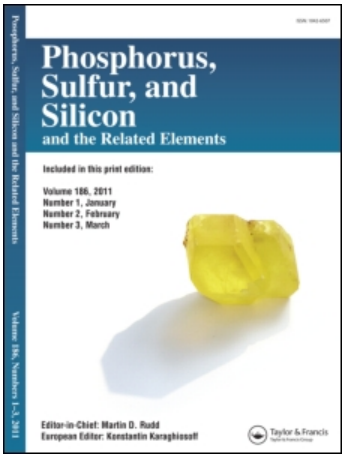

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

FUSED CYANOPYRIMIDINES: PART II SYNTHESIS AND REACTIONS OF FUSED CYANOPYRIMIDINE DERIVATIVES AS AFFECTING ENZYMATIC AGENTS

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To cite this Article Abdel-aziz, S. A. , Allimony, H. A. , El-shaaer, H. M. , Ali, Usama F. and Abdel-rahman, R. M.(1996) 'FUSED CYANOPYRIMIDINES: PART II SYNTHESIS AND REACTIONS OF FUSED CYANOPYRIMIDINE DERIVATIVES AS AFFECTING ENZYMATIC AGENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 113: 1, 67 — 77
To link to this Article: DOI: 10.1080/10426509608046379
URL: http://dx.doi.org/10.1080/10426509608046379

Phosphorus, Sulfur, and Silicon, 1996, Vol. 113, pp. 67–77
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FUSED CYANOPYRIMIDINES: PART II SYNTHESIS AND REACTIONS OF FUSED CYANOPYRIMIDINE DERIVATIVES AS AFFECTING ENZYMATIC AGENTS

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(Received August 10, 1995; in final form December 2, 1995)

Some new fused heterobicyclic systems, such as thiazolo[3,2-a]-pyrimidin-5-one (**3**), 2,3-tetrahydrothiazolo[3,2-a]pyrimidin-5-one (**5**), 2,4-tetrahydrothiazino[3,2-a]pyrimidin-3,6-dione (**6**), 3-dihydrothiazino[3,2-a]pyrimidin-2,4,6-trione (**7**), 3-arylidenethiazino[3,2-a]pyrimidin-2,4,6-trione (**8**) and/or the related nitrogen compounds, such as 2,3-tetrahydroimidazolo[3,2-a]-pyrimidin-5-one (**9**), 1-aryl-2,3-tetrahydroimidazolo[3,2-a]pyrimidin-5-one (**11**), quinazolino[3,2-a]pyrimidin-6,8-dione (**12**) and 3-mercapto-1,2,4-triazolo[4,3-a]pyrimidin-5-one (**14**) have been synthesized by the interaction of 2-mercapto-4-arylidene-5-cyanopyrimidin-6(1H)one (**1**) with α,β-bifunctional nitrogen, oxygen and/or sulfur compounds. The structures have been characterized by elemental analyses, IR, UV, ^{1}H NMR and mass spectral data. Some newly prepared compounds revealed a moderate effect on the activity of cellobiase produced by *Aspergillus nidulans*.

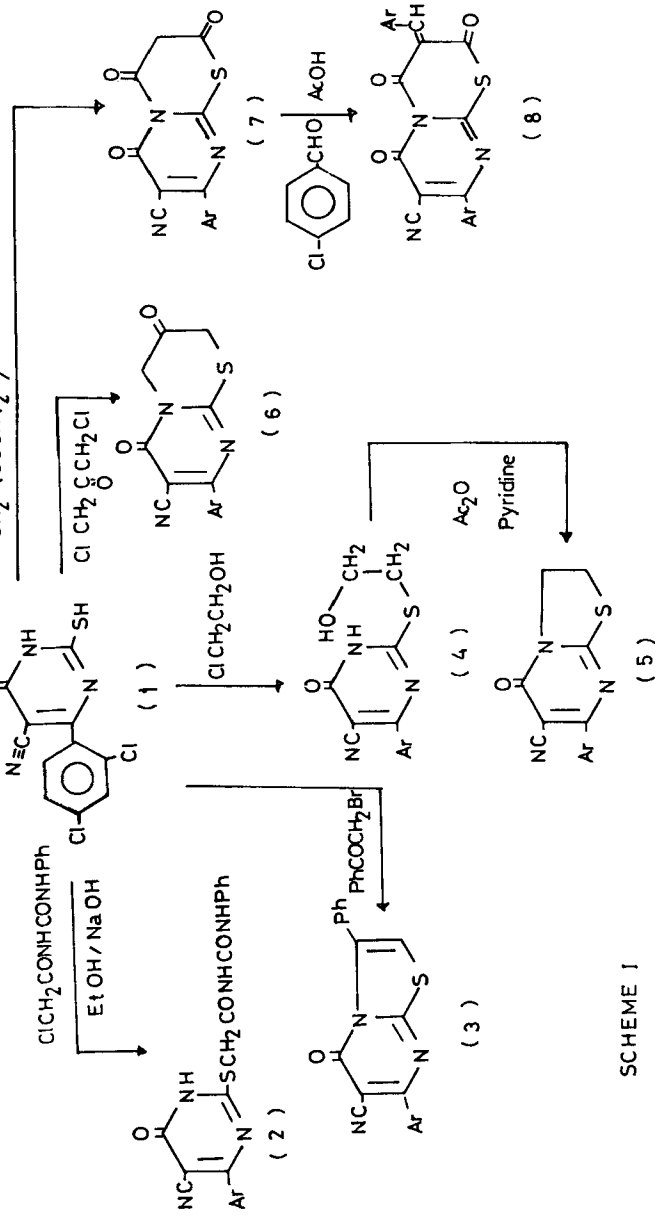
Key words: Fused-cyanopyrimidine, heterobicyclic systems, NMR spectra, UV spectra, IR spectra, biological activity.

INTRODUCTION

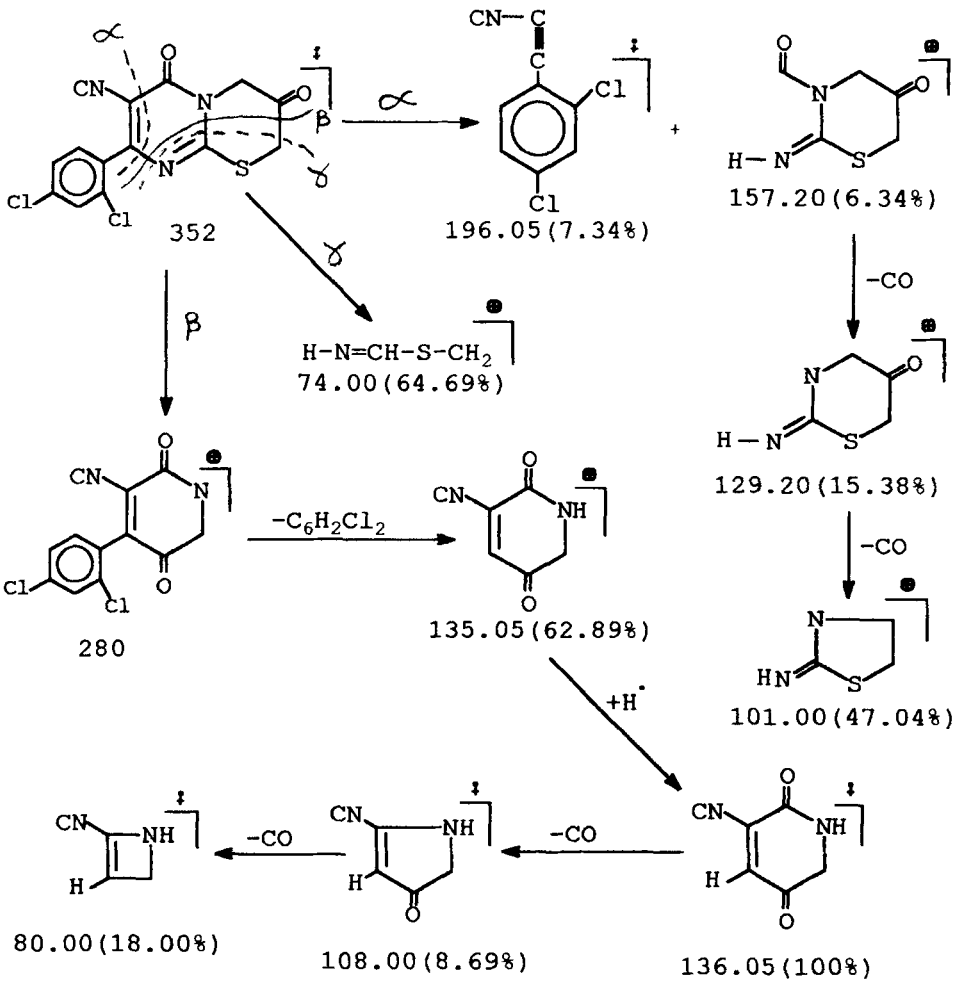
Sulfur compounds containing heterocyclic systems, such as the 2-thiouracil moiety play a vital role in many biological processes and are used as intermediates for the synthesis of drugs. In continuation of our interest in the chemistry of pyrimidines, owing to their considerable biological activities,[1–6] we report the syntheses of some new fused cyanopyrimidines and the effect of these compounds on cellobiase activity produced by *Aspergillus nidulans*.

RESULTS AND DISCUSSION

Reaction of compound **1** with alkylating agents,[7] such as, chloroacetyl-N-phenylurea in ethanolic NaOH gave the chloroacetylurea derivative **2**, while alkylation of **1** using phenacyl bromide under the same conditions, led to the direct formation of 3-phenyl-7-(2′,4′-dichlorophenyl)-6-cyano-thiazolo[3,2-a]pyrimidin-5-one (**3**). Compound **1** on treatment with 2-chloroethanol in DMF afforded the asymmetrical thioether **4** which underwent cyclization on refluxing with a mixture of acetic anhydride-pyridine to give 2,3-tetrahydro-6-cyano-7-(2′,4′-dichlorophenyl)thiazolo[3,2-a]pyrimidin-5-one (**5**) (Scheme I).



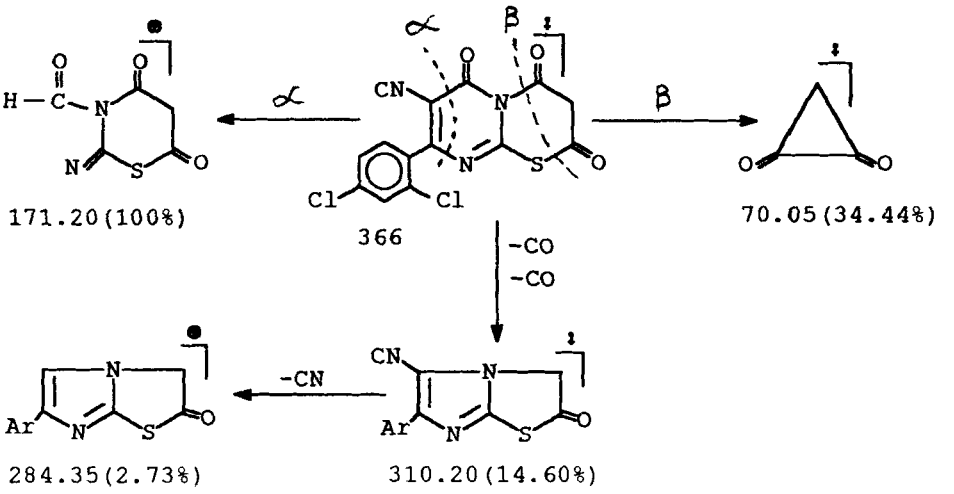
SCHEME I



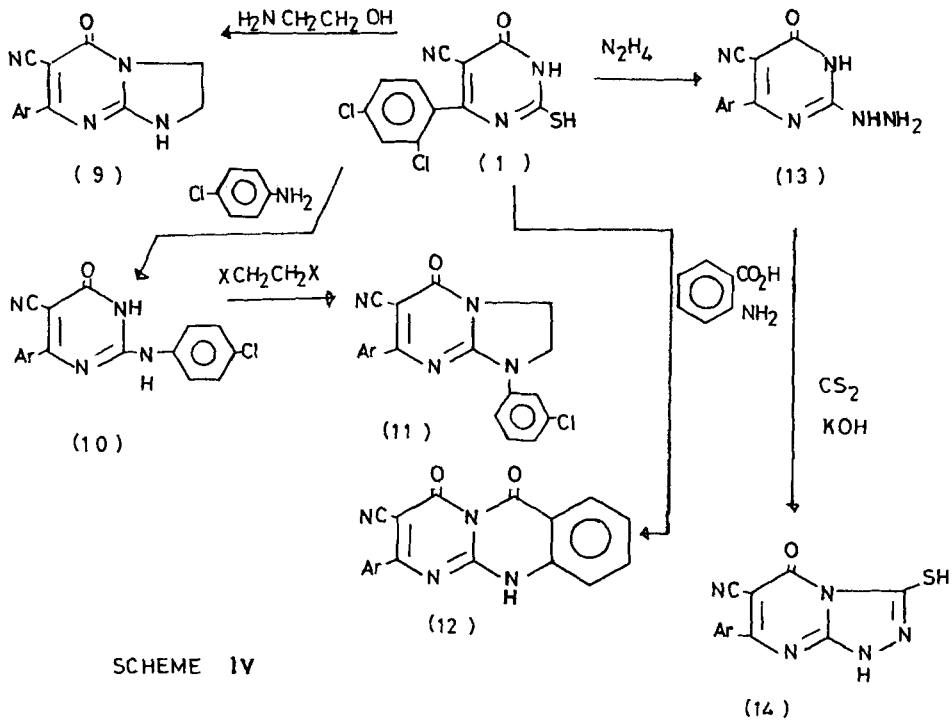
Scheme-II Mass Fragmentation Pattern of Compound 6

The structures of compounds **2–5** were elucidated by elemental analysis, IR and ^{1}H NMR spectral studies. IR spectra of **2** and **4** showed peaks at 3453 (OH), 3176 (NH), in addition to the deformation absorption band at 1472 (deformation acyclic CH_2) and 1171 cm^{-1} (C—S), while IR spectra of **3** and **5** revealed the absence of absorption bands corresponding to OH, NH and acyclic CH_2 groups. The ^{1}H NMR spectrum of **5** showed signals at δ 3.2–3.5 and 7.2–7.7 ppm attributed to —CH_2—CH_2 and the aromatic protons, respectively.

The original objective of the present work was the formation of fused cyanopyrimidines containing a sulfur atom. Thus, the interaction of compound **1** with 1,3-dichloroacetone in DMF resulted in the formation of 2,4-tetrahydro-7-cyano-8-(2′,4′-dichlorophenyl)-1,3-thiazino[3,2-a]pyrimidin-3,6-dione (**6**) (Scheme I). The structure of **6** was deduced from elemental analysis and spectral data. The IR spectrum showed bands characteristic to OH, CH_2, CN, def. CH_2 and C—S vibrations. ^{1}H NMR spectrum of compounds **6** showed signals at δ 2.7, 2.9 and 3.2–3.5 ppm due to two CH_2

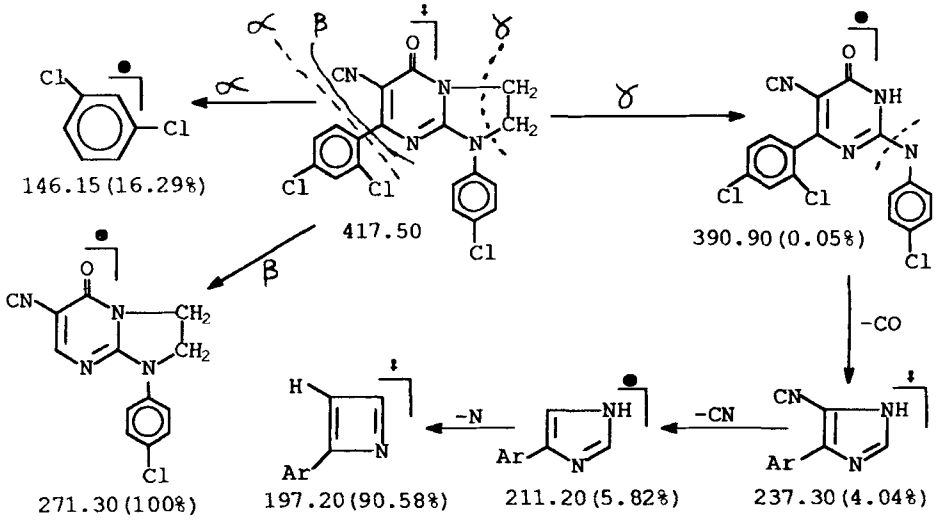


Scheme-III Mass Fragmentation Pattern of Compound 7



SCHEME IV

and coupling CH_2—CH_2 protons, in addition, two signals at 7.2–7.7 and 7.9 ppm correspond to aromatic and OH protons, respectively. While mass spectra of **6** revealed the m/z at 354 (M+2) due to the presence of chlorine and sulfur atoms. It is proposed that the ion of 136 (100%), due to cyanopyridindione moiety, undergoes fragmentation according to the sequence in Scheme II.



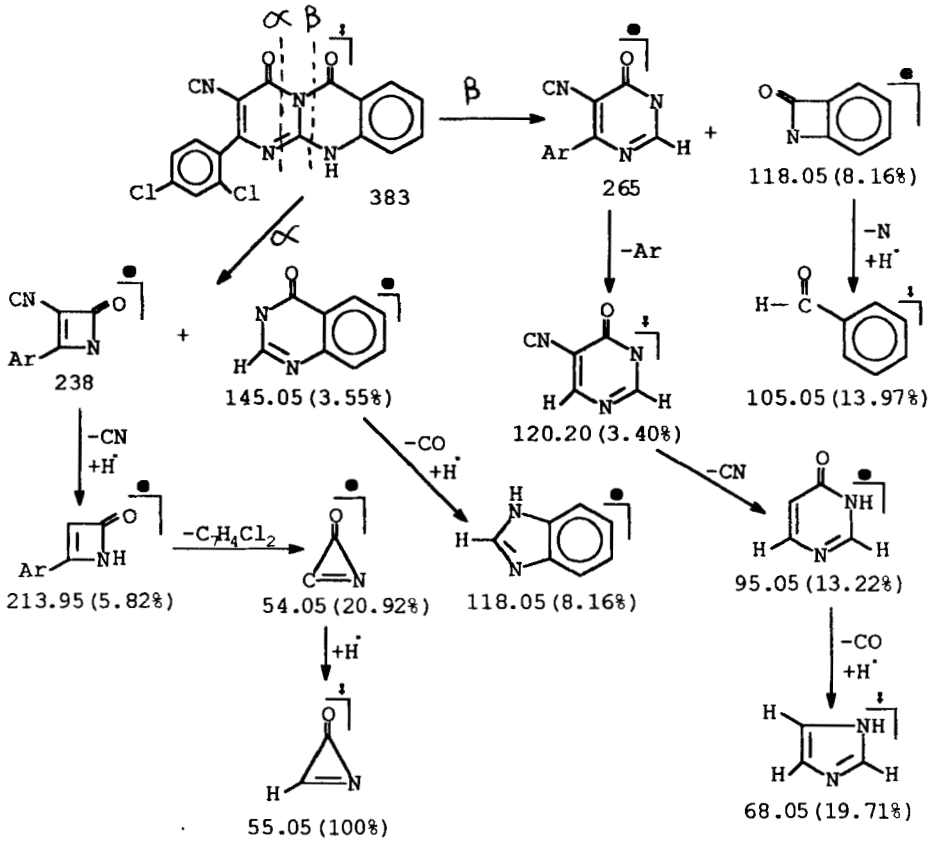
Scheme-V Mass Fragmentation Pattern of Compound 11

Also, compound **1** on treatment with malonic acid in the presence of acetyl chloride gave 3-dihydro-7-cyano-8-(2′,4′-dichlorophenyl)-1,3-thiazino[3,2-a]pyrimidin-2,4,6-trione (**7**) (Scheme I). The presence of active CH_2 group in compound **7** was established from condensation with *p*-nitrobenzaldehyde in the presence of glacial acetic acid-fused sodium acetate to give the arylidene derivative **8**.

The structures of **7** and **8** were established by elemental analysis and spectral data. IR spectra of **7** and **8** showed the absence of NH, SH and OH functional groups. The UV spectrum of **8** showed an intense band at 305 nm (A 0.75) and another less prominent band at a lower wavelength of 275.8 nm (A 3.452), while the UV spectrum of **7** showed only one band at 276.3 nm (A 3.219), which revealed the presence of the conjugated system in **8**. The structure of compound **7** was deduced from the mass spectral fragmentation pattern of the molecular ion at 369 (M+3) and the base peak at 171 (100%) (Scheme III).

A few displacement reactions of the mercapto group[8] in compound **1** were also investigated. Thus 1H-2,3-tetrazino-6-cyano-7-(2′,4′-dichlorophenyl)imidazolo[3,2-a]pyrimidin-5-one (**9**) was obtained from refluxing compound **1** with ethanolamine in isopropanol-Ac_2O, while the interaction between compound **1** and *p*-chloroaniline in isopropyl alcohol produced 2-(*p*-chlorophenylamino)-5-cyano-4-(2′,4′-dichlorophenyl)pyrimidin-6(1H)one (**10**), which underwent ring closure reaction by treatment with 1,2-dibromoethane in ethanolic KOH to form 1-(*p*-chlorophenyl)-2,3-tetrahydro-6-cyano-7-(2′,4′-dichlorophenyl)imidazolo[3,2-a]pyrimidin-5-one (**11**) (Scheme IV).

Structures of compounds **9**–**11** were established on the basis of elemental analyses and spectral data. IR spectra of both **9**, **10** and/or **11** lack any significant absorption bands characteristic of SH, OH and/or NH_2 groups. In addition, compound **9** and **10** showed a broad band due to NH at 3174 cm^{-1}. ^1H NMR of **10** showed signals at δ 5.0 (OH), 7.2–7.5, 7.7–7.9 (aromatic) and at 10.0 and 11.3 ppm correspond to the cyclic and acyclic NH protons, respectively.



Scheme-VI Mass Fragmentation Pattern of Compound 12

The IR spectrum of **11** displayed absorption bands in the range 2958, 2928, 2845, 1477 and 1466 cm^{-1} due to the stretching and bending vibrations of CH_2—CH_2 with absence of OH and NH groups. The ^1H NMR spectrum of **11** displayed signals due to CH_2—CH_2 and aromatic protons. The structure of **11** was supported by mass spectral data. The characteristic m/z at 417 (0.02%) and the base peak at 271 (100%) are attributed to imidazolopyrimidine (Scheme V).

The target heterobicyclic nitrogen system, such as quinazolino[3,2-a]pyrimidindione (**12**) has been obtained from the interaction between compound **1** with anthranilic acid in the presence of sodium ethoxide. The structure of **12** was deduced from the elemental analysis and spectral data. The IR spectrum, showed the absorption bands at 3177 (NH), 2300 (C≡N), 1786, 1694 (two C=O) and 920, 860 and 780 cm^{-1} (aryl groups), also compound **12** did not give the acidity test. The mass spectrum of **12** exhibited a molecular ion peak at m/z 384 (M+1) and a base peak at m/z 55. The fragmentation process of **12** supported the postulated structure (Scheme VI).

Hydrazinolysis of compound **1** by refluxing with hydrazine hydrate in isopropyl alcohol gave 2-hydrazino-5-cyano-4-(2′,4′-dichlorophenyl)pyrimidin-6(1H)one (**13**), which underwent treatment with CS_2 in ethanolic KOH led to the direct forma-

TABLE I

Physical and spectral data of the newly synthesized compounds **1–14**

Compd. No.	Yield %	M.P. °C	Solvent	Molecular formula	Analysis Found/(Calcd.)%					IR (KBr) cm^{-1}
					C	H	N	S	Cl	
1	75	250-51	EtOH-DMF	$C_{11}H_5N_3OSCl_2$	44.0 (44.3)	1.7 (1.7)	14.0 (14.1)	10.9 (10.7)	23.5 (23.8)	3300-3100 (br., OH, NH), 2220 (C≡N), 1200 (C-S).
2	40	260-61	EtOH	$C_{20}H_{13}N_5O_3SCl_2$	50.6 (50.6)	2.9 (2.7)	14.8 (14.8)	6.9 (6.8)	14.7 (15.0)	3453 (OH), 3176 (NH), 1472 (def. CH_2), 1171 (C-S).
3	70	141-42	Dil. MeOH	$C_{19}H_9N_3OSCl_2$	57.4 (57.3)	2.0 (2.3)	10.6 (10.6)	8.2 (8.0)	17.6 (17.8)	2250 (C≡N), 1668 (C=O), 1633 (C=N), 1178 (C-S).
4	80	243-44	MeOH	$C_{13}H_9N_3O_2SCl_2$	45.9 (45.6)	2.8 (2.6)	12.4 (12.3)	9.4 (9.4)	20.6 (20.8)	3538-3180 (br., OH, NH), 2942-2893 (CH_2), 1472 (def. CH_2).
5 [a]	40	180-81	EtOH	$C_{13}H_7N_3OSCl_2$	48.1 (48.1)	2.4 (2.2)	13.2 (13.0)	10.0 (9.9)	21.6 (21.9)	2916, 2848 (CH_2), 1696 (C=O), 1471 (def. CH_2), 1174 (C-S).
6 [b]	60	> 290	Dil. DMF	$C_{14}H_7N_3O_2SCl_2$	47.8 (47.7)	1.9 (2.0)	11.8 (11.9)	9.3 (9.1)	20.0 (20.2)	3405 (OH), 2927 (CH_2), 2216 (C≡N), 1664 (C=O), 1162 (C-S).
7 [c]	50	261-62	Dil. DMF	$C_{14}H_5N_3O_3SCl_2$	46.2 (45.9)	1.4 (1.4)	11.3 (11.5)	8.8 (8.7)	19.2 (19.4)	2945 (CH_2), 1786, 1696 (C=O), 1559 (C=N), 1171 (C-S).
8 [d]	40	257-58	Dil. DMF	$C_{21}H_8N_4O_5SCl_2$	50.8 (50.5)	1.8 (1.6)	11.4 (11.2)	6.4 (6.4)	14.0 (14.2)	2946 (CH_2), 1786, 1696 (C=O), 1630 (CH=C), 1503, 1366 (NO_2).
9	55	262-63	EtOH	$C_{13}H_8N_4OCl_2$	51.0 (50.8)	2.6 (2.6)	18.2 (18.2)	-- --	23.0 (23.1)	3174 (NH), 2943 (CH_2), 1696 (C=O), 1569 (C=N), 1472 (def. CH_2).

TABLE I (*Continued*)

Compd. No.	Yield %	M.P. °C	Solvent	Molecular formula	Analysis Found/(Calcd.)%					IR (KBr) cm^{-1}
					C	H	N	S	Cl	
10 [e]	60	263-64	EtOH-DMF	$C_{17}H_9N_4OCl_3$	52.1 (52.1)	2.3 (2.3)	13.5 (14.3)	-- --	27.1 (27.2)	3175 (NH), 3075 (NH), 1696 (C=O), 1572 (C=N), 703 (C-Cl).
11 [f]	67	189-90	EtOH	$C_{19}H_{11}N_4OCl_3$	54.8 (54.6)	2.6 (2.6)	13.5 (13.4)	-- --	25.1 (25.5)	2958-2845 (CH_2), 1719 (C=O), 1477, 1466 (def. CH_2).
12	74	262-63	Dil. DMF	$C_{18}H_8N_4O_2Cl_2$	56.2 (56.4)	2.1 (2.1)	14.7 (14.6)	-- --	18.3 (18.5)	3177 (NH), 2300 (C≡N), 1786, 1694 (C=O), 920-780 (phenyl).
13	44	191-92	EtOH	$C_{11}H_7N_5OCl_2$	44.3 (44.6)	2.4 (2.4)	23.5 (23.6)	-- --	23.8 (24.0)	3428 (NH_2), 3274 (NH), 1725 (C=O), 1632 (def. NH_2).
14	65	212-13	DMF	$C_{12}H_5N_5OSCl_2$	42.6 (42.6)	1.6 (1.5)	20.7 (20.7)	9.6 (9.5)	20.8 (21.0)	3092 (NH), 1693 (C=O), 1617, 1583 (C=N), 1180 (C-S).

a) ^{1}H NMR (δ): 3.2-3.5 (m, CH_2-CH_2), 7.2-7.7 ppm (m, aromatic protons).

b) ^{1}H NMR (δ): 2.7, 2.7 (each s, $2CH_2$), 3.2-3.5 (m, coupling CH_2-CH_2), 7.2-7.7 (m, aromatic protons), 7.9 ppm (s, OH proton).

c) UV: 276.3 (3.219) nm

d) UV: 305 (0.75), 275.8 (3.452) nm.

e) ^{1}H NMR (δ): 5.0 (OH), 7.2-7.5, 7.7-7.9 (each m, aromatic potons), 10.0, 11.3 ppm (each s, NH protons).

f) ^{1}H NMR (δ): 2.5, 2.7 (each s, $2CH_2$), 7.2-7.7, 8.2-8.5 ppm (each m, aromatic protons).

TABLE II

The effect of some synthesized compounds on cellobiase activity produced by *Aspergillus nidulans*

Compound No.	1000 μg/mL	100 μg/mL	10 μg/mL
1	0.17	0.17	0.35
2	0.22	0.17	0.30
5	0.14	0.13	0.32
7	0.16	0.21	0.28
10	0.12	0.30	0.34
14	0.35	0.33	0.38

DMF: 0.04 μg/mL reducing sugar.

Control: 0.31 μg/mL reducing sugar.

tion of 3-mercapto-6-cyano-7-(2′,4′-dichlorophenyl)-1,2,4-triazolo[4,3-a]pyrimidin-5(1H)one (**14**) (Scheme IV).

Structures of both compounds **13** and **14** were supported by the IR spectral data: **13** showed bands at ν 3428 (NH_2), 3274 (NH), 1725 (C═O) and 1632 (def. NH_2), while **14** revealed the absorption bands at 3092 (NH), 1693 (C═O), 1617, 1583 (C═N) and at 1180 cm^{-1} (C—S).

BIOLOGICAL ACTIVITY

The effect of some synthesized compounds on the activity of cellobiase produced by *Aspergillus nidulans* was studied. The fungus was grown on Czapeck's medium fortified with cellulose as a carbon source and incubated for 8 days at 45°C. The filtrate was then assayed for cellobiase activity according to the method described by Reese and Mandels.[10] Each compound was dissolved in an appropriate amount of DMF to give three different concentrations and then was added separately to an assay mixture consisting of the enzyme solution and the substrate (cellobiose) dissolved in citrate phosphate buffer at pH 4.8 and incubated at 50°C for one hour. The released reducing sugar was estimated colorimetrically at 540 nm as an indication for the enzyme activity. The results are shown in Table II. The tested compounds adversely affected the enzyme (cellobiase) activity compared with the control. Generally, the lower concentrations increased the enzyme activity, while the higher concentrations inhibited the enzyme activity except for compounds **10** and **14**, which increased the enzyme activity at the concentration 100 μg/mL for the former compound and at both concentrations of 100 and 1000 μg/mL for the latter one.

EXPERIMENTAL

Melting points reported are uncorrected. UV spectra were recorded in pure DMF on a Perkin-Elmer, Lambda 4B controller Accessory Interface, uv-vis spectrophotometer (λ_{max} in nm). IR spectra in KBr were recorded in a Perkin-Elmer, 1430 Ratio Recording spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded on Bruker 200 MHz/52 MM spectrometer using DMSO-d_6 as a solvent and TMS as internal reference (Chemical shift in δ, ppm). Mass spectra were recorded using Hewlett-Packard model: MS 5988 spectrometer (70 eV). Compound **1** was prepared according to the described method.[9]

Synthesis of 2-mercapto-4-arylidene-5-cyanopyrimidin-6(1H)one (**1**)

A mixture of ethyl cyanoacetate (0.01 mole), thiourea (0.01 mole), 2,4-dichlorobenzaldehyde (0.01 mol) and sodium ethylate (0.5 g Na/20 mL abs. ethanol) was stirred for 1 h at room temperature. The reaction mixture was poured gradually onto HCl-ice. The solid thus separated was filtered off and recrystallized (see Table I for details).

Synthesis of Chloroacetylurea Derivative (**2**)

A mixture of compound **1** (0.01 mole), ethanolic sodium hydroxide (50 mL, 5%) and chloroacetylphenylurea (0.01 mole) was heated under reflux for 3 h, cooled, and then poured onto HCl-ice. The separated solid was filtered off and recrystallized to give **2** (Table I).

Synthesis of **3**

Phenacyl bromide (0.01 mole) was added to a solution of **1** in DMF, which was immersed in ice. Ethanolic sodium hydroxide (50 mL, 5%) was added and the reaction mixture was refluxed for 2 h, cooled, and poured onto HCl-ice. The solid obtained was filtered off and recrystallized to give **3** (Table I).

Synthesis of **4**

Compound **1** (0.01 mole) and 2-chloroethanol (0.01 mole) in DMF (20 mL) were heated under reflux for 4 h, cooled, and poured onto ice. The separated solid was filtered off and recrystallized to give **4** (Table I).

Cyclization of **4**: *Formation of 2,3-tetrahydro-6-cyano-7-(2',4'-dichlorophenyl)thiazolo[3,2-a]pyrimidin-5-one* (**5**)

A mixture of compound **4** in 50 mL of acetic anhydride-pyridine mixture (1:1) was refluxed for 4 h, cooled, and then diluted with cold water. The solid obtained was recrystallized to give **5** (Table I).

Synthesis of **6**

1,3-Dichloroacetone (0.01 mole) was added to a solution of **1** in DMF, which was immersed in ice. The mixture was then heated under reflux for 2 h, cooled, and poured onto ice. The solid was filtered off and recrystallized to give **6** (Table I).

Synthesis of 3-dihydro-7-cyano-8-(2',4'-dichlorophenyl)-1,3-thiazino[3,2-a]pyrimidin-2,4,6-trione (**7**)

Malonic acid (0.01 mole) was added to an ice-cold solution of **1** in DMF. The mixture was heated under reflux on a water-bath in the presence of acetyl chloride (3 mL) for 6 h. The reaction mixture was concentrated into its half volume. The separated solid was filtered off and recrystallized to give **7** (Table I).

Condensation of **7** *with p-nitrobenzaldehyde: Synthesis of* **8**

A mixture of equimolar amounts of compound **7**, *p*-nitrobenzaldehyde and sodium acetate (2 gm) in acetic acid (20 mL) was heated under reflux for 3 h. The reaction mixture was poured onto ice. The solid obtained was filtered off and recrystallized to give **8** (Table I).

Synthesis of 1H-2,3-tetrazino-6-cyano-7-(2',4'-dichlorophenyl)imidazolo[3,2-a]pyrimidin-5-one (**9**)

A mixture of **1** and ethanolamine in isopropyl alcohol (20 mL) was refluxed for 4 h, then added acetic anhydride (20 mL) and heated for 2 h. The reaction mixture was poured onto ice and filtered off. The separated solid was recrystallized to give **9** (Table I).

Synthesis of **10**

A compound **1** (0.01 mole) and *p*-chloroaniline (0.01 mole) in isopropyl alcohol (20 mL) were heated under reflux for 10 h. The solid obtained was filtered off and recrystallized to give **10** (Table I).

Cyclization of **10**: *Synthesis of 1-(p-chlorophenyl)-2,3-tetrahydro-6-cyano-7-(2',4'-dichlorophenyl)imidazolo[3,2-a]pyrimidin-5-one* (**11**)

A mixture of **10** (0.01 mole) and 1,2-dibromoethane (0.01 mole) in ethanolic potassium hydroxide (50 mL, 5%) was heated under reflux for 2 h. The reaction mixture was neutralized with dilute HCl. The solid obtained was filtered off and recrystallized to give **11** (Table I).

Synthesis of **12**

A mixture of equimolar amounts of **1** and anthranilic acid in sodium ethoxide (0.5 g Na/20 mL abs. ethanol) was heated under reflux for 8 h. The product was poured onto ice-cold dilute HCl. The separated solid was recrystallized to give **12** (Table I).

Synthesis of 2-hydrazino-5-cyano-4-(2',4'-dichlorophenyl)pyrimidin-6-(1H)one (**13**)

A solution of **1** (0.01 mole) in isopropyl alcohol (20 mL) and hydrazine hydrate (0.01 mole) was heated under reflux for 9 h, cooled, and poured onto crushed-ice. The solid obtained was recovered by filtration and recrystallized to give **13** (Table I).

Cyclization of **13**: *Synthesis of* **14**

Compound **13** (1 g), carbon disulphide (1 mL) and an ethanolic solution of potassium hydroxide (1 g/7 mL H_2O and 15 mL ethanol) were heated under reflux for 4 h. The reaction mixture was poured onto ice-HCl. The separated solid was filtered off and recrystallized to give **14** (Table I).

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