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Studies on the Reactivity of Fused Thiazole Toward Nucleophilic Reagents: Synthesis of New Thiazolo-Derivatives of Potential Antischistosomal Activity

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ABSTRACT: *Schistosomiasis is considered one of the most important human helminth infection in terms of morbidity and infectivity (Chitsulo et al. Acta Trop 2000, 77, 41; Engles et al. Acta Trop 2002, 82, 139; Shelly et al. Mol Biochem Parasitol 1993, 60, 93). Derivatives of 2-amino-5-nitrothiazoles have shown activity against Schistosoma mansoni (S. mansoni) and Schistosoma haematobium (S. haematobium), but due to their toxic effect we synthesized new derivatives of a heteroaromatic amine with thiazole moiety. Required thiazole derivatives were prepared via* **1** *and* **2**. *In this work, two batches of animals were used to test the efficacy of 10 derivatives of thiazole against schistosomiasis. The first batch of Swiss albino mice was infected with S. mansoni and was treated with 5 × 50 mg/kg b.w. The second batch of golden hamsters was infected with S. haematobium and was treated with 5 × 100 mg/kg b.w. Parasitological parameters, biochemical studies, and granuloma diameter were estimated. Results indicated that in the case of S. mansoni infected mice, compounds* **2** *(2-amino-4-thiazoliniminium chloride) and* **20** *(2,4-diamino thiazole) showed moderate efficacy (50% worm reduction). While compounds* **18** *(4-dicyanomethylene-4, 5-dihydrothiazo-2-yl)-N,N-dimethylimidoformamide) and* **21** *2-(dimethylamino) methylene-1,3-thiazol-4-yl)-N,N-dimethylimidoformamide) showed 83% and 90% worm reduction with some normalization of liver function and significant reduction in hepatic granuloma diameters. In the case of S. haematobium infected hamsters, compound* **15** *showed reduction of worms by about 50% with improvement in kidney function. The high effect of compounds* **18** *and* **21** *compared to* **2**, **15**, *and* **20** *could be attributed to the dimethylimidoformamide moieties combined with the thiazole ring.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:121–131, 2005; Published online in Wiley InterScience (www.interscience. wiley.com). DOI 10.1002/hc.20072

INTRODUCTION

Schistosomiasis is considered one of the most important human helminth in terms of morbidity and infectivity [1,2]. Approximately 220 million people are infected with *S. mansoni* that occurs in 58 countries in Africa, the Middle East, and South America, while about 90 million people are now infected with *S. haematobium* in 52 countries in Africa and the Middle East [3]. Derivatives of 2-amino-5-nitrothiazoles have shown activity against a variety of parasitic infections [4], and as a consequence a nitrothizole heterocyclic compound niridazole [5] has been introduced for the treatment of schistosomiasis. This compound showed considerable efficacy

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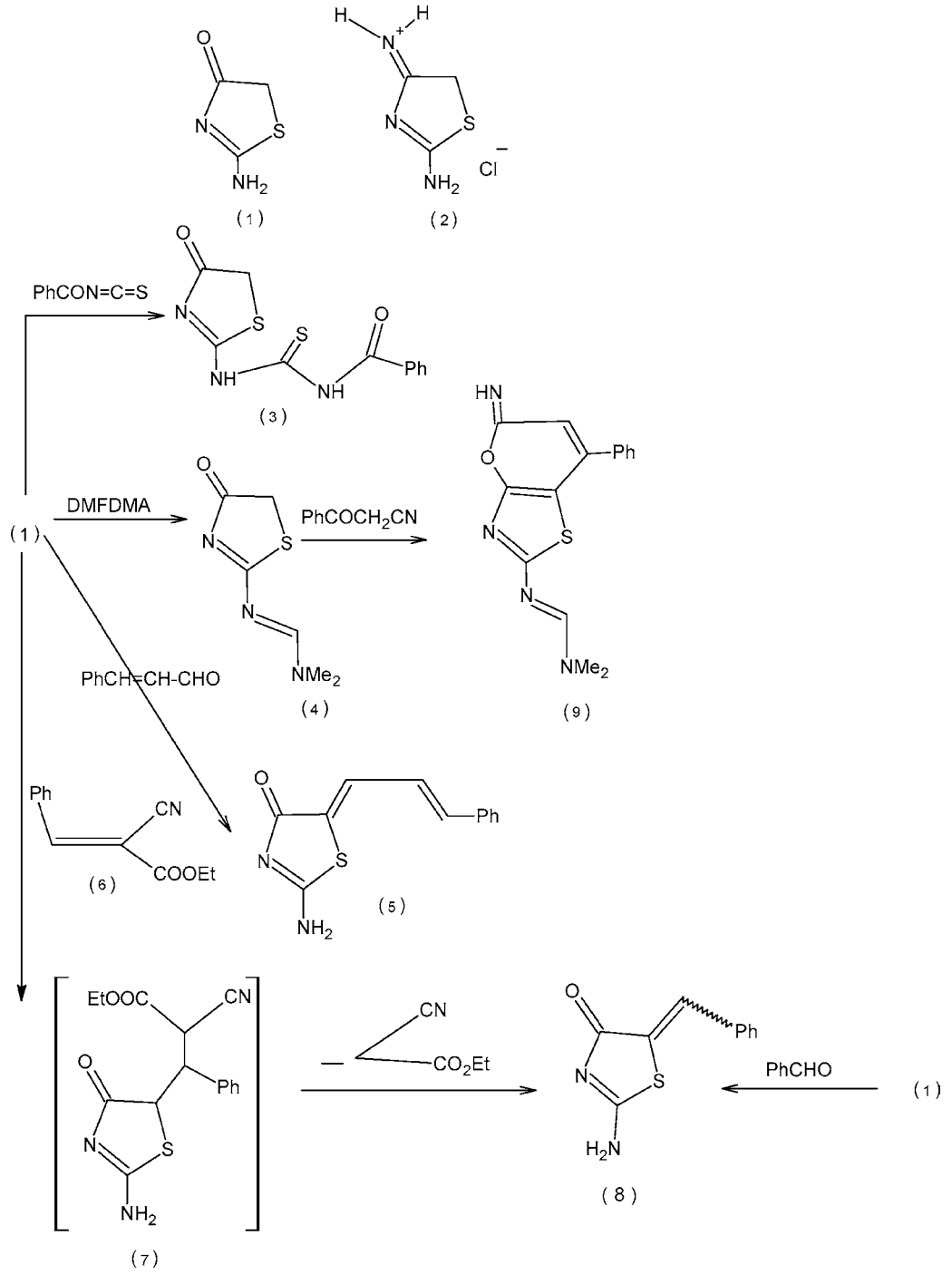
against *S. mansoni* and *S. haematobium* via oral administration, but due to its toxic effect [6] we synthesized new derivatives of a heteroaromatic amine with the thiazole moiety for our program. For the synthesis of some aminothizole for experimental evaluation as schistosomicidal agents, the required 2-aminothiazl-4-one **1** and 4- iniminium-4,5-dihydrothiazol-2-ylamine chlorid **2** were prepared following literature procedures [7,8]. Reaction of **1** with electrophilic reagents proved to depend on the nature of reagents (see Scheme 1). Whereas **1** reacts with benzoylisothiocyanate (prepared in situ) and with *N*,*N*-dimethyl formamide dimethylacetal to yield products of addition or condensation at the



SCHEME 1

amino function (CF compounds **3** and **4**), it reacts with cinnamaldehyde affording only the cinnamylidene derivative **5**. Attempt of addition of ethyl benzylidenecyanoacetate **6** to compound **1** has resulted only in the formation of arylidene derivative **8**. This most likely has occurred via addition of the active methylene moiety in **1** to activated double bond system and subsequence elimination of ethyl cyanoacetate. Similar reaction sequence has been previously observed on reacting ethyl arylidene cyanoacetate with active methylene reagents [9]. Compound **8** has also been obtained via reacting **1** with benzaldehyde in acetic acid solution in the presence of sodium acetate. Attempt of reacting **4** with benzoylacetonitrile has, in our hand, resulted in only the formation of the condensed isomeric pyranothiazol product **9**. This structure is supported by the presence of NH function at ^{1}H NMR and disappearance of CO group in IR spectrum. In recent work [10] it has been showed that the amino function in **2** is readily replaceable by electropilies. We have found that this amino function is also replaceable by carbanionic species in sodium hydroxide solution, compound **2** with malononitrile afforded dicyanomethylene derivative **10** [10]. This product condensed with a variety of electrophilic reagents enabling the synthesis of several new biologically interesting thiazole derivatives. Condensation of **10** with 4-methyl benzaldehyde has resulted in the formation of arylidene derivative **11**, the isomeric Shiff's condensation product was excluded based on ^{1}H NMR that revealed acetylation of amino function, thus irradiating of methyl signal at δ 2.3 while no NH_2 protons was observed. Reaction of **10** with 3-dimethylamino propiophenone hydrochloride afforded product of molecular formula $C_{23}H_{15}N3S$. This was assigned structure **15** and is assumed to be formed via initial addition of two molecules of methylvinyl ketone formed on heating **12** and subsequent cyclization loss of HCN and water (see Seheme 2). This structure was established based on ^{1}H NMR which is consistent with the proposed structure. This to our knowledge is the first reported synthesis of benzothiazole from thiazole intermediate and clearly opens the way to synthesis functionally substituted amino benzothiazoles. The reaction of **10** with excess of CS_2 in dimethyl formamide in the presence of triethylamine has resulted in the formation of product of molecular formula $C_7H_5N_3O_2S_3$. The IR spectrum revealed the absence of CN signal, structure **17** could be proposed; it is believed that CS_2 initially added to active methylene at C-5 of thiazole ring formed dithiocarboxylic acid **16** which was cyclized to the amino thiopyranothiazole **17** (Scheme 3), in analogy with the Gewald reaction [11]. The reaction of **10** with DMFDMA yielded a product of molecular formula $C_9H_9N_5S$ (*m/z* 219) that is formulated as **18** rather than **19** on the basis of its ^{1}H NMR spectrum, which revealed thiazol-H_5 with no enhancement of NH_2 protons. Stirring the salt **2** with 1 N sodium hydroxide results in formation of 2,4-diamino thiazole **20** [12] and condensation of DMFDMA with **20** results in the formation of di-amidine structure **21** (Scheme 4).

BIOLOGICAL ACTIVITY

Effect of Treatment with Thiazolo Derivatives Against S. mansoni Infection (First Batch)

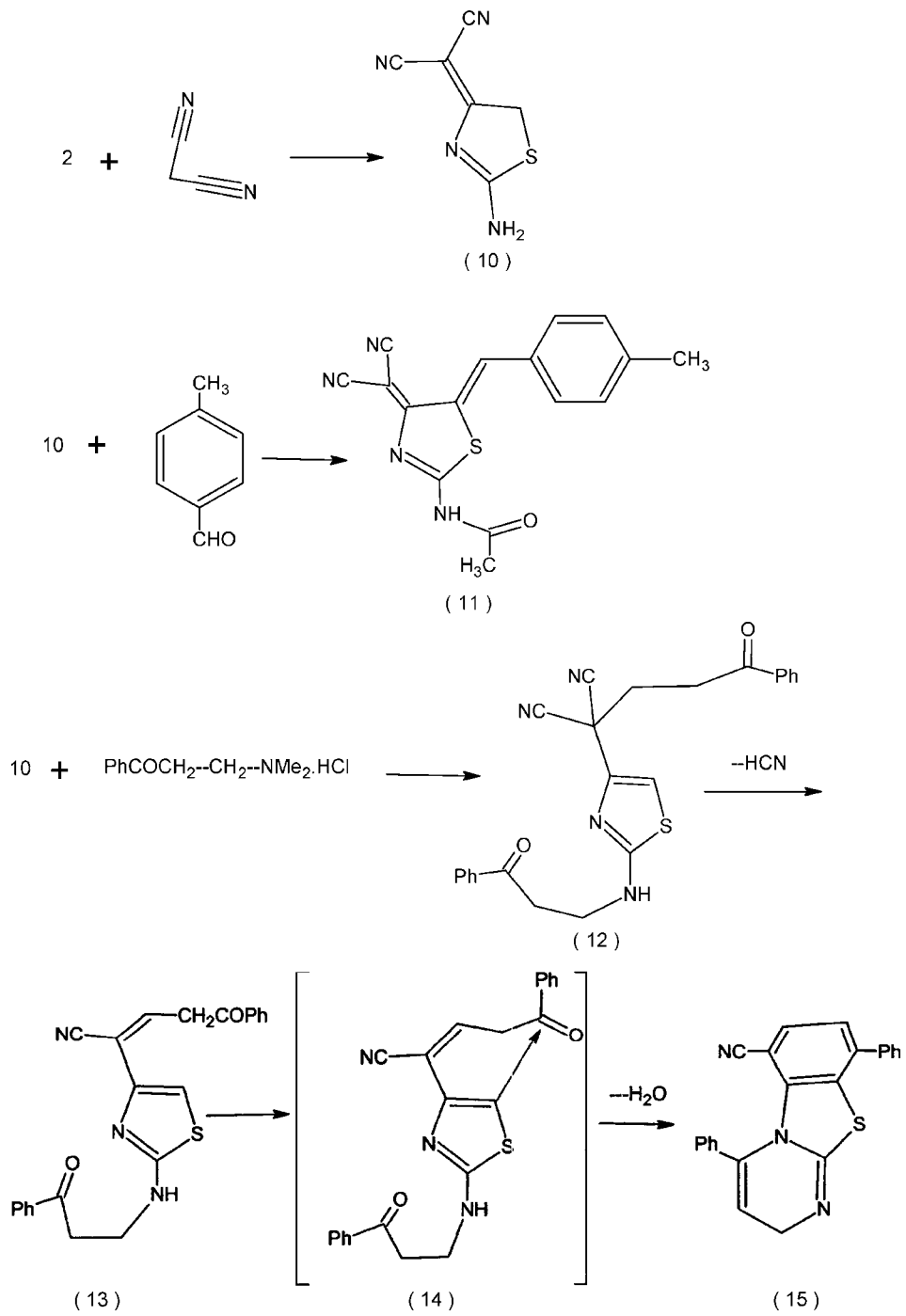
Experimental Animals and Infection. Swiss albino mice were infected with 80 ± 10 cercariae per mouse of an Egyptian strain of *S. mansoni* taken from Experimental animal research unit of Biological Supply Program at Theodore Bilharz Research Institute (BSP, TBRI) Giza, Egypt. Infection was done by body immersion method [13].

Treatment. After 7 weeks of infection, treatment was started with 50 mg/kg orally for five consecutive days from each compound (synthetic thiazolo derivatives). Total dose of 250 mg/kg body weight. Praziquantel was given in a dose of 500 mg/kg for two consecutive days [14].

Animal Sacrifice. Animals were sacrificed by decapitation 1 and 2 weeks after treatment, blood was collected, and serum was separated by centrifugation at 3000 r.p.m. and used for determination of ALT [15] and GGT [16]. Animals were perfused with saline to the hepatic and protomesenteric vessels [17] and worm were collected, counted and classified. Ova count were done in 0.2–0.5 g specimen of liver and intestine in 5% KOH at 37°C [18]. Percent egg developmental stages of ova were examined under microscope in three specimens of small intestine per mouse [19]. Small part of liver was put in 10% formaline for measuring granuloma diameters. Level of reduced glutathion (GSH) was estimated in liver homogenate [20].

Effect of Treatment with Thiazolo Derivatives Against S. haematobium Infection (Second Batch)

Experimental Animals and Infection. Golden hamsters, 6–8 weeks old, were exposed individually to 150 ± 10 cercariae of Egyptian strain of *S. haematobium*. The hamsters were infected using a ring method of exposure. Each animal was weighed and anesthetized by intraperitoneal injection with 0.5 mg/kg b.w. sodium thiopental diluted 1:10 in

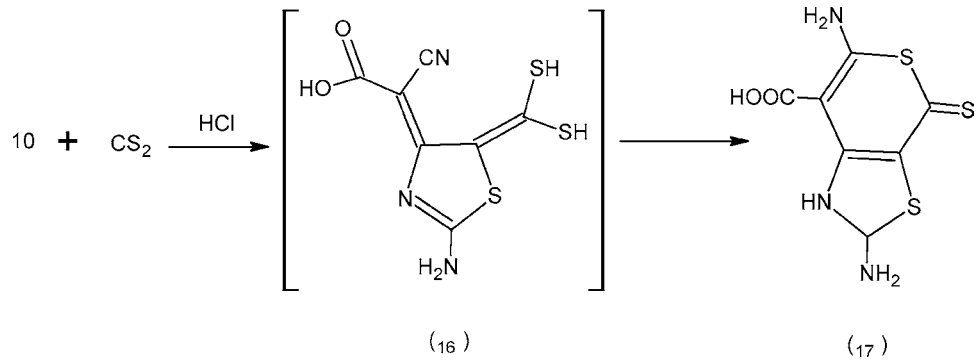


SCHEME 2

physiological saline. Then each hamster was placed on its back, in a wooden frame for support, and a heavy metal ring (nickel-plated brass, measuring 3 cm inside diameter weighing 25 gm and holding 5.0 mL of water) was put on the lower dampened abdomen. The appropriate suspension of cercariae was then pipette into each ring and left for a period of 1 h.

Treatment. After 13 weeks of infection treatment was started with 100 mg/kg orally for five consecutive days from each compound (synthetic thiazolo derivatives). Praziquantel was given in a dose of 150 mg/kg for two consecutive days.

Animal Sacrifice. Animals were sacrificed by decapitation 1 and 2 weeks after treatment, blood was

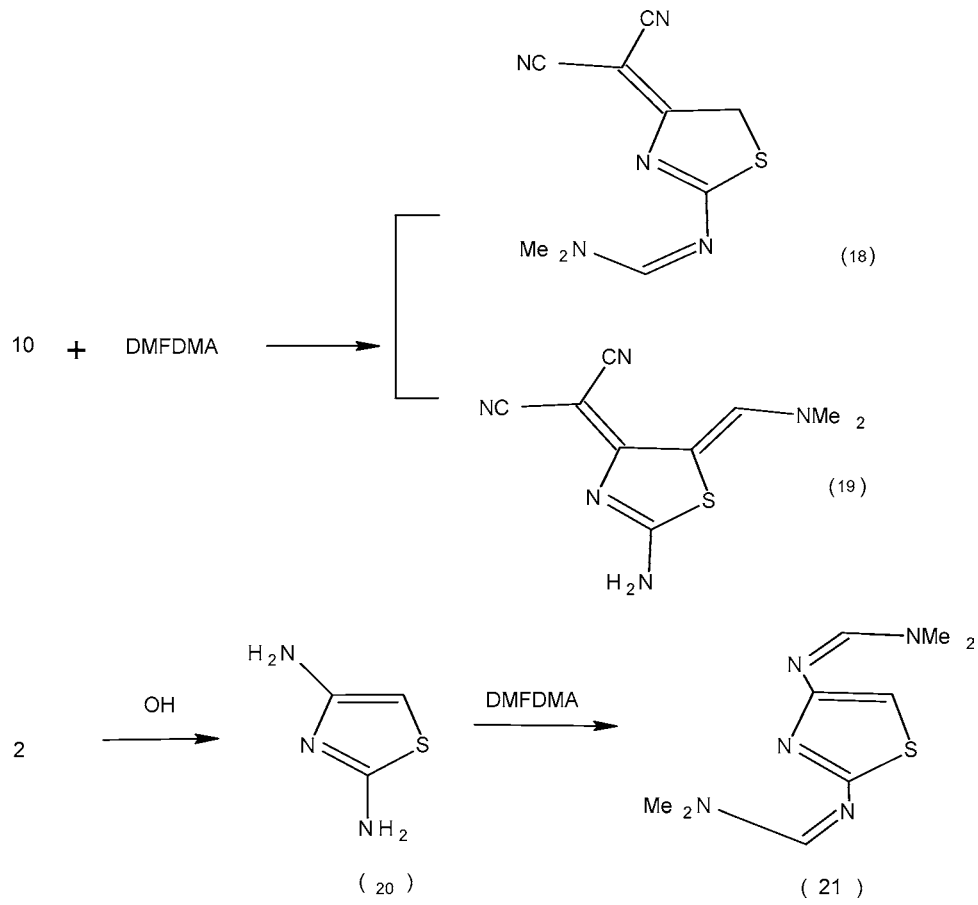


SCHEME 3

collected and serum was separated, and all parasitological parameters were done as in first batch. Body of each hamster was weighed before sacrificed and liver, spleen, heart, kidneys, and lungs were weighed after sacrifice. Serum level of creatinine [21] and alkaline phosphatase [22], urea [23], and thiol [24] were estimated.

EXPERIMENTAL DESIGN

We choose compounds **4, 5**, and **8** derivatives from **1** as they have a variety of modifications from **1**. We choose compounds **15, 18**, and **21** that are novel compounds as a derivatives from **2** to be compared to **10** and **20**. The two batches of infected mice or



SCHEME 4

hamsters were divided into 12 groups: infected control group, animals received the vehicle of drugs. Second group received praziquantel suspended in 2% cremophore–El. Groups from 3–12 received compounds **1, 2, 4, 5, 8, 10, 15, 18, 20**, and **21** respectively. All compounds dissolved in water except compounds. **5** and **8** that were suspended in gum acacia 2.5%.

Statistical Analysis

All values were expressed as mean ± standard error of the mean. Independent Student *t*-test was applied to analyze the significance of differences between mean values, and a critical *p* value was considered to be significant at <0.05.

RESULTS

First Batch

Infection with *S. mansoni* produced about 18.7 ± 1.4 worms with equal number of males and females. Treatment with compounds **1, 4, 5, 8**, and **15**, produced no significant changes in worm distribution, while compound **2** and **20** reduced the total number of worms by 50.8% and 56.7% respectively (Table 1). Worm reduction was more after treatment with compounds 18 and 21 (83.4% and 90.9%) with 83.9% and 82.4% hepatic shift. These results were, 2 weeks after treatment, pronounced than group sacrificed 1 week after treatment. Compounds **18** and **21** reduced the total number of ova by about 85.3% and 83.6% and increased the percent of dead ova to be 58.9% and 52.4% (Table 2). These results were compared with PZQ that reduced the total number of worms and eggs by 96.3% and 86.8%, respectively with 85.7% hepatic shift. Infection with *S. mansoni* was found to increase the serum level of ALT and GGT by 83.1% and 188.9% and decrease liver GSH by 32.8%. No significant reduction was observed in serum level of ALT and GGT after treatment with compounds **4, 8**, and **5**, while compound **18** produced (36.1% and 53.8%) reduction. Compound **21** produced more reduction 40.3% and 59.6%, respectively. The level of GSH increased after compounds **18** and **21** by 30.4% and 35.6%. These were compared with PZQ that tend to normalize ALT, GGT, and GSH. Slight reduction in hepatic granuloma diameter was observed in group treated with compound **18** (20.2%), while more reduction occurred in group treated with compound **21** (26.5%) (Table 3).

Second Batch

The total number of worms was 59.7 ± 8.5 after 13 weeks of infecting hamsters with *S. haematobium*. Oogram pattern showed 50.2%, 40.8%, and 9.0% of total immature, mature, and dead ova, respectively. The total number of ova per gram liver and intestine was found to be 53.5×10^3. Treatment with PZQ reduced the total number of worms by 98.1% with complete absence of mature and immature stages. Treatment with compounds **2, 15, 18**, and **20** reduced the total number of worms by about 50%, while the rest of compounds produced reduction from 33–41%. Also, compounds **2, 15, 18**, and **20** increased the percent of dead ova and reduced the total number of eggs by about 62%, 60%, 53%, and 70%, and respectively (Table 5). Also, infection increased liver and spleen weight 13 weeks post infection (w.p.i.) without significant change in

TABLE 1 Effect of Treatment of Thiazole Derivatives in a Dose of 50 mg/kg for 5 days and Praziquantel (PZQ) in a Dose of 500 mg/kg for 2 Days on Worm Distribution in *S. mansoni* Infected Mice

Animal Groups	*Total No. of Male mean + SE*	*Total No. of Female Mean + SE*	*Total No. of Couples Mean + SE*	*Total No. of Worms Mean + SE*	*% Worm Reduction*	*% Hepatic Shift*
Infected control	9.6 ± 0.7	9.1 ± 0.8	9 ± 0.4	18.7 ± 1.4	–	10.7
PZQ	0.6 ± 0.2*	0.1 ± 0.1*	0 ± 0*	0.7 ± 0.3*	96.3*	85.7*
1	8.2 ± 0.6	7.0 ± 0.6	8.0 ± 0.4	15.2 ± 1.2	18.7	15.4
2	5.0 ± 0.2*	4.2 ± 0.3*	3.0 ± 0.1*	9.2 ± 0.9*	50.8*	35.2*
4	6.6 ± 0.9	8.1 ± 0.9	6.1 ± 0.8	14.7 ± 1.9	21.42	31.3
5	8.6 ± 0.9	9.0 ± 0.5	4.6 ± 0.6	17.6 ± 1.1	5.9	27.8
8	8.9 ± 0.6	9.1 ± 1.6	7.3 ± 0.6	18.0 ± 1.3	3.7	20.6
10	8.0 ± 0.5	6.2 ± 0.5	6.3 ± 0.7	14.2 ± 1.1	24.1	29.3
15	7.0 ± 0.6	6.1 ± 0.4	5.3 ± 0.3	13.1 ± 1.0	29.9	22.1
18	2.1 ± 0.1*	1.0 ± 0.4*	0 ± 0*	3.1 ± 0.3*	83.4*	83.9*
20	4.1 ± 0.2*	4.0 ± 0.3*	2.6 ± 0.1*	8.1 ± 0.5*	56.7*	39.3*
21	0 ± 0*	1.7 ± 0.5*	0 ± 0*	1.7 ± 0.5*	90.9*	82.4*

*Significant difference from infected control at $p < 0.05$.

TABLE 2 Effect of Treatment of Thiazole Derivatives in a Dose of 50 mg/kg for 5 Days and Praziquantel (PZQ) in a Dose of 500 mg/kg for 2 Days on Percent Egg Developmental Stages and Tissue Egg Load in *S. mansoni* Infected Mice

Animal Groups	*% Egg Developmental Stages (Oogram Pattern)*			*Tissue Egg Load (No. of Ova/gm Tissue $\times 10^3$)*		
	% Immature	*% Mature*	*% Dead*	*Liver*	*Intestine*	*Total*
Infected control	43.9 ± 3.9	44.3 ± 4.1	11.8 ± 1.3	14.9 ± 1.3	25.9 ± 0.9	40.8 ± 1.1
PZQ	0 ± 0*	0 ± 0*	100 ± 0*	3.7 ± 0.2*	1.7 ± 0.5*	5.4 ± 0.4*
1	44.3 ± 3.8	44.7 ± 4.2	11 ± 1.5	13.5 ± 0.3	11.9 ± 1.4	25.4 ± 2.5
2	24.1 ± 2.5*	40.6 ± 3.2	35.3 ± 3.4*	8.2 ± 0.4*	2.5 ± 0.2*	10.7 ± 1.5*
4	45.2 ± 4.7	40.2 ± 3.2	14.6 ± 2.3	11.0 ± 0.5	23.9 ± 1.2	34.9 ± 1.1
5	44.1 ± 3.7	45.3 ± 4.2	10.7 ± 0.9	12.3 ± 0.9	23.9 ± 2.4	36.2 ± 2.1
8	35.7 ± 4.0	51.2 ± 3.7	13.1 ± 1.4	13.1 ± 0.8	22.4 ± 1.8	35.4 ± 2.5
10	30.2 ± 2.1	48.3 ± 2.5	21.5 ± 3.2*	12.1 ± 0.5	22.1 ± 2.3	34.2 ± 2.4
15	29.3 ± 2.5*	40.2 ± 5.3	30.5 ± 3.5*	10.7 ± 0.5	10.9 ± 1.6*	21.6 ± 2.6*
18	10.1 ± 4.3*	29.0 ± 2.1*	60.9 ± 6.1*	3.8 ± 0.4*	2.2 ± 0.3*	6.0 ± 0.2*
20	22.4 ± 2.1*	35.2 ± 3.2	43.4 ± 4.1*	7.8 ± 0.4*	2.4 ± 0.2*	10.2 ± 1.4*
21	16.5 ± 3.4*	21.1 ± 4.3*	62.4 ± 5.2*	4.2 ± 0.3*	2.6 ± 0.3*	67 ± 0.4*

*Significant difference from infected control at $p < 0.05$.

other organs compared with infected control groups (Table 4). There was a significant increase in creatinine, thiol, alkaline phosphatase, and urea compared to normal control. Treatment with compounds **2, 15, 18**, and **20** improved these enzymes significantly (Table 5).

DISCUSSION

Nitridazole was found to be effective against schistosomiasis [5] and due to its toxic effect [6], we synthesized 10 new compounds (derivatives of thiazole moiety) and their efficacy was tested against *S. mansoni* (batch 1) and *S. haematobium* (batch 2). Activity among derivatives of 2-aminothiazol-4-one **1** depends on the modification in structures, for example, replacement of amino group by *N, N*-dimethylimidoformamide as in compound **4** or the introduction of arylidene derivatives in 5-position as in compounds **5** and **8** resulted in loss of activity against *S. mansoni* and *S. haematobium*. This may be due to the presence of carbonyl group in 4-position of thiazole ring. A wide variety of structural modification in 4-iminium-4,5-dihydrothiazol-2-yl amine chloride **2** produced compounds **10, 15**, and **20** which showed a limited activity against *S. mansoni* and *S. haematobium*. The increase in reactivity in compound **18** is due to the replacement of

TABLE 3 Effect of Treatment of Thiazole Derivatives in a Dose of 100 mg/kg for 5 Days and Praziquantel (PZQ) in a Dose of 500 mg/kg for 2 Days on % Reduction in Granuloma Diameter and On serum ALT, GGT, and Liver Content of GSH in *S. mansoni* Infected Mice

Animal Groups	*% Worm Reduction*	*% Reduction in Granuloma Diameter*	*ALT (Unit/mL)*	*GGT(U/L)*	*GSH (Umol/g Liver)*
Normal control	–	–	66.8 ± 3.4	1.8 ± 0.5	2.01 ± 0.11
Infected control	–	–	122.3 ± 5.6	5.2 ± 0.6	1.35 ± 0.09
PZQ	96.3*	34.1	72.1 ± 3.4	2.2 ± 0.2	1.90 ± 0.2
1	18.7	5.1	110.2 ± 3.5	4.5 ± 0.2	1.33 ± 0.12
2	50.8*	10.0*	91.5 ± 6.6	3.0 ± 0.2	1.59 ± 0.10
4	21.42	4.2	100.3 ± 7.1	4.0 ± 0.3	1.53 ± 0.18
5	5.9	2	110.3 ± 6.5	4.7 ± 0.4	1.24 ± 0.11
8	3.7	2.5	113.4 ± 6.3	5.0 ± 0.2	1.25 ± 0.17
10	24.1	5.2	102.3 ± 4.5	4.1 ± 0.6	1.29 ± 0.08
15	29.9	6.1	100.0 ± 4.3	3.6 ± 0.2	1.30 ± 0.13
18	83.4*	20.2*	78.1 ± 5.5*	2.4 ± 0.6*	1.76 ± 0.19
20	56.7*	12.0*	82.2 ± 3.9*	2.8 ± 0.1*	1.55 ± 0.16
21	90.9*	26.3*	73.4 ± 3.5*	2.1 ± 0.3*	1.83 ± 0.17

*Significant difference from infected control at $p < 0.05$.

amino group in **2** by *N, N*-dimethylimidoformamide with dicyanomethylene in 4-position. Also the high activity of compound **21** could be attributed to 2-dimethylimidoformamide moieties combined with position 2,4 in thiazole ring.

First Batch

Infection with *S. mansoni* produced worms hepatic and portomesenteric vessels, female worms laid thousands of eggs that produced toxins and marked histopathological changes in liver, massive hepatic fibrosis [25], and produced disturbances in liver enzymes.

In the present study, infection with *S. mansoni* was found to increase the level of ALT. This elevation was in accordance with previous findings [26]. The level of GGT was elevated, and these results agree with those of Mahmoud [26]. This elevation seems to be due to the damage of hepatic cells and/or impaired permeability of cell membranes or due to heavy schistosome egg deposition [27]. Infection increased the level of GSH in liver homogenate significantly. This elevation functions to protect liver cells from toxins produced by bilharizial ova [28] and protect cells from lethal effects of toxic and carcinogenic compounds [29]. Treatment with compound **18** produced worm reduction by about 36 and 54%, whereas compound **21** produced more reduction (40% and 60%). Improvement in ALT and GGT is mainly due to eradication of worms with its damage effect of their ova that secrete toxins. Elevation of GSH was reduced and tends to normalize after treatment with compounds **18, 21**, and PZQ. Reducing effect of PZQ on GSH level in liver homogenate of *S. haematobium* infected hamster was observed by Ebeid et al. [30]. Reduction in granuloma diameters after compounds **18** and **21** may be attributed to the eradication of worms with consequent stopping of further deposition of new eggs.

Second Batch

Infection with *S. haematobium* causes marked histopathological changes in the liver. In addition to massive hepatic fibrosis, there was liver damage and an association between schistosomal infection and bladder cancer [31]. In the present work, infection with *S. haematobium* produced worms in the portomesenteric vessels. Praziquantel is now recognized as a powerful therapeutic agent that causes death of schistosomes [32,30] and can dramatically lower egg output [33]. It reduced the total number of worms by about 98% and the total number of eggs by about 86%, and all eggs present were dead. Total number of worms was reduced to about 50% after treatment with compounds **2, 15, 18**, and **20** (Table 5). Infection causes an increase in liver and spleen weight, and these might be due to histopathological changes caused by egg deposition, infiltration of reticuloendothelial cells, and development of fibrogranulomatous tissues. These changes are associated with blockage in hepatic venules and reduction in hepatic flow [34]. Compounds **2, 15, 18**, and **20** reduced liver and spleen weight, which might be due to improvement in liver pathology and reduction in worms and eggs (Table 4). Concerning the effect of infection on kidney functions, there was a significant increase in creatinine, thiol, alkaline phosphatase, and urea at 13 w.p.i compared to normal control

TABLE 4 Effect of Treatment of Thiazole Derivatives in a Dose of 100 mg/kg for 5 Days and Praziquantel (PZQ) in a Dose of 500 mg/kg for 2 Days on Body and Organs Weight in *S. haematobium* Infected Hamster

Animal Groups	*Organs Weight*					
	Body	*Liver*	*Spleen*	*Kidney*	*Heart*	*Lungs*
Normal control	133.91 ± 7.3	5.6 ± 0.6	0.15 ± 0.13	1.21 ± 0.11	0.61 ± 0.03	0.92 ± 0.22
Infected control	154.3 ± 6.4	7.4 ± 0.4	0.35 ± 0.09	1.43 ± 0.09	0.65 ± 0.04	1.22 ± 0.11
PZQ	137.22 ± 6.1	5.8 ± 0.5	0.19 ± 0.12	1.28 ± 0.10	0.60 ± 0.02	1.0 ± 0.13
1	148.4 ± 5.3	6.8 ± .3	0.32 ± 0.1	1.35 ± 0.08	0.66 ± 0.05	1.05 ± 0.17
2	143.5 ± 6.4	6.1 ± 0.7*	0.25 ± 0.05	1.41 ± 0.07	0.56 ± 0.06	1.22 ± 0.07
4	149.1 ± 5.5	6.9 ± 0.5	0.30 ± 0.09	1.36 ± 0.06	0.59 ± 0.04	1.14 ± 0.14
5	151.5 ± 9.5	7.1 ± 0.6	0.33 ± 0.07	1.30 ± 0.09	0.61 ± 0.03	1.05 ± 0.15
8	149.9 ± 10.1	6.6 ± 0.5	0.31 ± .05	1.29 ± 0.08	0.65 ± 09	1.00 ± 0.21
10	150.1 ± 9.1	7.0 ± 0.6	0.29 ± 0.06	1.26 ± 0.10	0.66 ± 0.08	1.09 ± 0.08
15	151.1 ± 8.9	6.1 ± 0.8*	0.26 ± 0.05*	1.23 ± 0.15	0.60 ± 0.09	1.11 ± 0.20
18	141.3 ± 10.1	6.3 ± 0.5*	0.28 ± 0.05*	1.26 ± 0.16	0.64 ± 0.07	1.21 ± 0.30
20	142.9 ± 9.9	5.9 ± 0.8*	0.24 ± 0.07*	1.33 ± 0.13	0.61 ± 0.09	1.12 ± 0.09
21	139.5 ± 9.3	6.9 ± 0.7	0.30 ± 0.03	1.40 ± 0.12	0.63 ± 0.1	1.09 ± 0.20

*Significant difference from infected control at $p < 0.05$.

animals. This increase is due to schistosomal infection that may damage the kidneys because of immune complex deposition in the glomeruli resulting in a true glomerulonephritis [35]. Administration of PZQ to infected hamsters produced a significant decrease in serum level of creatinine, thiol, alkaline phosphatase, and urea 2 weeks after treatment. This improvement agrees with the findings of El-Badrawy et al. [36] who attributed these improvements to stopping of egg deposition and eradication of the parasites. Significant reduction in serum level of creatinine, thiol, alkaline phosphatase, and urea was observed after treatment with compounds **2, 15, 18**, and **20** which might be due to death of 50% of *S. haematobium* worms (Table 5).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using Bruker vector 22 Germany. ^{1}H NMR spectra were recorded on Varian mercury 300 MHz with DMSO-d_6 a solvent and TMs as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on. Gc Ms-QP1000EX. Microanalysis was performed in National Research Center, Doki Giza, Egypt.

The preparation of 2-aminothiazol-4-one **1** and 4-iniminium-4,5-dihydrothiazol-2-yl amine chloride **2** has been reported before [8,9].

*1-Benzoyl-3-(4-oxo-thiazolidin-2-yl)-thiourea (**3**)*

A solution of benzoyl isothiocyante (prepared in situ) and compound **1** (1.6 g, 0.01 mol) was poured in acetonitrile (10 mL). The reaction mixture was refluxed for 3 h, the solid product so formed was filtered off and crystallized from methanol as white crystals; yield 55% mp 300°C, IR: 3100, 3000 cm^{-1} (NH, NH); 1780,1680 cm^{-1}, ^{1}H NMR (DMSO-d_6): δ 3.9 (S, 2H, CH_2), 7.4–7.6 (m,6H, aromatic-H+NH), 9.6 (S, 1H, CONH). Found: C, 47.29, H, 3.29; N, 15.03; S, 22.99% calcd for: $C_{11}H_9N_3O_2S_2$: C, 47.29, H, 3.24, N, 15.04, S, 22.95%.

*N, N-Dimethyl-N′-(4-oxo-4,5-dihydrothiazol-2-yl)imidoformamide (**4**)*

A mixture of compound **1** (1.61 g, 0.01 mol) and dimethyl formamid dimethyl acetal (1.19, 0.01 mol) was heated at 120°C for 30 min. The reaction mixture was left to cool then triturated with ethanol. The solid product, so formed, was collected by filtration and crystallized from ethanol as a brown crystals; yield 45% mp 230°C dec. IR: 1680 cm^{-1} (CO), 1660 cm^{-1} (C=N): ^{1}H NMR (DMSO-d6): δ 3.4 (S, 6H, $2CH_3$), 3.9 (S, 2H, CH_2), 8.8 (S, ^{1}H, CH, formyl-H). Found: C, 41.99, H, 5.30; N, 24.53; S, 18.70, calcd for $C_6H_9N_3OS$: C, 42.08; H, 5.29; N, 24.54; S, 18.72%.

*2-Amino-5-(3-phenyleneallylidene)-thiazol-4-one (**5**)*

A solution of **1**(1.16 g, 0.01 mol) and cinnamaldehyde (1.32 g, 0.01 mol) in pyridine (30 mL) was heated under reflux for 4 h. The solvent was then evaporated in vacuum, and the remaining solid product was collected by filtration and crystallized from DMF as yellow crystals of yield 52% mp 285°C. IR: 3200 cm^{-1} (NH_2), 3050 cm^{-1} olefines CH, 1680 cm^{-1} (CO), 1600 cm^{-1} aromatic ring. ^{1}H NMR (DMSO-d_6): δ 6.8–7.6 (m, 8H-aromatic −H+propenyl-H), 9.0 (S,1H, NH_2). Found: C, 62.59, H, 4.37; N, 12.15, S,

TABLE 5 Effect of Treatment of Thiazole Derivatives in a Dose of 100 mg/kg for 5 Days and Praziquantel (PZQ) in a Dose of 500 mg/kg for 2 Days on % Worm Reduction and Some Biochemical Aspects in *S. haematobium* Infected Hamster

Animal Groups	*% Worm Reduction*	*% Egg Reduction*	*Alkaline Phosphatase (Kind and King Units/mL)*	*Creatinine (Units/mL)*	*Thiol (Umol/L)*	*Urea (Units/mL)*
Normal control	–	–	20.3 ± 1.36	0.65 ± 0.03	863.55 ± 60.66	59.9 ± 2.5
Infected control	0	0	31.2 ± 2.34	1.91 ± 0.18	663.82 ± 32.87	72.3 ± 3.6
PZQ	98.1*	85.9*	21.9 ± 1.30*	0.68 ± 0.05*	851.22 ± 41.21*	61.4 ± 2.9*
1	37.5	32.5	29.3 ± 1.43	1.72 ± 0.11	690.88 ± 37.54	67.3 ± 2.7
2	50.9*	62.3*	24.3 ± 2.05*	1.01 ± 0.13*	824.43 ± 40.41*	64.4 ± 2.5*
4	41.9	36.1	30.3 ± 2.10	1.81 ± 0.14	721.89 ± 43.5	67.0 ± 2.3
5	33.3	29.1	30.1 ± 2.51	1.81 ± 0.15	705.77 ± 30.45	68.4 ± 5.3
8	40.4	35.2	29.7 ± 1.41	1.75 ± 0.13	720.63 ± 39.53	67.5 ± 3.7
10	38.5	32.4	28.3 ± 1.63	1.41 ± 0.09	689.11 ± 51.37	68.2 ± 4.1
15	48.1*	60.1*	25.3 ± 1.91*	1.01 ± 0.08*	828.21 ± 47.27*	64.9 ± 5.1*
18	46.9*	53.4*	26.1 ± 1.54	1.33 ± 0.03*	823.44 ± 50.33*	66.3 ± 4.1
20	55.3*	70.3*	22.3 ± 2.04*	0.81 ± 0.07*	829.31 ± 49.55*	63.3 ± 4.3*
21	39.7	34.8	27.5 ± 2.03	1.22 ± 0.05	692.35 ± 43.34	67.8 ± 3.1

*Significant difference from infected control at $p < 0.05$.

13.95; calcd for $C_{12}H_{10}N_2OS$: C, 62.58, H, 4.37; N, 12.16; S, 13.92%.

*2-Amino-5-benzlidene-thiazol-4-one (**8**)*

A solution of 2-amino-4,5-dihydrothiazole-4-one **1** (1.16 g, 0.01 mol) in pyridine (50 mL was treated with ethylbenzylidene cyanoacetate (2.01 g, 0.01 mol) the reaction mixture was refluxed for 3 h, poured into ice-cold water. The solid product, so formed was collected by filtration and crystallized from dioxane as white crystals; yield 65% mp 285°C. IR: 3200 cm^{-1} (NH_2), 1680 cm^{-1} (CO). ^1H NMR (DMSO-d_6) δ 4.4 (S, 1H, CH) 7.2–7.9 (m,5 H, aromatic-H.), 9.4 (S,2H, NH_2). Found C, 58.82; H, 3.91; N, 13.77; S, 15.69%, calcd for: $C_{10}H_8N_2OS$: C, 58.80, H, 3.94, N, 13.71; 15.70%.

*N′-(5-Imino-7-phenyl-5H-pyrano[2,3-d] thiazol-2-yl) N,N-dimethylformamidine (**9**)*

A mixture of compound **4** (1.71 g, 0.01 mol) and benzoyl acetonitrile (1.45 g, 0.01 mol) in pyridine (50 mL) was refluxed for 3 h. The reaction mixture was evaporated under vacuum, and the solid product so formed was collected and crystallized from benzene pet ether 1:1 as pale brown crystals, yield 46%, mp 110–112°C. IR: 3229 cm^{-1} (NH), ^1H NMR (DMSO-d_6): δ 3.0 (S, 3H, Nme), 3.4 (S, 3H, Nme), 4.8 (S, 1H, CH), 7.3–76 (m; 5H, aromatic-H), 8.0 (S, 1H, formyl-H), 11.6 (brs, 1H, NH). Found : C, 60.36; H, 4.75; N, 18.75; S, 10.75, calcd for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.72; N, 18.77; S, 10.74%.

*2-(2-Aminothiazol-4-ylidene)malononitrile (**10**)*

A mixture of 2-amino-4-thiazoliniminium chloride **2** (1.51 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) are stirred in 100 mL 2N NaOH for 2 h at room temperature. The crystalline products formed during this procedure are isolated by suction and crystallized for purification. Compound **10** was obtained as brown crystals; yield 79% mp over 350 L > 360°C. IR: 3264 cm^{-1} (NH_2); 2214 cm^{-1} (CN). ^1H NMR (DMSO-d_6): δ 4.6 (S, 2H, CH_2), 9.6 (S, 2H, NH_2) . Found: C, 43.85; H, 2.41; N, 34.15; S, 19.50, calcd for $C_6H_4N_4S$: C, 43.89; H, 2.45; N, 34.12; S, 19.52%.

*N-(5Z)-4-(Dicyanomethylene)-5-[4-(methyl-benzylidene]-4,5-dihydrothiazole-2-yl Acetamide (**11**)*

A mixture of 2-amino-4-dicyanomethylene-4,5-dihydrothiazole (1.64 g, 0.01 mol) and 4-methyl benzaldehyde (1.20 g, 0.01 mol) in acetic anhydride (20 mL) was refluxed for 10 min. After cooling, the product so formed was collected by filtration and crystallized from ethanol as green crystals; yield 65% mp 275°C IR: 3172 cm^{-1} (NH), 2221 cm^{-1} (CN), 1721 cm (CO). ^1H NMR (DMSO-d_6): δ 2.3 (S, 3H, $COCH_3$), 6.7–6.9 (d, 2H, CH), 7.5–7.6 (d, 2H, CH), 8.4 (S, 1H, CH), 13.1 (S, 1H, NH) MS: *m/z* 308 (M^+). Found: C, 62.33, H,3.93; N,18.17; S,10.42.%, Calcd for $C_{16}H_{12}N_4OS$: C, 62.3 2; H,3.92; N,18.17, S,10.4 0%.

*4,8-Diphenyl-2H-pyrimido[2,1-b] benzothiazol-5-carbonitile (**15**)*

To a solution of **10** (1.64 g, 0.01 mol) in DMF (10 mL), 3-dimethyl amino propiophenone hydrochloride (2.13 g, 0.01 mol) was added. The reaction mixture was refluxed for 3 h, poured into ice-cold water. The solid product so formed was collected by filtration and crystallized from ethanol as brown crystals; yield 64% ; mp 90°C IR: 2208 cm^{-1} (CN). ^1H NMR (DMSO-d_6): δ 3.7 (m, 1H, H-3), 3.9 (m, 2H, H-2), 7.3–7.5(m,10H, aromatic-H), 6.7 (d,1H, H-7), 8.0 (d, 1H,H-8); MS: *m/z* 364 (+M*). Found: C, 75.59; H, 4.1 5; N,11.51; S, 8.63%, calcd for $C_{23}H_{15}N_3S$: C,75.59; H, 4.14; N,11.50; S, 8.77%.

*2,6-Amino-4-thioxo-4H-thiopyrano[4,3-d] thiazol-7-carboxylic acid (**17**)*

To a suspension of 2-amino-4-dicyanomethylene-4,5-dihydrothiazole (**10**) (16.4 g, 0.1 mol) in DMF (50 mL), carbon disulfide (11.5 g, 0.15 mole) and triethyl amine (25.39, 0.25 mol) were added dropwise under stirring at room temperature for 1 h; the solution was neutralized with dil. HCl. The precipitate formed was collected by filtration, washed with hot ethanol and dried as red crystals. Yield 70%, mp 140°C; IR: 3175, 3140 cm^{-1} (NH_2)2. ^1H NMR (DMSO-d_6)δ 3.2(s, 2H, NH_2), 9.1 (S, 2H, NH_2-thiazole) 12.4 (S, 1H,COOH); MS: *m/z* 258 (+M*). Found: C, 32.44; H, 1.93; N, 16.22; S, 37.07%, calcd for: $C_7H_5N_3O^2S_3$: C,32.41; H, 1.94; N, 16.20; S, 37.09%.

*N′-[4-(Dicyanomethylene)-4,5-dihydrothiazol-2-yl]-N,N-dimethylimidoformamide (**18**)*

Compound **10** (1.64 g, 0.01 mol) was treated with *N,N*-dimethylformamide dimethylacetal (1.19 g, 0.01 mol) in dioxane (30 mL). The reaction mixture was refluxed for 1 h, left to cool, and triturated with ethanol. The solid product, so formed was collected by filtration and washed by hot ethanol; yield 45% dec 290°C. IR: 2223 cm^{-1}(CN); 1621 cm^{-1} (C=N).

^{1}H NMR (DMSO-d_6) δ 3.1 (S, 3H, CH_3), 3.2 (S, 3H, CH_3); 4.7 (S, 2H, CH_2), 8.5 (S, 1H, formyl-H), MS: *m/z* 219 (M^+). Found: C, 49.30; H, 4.15; N, 31.90; S, 14.60%; Calcd for $C_9H_9N_5S$: C,49.29; H, 4.13; N, 31.94; S, 14.62%.

*N′-(2- [(1Z)-(Dimethylamino)methylene]amino-thiazol-4-yl)-N,Ndimethylimidoformamide (**21**)*

Compound **20** [12] (1.15 g, 0.01 mol) was treated with *N*,*N*-dimethyl formamide dimethyl acetal (1.19 g, 0.01 mol) in dioxane (50 mL). The reaction mixture was refluxed for 1 h, then left to cool and triturated with ethanol. The solid product, so formed was collected by filtration and crystallized from ethanol as brown crystals; yield 70% mp=170°C. IR: 1662 cm^{-1} (C=N), 1625 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6) δ 2.9 (S, 6H, NMe), 3.2 (S, 6H, NMe) 7.2 (S, 1H, thiazole-H_5), 8.1 (S, 1H, formyl-H), 8.6 (S, 1H, formyl-H), MS: *m/z* 225 (M^+). Found: C, 47.96; H, 6.70; N, 31.06; S, 14.21%, calcd for $C_9H_{15}N_5S$: C, 47.97; H, 6.71; N,31.08; S,14.22%.

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