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Synthesis of some new benzothiazole derivatives as potential antimicrobial and antiparasitic agents

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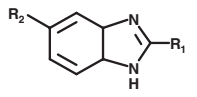
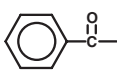
Several thiazolidinonyl benzothiazoles **8a**–**b** and thiazolinylbenzothiazoles **9a**–**j** were synthesized by the reaction of 2-(*N*-substituted thiocarbamoyl hydrazino) benzothiazoles **7a**–**d** with chloroacetic acid or phenacyl bromide respectively. The intermediate compounds **7a**–**d** were prepared in a good yield by the reaction of 2-hydrazinobenzothiazole (**6**) with phenylisothiocyanates. Synthesis of hydrazones **10a**–**c** were performed by the reaction of **6** with the corresponding aldehydes. Trials to cyclize the obtained hydrazones **10a**–**c** into the corresponding triazolo derivatives **11a**–**c** were unsuccessful. Addition of 4-morphylino carbonyl chloride to compound **6** yielded the corresponding 2-acid hydrazide derivative **12**. Some of the prepared compounds were screened for their anti-parasitic activity. Most of them showed reasonable antinematodal or schistosomicidal activity. In addition, antimicrobial screening of all of the prepared new compounds was performed against *Staphylococcus aeurus* ATCC 6538, *Escherichia coli* ATCC 8735 and *Candida albicans* ATCC 10321 but non of them was active.

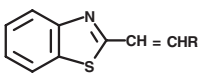
1. Introduction

Human trichinosis is a dangerous disease, the manifestations of which are related to larval migration and subsequent encystation within striated muscles [1]. Albendazole (**1**) and other benzimidazoles (thio-bendazole (**2**) and mebendazole (**3**)) are effective against the intestinal forms of *T. spiralis* present in early stages of infection [2]. The efficacy of these agents or any anthelmintic agents on larvae that have migrated to muscle is questionable. Corticosteroids and antimitotics may be of considerable value in controlling the acute and dangerous manifestation of an established infection [2]. It is obvious that there is a need for more effective and less toxic agents for the treatment of human trichinella.

Benzothiazole derivatives (the isoster of benzimidazole) were reported to possess versatile pharmacological activities. They have been reported as potential anthelmintic [3, 4], antimicrobial [5, 6] as well as antifungal [7–9] agents. Interestingly, an Egyptian study reported potent schistosomicidal activity of a series of benzothiazole analoges [10] **4** and **5**. These information encourage the synthesis of a new series of benzothiazoles in order to investigate their antimicrobial activity beside their possible effect against human trichinosis and schistosoma.



	R_1	R_2
1 Albendazole	$-NHCO_2CH_3$	$CH_3CH_2CH_2S-$
2 Thiobendazole		H
3 Mebendazole	$-NHCO_2CH_3$	



4 R = CO NHN = CH-4-C_6H_4(Cl)

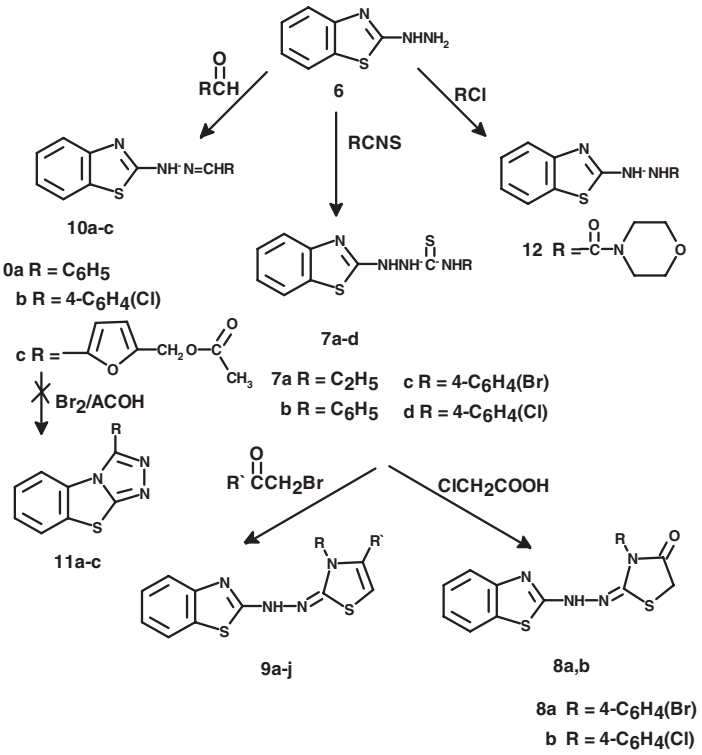
5 R = CO $NHNHCSNHC_6H_5$

2. Investigations, results and discussion

2.1. Chemistry

The sequence of reactions followed for the synthesis of the target compounds is illustrated in the Scheme. The intermediates **7a**–**d** were prepared according to a reported procedure [11] by the reaction of 2-hydrazinobenzothiazole [4] with the appropriate isothiocyanate derivatives in absolute ethanol. Cyclization of the 1-benzothiazolyl-4-substituted thiosemicarbazides **7d**–**c** by refluxing with chloroacetic acid and anhydrous sodium acetate in absolute ethanol yields the pertinant 2-[(3-substituted-4-oxothiazolidin-2-ylidene)hydrazino]benzothiazoles **8a**, **b**. The

Scheme



	R	R`
9a	$-C_2H_5$	4-$C_6H_4(NO_2)$
b	$-C_6H_5$	C_6H_5
c	C_6H_5	4-C_6H_4(Br)
d	C_6H_5	4-$C_6H_4(NO_2)$
e	4-C_6H_4(Br)	$-C_6H_5$
f	4-C_6H_4(Br)	4-C_6H_4(Br)
g	4-C_6H_4(Br)	4-$C_6H_4(NO_2)$
h	4-C_6H_4(Cl)	C_6H_5
i	4-C_6H_4(Cl)	4-C_6H_4(Br)
j	4-C_6H_4(Cl)	4-$C_6H_4(NO_2)$

IR spectra of the thiazolidinones **8a**, **b** showed characteristic absorption bands at 1700–1720 (C=O). The ^{1}H NMR spectra of these compounds showed a doublet at 3.3–3.4 for C_5-H_2 of thiazolidinone which are magnetically non equivalent.

On the other hand, refluxing **7a**–**d** for 8 h with monoequivalent of phenacylbromide derivatives afforded the 3,4-disubstituted thiazoline derivatives **9a**–**j**. The chemical structure of **9a**–**j** was confirmed by the appearance of a singlet band at 6.4–7.1 ppm corresponding to thiazoline C_5-H protons in the ^{1}H NMR spectra. The hydrazones **10a**, **c** were synthesized as reported [11], by equimolar reaction of the hydrazine derivative **6** with the corresponding aldehyde. The structure of compound **10c** was confirmed by the presence of two singlets at ppm 8 and 12.2 for N=CH and NH, respectively. However, trials to obtain the triazolo analoges **11a**–**c** from the hydrazones **10a**–**c** using Br_2/AcOH or refluxing in acetic anhydride were unsuccessful. Compound **12** was obtained from **6** by reaction with 4-morpholinocarbonylchloride in the presence of Et_3N. The IR spectrum of **12** showed a strong absorption band at 1677 cm^{-1} for the C=O, while the ^{1}H NMR spectrum showed two triplets at 2.8 and 3.7 ppm for the morpholine ring protons.

2.2. Antiparasitic activity

2.2.1. Antinematodal activity

Compounds **7d**, **8a**, **9j**, **9h**, **10b** and **10c** were subjected to *in vivo* antiparasitic evaluation against *Trichenilla spiralis*. The percentage reduction in the number of adult parasites in the intestine of treated mice compared with control (untreated infected mice) was calculated. The thiosemicarbazide analoge **7d** bearing a 4-chlorophenyl group as substituent, showed 87.8% reduction of adult worm number (Table 2). Cyclization of the former compound to a thiazoline derivative **9h** (R = 4-chlorophenyl, R′ = phenyl, Scheme) reduced antiparasitic activity considerably (46.4% reduction). The activity was restored in compound **9j** (91.2% reduction) having the same chemical back bone as **9h** (thiazoline) but 4-nitrophenyl instead of the phenyl ring.

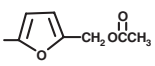
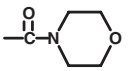
This observation suggested that for the same substituent the open chain thiosemicarbazide derivatives will possess higher activity than the corresponding cyclized thiazolines. On the other hand, the 4-oxo-thiazolidinone derivative **8a** exhibited almost the same activity (86.1% reduction) as the open chain thiosemicarbazide **7d**. The hydrazone derivative **10c** (R = 5-acetoxymethylfurane), the most active compound, exhibited 96.6% reduction of adult worm in the intestine while its analoge **10b** (R = 4-chlorophenyl) produced 69.9% reduction. Comparing the great difference in activity of these two analoges **10b** and **10c** with their difference in chemical structure, will actually emerge the important effect of the 5-acetoxymethylfurane moiety for high antinematodal activity.

In conclusion, it can be stated that the thiosemicarbazide, the hydrazone as well as the thiazolidinone derivatives were more active against *Trichenilla spiralis* than the thiazoline analoges. Mebendazole, a current drug of choice for the treatment of *T. spiralis*, produced a mean worm reduction of 98, 99.7 and 99.7% at 10, 50 and 100 mg respectively when administered to infected mice for three consecutive days [10]. This information actually indicates that the hydrazone derivative **10c** (96.6% reduction at 20 mg/kg) is a promising antinematodal compound.

2.2.2. Schistosomal activity

Two intermediate compounds **7c** and **7d** (Scheme) were selected to be evaluated as antischistosomal agents. This selection was based on their structure similarity to the most active compounds previously reported (**4**, **5**) which

Table 1: Yields, physical data and crystallization solvents of the new compounds

Compd.	R	R′	M. Formula M. wt.	Mp (°C) cryst. solv.*	Yield (%)
8a	4-C_6H_4(Br)	–	$C_{16}H_{11}BrN_4OS_2$ 419.3	201–2 Et	37
8b	4-C_6H_4(Cl)	–	$C_{16}H_{11}ClN_4OS_2$ 474.9	172–4 Et	33
9a	C_2H_5	4-$C_6H_4(NO_2)$	$C_{18}H_{15}N_5O_2S_2$ 397.5	201–3 Aq. Et	31
9b	C_6H_5	C_6H_5	$C_{22}H_{16}N_4S_2$ 400.5	149–51 Aq. Et	58
9c	C_6H_5	4-C_6H_4(Br)	$C_{22}H_{15}BrN_4S_2$ 479.4	160–2 Et/Pt.E	47
9d	C_6H_5	4-$C_6H_4(NO_2)$	$C_{22}H_{15}N_5O_2S_2$ 445.5	213–14 B/Pt.E	61
9e	4-C_6H_4(Br)	C_6H_5	$C_{22}H_{15}BrN_4S_2$ 479.4	218–20 B/Pt.E	53
9f	4-C_6H_4(Br)	4-C_6H_4(Br)	$C_{22}H_{14}Br_2N_4S_2$ 558.3	217–19 Aq. Et	72
9g	4-C_6H_4(Br)	4-$C_6H_4(NO_2)$	$C_{22}H_{14}BrN_5O_2S_2$ 524.4	132–4 Aq. Et	64
9h	4-C_6H_4(Cl)	C_6H_5	$C_{22}H_{15}ClN_4S_2$ 434.9	197–200 Et	47
9i	4-C_6H_4(Cl)	4-C_6H_4(Br)	$C_{22}H_{14}BrClN_4S_2$ 513.8	129–30 Et/Pt.E	65
9j	4-C_6H_4(Cl)	4-$C_6H_4(NO_2)$	$C_{22}H_{14}ClN_5O_2S_2$ 479.9	220–1 Et/Pt.E	59
10c		–	$C_{15}H_{13}N_3O_3S$ 315.3	179–81 Et	91
12		–	$C_{12}H_{14}N_4O_2S$ 278.3	98–100 Et	53

Aq. Et = aqueous ethanol, B = benzene, Et = ethanol, Pt. E = petroleum ether

showed 83.9% reduction of adult worm count [11]. The author indicated that the presence of a substituted thiosemicarbazide or p-chlorobenzylidene moiety attached to the benzothiazole ring is a requirement for high schistosomicidal activity.

It was found that compound **7c** (R = 4-bromophenyl), showed very high antischistosomal activity (91.7% reduction, Table 3), while, compound **7d** possesses intermediate activity (77.5% reduction). Praziquantel, the drug of device for the treatment of human schistosomiasis, was mentioned to exhibit 57% reduction in worm number when administered in 100 mg/kg on days 35 and 37 post infection [12]. More detailed information about the antiparasitic activity and toxicity of all the examined compounds will be published later.

Table 2: Mean number and percentage reduction of adult of *T. spiralis* in the intestine in the different groups

Group/Compd.	Worms count	
	X[a]	% r[b]
GI (**7d**)	9.1	87.8
GII (**8a**)	10.3	86.1
GIII (**9h**)	39.7	46.4
GIV (**9j**)	6.5	91.2
GV (**10b**)	22.3	69.9
GVI (**10c**)	2.5	96.6
Control	74	–

[a] the mean number, [b] percentage reduction

Table 3: Mean adult aworm load of *S. mansoni* in the different groups

Group/Comp.	Adult worm load[a]	
	X[b]	% r[c]
GI (**7c**)	3	91.7
GII (**7d**)	8.1	77.5
Control	36	–

[a] adult worm was obtained from the portal system of mice, [b] the mean number, [c] percentage reduction

3. Experimental

3.1. Chemistry

Melting points were determined in open glass capillaries and are ucorrected. IR spectra (KBr) were measured on a Perkin-Elmer 1430. ^{1}H NMR spectra were recorded on a Varian EM-390–90 MHz or Varian Gemini 200 MHz spectrometers in DMSO-d_6 using TMS as an internal reference. Elementary analyses were carried out using a Perkin-Elmer RE 2400 CHNS analyzer. All values of C, H, N and S are within ±0.4% of the calculated data. The intermediates **7a–d** [13] and **10a**, **c** [14] were prepared as reported. The yields, physical constants and crystallization solvents are listed in Table 1.

3.1.1. 2-[(3-Substituted-4-oxothiazolidin-2-ylidene)hydrazino]benzothiazoles (**8a**, **b**)

To a solution of **7c**, **d** (10 mmol) in abs. EtOH (20 ml), chloroacetic acid (0.94 g, 10 mmol) and anhydrous CH_3COONa (0.82 g, 10 mmol) were added. The reaction mixture was refluxed for 8 h and cooled. The product

obtained was filtered washed with ethanol, dried and recrystallized from the proper solvent.
8a: IR (KBr cm^{-1}): 3297, 3253 (NH); 1710 (C=O); 1664 (C=N); 1614, 1522 (C=C); 1545 (δ NH). ^{1}H NMR: δ ppm 3.35 (d, 2 H, J = 6 Hz, thiazolidinone-C_4H_2 magnetically non equivalent), 6.7–7.8 (m, 8 H, Ar-H and benzothiazole-H), 8.65 (s, br, 1 H, D_2O exchangeable, NH).
8b: IR (KBr cm^{-1}): 3290, 3256 (NH); 1700 (C=O); 1658 (C=N), 1620, 1515 (C=C), 1541 (δ NH). ^{1}H NMR: δ ppm 3.4 (d, 2 H, J = 6 Hz, thiazolidinone C_4H_2 magnetically non equivalent), 6.6–7.8 (m, 8 H, Ar-H and benzothiazole-H), 8.5 (s, br, D_2O exchangeable NH).

3.1.2. 2[(3,4-Disubstituted-thiazolin-2-ylidene)hydrazino)benzothiazoles **9a–j**

A mixture of **7a–d** (10 mmol), selected phenacyl bromide (10 mmol) and anhydrous CH_3COONa (0.82 g, 10 mmol) in 20 ml abs. EtOH, was refluxed for 12 h. After cooling, the separated solid was filtered dried and recrystallized from the proper solvent.
9a: IR (KBr cm^{-1}): 3318 (NH); 1656 (C=N); 1597, 1528 (C=C); 1556 (δ NH); 1538, 1344 (NO_2). ^{1}H-NMR: δ ppm 1.1 (t, J = 6.9 Hz, 3 H, CH_2CH_3), 1.4 (q, J = 7 Hz, 2 H, CH_2–CH_3), 6.4 (s, 1 H, thiazoline-C_5–H), 6.9 (m, 2 H, benzothiazole-$C_{6,7}$-H), 7.13 (t, J = 7.6 Hz, 1 H, benzothiazole C_5–H), 7.41 (d, J = 7.9 Hz, 1 H, benzothiazole C_4–H), 7.73 (d, J = 8.5 Hz, 2 H, Ar-$H_{2,6}$), 8.3 (d, J = 8.5, 2 H, Ar-$H_{3,5}$), 11.3 (s, br, 1 H, D_2O exchangeable, NH).
9b: IR (KBr cm^{-1}): 3374 (NH), 1676 (C=N), 1551, 1506 (C=C), 1558 (δNH). ^{1}H NMR: δ ppm 6.8 (s, 1 H, thiazoline-C_5-H), 7–7.9 (m, 14 H, Ar-H and benzothiazole-H), 11.1 (s, br, D_2O exchangeable, NH).
9c: IR (KBr cm^{-1}): 3360 (NH), 1662 (C=N), 1584, 1507 (C=C), 1549 (δNH). ^{1}H NMR: δ ppm 6.7 (s, 1 H, thiazoline-C_5-H), 7–7.9 (m, 13 H, Ar-H and benzothiazole-H), 11.4 (s, br, 1 H, D_2O exchangeable, NH).
9d: IR (KBr cm^{-1}): 3295 (NH), 1658 (C=N), 1591, 1505 (C=C), 1539 (δNH), 1535, 1443 (NO_2). ^{1}H NMR: δ ppm 7 (s, 1 H, thiazoline-C_5–H), 7.2–8.6 (m, 13 H, Ar-H and benzothiazole-H), 11.3 (s, br, 1 H, D_2O exchangebale, NH).
9e: ^{1}H NMR: δ ppm 6.7 (s, 1 H, thiazoline-C_5–H), 7–7.9 (m, 13 H, Ar-H and benzothiazole-H), 11.4 (s, br, 1 H, D_2O exchangeable, NH).
9f: ^{1}H NMR: δ ppm 6.8 (s, 1 H, thiazoline-C_5–H), 7.1–7.8 (m, 12 H, Ar-H and benzothiazole-H), 11 (s, br, 1 H, D_2O exchangeable, NH).
9g: ^{1}H NMR: δ ppm 7.1 (s, 1 H, thiazoline-C_5–H), 7.2–8.8 (m, 12 H, Ar-H and benzothiazole-H), 11.3 (s, br, 1 H, D_2O exchangeable, NH).
9h: IR (KBr cm^{-1}): 3284 (NH), 1622 (C=N), 1598, 1504 (C=C), 1571 (δ NH), 885 (C–Cl). ^{1}H NMR: δ ppm 6.7 (s, 1 H, thiazoline-C_5–H), 7–7.9 (m, 13 H, Ar-H and benzothiazole-H), 11 (s, br, 1 H, D_2O exchangeable, NH).
9i: IR (KBr cm^{-1}): 3100 (NH); 1650 (C=N); 1603, 1503 (C=C), 1565 (δ NH); 811 (C–Cl). ^{1}H NMR: δ ppm 6.8 (s, 1 H, thiazoline-C_5–H), 7.2–8 (m, 12 H, Ar-H and benzothiazole-H), 11.2 (s, br, 1 H, D_2O exchangeable, NH).
9j: ^{1}H NMR: δ ppm 6.85 (s, 1 H, thiazoline C_5-H); 6.85–6.9 (m, 4 H, benzothiazole-$C_{6,7}$-H and 4-Cl–C_6H_4–$C_{3,5}$–H); 7.15 (t, J = 7.8 Hz, 1 H, benzothiazole-C_5–H), 7.3 (d, J = 7.9 Hz, 2 H, 4-Cl–C_6H_4–$C_{2,6}$–H); 7.4 (d, J = 7.8 Hz, 1 H, benzothiazole-C_4–H), 7.45 and 8.15 (two d, J = 8.7, each 2 H, 4-NO_2–C_6H_4); 11.35 (s, br, 1 H, D_2O exchangeable, NH).

3.1.3. N-Benzothiazol-2-yl-N′(5-acetoxymethylfurano-2-yl)methinehydrazone (**10c**)

A mixture of benzothiazol-2-hydrazine **6** (0.25 g, 1.5 mmol), 5-acetoxymethyl-2-furanaldehyde (0.27 g, 1.6 mmol) and absolute EtOH (15 ml) were allowed to stirr at room temperature for 1 h. The product was collected by filtration, dried and recrystallized from the appropriate solvent.
IR (KBr cm^{-1}): 3310 (NH), 1742 (C=O), 1661 (C=N), 1573, 1506 (C=C), 1237, 1020 (C–O–C). ^{1}H NMR: δ ppm 2.1 (s, 3 H, $COCH_3$), 5.1 (s, 2 H, CH_2O), 6.68 and 6.85 (two d, each for 1 H, J = 3.4 Hz, furane $C_{3,4}$–H), 7.1 (t, 1 H, J = 6.3 Hz, benzothiazole-C_6–H), 7.3 (t, 1 H, J = 7 Hz, benzothiazole-C_5–H), 7.4 (d, 1 H, J = 7.8 Hz, benzothiazole-C_7–H), 7.76 (d, 1 H, J = 7.4 Hz, benzothiazole-C_4–H), 8 (s, 1 H, N=CH), 12.2 (s, br, 1 H, D_2O exchangeable NH).

3.1.4. 2-(Morpholinocarbonylhydrazino)benzothiazole (**12**)

4-Morpholinocarbonylchloride (0.15 g, 1 mmol) and Et_3N (0.05 ml) were added to a cold solution of **6** (0.17 g, 1 mmol) in 5 ml $CHCl_3$. The reaction mixture was stirred for 1 h and the solvent was then evaporated in vacuo. The residue was digested with H_2O and recrystallized from the appropriate solvent.
IR (KBr cm^{-1}): 3104 (NH), 1677 (C=O); 1645 (C=N); 1603, 1524 (C=C), 1544 (δ NH). ^{1}H NMR δ ppm: 2.8 (t, 4 H, J = 7 Hz, morpholine-$C_{3,5}$–H), 3.7 (t, 4 H, J = 7 Hz, morpholine-$C_{2,6}$–H), 6.6–7.6 (m, 4 H, benzothiazole-H), 8.7 (s, br, 1 H, D_2O exchangeable, N*H*–NHCO), 10.3 (s, 1 H, br, D_2O exchangeable, N*H*CO).

3.2. Parasitology

3.2.1. Nematodal study

Trichenilla spiralis larvae were obtained from infected pigs from Alexandria slaughter house and maintained in the laboratory by several passage in Swiss strain albino mice. Each mouse was infected with 300 T. spiralis larvae.
The drugs **7d**, **8a**, **9j**, **9h**, **10b** and **10c** were given orally in a dose of 20 mg/kg for 3 successive days. The later dose was chosen according to a pilot study using 10, 20, 50 g and 100 mg/kg. The chosen dose (20 mg) proved to be the most efficient dose. All of the compounds were insoluble in aqueous medium and were administered to mice as a suspension in 10% Cremophor EL (Sigma) after ultrasonication to produce a uniform suspension.
Mice were divided into six groups. Groups I, II, III, IV, V and VI received, on the second day post infection (PI), compounds **7d**, **8a**, **9h**, **9j**, **10b** and **10c** respectively, for 3 successive days in order to test the effect on adult worms.
Infected but non treated mice were sacrificed simultaneously with each experimental group (7 day PI). Also a control group treated with 10% Cremophor EL solution only was included.
Assessment of results was done by the parasitological studies [15]. Worms were counted in the intestines after 7 days PI in all groups.

3.2.2. Schistosomal study

Schistosoma mansoni cercariae were obtained from infected *Biomphalaria alexandrina* snails, purchased from the Biological Unit, Theodor-Bilharz Research Institute. Imbaba, Giza, Egypt. Each mouse was infected by 150 cercariae using the tail method [16].
Two groups of infected mice (GI and GII) received compounds **7c** and **7d** respectively. These compounds were administered in a dose of 20 mg/kg for three successive days. Again this dose proved to be the most efficient dose according to a pilot study with 10, 20, 50 and 100 mg/kg. Another group of infected non-treated mice served as a control.
Adult worms are recovered by the perfusion technique [17] in order to determine the reduction in worm burden.

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