonium bromide with sodium nitrite and hydrochloric acid in dioxane. Compound **15** reacted with α-(1,3-benzothiazol-2-yl) cinnamonitrile **14** afforded the isoxazole derivatives **16**. Reaction of coumarin derivative **5** with anthranilamide, pyrimidine diamine, thiosemicarbazide, acetylacetone, and hydrazine hydrate yielded quinazoline-2-one **17,** purine **18,** triazole **19**, 2-acetyl naphthalene-2-one **20**, and N-aminoquinoline-2-one **21** derivatives.*

Keywords Cinamonitrile; coumarin; 2-cyanomethyl-1,3-benzothiazole and its derivatives; cyanothioacetamide; ketonitrile; thioamide

INTRODUCTION

Heterosulfur compounds now find a wide variety of applications ranging from antitumor,[1–3] bacteriostatic,[4,5] antibiotic,[6,7] and CNS regulant[8] to high ceiling diuretics.[9] These considerable biological activities have stimulated interest in the synthesis and chemistry of a new class of thiazole derivatives.[10]

Received 2 June 2008; accepted 13 October 2008.
Address correspondence to A. Y. Hassan, Chemistry Department, Faculty of Science (Girls), Al-Azhar University, Nasr City, Cairo, Egypt. E-mail: helali_aisha@yahoo.com

RESULTS AND DISCUSSION

Compound **1**[11] reacted with α,β-unsaturated nitrile to yield 1:1 adducts, for which structure **2a,b** can be considered. Structure **2a,b** could be established from the ^{1}H NMR spectrum, which revealed a signal at δ 4.28 ppm for pyridine (H-4). The formation of **2a,b** from compound **1** and α,β-unsaturated nitrile is assumed to proceed via Michael addition of the active methylene group to the activated double bond to yield acyclic intermediate **2′a,b**, which cyclizes give **2a,b** via the addition of ring NH to the cyano group. 1-Oxo-1H-pyrido [2,1-*b*]-1,3-benzothiazole **3** was prepared by the reaction of compound **1** with α-chloro ethyl acetoacetate. 2-Aminobenzaldehyde, upon condensation with compound **1** in the presence of piperidine without any solvent at room temperature,[12] resulted in the formation of 2-amino-3-(1,3-benzothiazol-2-yl)-quinoline **4**.

In addition, compound **1** reacted with 5-chlorosalicyladehyde in ethanol piperidine[13] to give the corresponding coumarin derivative **5**. The structures of compounds **3**, **4**, and **5** were established by IR, ^{1}H NMR, and mass spectrometry (cf. Scheme 2 and Table II).

The synthesis of highly substituted cyclohexanol derivatives has been accomplished in a single step reaction[14] of 2-cyanomethyl-1,3-benzothizaole **1** and α,β-unsaturated ketones (1:2) using sodium ethoxide in anhydrous diethyl ether at room temperature to give 3-aroyl-1,2,4,6-tetraaryl-4-hyroxcyclohexane carbonitrile derivatives **6a,b**. The isolated products indicated that the reaction could involve a double Michael addition of benzothiazol-2-yl-acetonitrile carbonion to two moles of α,β-unsaturated ketones followed by cyclization. A suggested reaction mechanism is also outlined in that scheme in which the 1,7-diketone **6′a,b** undergoes an intramolecular aldol cyclization to give the cyclohexanol **6a,b**. The structure of the products **6a,b** was elucidated on the basis of their elemental analysis, ^{1}H NMR, and IR data (cf. Table II).

2-(1,3-Benzothiazol-2-yl) methylidene-(1,3-benzothiazole) **7** was prepared, albeit in low yield, from (1,3-benzothiazol-2-yl)-acetonitrile and 2-aminobenzothiol hydrochloride. The mass spectral data for this product revealed a molecular formula ($C_{15}H_{10}N_2S_2$), m/z = 282 (7.92%). Three tautomeric structures were considered. The structure of **7a** was readily ruled out based on the ^{1}H NMR spectrum that revealed one proton signal at δ = 5.39 ppm; this signal can only interpreted in terms of the **7b,c**. The 2-thiazole derivative target was prepared from 2-cyanomethyl-1,3-benzothiazole **1** that was converted to thioamide **8** by reaction with HCl and thioacetamide in DMF.[15] Cyclization of

TABLE I Characterization Data of Newly Synthesized Compounds

Comp. No.	Mp°C	Yield%	Mol. Formula MW	% Analysis = Calcd/found C	H	N	S	
2a*	160	75	$C_{19}H_{11}ClN_4S$	62.89	3.03	15.44	8.82	
			362.5	62.50	3.00	15.70	8.80	
2b	220	60	$C_{19}H_{15}N_3O_2S_2$	59.84	3.93	11.02	16.79	
			381	60.00	3.14	11.00	17.00	
3**	260	62	$C_{13}H_7ClN_2OS$	56.83	2.55	10.20	11.65	
			274.5	56.70	2.10	10.50	11.80	
4	310	80	$C_{16}H_{11}N_3S$	69.31	3.97	15.16	11.55	
			277	70.00	4.00	15.35	11.90	
5***	210	85	$C_{16}H_8ClNO_2S$	61.24	2.55	4.46	10.20	
			313.5	61.00	2.73	4.70	10.75	
6a	>360	70	$C_{31}H_{22}N_2O_2S_5$	60.58	3.58	4.56	26.05	
			614	60.55	3.13	4.80	26.80	
6b	>360	75	$C_{31}H_{22}N_2O_6S$	67.63	4.00	5.09	5.81	
			550	67.30	3.85	4.93	6.12	
7	70	40	$C_{15}H_{10}N_2S_2$	63.82	3.54	9.92	22.69	
			282	63.90	3.50	10.00	22.20	
8	240	75	$C_9H_8N_2S_2$	51.92	3.84	13.46	30.76	
			208	52.00	3.80	13.00	30.35	
9a	290	40	$C_{17}H_{12}N_2S_2$	66.23	3.89	9.09	20.77	
			308	66.12	3.90	9.00	20.80	
9b	310	45	$C_{12}H_{10}N_2S_2$	58.53	4.06	11.38	26.01	
			246	58.61	4.00	11.50	26.50	
10	230	60	$C_{11}H_8N_2OS$	61.11	3.70	12.96	14.81	
			216	61.00	3.30	12.96	14.21	
11	80	30	$C_{11}H_{10}N_4S$	57.39	4.34	24.34	13.91	
			230	57.50	4.40	24.70	13.50	
12	>360	75	$C_{16}H_{10}ClN_3S_2$	55.89	2.91	10.33	12.22	18.63
			343.5	55.80	3.00	10.00	12.50	18.60
13	220	90	$C_{24}H_{16}ClN_3OS_2$	62.40	3.46	7.69	9.10	13.86
			461.5	62.60	3.50	7.70	9.00	14.00
15	>360	80	$C_8H_6ClNO_2$	52.31	3.26	19.34	7.62	—
			183.5	52.30	3.50	19.90	7.60	—
16	225	30	$C_{23}H_{14}N_2O_2S$	72.25	3.66	—	7.32	8.37
			382	72.30	3.84	—	7.30	8.80
17	>360	65	$C_{23}H_{12}ClN_3OS$	66.74	2.90	8.58	10.15	7.73
			413.5	66.60	3.00	8.77	10.00	7.80
18	180	40	$C_{20}H_{10}ClN_5S$	61.93	2.58	9.16	18.06	8.25
			387.5	61.50	2.58	9.00	18.50	8.11
19	140	55	$C_{17}H_9ClN_4S_2$	55.35	2.44	9.63	15.19	17.36
			368.5	55.50	2.58	9.80	15.00	17.61
20	120	40	$C_{19}H_{12}ClNO_2S$	64.49	3.39	10.04	3.96	9.05
			353.5	64.50	3.30	10.15	4.00	9.51
21	280	60	$C_{16}H_{10}ClN_3OS$	58.62	3.05	10.83	12.82	9.77
			327.5	53.80	3.00	10.90	12.60	10.00

*Cl:Calcd = 9.79, Found = 9.80.
**Cl:calcd = 12.93, Found = 13.00.
***Cl:Calcd = 11.32, Found = 11.50.

TABLE II Spectroscopic Characterization Data for the Reported Compounds

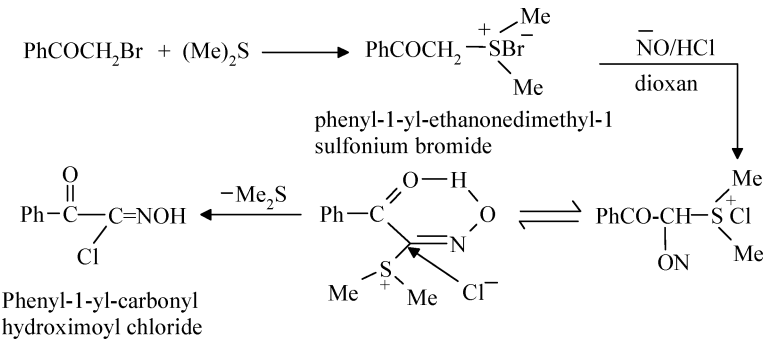
Comp. no.	IR (cm^{-1})	H^1 NMR δ(ppm)/^{13}C NMR δ(ppm)/m.s.
2a	3420, 3390 (NH_2), 3090 (CHAr), 2220 (CN).	4.28 (s, 1H, pyridine, H–4), 6.50 (s, 2H, NH_2), 7.10–8.33 (m, 9H, Ar–H and NH). ms : m/z = 362 (7.11%).
2b	3400, 3310 (NH_2), 3088 (CH–Ar), 2900 (CH aliph.), 2200 (CN), 1710 (CO).	1.30 (t, 3H, CH_2CH_3, J = 7.70 Hz), 4.22 (q, 2H, CH_2CH_3, J = 8.21 Hz), 4.92 (s, 1H, pyridine–H-4), 5.82 (s, 2H, NH_2), 7.44–8.00 (m, 7H, Ar–H and NH) ^{13}C: 14.42 (CH_3), 44.11 (CH_2). 63.01 (CH), 117.11 (CN), 168.20 (CO) and $C_{aromatic}$ 129.00, 130.11, 130.88, 132.22, 133.05, 134.95, 135.84.
3	3087 (CH-Ar), 2910 (CH aliph.), 2219 (CN), 1670 (CO), 1590 (C=C).	2.60 (s, 3H, CH_3), 7.65–7.80 (m, 4H, Ar-H). ^{13}C: 19.10 (CH_3), 115.00 (CN), $C_{aromatic}$ 128.92, 130.92, 132.22 133.00 and 174.84 (CO) ms: m/z = 274 (11.13%), 276 (4.03%).
4	3411, 3310 (NH_2), 3055 (CH-Ar), 1620 (C=N)	5.80 (s, 2H, NH_2), 7.00–7.88 (m. 9H, Ar-H). Ms: m/z = 277 (0.81%).
5	3050 (CH-Ar), 1680 (C=O), 1600 (C=C).	7.00—8.22 (m, 8H, Ar-H). ms: m/z = 313 (7.74%).
6a*	3440 (OH), 3075 (CH-Ar), 2900 (CH-aliph.), 2235 (CN), 1660 (C=O).	2.30 (dd, 1H, H_b, J = 11.80 Hz), 3.11 (dt, 1H, H_c, J = 13.14Hz), 4.20 (dd, 2H, H_d, H_c, J = 11.00Hz), 5.00 (d, 1H, H_f, J = 12.14Hz), 5.80 (d, 1H, H_a, J = 4.88 Hz), 6.75–7.82 (m, 16H, Ar-H). ^{13}C: 119.10 (CN), 208.50 (C=O) and cyclohexane carbons 42.00, 46.16, 50.55, 52.38, 58.26, 74.71; ms: m/z = 614 (6.32%).
6b*	3465 (OH), 3099 (CH-Ar), 2888 ($CH_{aliph.}$), 2222 (CN), 1665 (C=O).	2.33 (dd, 1H, Hb, J = 13.11 Hz), 2.80 (dd, 1H, H_C, J = 11.14 Hz), 4.00 (dd, 2H, H_d, H_C, J = 9.44 Hz), 5.32 (d, 1H, H_f, J = 7.35 Hz), 6.22 (d, 1H, H_a, J = 3.88 Hz), 7.22–8.55 (m, 16H, Ar-H). ms: m/z = 550 (6.37%).
7	3072 (CH-Ar), 2880 (CH-aliph.), 1630 (C=N)	5.39 (s, 1H, CH), 7.25–8.09 (m, 8H, Ar-H) Ms: m/z = 282 (7.92%) and base peak at m/z = (148.11, 100%)
8	3300, 3280 (NH_2), 3082 (CH-Ar), 2888 (CH aliph.)	4.05 (s, 2H, CH_2), 5.80 (s, 2H, NH_2), 7.28–7.77 (m, 4H, Ar-H).

(Continued on next page)

TABLE II Spectroscopic Characterization Data for the Reported Compounds *(Continued)*

Comp. no.	IR (cm^{-1})	H^1 NMR δ(ppm)/^{13}C NMR δ(ppm)/m.s.
9a	3088 (CH-Ar), 2875 (CH aliph.), 1630 (C=N)	4.40 (s, 2H, CH_2), 7.20–7.75 (m, 9H, Ar-H), 11.80 (s, 1H, CH-thiazole ring) ms: m/z 308 (22.13%) and base peak at m/z = (148.00, 100%).
9b	3086 (CH-Ar), 2900 (CH-aliph.), 1625 (C=N)	4.80 (s, 2H, CH_2), 2.33 (s, 3H, CH_3), 7.00–7.78 (m, 4H, Ar-H), 11.00 (s, 1H, CH-thiazole ring) ^{13}C: 23.11 (CH_3), 55.18 (CH_2) and $C_{aromatic}$, 127.11, 128.82, 129.33, 130.80, 133.44.
10	3060 (CH-Ar), 2800 (CH-aliph.), 2219 (CN) 1680 (C=O)	2.38 (s, 3H, CH_3), 5.15 (s, 1H, CH), 7.22–7.83 (m, 4H, Ar-H).
11	3377, 3297 (NH_2, NH), 3062 (CH-Ar), 1630 (C=N), 1580 (C=C)	2.15 (s, 3H, CH_3), 6.20 (br.s, 2H, NH_2), 7.22–7.80 (m, 4H, Ar-H), 13.80 (br.s, 1H, NH) ms: m/z = 230 (11.08%).
12	3330 (NH), 3048 (CH-Ar), 2219 (CN),	5.11 (s, 1H, CH), 7.50–8.00 (m, 8H, Ar-H), 11.80 (s, 1H, NH). ^{13}C : 70.12 (CH) and $C_{aromatic}$ 127.13, 128.00, 130.11, 131.08, 132.12, 133.88, 134.81, 135.00 and115.80 (CN), 208.00 (C = S),
13	3450 (OH), 3296 (NH), 3055 (CH-Ar), 1680 (C=O), 1600 (C=C).	6.28 (br.s, 2H, NH_2), 7.22–8.11 (m, 13H, Ar-H), 9.80 (s, 1H, NH) ms: m/z = 461 (4.11%).
15	3300–3200 (OH) 3050 (CH-Ar), 1665 (C=O), 1635 (C=N)	7.42–8.11 (m, 5H, Ar-H), 13.74 (br.s, 1H, OH).
16	3085 (CH-Ar), 1700 (C=O), 1620 (C=N)	7.55–8.11 (m, 14H, Ar-H) ms: m/z = 382 (18.08%).
17	3078 (CH-Ar), 1700 (C=O), 1630 (C=N)	7.33–8.11 (m, 12H-Ar-H) ms: m/z = 413 (6.31%).‘
18	3090 (CH-Ar), 1640 (C=N), 1580 (C=C)	7.55–8.22 (m, 10 H, Ar-H) ms: m/z = 387 (9.12%).
19	3300 (NH), 3042 (CH-Ar), 1630 (C=N).	7.22–7.82 (m, 8H, Ar-H), 11.80 (s, 1H, NH).
20	3300 (OH-enol form) 3088 (CH-Ar), 2980 (CH aliph.), 1680 (C=O)	3.01 (s, 3H, CH_3), 6.20 (br, 1H, CH) 7.15–7.88 (m, 8H, Ar-H) ^{13}C: 19.13 (CH_3), 74.22 (CH), and $C_{aromatic}$ 127.11, 127.90, 128.33, 130.00, 131.13, 132.00, 133.1o%) and 188.00 (C=O), 177.00 (C=O),
21	3380, 3230 (NH_2) 3080 (CH-Ar), 1680 (C=O), 1580 (C=C).	5.80 (s, 2H, NH_2) 7.33–7.82 (m, 7H, Ar-H) ms: m/z = 327 (11.08%)

*^1H and ^{13}C NMR for compound **6a,b** in ($CDCl_3$).



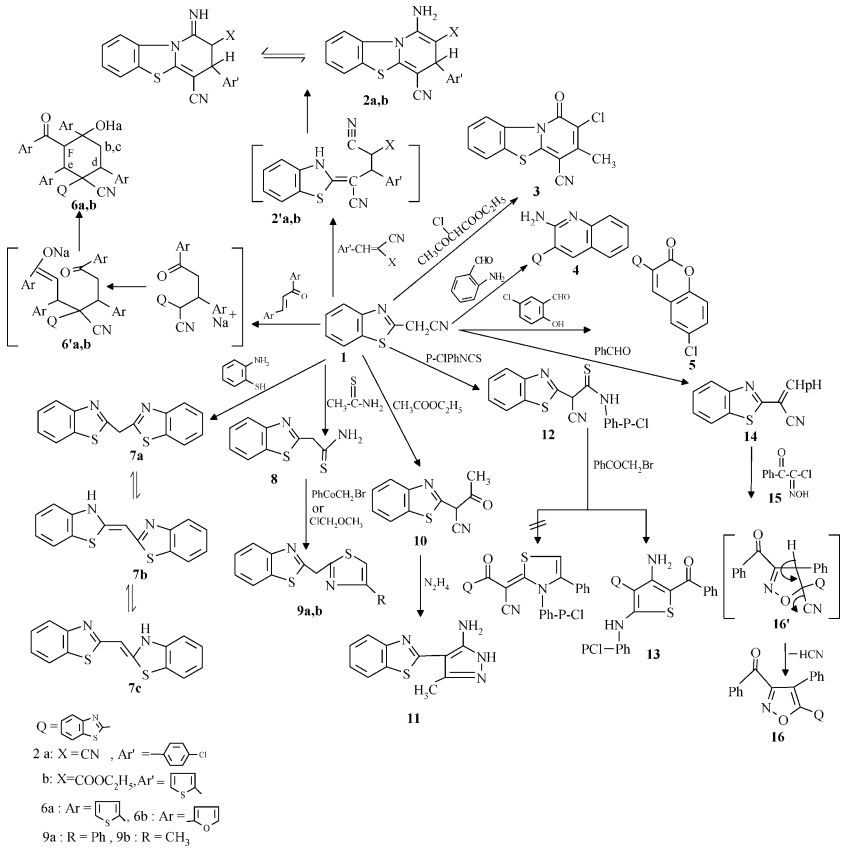
SCHEME 1

this thioamide with an phencyl bromide or chloroacetone gave the 2-thiazolyl derivatives **9a,b**.

Compound **1** was acetylated in the presence of sodium metal and ethyl acetate[16] to yield ketonitrile **10**. Treatment of **10** with hydrazine hydrate in refluxing toluene[16] afforded aminopyrazole derivative **11.** The structures of the newly synthesized derivatives were established on the basis of elemental analysis and spectral data (cf. Scheme 1 and Table II). 2-Cyanomethyl-1,3-benzothiazole **1** reacted efficiently with p-chlorophenylisothiocyanate in dioxan[17] to give compound **12**. Alkylation of compound **12** at sulfur with phencylbromide yielded 3-aminothiophene derivative **13**. However, it has been found in contrast to the reported behavior.[18] Structure **13** finds support from the MS spectra, which revealed a molecular formula ($C_{24}H_{16}ClN_3OS_2$), m/e = 461 (4.11%). The ^{1}H NMR spectra revealed one amino function at δ 6.28 ppm and a signal at δ 9.80 ppm for the NH group.

α-(1,3-Benzothiazol-2-yl)-cinnamonitrile **14**[19] was treated with phenyl-1-yl-carbonyl hydroximoyl chloride **15** in toluene and triethylamine at room temperature to furnish a single product identified as 3-benzoyl-5-(1,3-benzothiazol-2-yl)-4-phenyl isoxazoline intermediate **16′**, but was unsuccessful. The IR spectrum of the reaction product was free of the nitrile absorption band and revealed only a carbonyl band at 1700 cm^{-1}. Its ^{1}H NMR spectrum displayed only a multiplet in the region δ 7.55–8.11 ppm due to aromatic protons.

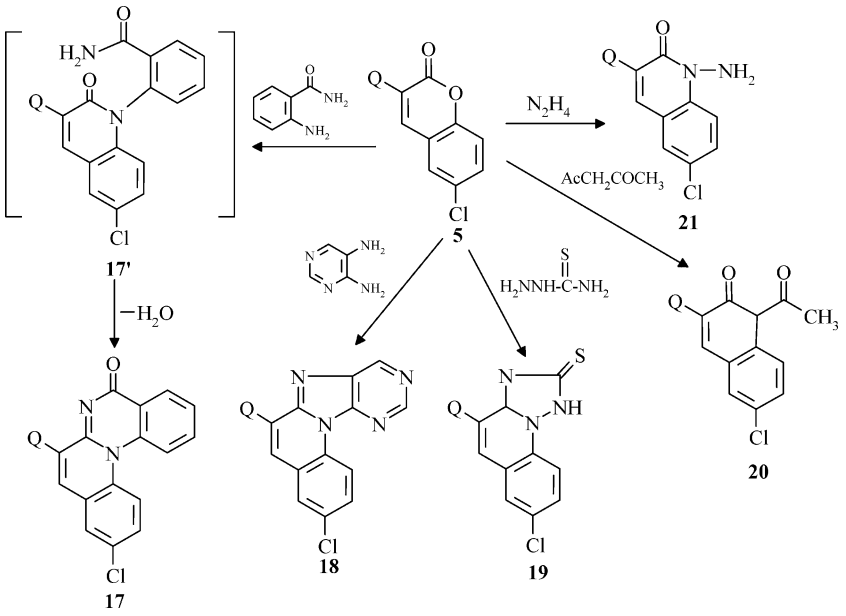
The IR spectrum of compound **15** revealed a abroad band in the region of 3300–3200 cm^{-1} due to the hydroxyl group and a strong band at 1665 cm^{-1} due to the carbonyl group. Its ^{1}H NMR spectrum displayed also a base-broad singlet at δ 13.74 ppm and a multiplet at δ 7.42–8.11 ppm assignable to hydroxyl and aromatic protons, respectively. A



SCHEME 2

plausible mechanism for the formation of the hdyroximoyl chloride **15** is depicted in Scheme 1.

The interaction of compound **5** with anthranilamide, pyrimidine diamine, and thiosemicarbazide in glacial acetic acid and in the presence of fused sodium acetate[20] yielded quinazolinone **17**, purine **18**, and triazole **19** derivatives, respectively. However, formation of the quinazolinone **17** was mediated, most likely by intermediate **17′**, which could undergo cyclodehydration to afford **17**. The IR spectrum of **17** exhibited bands at 1700 cm^{-1} (C=O) and 1630 cm^{-1} (C=N), and the mass spectrum of **17** showed a molecular ion peak m/z 413 (16.31%). The IR spectrum of compound **18** showed the absence of C=O and the presence of C=N at 1640 cm^{-1}. Extending the reaction to include acetylacetone using sodium ethoxide[21] as a catalyst gave 2-acetyl-8-



SCHEME 3

(1,3-benzothiazol-2yl)-5chloro-naphthalene-1-one **20** in low yields. Condensation of **5** with hydrazine hydrate gave 3-(1,3-benzothiazol-2-yl)-N-amino-4-chloro quinoline-2-one **21**. The IR spectrum of **21** showed the presence of (NH_2) at 3380, 3230 cm^{-1} and C=O at 1680 cm^{-1} (cf. Scheme 3 and Table II).

EXPERIMENTAL

All melting points were recorded on a Gallen Kamp melting apparatus and uncorrected. The IR spectra were recorded on a pye-unicam Sp-3–100 spectrophotometer using KBr Wafer Technique. ^1H and ^{13}C NMR spectra were recorded on a Brucker 400 MHz with DMSO-d_6 as solvent and tetramethysilane as an internal standard; chemical shifts are as δ units (ppm). The mass spectra were recorded on Ms-S 988 operaing at 70eV. Elemental analysis was determined using a Perkin-Elmer 240C microanalyses. The newly synthesized compounds were screened for in vitro antitumor activity at Cairo University, National Center Institute, Cancer Biology Department Pharmacology unit.

Compounds **1** and **14** were prepared according to the procedure in the literature.[11,19]

1-Amino-3(p-chlorophenyl)-4-cyano-3H-pyrido[2,1-*b*]benzothiazole-2-carbonitrile 2a or Ethyl-1-amino-3(2-thienyl) 4-cyano-3H-pyrido[2,1-*b*]benzothiazole-2-carboxylate 2b

Equimolecular amounts (0.01 mol) of **1** with the appropriate cinnamonitrile were refluxed in ethanol (50 mL) in the presence of piperidine (0.1 mL) for 3 h. The solid product so formed was filtered off and recrystallized from ethanol.

2-Chloro-4-cyano-3-methyl-1-oxo-1H-pyrido [2,1-*b*]-1,3-benzothiazole 3

A solution of **1** (0.01 mol) in ethanol (20 mL), α-chloro ethyl-acetoacetate (0.01 mol), and piperidine (3 drops) was refluxed for 6 h. The reaction mixture was left to cool at room temperature and recrystallized from ethanol.

2-Amino-3-(1,3-benzothiazol-2-yl)quinoline 4

A mixture of 2-aminobenzaldehyde (0.01 mol), compound **1** (0.01 mol), and piperidine (5 drops) was ground by pestle and mortar at room temperature for 30 min and treated with water. The resultant product was filtered, washed with water, and recrystallized from methanol.

6-Chloro-3-(1,3-benzothiazol-2-yl)-coumarin 5

A mixture of the appropriate **1** (0.005 mol) and 5-chloro-salicylaldehyde (0.005 mol) in absolute ethanol (35 mL) containing piperdine (5 drops) was refluxed for 4 h. The reaction mixture was cooled and then acidified with dilute hydrochloric acid. The solid so formed was collected and recrystallized from ethanol.

3-Aroyl-1-(1,3-benzothiazole)-2,4,6-triaryl-4-hydroxycyclohexane carbonitrile 6a,b

To a suspension of sodium ethoxide (0.01 mol) in anhydrous ether (150 mL) containing compound **1** (0.01 mol), chalcone[22] (0.02 mol) was added. The mixture was stirred at room temperature for 20–24 h, the solid formed was filtered and recrystallized from dioxan. The filtrate was poured into water (100 mL), the organic layer was separated, dried with sodium sulfate, and evaporated to give the crude unreacted starting materials.

2-(1,3-Benzothiazol-2-yl)methylidene-(1,3-benzothiazole) 7

A solution of **1** (28 mmol) and 2-aminobenzenthiol hydrochloride (5.0 g, 30 mmol) in ethanol (75 mL) was heated at reflux for 48 h. The solvent was evaporated in vacuo, and the solid was collected and recrystallized from cyclohexanone.

1-(Benzothiazol-2-yl)thioacetamide 8

A solution of **8** (120 mmol) and thioacetamide (40 mmol) in DMF (75 mL) was heated in an oil bath to 90–100°C for about 2 h, while HCl gas was being bubbled into the reaction mixture. The solvent was evaporated in vacuo, and the residue was triturated with acetone to give crude product. This material was recrystallized from ethanol.

[5-(Phenylthiazol-2-yl)methyl]-2-(1,3-benzothiazol-2-yl) 9a and [(5-Methylthiazol-2-yl) methyl]-2-(1,3-benzothiazol-2-yl) 9b

A solution of 8 (26 mmol) and phencyl bromide or chloroacetone (45.6 mmol) in ethanol (25 mL) was heated at reflux for 6 h. After the starting material had been consumed as judged by TLC, the reaction mixture was cooled and the crude product was collected by filtration. Chromatography on silica (90:9:1, $CHCl_3$:MeOH:NH_4OH) yielded a yellow oil, which was dissolved in MeCN and treated with diethyl ether. The solid was collected and recrystallized from ethanol.

1-Cyano-1-(1,3-benzothiazole)-propan-2-one 10

To a solution of **1** (0.22 mol) in ethyl acetate (200 mL), sodium metal (6.43 g, 0.28 mol) was added portionwise at room temperature. Ethylacetate (400 mL) was added to the reaction suspension to facilitate stirring, and the resultant mixture was stirred at room temperature for 48 h. The collected solid was washed with copious amounts of diethyl ether and recrystallized from ethanol.

5-Amino-4-(1,3-benzothiazole)-3-methyl-pyrazole 11

A mixture of **10** (80.3 mmol), hydrazine monohydrate (120.45 mmol), acetic acid (14.9 mL, 200.75 mmol), and toluene (300 mL) was heated at reflux using a Dean-Stark trap for 5 h. The reaction mixture was cooled to room temperature. The solid was collected and recrystallized from benzene.

1-(2-(1,3-Benzothiazole)-N-(p-chlorophenyl cyanothioacetamide) 12

A mixture of 1 (0.01 mol), finely divided sodium metal (0.01 mol), and *p*-chlorophenyl isothiocyanate (0.01 mol) was refluxed for 7 h in dry dioxan (50 mL), then allowed to cool, poured onto cold water, and neutralized with dilute HCl. The precipitated was filtered off and recrystallized from ethanol.

4-Amino-5-(benzoyl)-3-(1,3-benzothiazol-2-yl)-2-*p*-chlorophenyl-aminothiophene 13

A mixture of **12** (0.01 mol), sodium ethoxide (0.005 mol), and phencyl bromide (0.01 mol) in 50 mL ethanol was heated under reflux for 22 h, and the reaction mixture was poured into ice cold dilute HCl. The product was crystallized from ethanol.

Phenyl-1-yl-carbonylhydroximoyl Chloride 15

To a stirred solution of the sulfonium bromide (20 mmol) and sodium nitrite (1.4 g, 20 mmol) in dioxan (25 mL) and water (25 mL), concentrated hydrochloric acid (50 mL) was added portionwise over a period of 1 h. The reaction mixture was stirred for a further 2 h at room temperature during which the sulfonium bromide dissolved and the precipitated which was filtered off, washed with water, dried, and recrystallized from AcOH.

3-Benzoyl-5-(1,3-benzothiazol-2-yl)-4-phenylisoxazole 16

A mixture of the hydroximoyl chloride **15** (2 mmol) and α-(benzothiazol-2-yl) cinnamonitrile **14** (2 mmol) in dry toluene (15 mL) and triethylamine (0.2 mL) was stirred for 6 h. The solvent was evaporated under reduced pressure, and the residue was triturated with methanol. The solid so formed was collected by filtration, washed with ethanol, dried, and finally recrystallized from DMF.

Formation of Quinazolinone 17, Purine 18, and Triazole 19 Derivatives

A mixture of **5** (0.01 mol), anthranilamide, pyrimidine diamine, and/or thiosemicarbazide (0.01 mol) and fused sodium acetate (1 g) was refluxed in glacial acetic acid (25 mL) for 12 h. After cooling, the reaction mixture was poured onto ice cold water (100 mL). The solid so formed

was isolated, dried, and crystallized from ethanol for compound **18** and **19**, but for compound **17** was recrystallized from acetic acid.

1-(1,3-Benzothizol-2-yl)-3-acetyl-6-chloro-naphthalene-2-one 20

A mixture of **5** (0.01 mol) in sodium ethoxide (0.01 mol) and acetyl acetone (0.01 mol) in (50 mL) ethanol was heated under reflux for 18 h. The reaction mixture was poured into ice cold diluted HCl. The product was crystallized from ethanol and acetic acid.

3-(1,3-Benzothiazol-2-yl)-N-amino-4-chloroquinoline-2-one 21

A solution of **5** (0.01 mol) and hydrazine hydrate (0.02 mol) in (30 mL) ethanol was heated under reflux for 6 h. The product obtained after cooling was crystallized from ethanol.

BIOLOGICAL RESULTS

Antitumor Activity (In Vitro Study)[23]

Ehrlich A sites carcinoma cells (EAC) were drawn from mice, in sterile test tube, where 2.5×10^5 tumor cells/mL were suspended in phosphate buffer saline at three different concentrations for each compound (25, 50, and 100 μg/mL). The 2.5×10^5 tumor cells for each test tube were added at 37°C for 2 h. The cells were tested for viability and contamination by staining a certain cell volume of this fluid by an equal volume of the working solution of trypan blue dye and examined under microscope. The dead cells stained blue and live cells not stained were then carried out to calculate the percentage of nonviable cells. Compounds producing more than 70% nonviable cells are considered active (see Table III)[24]:

$$\% \text{ of non-viable cells} = \frac{\text{no. of nonviable}}{\text{Total No. of cell}} \times 100$$

Compounds **6b**, **7**, **11**, and **13** are more effective than the positive control (doxorubicin) and were able to reduce the magnitude of activity to 90%. Compounds **2a,b**, **4**, and **9b** possess moderate activity against tumor cell lines, while compounds **16**, **17**, **18**, **19**, and **20** did not show any activity at different concentration, probably because of a solubility problem in the used culture media. On the basis of the structure of the tested compounds, one can conclude structure–activity relationships provided evidence that geometry, size, and shape of the compounds is an

TABLE III In Vitro Cytotoxic Activity of Synthesized Compounds

	Nonviable cells (%) concentration (μg/mL)		
Compound no.	100	50	25
2a	50%	40%	20%
2b	50%	40%	30%
3	−ve	−ve	−ve
4	70%	60%	55%
5	−ve	−ve	−ve
6a	−ve	−ve	−ve
6b	100	100%	95%
7	90%	85%	80%
8	−ve	−ve	−ve
9a	−ve	−ve	−ve
9b	50%	40%	25%
10	−ve	−ve	−ve
11	90%	85%	70%
12	−ve	−ve	−ve
13	90%	80%	75%
16	−ve	−ve	−ve
17	−ve	−ve	−ve
18	−ve	−ve	−ve
19	−ve	−ve	−ve
20	−ve	−ve	−ve
Doxorubicin[25]	100%	55%	20%

important as their substituents. These heterocycles could be considered as a useful template for further development and further derivatization or modification to obtain more potent and selective antitumor agents.

REFERENCES

[1] E. Marco and F. Gago, *J. Mol. Pharmacol.* **68**(6), 1559 (2005).
[2] A. B. Herrero, M. Castellahous, E. Marco, F. Gago, and S. Moreno, *Cancer Res.*, **66**(16), 8155 (2006).
[3] J. Bendnarski, *J. Des Pharmazie*, **341**(2), 121–125 (2008).
[4] M. M. Ghorab and A. Y. Hassan, *Phosphous, Sulfur, and Silicon*, **141,** 251 (1998).
[5] S. Suzen and E. Buyukbingol, *Il Farmaco*, **55,** 246 (2000).
[6] R. M. Harnden, S. Baiky, R. M. Boyd, R. D. Taylor, and D. N. Wright, *J. Med. Chem.*, **21,** 82 (1977).
[7] I. Hyakawa, Y. Tanaka, and Y. Nagata; *Tap, P. 77*, **83,** 588 (1976); *Chem. Abstr.*, **88**, 37785c (1987).
[8] A. A. Deshmukh, M. K. Mody, T. Ramalingam, and P. H. Sattur, *Indian J. Chem.*, **25B,** 793 (1985).

[9] A. Andereani, M. Ramboldi, A. Locattelli, and A. M. Isettam, *Eur. J. Med. Chem.*, **26,** 335 (1991).
[10] A. A. Elagamey, F. A. El-Taweel, F. A. Amer, and H. H. Zoorob, *Arch. Pharm.*, **320,** 246 (1987).
[11] K. Saito, S. Kampe, and Y. Nanano, *Synthesis*, 210 (1983).
[12] K. Mogilaiah, H. Ramesh Babu, and N. V. Reddy, *J. Synth. Commun.*, **32**(15), 2377 (2002).
[13] A. O. Abd El-Hamid, *Phosphorus, Sulfur, and Silicon*, **88,** 217 (1994).
[14] M. M. Al-Arab, B. S. Ghanem, and M. M. Olmstead, *Synthesis*, 1003 (1992).
[15] R. E. Boyd, J. B. Press, C. R. Ramsussen, R. B. Raffa, E. E. Cood, C. D. Connelly, D. J. Bennet, A. L. Kirrifides, J. F. Gardocki, B. Reynolds, J. T. Hortenstein, and A. B. Reitz, *J. Med. Chem.*, **42,** 5064 (1999).
[16] L. He, P. J. Gilligan, R. Zaczek, L. W. Fitzgerald, J. Mcelroy, H. S. L. Shen, J. A. Saye, N. H. Kalin, S. Shelton, D. Christ, G. Trainor, and P. Hartig, *J. Med. Chem.*, **43,** 449 (2000).
[17] F. Zaragoza, *Tetrahedron Lett*., **37,** 6213 (1996).
[18] R. Laliberte and G. Medawar, *Can. J. Chem.*, **48,** 2704 (1970).
[19] A. M. Farag, K. M. Dawood, and A. O. Abdelhamid, *Tetrahedron Lett*., **53,** 17461 (1997).
[20] M. M. Ghorab, O. M. Nassar, and A. Y. Hassan, *Phosphorus, Sulfur, and Silicon*, **134–135,** 57 (1998).
[21] M. M. Hamad, S. A. Said, A. F. El-Farargy, and G. M. Gendy, *Pak. J. Sci. Ind. Res.*, **36**(6–7), 228 (1993).
[22] N. R. E-Rayyes, *J. Heterocycl. Chem.*, **19,** 415 (1982).
[23] The method used is that of trypan blue exclusion, Mclimans et al. , *J. Immunol.* **79,** 428 (1957).
[24] M. M. El-Merzabani, A. A. El-Aaser, A. K. El-Dueini, and A. M. Ghazal, *Planta Medica*, **36,** 150 (1979).
[25] F. A. Fornair, J. K. Randolph, J. C. Yalowich, M. K. Ritke, and D. A. Gewirtz, *J. Molec. Pharmacol.*, **456,** 649 (1999).