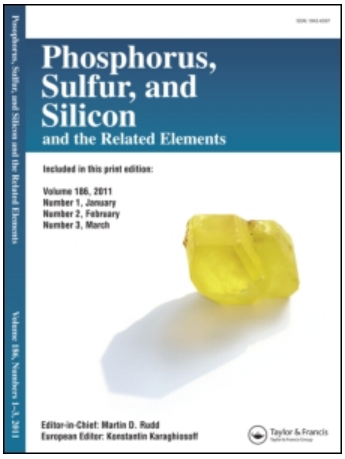

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis, Antimicrobial Activity of Some New 2-Amino-4-(4'-phenylsulfanyl-phenyl)-thiazole Derivatives and Theoretical Studies of Their Schiff's Base

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Online publication date: 18 June 2010

To cite this Article Abdel-Hafez, Sh. H.(2003) 'Synthesis, Antimicrobial Activity of Some New 2-Amino-4-(4'-phenylsulfanyl-phenyl)-thiazole Derivatives and Theoretical Studies of Their Schiff's Base', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 12, 2563 — 2579
To link to this Article: DOI: 10.1080/714040970
URL: http://dx.doi.org/10.1080/714040970

Phosphorus, Sulfur, and Silicon, 178:2563–2579, 2003

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500390248060

SYNTHESIS, ANTIMICROBIAL ACTIVITY OF SOME NEW 2-AMINO-4-(4′-PHENYLSULFANYL-PHENYL)-THIAZOLE DERIVATIVES AND THEORETICAL STUDIES OF THEIR SCHIFF'S BASE

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(Received June 9, 2003; accepted July 1, 2003)

*2-Amino-4-(4′-phenylsulfanyl-phenyl)-thiazole (**2**) has been obtained from reaction of 4-chloroacetyl diphenyl sulfide (**1**) with thiourea. Compound (**2**) reacted with active methylene derivatives, e.g., diethylmalonate or ethylcyano acetate to give fused thiazolo-pyrimidines (**3–6**) under variable conditions. Other substituted thiazolo-pyrimidines (**7–9**) also have been prepared by the reaction of (**2**) with some arylidine malonitriles (benzylidinemalononitrile and ethylbenzylidinecyanoacetate). On treatment of schiff's bases (**$10_{a–c}$**) with phenylisothiocyanate, the corresponding thiazolo-s-triazines (**$11_{a–c}$**) were formed. Reaction of (**2**) with carbon disulfide in the presence of concentrated aqueous sodium hydroxide and DMF as solvent gave the sodium salt of dithiocarboimidic acid which, on treatment with 1 mmol of ethyl iodide, gave monoethylated product (**12**). Reaction of (**12**) with anthranilic acid yielded (**13**). Interaction of (**2**) with 2 mmol of ethyl iodide afforded the diethylated product (**14**) which reacted with potassium salt of anthranilic acid to give (**15**). Also, (**14**) reacted with o-phenylenediamine yielded (**16**). The substituent effect on the stereochemistry of Schiff's bases (**$10_{a–c}$**) was studied using Hyperchem (version 5). Compounds (**2, 4, 6, 10_b, 12, 13, 14, 15**) were tested to evaluate their antimicrobial activity.*

Keywords: Antimicrobial activity; Schiff's base; stereochemistry; synthesis; thiazolopyrimidines

This work was carried out[1–4] according to the literature on the heterocycles containing thiazole rings. These are associated with a particulary wide range of biological properties including antiprotozoal[5] anticonvulsants activity,[6] as well as with a depressant effect on the central

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nervous system,[7] antihelminthic,[8] antidiabetic,[9] and as inhibitors of dihydrofolate.[10] It was of interest to incorporate the moiety of thiazole rings into the well-known antimicrobial diphenyl sulfides.[11–13] We have synthesized some heterocyclic compounds containing diphenyl sulfides and thiazole moieties for their useful biological application. Furthermore, a search of the literature revealed the lack of information concerning the stereochemistry studies of Schiff's bases ($\mathbf{10_{a-c}}$) derivatives.[14] We have applied Hyperchem (version 5)[15] to evaluate the stability of different isomers (syn or anti).

RESULTS AND DISCUSSION

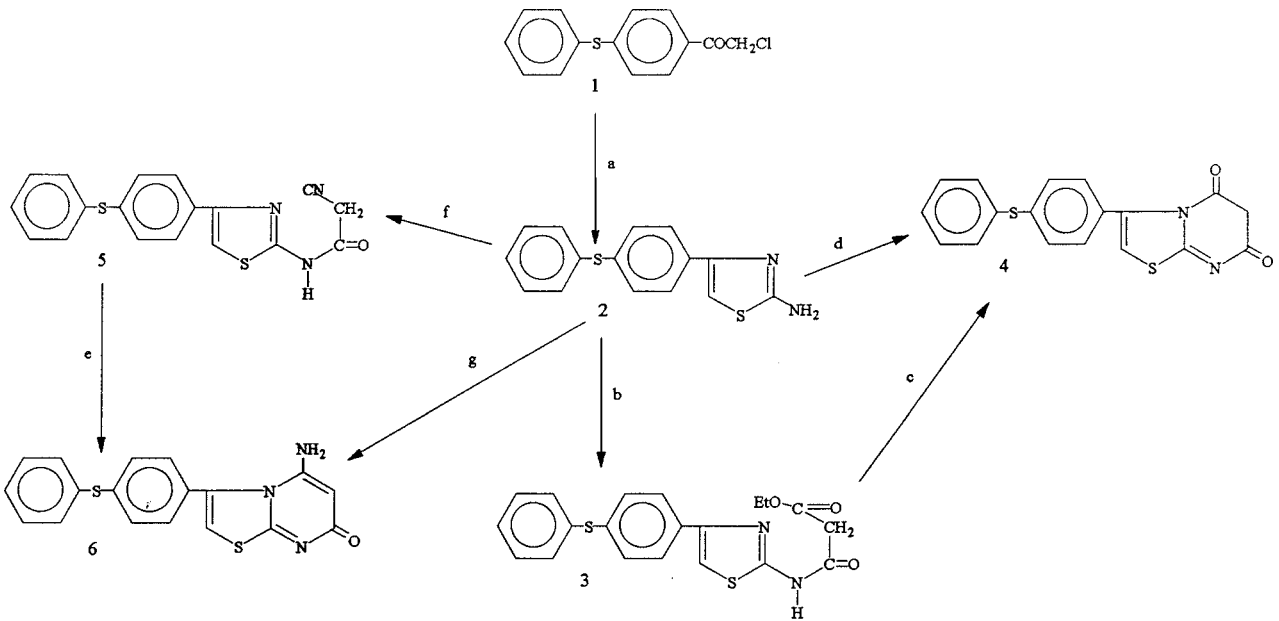
Synthesis of 4-chloroacetyl diphenyl sulfide (**1**) was done according to the similar method for other products given in the literature.[16] The forthcoming synthesis and studies was based on 2-amino-4-(4′-phenylsulfanyl-phenyl)-thiazole (**2**), which was prepared by refluxing equimolar amounts of (**1**) and thiourea in absolute ethanol as modified process to that known in literature.[17] Elucidation of the structures (**1**) and (**2**) was based on elemental analyses and spectral data.

IR spectrum of (**2**) displayed characteristic absorption bands at 3430–3290 cm^{-1} due to ν (NH_2) and 1625 cm^{-1} ν (C=N). The absence of absorption band for carbonyl group in spectrum of (**2**) supports its cyclic structure. The mass spectrum of (**2**) revealed a molecular ion peak at m/z = 284 with 40% relative abundance corresponding to the formula $C_{15}H_{12}N_2S_2$.

In accord to the well-known cyclocondensation reaction of 2-amino-thiozoles with β-bifunctional reagents to yield thiazolo [3,2-a]. Pyrimidines,[18] compound (**2**), reacted with diethylmalonate or ethyl-cyanoacetate to yield 3-(4′-phenylsulfanyl-phenyl)-5,7-dioxo-thiazolo [3,2-a]-4,5,6,7-tetrahydropyrimidine (**4**) and 3-(4′-phenylsulfanylphenyl)-5-amino-7-oxo-thiazolo[3,2-a]-4,7-dihydropyrimidine (**6**) respectively.

The formation of derivatives (**4**, **6**) may be done via cyclization through the amino group of (**2**) to give the intermediates (**3**, **5**), which were isolated and identified. On fusion of (**3**, **5**) over its melting points, or fusion of (**2**) with the active methylene derivative products, (**4**, **6**) were isolated (Scheme 1). The structures of (**4**, **6**) were assigned on the basis of elemental analyses and spectral data (IR, ^{1}H NMR).

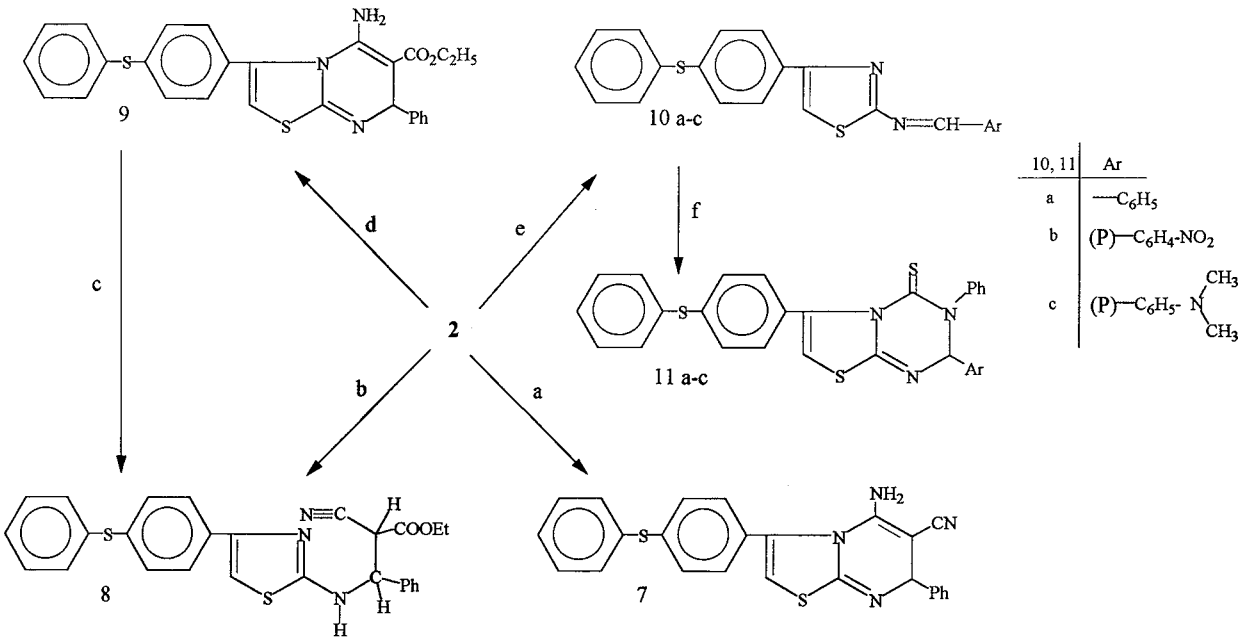
Compound (**2**) was reacted with benzylidinemalonoitrile to give 3-(4′-phenylsulfanyl-phenyl)-5-amino-6-cyano-7-phenyl-thiazolo [3,2-a]-4,5-dihydro-pyrimidine (**7**). Structure (**7**) was assigned on the basis of elemental analyses and spectral data.



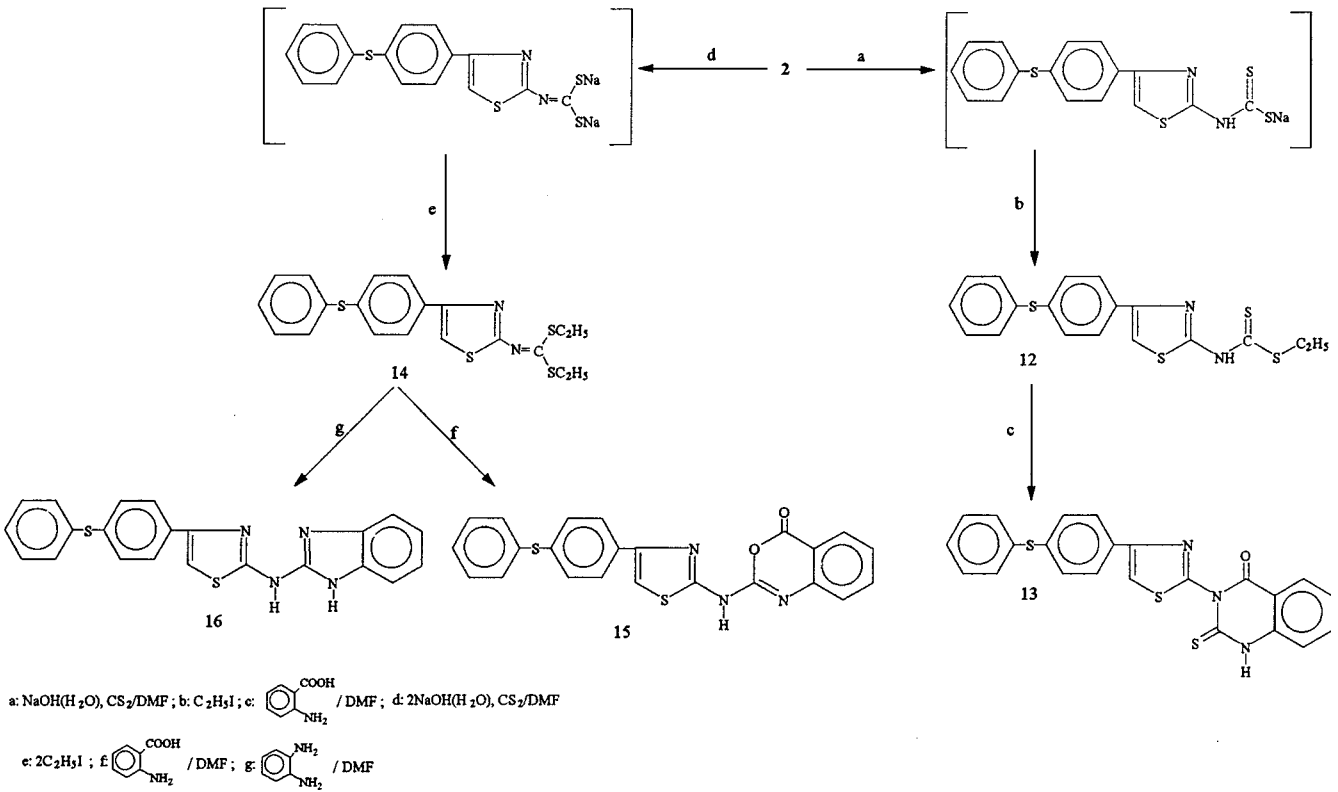
a: thiourea / abs. EthOH ; b: $CH_2(COOC_2H_5)_2$/excess ; c: fusion ; d: $CH_2(COOC_2H_5)_2$/fusion ;

e: fusion ; f: $NC\text{-}CH_2COOC_2H_5$; g: $NC\text{-}CH_2COOC_2H_5$ / fusion

SCHEME 1



SCHEME 2



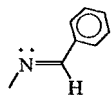
SCHEME 3

Interaction of ethylarylidinecyanoacetate gave 3-(4′-phenylsulfanyl-phenyl)-5-amino-6-carboethoxy-7-phenyl-thiazolo [3,2-a]-4,5-di-hydro-pyrimidine (**9**) through the formation of the intermediate 2-benzyl-idinethylcyanoacetate-amino-4-(4′-phenylsulfanyl-phenyl)-thiazole (**8**), which was separated and identified. On treatment of (**2**) with some aromatic aldehydes such as (bezaldehyde, p-nitrobenzaldehyde, N,N-dimethylaminobenzaldehyde), the corresponding 2-arylidine-aminothiazole derivatives (**10$_{a–c}$**) were formed. Reaction of (**10$_{a–c}$**) with phenylisothiocyanate in refluxing toluene gave 6,7-disubstituted-thiazolo [3,2-a]-s-triazine-5-thioxo-derivatives[19] (**11$_{a–c}$**) (Scheme 2).

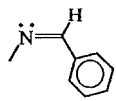
Reaction of (**2**) with CS_2/NaOH in dimethylformamide[20] in presence of 1 mmol ethyl iodide gave the monoethylated derivative (**12**) which reacted with anthranilic acid to give (**13**).

The diethylated product (**14**) also was obtained using 2 mmol of ethyl iodide. The structure of (**14**) was assigned on the basis of analytical and spectral data. The mass spectrum of (**14**) revealed a molecular ion peak at m/z = 416 with 1.5% relative abundance. This reflex the unstability of this molecular ion under electron impact. Reaction of (**14**) with anthranilic acid or o-phenylenediamine gave (**15**, **16**) respectively[21] (Scheme 3).

It was established that the Schiff's bases are present in two forms, i.e., anti and syn isomers.[14]



Anti



Syn

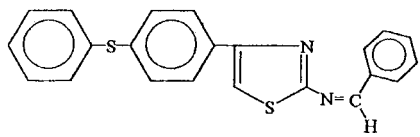
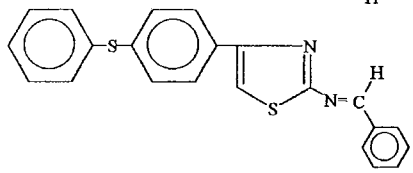
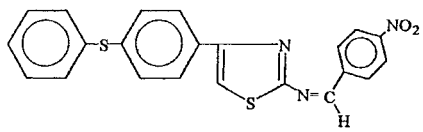
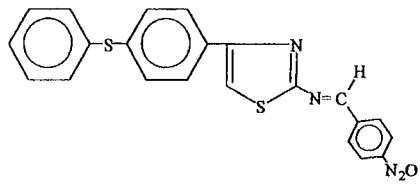
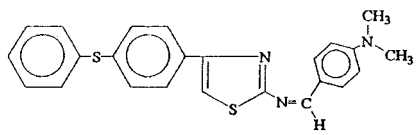
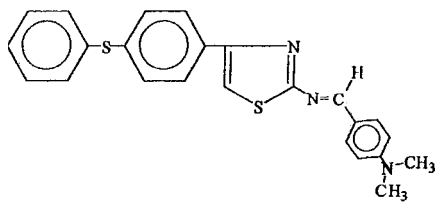
We have extended our study using Hyperchem (version 5) to estimate the relative stability of both forms. The calculation are listed in Table I and Figures 1–6, which reveal that the both forms are highly related in the absence energy of substituent on benzylidine amino groups. Introduction of different substituent on the later affect the stability of both isomer.

Generally, the anti isomer form is more stable than the syn isomer.

Antimicrobial Activities

Some of the newly synthesized compounds (**2**, **4**, **6**, **10$_b$**, **12–15**) were screened for the antifungal activity against two species of fungi, namely *Penicillium oxalicum* and *Aspergillus parasiticus*, and for antibacterial activity against Gram positive bacteria *(Streptococcus* and *Staphylococcus aureus)* and Gram negative bacteria *(Serratia*

TABLE I Theoretical Data of Compound $\mathbf{10_{a–c}}$ and the Relative Stability (ΔE Kcal/mol) of Two Geometrical Isomers

Compound no.	Structure	Energy (ΔE), Kcal/mol (E)	Gradient (G)
$\mathbf{10_a}$ (syn)		21.382162	0.099353
$\mathbf{10_a}$ (anti)		22.83859	0.094213
$\mathbf{10_b}$ (syn)		24.050827	0.099518
$\mathbf{10_b}$ (anti)		21.764473	0.08784
$\mathbf{10_c}$ (syn)		163.1243	0.091080
$\mathbf{10_c}$ (anti)		26.33323	0.092228

marcescems and *Pseudomonas aeruginosa*) using the filter paper disc method.[22]

The results are illustrated in Table II, which revealed that comparison of the antifungal activity of thiazolopyrimidine derivatives (**4**, **6**), quinoxaline and dithiocarbamate (**13**, **14**) induces more fungitoxicity

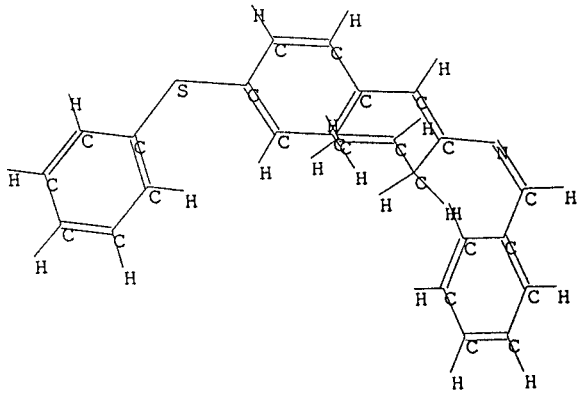


FIGURE 1 Stick model of the syn isomer ($\mathbf{10_a}$) according to the Hyperchem calculations.

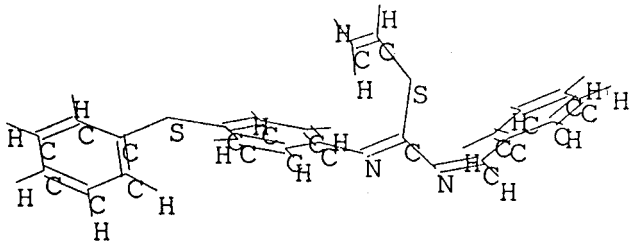


FIGURE 2 Stick model of the anti isomer ($\mathbf{10_a}$) according to the Hyperchem calculations.

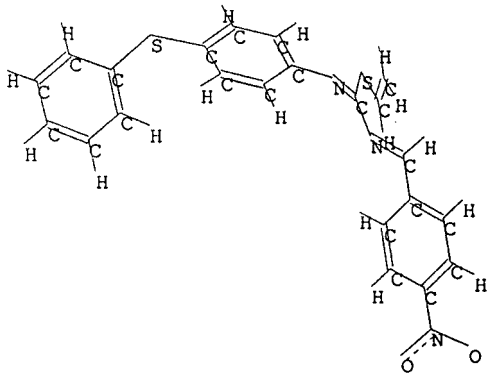


FIGURE 3 Stick model of the syn isomer ($\mathbf{10_b}$) according to the Hyperchem calculations.

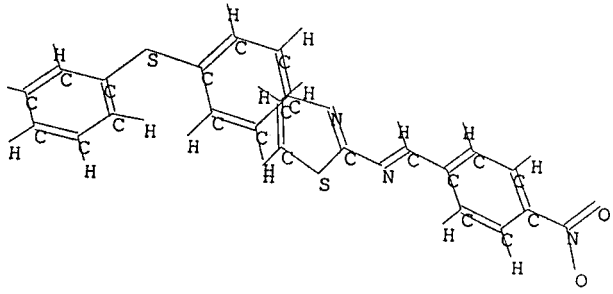


FIGURE 4 Stick model of the anti isomer ($\mathbf{10_b}$) according to the Hyperchem calculations.

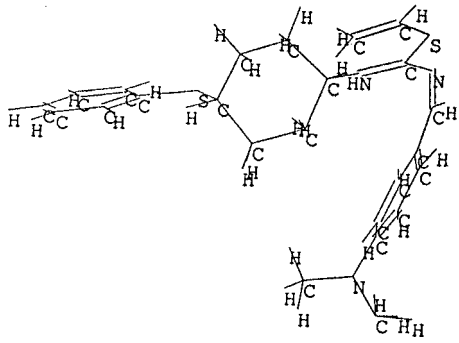


FIGURE 5 Stick model of the syn isomer ($\mathbf{10_c}$) according to the Hyperchem calculations.

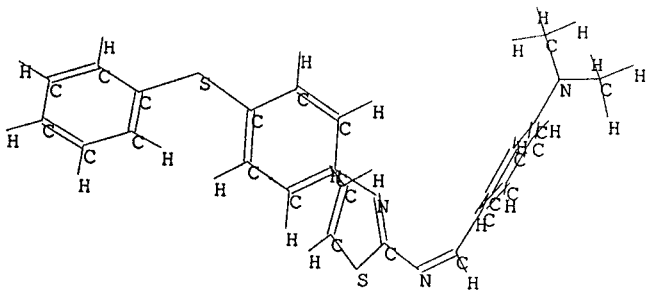


FIGURE 6 Stick model of the anti isomer ($\mathbf{10_c}$) according to the Hyperchem calculations.

TABLE II Minimum Inhibitory Concentration of Compounds (**2**, **4**, **6**, **10_b**, **12–15**) Against Different Organisms Mic (mm)

	Fungi species					
Compound no.	*Pencillium oxalicum*	*Aspergillus parasiticus*	*Strepto-coccus* (+ve)	*Serratia marcescems* (−ve)	*Staphyloc occus aureus* (+ve)	*Pseudo-monas aeruginosa* (−ve)
2	—	7	14	—	14	12
4	8	—	—	—	—	8
6	9	—	—	—	9	13
10_b	—	—	—	—	—	—
12	—	—	7	—	11	—
13	—	11	—	—	—	—
14	—	14	—	—	35	—
15	—	—	—	—	—	—

Conclusion: Thiazolopyrimidine derivatives were synthezied that have a useful biological application. The biological activity of some selected compounds were investigated against fungi and as antibacteria and were shown a good results. Application of Hyperchem to estimate the stability of different isomers showed that the anti isomers form are more stable than the syn isomers.

against *Aspergillus parasiticus* and *Penicillium oxalicum* than its parent compound **2**.

Compound (**14**) showed the strongest inhibition activity against *Staphylococcus aureus* and compounds (**2**, **4**, **6**) exhibited a moderate activity against *Streptoccus, Pseudomonas aeruginosa*, and *Staphylococcus aureus* respectively. The remaining compounds have no significant antibacterial activity. This is may be attributed to the function group dithiocarbamate in compound (**14**) which works better than the amino group alone in compound (**2**) and their fused derivatives (**4**, **6**).

Experimental Procedure

The time period required for the completion of the reaction and the purity of the prepared compounds were controlled by means of TLC. Melting points were determined on Fisher-Johns melting points apparatus and were uncorrected. Elemental analysis were performed on a Perkin-Elmer 240 C elemental analyzer and all the results were in an acceptable range. The characterization data of all synthesized compounds are given in Table III. IR spectra were recorded on a Bye-Unicom SP3-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on GNM-LA 400-MHZ-NMR spectrophotometer in suitable deuterated solvent using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on Jeol JMS-600 mass spectrometer.

4-Chloroacetyl Diphenyl Sulfide (1)

To a conical flask containing (2.00 g, 0.01 mmol) of diphenyl sulfide and (0.85 ml, 0.01 mmol) of chloroacetyl chloride dissolved in 30 ml carbon dislfide, anhydrous $AlCl_3$ (2.14 g, 0.016 mmol) was added in small portions. The reaction mixture was stirred in an ice bath for 6 h. The reaction mixture was evaporated under vacuum and the residue was poured onto a mixture of ice and conc. HCl, pale yellow precipitate was formed collected and crystallized from pet. ether 60–80°C as a colourless flakes;yield (1.12 g, 0.001 mol).

Anal. Cal. for $C_{14}H_{11}ClOS$: C, 64.00; H, 4.19; Cl, 13.52; S, 12.19. Found: C, 63.98; H, 4.10; Cl 13.41; S, 12.02.

2-Amino-4-(4′-phenylsulfanyl-phenyl)-thiozole (2)

A mixture of **1** (1 g, 0.038 mmol) and (0.28 g, 0.038 mmol) of thiourea in 20 ml absolute ethanol was refluxed for 4 h. The clear solution was poured onto cold sodium acetate solution and the precipitated product was collected by filtration and crystallized from pet. ether 60–80° as pale yellow crystals; yield (0.54 g, 0.001 mmol).

TABLE III Characterization Data of the Synthesized Compounds

Comp. no.	m.p. (°C) (yield %)	Mol. form. (m. wt.)	IR cm^{-1}	^1H NMR (δ; ppm)
1	66–68 (40)	$C_{14}H_{11}ClOS$ (262.5)	1720 (C=O)	($CDCl_3$): 4.68 (s, 2H, CH_2); 7.23–7.87 (m, 9H, Ar—H)
2[a]	116–118 (50.5)	$C_{15}H_{12}N_2S_2$ (284)	3290–3430 (NH_2); 1625 (C=N)	($CDCl_3$): 5.52 (5, 2H, NH_2); 665 (s, 1H, CH Thiazole); 7.28–782 (m, 9H, Ar—H)
3	240–242 (62)	$C_{20}H_{18}N_2O_3S_2$ (398)	3300 (NH); 1725 (CO-ester); 1670 (C=O)	($CDCl_3$): 1.30 (t, 3H, $COOCH_2\underline{CH_3}$); 3.54 (s, 2H, CH_2); 4.25 (q, 2H, $COO\underline{CH_2}CH_3$); 7.05 (s, 1H, CH. thiazole); 7.28–7.85 (m, 9H, Ar.H); 10.61 (s, 1H, NH)
4	235–237 (65)	$C_{18}H_{12}N_2O_2S_2$ (352)	1700 (C=O); 1610 (C=N)	($CDCL_3$): 6.55(s, 1H, CH-thiazole); 7.91 (s, 2H, CH_2 Pyrimidine); 7.30–7.89 (m, 9H, Ar—H)
5	280–282 (64)	$C_{18}H_{13}N_3OS_2$ (351)	3300 (NH); 2200 (C≡N); 1700 (C=O)	($CDCl_3$); 3.97 (s, 2H, $COCH_2CN$); 6.83 (s, 1H, CH-thiazole); 7.01–7.87 (m, 9H, Ar—H); 10.55 (s, 1H, NH)
6	200–202 (67)	$C_{18}H_{13}N_3OS_2$ (351)	3400–3300 (NH_2); 1700 (C=O); 1600 (C=N)	($CDCl_3$); 3.68 (s, 2H, NH_2); 6.90 (s, 1H, CH-thiazole); 7.01–7.98 (m, 10H, Ar—H)
7	185–187 (34)	$C_{25}H_{18}N_4S_2$ (438)	3350–3290 (NH_2); 2200 (C=O); 1610 (C=N)	($CDCl_3$); 6.51 (s, 2H, NH_2); 6.91 (s, 1H, CH.thiazole); 7.08–8.54 (m, 15H, Ar—H)
8	260–262 (54)	$C_{27}H_{23}N_3O_2S_2$ (485)	3300 (NH); 2200 (C≡N); 1720 (CO ester)	(DMSO-d_6); 1.40 (t, 3H, $COOCH_2\underline{CH_3}$); 4.25 (q, 2H, $COO\underline{CH_2}CH_3$); 6.51 (s, 1H, CH-thiazole); 7.00–8.00 (m, 16H, Ar—H); 10.41 (s, 1H, NH)
9	180–182 (50.5)	$C_{27}H_{23}N_3O_2S_2$ (485)	3450–3340 (NH_2); 1710 (CO ester)	(DMSO-d_6); 1.38 (t, 3H, $COOCH_2\underline{CH_3}$); 3.40 (s, 2H, NH_2); 4.73 (q, 2H, $COO\underline{CH_2}$, CH_3, 6.57 (s, 1H, CH-thiazole); 7.32–7.98 (m, 15H, Ar—H)
10a[b]	137–175 (55)	$C_{22}H_{16}N_2S_2$ (372)	1610, 1580 (C=N)	($CDCl_3$); 6.68 (s, 1H, CH.thiazole); 7.27–7.97 (m, 14H, Ar—H); 9.57 (s, 1H, —N=CH)

10$_b$[b]	184–185 (53)	$C_{22}H_{15}N_3O_2S_2$ (417)	1600, 1580 (C=N);	($CDCl_3$); 6.68 (S, 1H, CH-thiazole); 7.01–8.01 (m, 13H, Ar–H); 10.50 (s, 1H, –N=CH–)
10$_c$[b]	190–191 (50)	$C_{24}H_{21}N_3S_2$ (415)	1610, 1580 (C=N)	($CDCl_3$); 1.80 (s, 6H, –N(–CH_3)–CH_3); 6.65 (s, 1H, CH-thiazole); 7.01–7.99 (m, 13H, Ar–H); 8.50 (s, 1H, –N=CH)
11$_a$[b]	200–202 (57)	$C_{29}H_{21}N_3S_3$ (507)	1610, 1580 (C=N); 1500 (C=S)	(DMSO-d_6); 6.87 (s, 1H, CH-thiazole); 7.01–8.11 (m, 20H, Ar–H)
11$_b$[b]	210–211 (55)	$C_{29}H_{20}N_4O_2S_3$ (552)	1610, 1580 (C=N); 1510, 1340 (NO_2)	(DMSO-d_6); 6.65 (s, 1H, CH-thiazole); 7.26–7.98 (m, 19H, Ar–H)
11$_c$[b]	217–219 (49)	$C_{31}H_{26}N_4S_3$ (550)	1610, 1580 (C=N); 1500 (C=S)	(DMSO-d_6); 1.93 (s, 6H, –N(–CH_3)–CH_3); 6.68 (s, 1H, CH-thiazole); 7.01–7.95 (m, 19H, Ar–H)
12	300 decom. (20)	$C_{18}H_{16}N_2S_4$ (388)	3320 (NH); 1610 (C=N)	(DMSO-d_6); 1.28 (s, 3H, $CH_2\underline{CH_3}$); 3.53 (s, 1H, NH); 4.20 (q, 2H, $CH_2\underline{CH_3}$); 6.68 (s, 1H, CH-thiazole); 7.01–7.89 (m, 9H, Ar–H)
13	120–122 (45)	$C_{23}H_{15}N_3OS_3$ (445)	3380 (NH); 1700 (C=O); 1610 (C=N)	(DMSO-d_6); 3.66 (s, 1H, NH); 6.68 (s, 1H, CH-thiazole); 7.10–8.00 (m, 13H, Ar–H)
14[a]	>360 (22)	$C_{20}H_{20}N_2S_4$ (416)	1610 (C=N)	(DMSO-d_6); 1.10 (t, 6H, $2CH_3$); 3.50 (q, 4H, $2CH_2$); 6.70 (s, 1H, NH); 7.17–7.90 (m, 9H, Ar–H)
15	135–137 (44)	$C_{23}H_{15}N_3O_2S_2$ (429)	3400 (NH); 1720 (C=O)	(DMSO-d_6); 3.12 (s, 1H, NH); 6.57 (s, 1H, CH-thiazole); 7.13–8.00 (m, 13H, Ar–H)
16	180–181 (45)	$C_{22}H_{16}N_4S_2$ (400)	3400 (NH); 1610 (C=N)	(DMSO-d_6); 3.15 (s, 1H, NH); 6.56 (s, 1H, CH-thiazole); 7.15–7.98 (m, 13H, Ar–H); 8.20 (s, 1H, NH-benzimidazole)

[a]The mass spectra of both (**2**, **14**) are shown in the text.

[b]**10$_a$**: crystallized from pet. ether 60–80°C; **10$_b$**, **10$_c$**: crystallized from ethanol; **11$_a$**, **11$_b$**: crystallized from ethanol; **11$_c$**: crystallized from dioxane.

Anal. Cal. for $C_{15}H_{12}N_2S_2$: C, 63.38; H, 4.22; N, 9.85; S, 22.53. Found: C, 63.11; H, 4.20; N, 9.65; S, 22.29.

Reaction of (2) with Active Methylene Derivatives (4) and (6)

General procedure. A mixture of **2** (0.035 mmol) and the corresponding ester (0.04 mmol) were heated at 180°C in an oil bath for 3 h. The reaction mixture was allowed to cool, whereby a solid mass was formed; this was washed several times with ether and then crystallized from the proper solvent. Spectral data are listed in Table III; comp. 4 yield (0.80 g, 0.002 mmol), whereas comp. 6 yield (0.82 g, 0.002 mmol).

Anal. Cal. for comp. **4** $C_{18}H_{12}N_2O_2S_2$: C, 61.36; H, 3.40; N, 7.95; S, 18.18. Found: C, 61.10; H, 3.22; N, 7.73; S, 18.01.

Anal. Cal. for comp. **6** $C_{18}H_{13}N_3OS_2$: C, 61.53; H, 3.70; N, 11.96; S, 18.23. Found: C, 61.09; H, 3.40; N, 11.49; S, 18.01.

Synthesis of the Intermediates (3) and (5)

General procedure. A mixture of **2** (0.035 mmol) with excess of ester (0.35 mmol) was heated under reflux for about 5–6 h. The reaction mixture was then allowed to cool, triturated with ethanol and the solid product was collected and recrystallized from the proper solvent. The results are tabulated in Table III; comp. 3 yield (0.86 g, 0.002 mmol) whereas comp. 5 yield (0.79 g, 0.002 mmol).

Anal. Cal. for comp. 3 $C_{20}H_{18}N_2O_3S_2$: C, 60.30; H, 4.52; N, 7.03; S, 16.08. Found: C, 60.12; H, 4.31; N, 6.88; S, 18.94.

Anal. Cal. for comp. 5 $C_{18}H_{13}N_3OS_2$: C, 61.53; H, 3.70; N, 11.96; S, 18.23. Found: C, 61.21; H, 3.45; N, 11.78; S, 18.00.

3-(4′-Phenylsulfanyl-phenyl)-5-amino-6-cyano-7-phenyl-thiazolo[3,2-a]-4,5-dihydropyrimidine (7)

A mixture of compound **2** (1 g, 0.035 mmol) and benzylidine malononitrile (0.54 g, 0.035 mmol) was heated under reflux for 8 h in absolute ethanol (30 ml) and 1 ml of piperidine. The reaction mixture was then allowed to cool to room temperature, poured onto crushed ice, and neutralized with conc. HCl. The precipitate was filtered and crystallized from ethanol; yield (0.52 g, 0.001 mmol).

Anal. Cal. for $C_{25}H_{18}N_4S_2$: C, 68.49; H, 4.10; N, 12.78; S, 14.61. Found: C, 68.33; H, 3.98; N, 12.55; S, 14.41.

3-(4′-Phenylsulfanyl-phenyl)-5-amino-6-carboethoxy-7-phenyl-thiazolo [3,2-a]-4,5-dihydropyrimidine (9)

A mixture of 2 (1 g, 0.035 mmol), benzylidinethylcyanoacetate (0.70 g, 0.035 mmol) and 1 ml piperidine in (30 ml) ethanol was heated under

reflux for 10 h. The reaction mixture was cooled, poured onto crushed ice, and neutralized with concn. HCl, the precipitate was isolated and crystallized from ethanol; yield (0.86 g, 0.001 mmol).

Anal. Cal. for $C_{27}H_{23}N_3O_2S_2$: C, 66.80; H, 4.74; N, 8.65; S, 13.19. Found: C, 66.73; H, 4.43; N, 8.38; S, 13.00.

2-Benzylidine Ethylcyanoacetate-4-(4′-phenylsulfanyl-pheny)-thiazole (8)

This was prepared following the preceding method for **9** with short refluxing time (3 h). The product **8** crystallized from dioxane; yield (0.92 g, 0.001 mmol).

Anal. Cal. for $C_{27}H_{23}N_3O_2S_2$: C, 66.80; H, 4.74; N, 8.65; S, 13.19. Found: C, 66.54; H, 4.45; N, 8.33; S, 12.89.

2-Arylidineamino Thiazole Derivatives ($10_{a–c}$)

General procedure. A mixture of 2 (0.017 mmol) and the appropriate aldehyde (0.019 mmol) such as (benzaldehyde, p-nitrobenzaldehyde, N,N-dimethyl aminobenzaldehyde) in 20 ml absolute ethanol in the presence of 1 ml piperidine as a catalyst was refluxed for 7–10 h. The precipitated product was collected by filtration and crystallized from proper solvent (cf. Table III) ; comp. $\mathbf{10_a}$ yield (0.72 g, 0.001 mmol), comp. $\mathbf{10_b}$ yield (0.77 g, 0.001 mmol), comp. $\mathbf{10_c}$ yield (0.73 g, 0.001 mmol).

Anal. Cal. for $\mathbf{10_a}$ $C_{22}H_{16}N_2S_2$: C, 70.96; H, 4.30; N, 7.52; S, 17.20. Found: C, 70.81; H, 4.21; N, 7.43; S, 17.00.

Anal. Cal. for $\mathbf{10_b}$ $C_{22}H_{15}N_3O_2S_2$: C, 63.30; H, 3.59; N, 10.07; S, 15.34. Found: C, 63.10; H, 3.33; N, 9.82; S, 14.98.

Anal. Cal. for $\mathbf{10_c}$ $C_{24}H_{21}N_3S_2$: C, 69.39; H, 5.06; N, 10.12; S, 15.42. Found: C, 69.12; H, 4.96; N, 10.00; S, 15.21.

6,7-Disubstituted-5-thioxo-thiazolo[3,2-a]-s-triazine Derivatives ($11_{a–c}$)

General procedure. An equimolar mixture of $\mathbf{10_{a–c}}$ (0.013 mmol) and phenylisothiocyanate in 20 ml toluene was refluxed for 4–6 h. The solvent was distilled under reduced pressure, the residue washed with small amount of ethanol followed by water and the product was crystallized from the proper solvent (cf. Table III); comp. $\mathbf{11_a}$ yield (0.77 g, 0.001 mmol), comp. $\mathbf{11_b}$ yield (0.72 g, 0.001 mmol), comp. $\mathbf{11_c}$ yield (0.64 g, 0.001 mmol).

Anal. Cal. for $\mathbf{11_a}$ $C_{29}H_{21}N_3S_3$: C, 68.63; H, 4.14; N, 8.28; S, 18.93. Found: C, 68.43; H, 4.00; N, 8.02; S, 18.63.

Anal. Cal. for $\mathbf{11_b}$ $C_{29}H_{20}N_4O_2S_3$: C, 63.04; H, 3.62; N, 10.14; S, 17.39. Found: C, 62.88; H, 3.19; N, 10.01; S, 17.10.

Anal. Cal. for **11c** $C_{31}H_{26}N_4S_3$: C, 67.63; H, 4.72; N, 10.18; S, 17.45. Found: C, 67.30; H, 4.61; N, 9.89; S, 17.13.

2-Ethyldithiocarbamate-4-(4′-phenylsulfanyl-phenyl)-thiazole (12)

To a well-stirred, cooled (ice/water) solution of **2** (1 g, 0.035 mmol) in dimethylformamide (5 ml) was successively added (a) aqueous 20 molar NaOH (0.14 ml); (b) carbon disulfide (0.42 ml); (c) aqueous 20 molar NaOH (0.211 ml) and after 30 min, ethyl iodide (0.54 g, 0.035 mmol) was added. Stirring was continued for 2 h. The mixture was poured onto water (50 cc) and neutrallized to litmus with 2 N hydrochloric acid. The solid obtained was filtered washed with water and crystallized from ethanol as orange crystals; yield (0.27 g, 0.0007 mmol).

Anal. Cal. for $C_{18}H_{16}N_2S_4$: C, 55.67; H, 4.12; N, 7.21; S, 32.98. Found: C, 55.50; H, 3.89; N, 7.11; S, 32.58.

3-[4-(4′-Phenylsulfanyl-phenyl)-thiazol-2-yl)]-2-thioxo-4-oxo-1,2,3,4-tetrahydroquinoxaline (13)

A mixture of **12** (1 g, 0.025 mmol) and anthranilic acid (0.35 g, 0.025 mmol) in dimethlformamide (20 ml) was heated under reflux for 4 h. The precipitate was filtered, washed with water, dried, and recrystallized from benzene/pet. ether 60–80° (5:5); yield (0.51 g, 0.001 mmol).

Anal. Cal. for $C_{23}H_{15}N_3O\ S_3$: C, 62.02; H, 3.37; N, 9.43; S, 21.57. Found: C, 61.88; H, 3.10; N, 9.18; S, 21.32.

2-Diethyldithiocarbamate-4-(4′-phenylsulfanyl-phenyl)-thiazole (14)

To a well-stirred solution of **2** (1 g, 0.035 mmol) in dimethylformamide (5 ml) was added (a), (b), (c), as mentioned above, for preparation of **12**. After 30 min ethyl iodide (1.09 g, 0.070 mmol) was added and stirring continued for 2 h. The mixture was poured onto (50 cc) water, the solid obtained was washed with water, and it was crystallized from ethanol; yield (032 g, 0.007 mmol).

Anal. Cal. for $C_{20}H_{20}N_2\ S_4$: C, 57.69; H, 4.80; N, 6.73; S, 30.76. Found: C, 57.38; H, 4.60; N, 6.57; S, 30.54.

2-[4-(4′-Phenylsulfanyl-phenyl)-thiazol-2-ylamino)-4-oxo-benzo[d][1,3]oxazin (15)

A mixture of compound **14** (1 g, 0.024 mmol), anthranilic acid (0.32 g, 0.024 mmol) in dimethylformamide (15 ml) and potassium hydroxide (0.096 g, 0.024 mmol) in water (2 ml) was heated under reflux for 6 h. After cooling the product was filtered, washed with water, air-dried,

and crystallized form ethanol-water as yellow crystals; yield (0.045 g, 0.001 mmol).

Anal. Cal. for $C_{23}H_{15}N_3O_2S_2$: C, 64.33; H, 3.49; N, 9.79; S, 14.91. Found: C, 64.11; H, 3.29; N, 9.49; S, 14.63.

(1H-Benzoimidazd-2-Yl)-[4-(4′-phenylsulfanyl-phenyl)-thiazole]-amine (16)

A solution of **14** (1 g, 0.024 mmol) in 15 ml dimethyl formamide and o-phenylenediamine (0.25 g, 0.024 mmol) was heated under reflux for 5 h. The reaction mixture was concentrated and cooled to room temperature. The solid product was filtered off and crystallized from ethanol as yellow crystals; yield (0.43 g, 0.001 mmol).

Anal. Cal. for $C_{22}H_{16}N_4S_2$: C, 66.00; H, 4.00; N, 14.00; S, 16.00. Found: C, 65.84; H, 3.88; N, 13.93; S, 15.94.

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