New heterocycles from thienopyridocinnolines

M.Z.A. Badr, A.A. Geies, M.S. Abbady, and A.A. Dahy

Abstract: 3-Cyano-4-(*p*-tolyl)pyrido[3,2-*c*]cinnolin-2(1*H*) thione **3** was reacted with α-halo ketones, esters, or amides to give the intermediates, S-alkylated products **5b**–**h**, respectively, which underwent intramolecular ring closure reactions with ethanolic sodium ethoxide to give thienopyridocinnolines **6a**–**h**. Pyrimidothienopyridocinnolines **9** and **11** were obtained by treatment of oxazino compound **8** with hydrazine hydrate and ammonium acetate. Treatment of hydrazino derivative **13** with acetylacetone, triethylorthoformate, carbon disulphide, ethyl chloroformate, and acetic anhydride afforded triazolopyrimidothienopyridocinnolines **14**–**16, 18,** and **21,** while with nitrous acid the corresponding tetrazolo compound **19** was produced.

Key words: thienopyridocinnolines; their pyrimido, triazolopyrimido, and heteroannelated systems.

Résumé : La 3-cyano-4-(*p*-tolyl)pyrido[3,2-*c*]cinnolin-2(1*H*) thione (**3**) réagit avec les α-halogéno cétones, esters ou amides pour conduire respectivement aux produits S-alkylés intermédiaires **5b**–**h** qui, sous l'influence de l'éthylate de sodium en solution dans l'éthanol, subissent des réactions de fermetures de cycle intramoléculaires fournissant les thiénopyridocinnolines **6a**–**h**. On a obtenu les pyrimidothiénopyridocinnolines **9** et **11** par traitement du composé oxazine **8** avec de l'hydrate d'hydrazine et de l'acétate d'ammonium. Le traitement du dérivé hydrazino **13** par de l'acétylacétone, de l'orthoformate d'éthyle, du disulfure de carbone, du chloroformate d'éthyle et de l'anhydride acétique conduit aux triazolopyrimidothiénopyridocinnolines **14**–**16, 18** et **21** alors que sa réaction avec l'acide nitreux conduit à la formation du composé tétrazolo correspondant **19**.

Mots clés : thiénopyridocinnolines; systèmes pyrimido, triazolopyrimido et hétérocycliques correspondants.

[Traduit par la rédaction]

Introduction

Cinnoline derivatives have been reported to constitute an important class of biologically active reagents (1). They have shown antibacterial (2), antifungal (3), and other microbicide (4) activities. Similarly, thienocinnolines and other derivatives have shown various pharmacological activities, such as acting as antihypertensive agents (5), bronchodilators (6), antioxylate drugs to improve brain functions (7), and immunostimulants (8), together with many other activities reported in the literature (9).

Results and discussion

As a continuation of our studies on the synthesis and chemistry of different new heteroannelated ring systems related to phthalazines, quinoxalines, pyrimidines, and other systems (10), we report in the present paper the synthesis and chemistry of a novel series of linear and angular tetra-, penta-, and hexaheterocyclic ring systems based on the cinnoline moiety. An approach to ring closure reactions leading to target compounds started from 4-amino-3-(*p*-methylbenzoylcinnoline **1** (11), which reacted with ethyl cyanoacetate and ammonium acetate to produce 3-cyano-4-(*p*-tolyl)pyrido[3,2-*c*]cinnolin-2(1*H*)-one **2**, which in turn, on refluxing with phosphorus pentasulphide in dry pyridine, gave the corresponding-2(1*H*)thione derivative **3**. Alkylation of **3** with alkyl (benzyl)halides or ethyl chloroformate in the presence of anhydrous sodium acetate gave the corresponding 2-alkylthio compounds **4a**–**d** (Scheme 1).

Similarly, treatment of **3** with α-halo ketones, esters, and (or) acylamides or acetanilides in basic medium gave the corresponding 2-substituted thio compounds **5b**–**h**, which in turn, as active starting materials, underwent nucleophilic ring closure reactions when treated with ethanolic sodium ethoxide solution to produce a new series of tetracyclic substituted thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnolines **6b**–**h**. The corresponding **6**a isomer was produced directly from treatment of **3** with α-chloroacetone without separation of the acyclic alkylthio intermediate **5a**. 3-Amino-2-ethoxycarbonyl-4-(*p*-tolyl)thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline **6c** was successfully used as a strategic starting material to synthesize the novel pentaheterocyclic target compound **11** together with other analogs **9** and **10** through the intermediate oxazine compound **8**.

Alkaline hydrolysis of 2-ethoxycarbonyl derivative **6c** gave the corresponding 2-carboxylic acid derivative **7**.

Ring closure reactions of the 3-amino-2-carboxylic acid compound **7** by heating with acetic anhydride gave the pentacyclic intermediate oxazino [4″,5″:4′,5′]thieno[3′,2′:5,6]-pyrido[3,2-*c*]cinnolin-11-one **8**. Refluxing of oxazino compound **8** with ammonium acetate in acetic acid produced pyrimido thienopyridocinnolin-11(10*H*)one **11**. Refluxing **8** with hydrazine hydrate in dry pyridine produced the corresponding 10-amino-11(10*H*)pyrimidone **9**, which condensed with aromatic aldehydes to give the corresponding arylideneamine derivatives **10a** and **10b.** Treatment of the 11-pyrimidone

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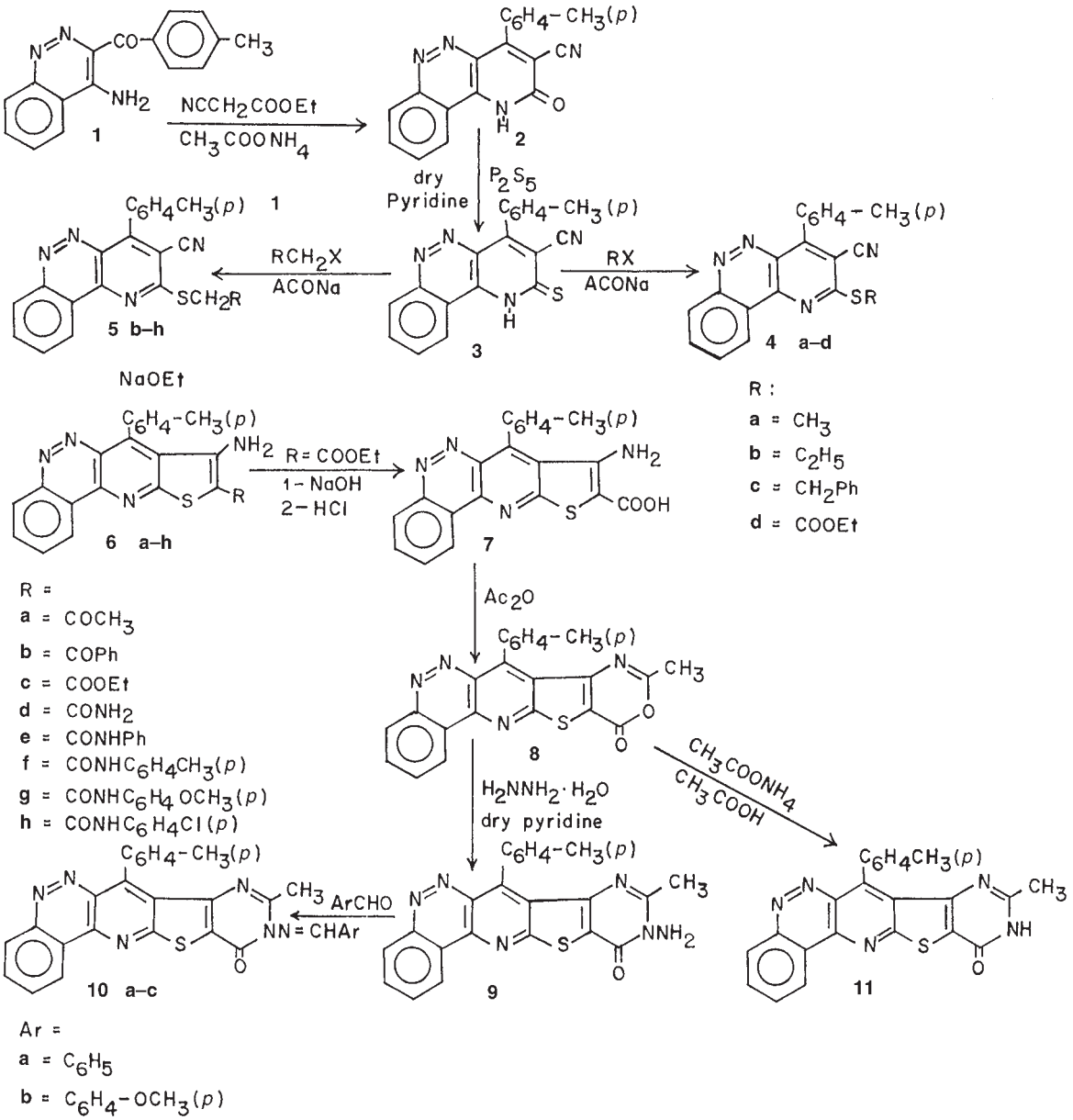
Scheme 1.



11 with phosphorus oxychloride gave the corresponding 11-chloropyrimidine derivative **12** (Scheme 2). The chlorine group of **12** underwent nucleophilic displacement by reflux with hydrazine hydrate in dioxane to produce 11-hydrazinopyrimidothienopyridocinnoline **13**, which condensed with aromatic aldehydes to give the corresponding 11-arylidinehydrazono derivatives **18a** and **18b**. Similarly, heating **13** with acetylacetone produced the corresponding 11-(3,5-dimethylpyrazolyl) derivative **14**.

The hydrazino compound **13** containing an active nitrogen nucleophile was used as strategy material and on treatment with carbonyl, thionyl, or other electrophilic reagents underwent ring closure reactions into a novel series of hexaheterocyclic target compounds. Such reactions favor the existence of the hydrazone tautomer **13** (12).

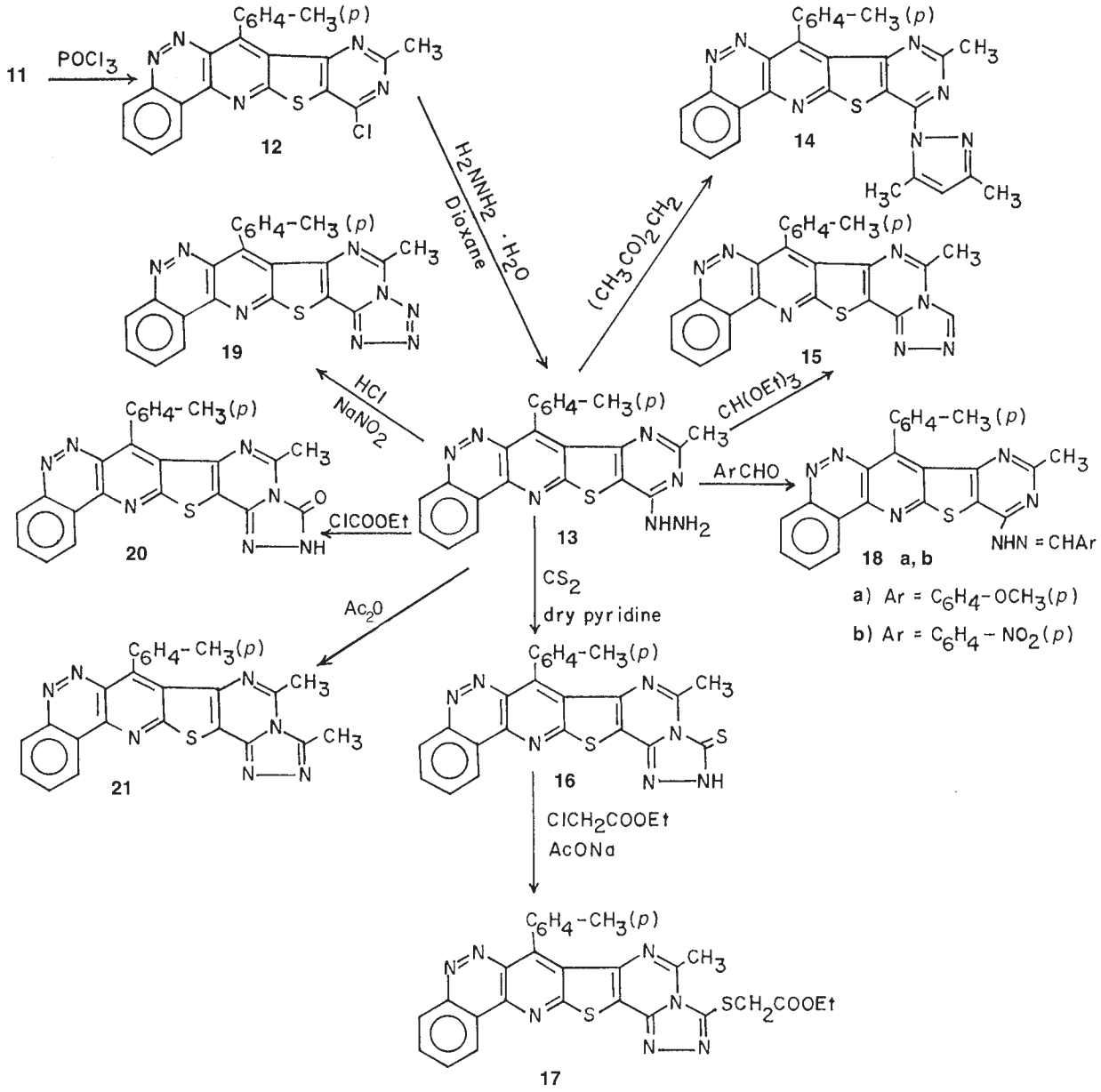
Treatment of **13** ⇌ **13′** with triethylorthoformate in acetic acid afforded 5-methyl-7-(*p*-tolyl)triazolo[3‴,4‴:1″,6″]-pyrimido[4″,5″:4′5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]-cinnoline **15**. The reaction between **13** and acetic anhydride produced the corresponding 3-methyltriazolo derivative **21**.

The interaction of **13** with carbon disulphide in pyridine produced the triazolopyrimidothienopyridocinnolin-3-thione **16**. The latter interacted with ethyl chloroacetate to give the 3-ethoxycarbonylmethylthio derivative **17**. On the other hand, condensation of **13** with ethyl chloroformate led to the formation of the correspondingtriazolo-3-one compound **20**. The interaction of **13** with sodium nitrite in dilute hydrochloric acid, while cooling, afforded the corresponding tetrazolopyrimidothieno-pyridocinnoline **19**.

Experimental

All melting points are uncorrected and were determined on an electric melting point (Gallenkamp) apparatus. IR spectra were

Scheme 2.



determined with a Shimadzu 470 IR spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a 90 MHz Varian EM-390 spectrometer in an appropriate solvent ($CDCl_3$, DMSO-d_6, or deuterated trifluoroacetic acid (TFA)) using TMS as internal standard. ^{1}H NMR signals for NH or NH_2 in TFA-*d* solvent were downfield. Chemical shifts are expressed in δ (ppm). Mass spectra were measured on a GC–MS QP 1000 EX spectrometer at an ionizing potential of 70 eV. Elemental analyses were carried out using a 240C Perkin Elmer analyser.

4-Amino-3-(*p*-methyl benzoyl)cinnoline (1)
A mixture of phenylhydrazonomalononitrile (0.1 mol), toluene (150 mL), and aluminium chloride (0.4 mol) was refluxed for 3 h. The separated product was crystallized from ethanol, mp 210°C (lit. (11) mp 210–212°C).

3-Cyano-4-(*p*-tolyl)pyrido[3,2-*c*]cinnolin-2(1*H*)-one (2)
A mixture of 1 (0.1 mol), ethyl cyanoacetate (0.03 mol), and ammonium acetate (0.05 mol) was heated under reflux for 3 h. After cooling, the precipitate was filtered off, washed with boiling ethanol, and recrystallized from dioxane as yellow crystals, mp >360°C, yield 56%. IR: 3100 (NH); 2200 (CN), 1650 (CO) cm^{-1}; ^{1}H NMR (DMSO) δ: 3.50 (s, 3H, CH_3) and 7.2–9.1 (m, 8H, ArH). Anal. calcd. for $C_{19}H_{12}N_4O$: C 73.07, H 3.87, N 17.94; found: C 72.92, H 3.76, N 17.62%.

3-Cyano-4-(*p*-tolyl)pyrido[3,2-*c*]cinnolin-2(1*H*)-thione (3)
A mixture of **2** (0.01 mol) and phosphorus pentasulphide (0.01 mol) in dry pyridine (20 mL) was refluxed for 4 h, then poured into ice-water. The precipitated solid was filtered, washed with water, and recrystallized from dioxane as orange crystals, mp 315–317°C, yield 86%. IR: 3280 (NH), 2200 (CN), 1250

Table 1. Analytical, spectral, and physical data of compounds, **4a**–**4d**.

Comp. no.	mp,°C	Color	Yield%	Mol. formula	Analysis calcd./found (%) C	H	N	S	Spectral data IR (KBr) cm^{-1}	^1H NMR δ (ppm)
4a[a]	306°C	Yellow	87	$C_{22}H_{14}N_4S$	70.15 69.89	4.12 4.07	16.36 16.08	9.36 9.18	(CN) 2200	^1H NMR (TFA-*d*) δ: 2.50 (s, 3H, *p*-CH_3), 3.20 (s, 3H, SCH_3), 7.5–9.5 (m, 8H, ArH)
4b	285°C	Yellow	80	$C_{21}H_{16}N_4S$	70.76 70.55	4.52 4.72	15.72 15.54	8.99 8.67	(CN) 2200	^1H NMR ($CDCl_3$) δ: 1.60 (t, 3H, CH_3 ester), 2.50 (s, 3H, *p*-CH_3), 3.60 (q, 2H, CH_2), 7.4–9.2 (m, 8H, ArH)
4c	265°C	Yellow	83	$C_{26}H_{18}N_4S$	74.60 74.50	4.30 4.18	13.39 13.56	7.66 7.38	(CN) 2200	^1H NMR ($CDCl_3$) δ: 2.50 (s, 3H, *p*-CH_3), 4.80 (s, 2H, CH_2), 7.2–9.2 (m, 13H, ArH)
4d	154°C	Yellow-orange	70	$C_{22}H_{16}N_4O_2S$	65.98 65.86	4.30 3.90	13.99 13.77	8.01 7.65	(CN) 2200, (CO) 1720	^1H NMR ($CDCl_3$) δ: 1.45 (t, 3H, CH_2CH_3), 2.55 (s, 3H, *p*-CH_3), 4.50 (q, 2H, CH_2), 7.25–9.3 (m, 8H, ArH)

[a] All products were recrystallized from ethanol except **4a** from acetic acid.

(C═S) cm^{-1}.^1H NMR (TFA-*d*) δ: 2.42 (s, 3H, *p*-CH_3) and 7.2–9.4 (m, 8H, ArH). Anal. calcd. for $C_{19}H_{12}N_4S$: C 69.5, H 3.68, N 17.06, S 8.76; found: C 69.65, H 3.80, N 17.12, S 8.68%.

2-Alkyl (aralkyl)thio-3-cyano-4-(*p*-tolyl)pyrido[3,2-*c*]-cinnoline (4a–d)

General procedure

A mixture of **3** (0.01 mol) and alkyl (or benzyl) halide or ethyl chloroformate (0.01mol) was refluxed in ethanol (30 mL) and anhydrous sodium acetate (2 g) for 1 h. The reaction mixture was concentrated to half volume and cooled. The precipitated solid was filtered and recrystallized from an appropriate solvent. The analytical, spectral, and physical data are summarized in Table 1.

3-Cyano-4-(*p*-tolyl)-2-substituted thiopyrido[3,2-*c*]cinnoline (5b–h)

The corresponding α-halo compound was treated with **3** following the same procedure as above. The separated solid was filtered, washed with water, and recrystallized from an appropriate solvent. The analytical, spectral, and physical data are summarized in Table 2.

3-Amino-2-substituted-4-(*p*-tolyl)thieno[3′,2′:5,6]pyrido-[3,2-*c*]cinnoline (6a–h)

General procedure

A mixture of each of the mercapto derivatives (**5b**–**h**) (0.01 mol) in ethanol (50 mL) and five drops of ethanolic sodium ethoxide was refluxed for 30 min. The solid product was filtered and recrystallized from a suitable solvent. **6a** was separated directly on treating α-chloracetone and **3** with anhydrous sodium acetate as above. The analytical, spectral, and physical data are summarized in Table 3.

2-(3-Amino-4-(*p*-tolyl)thieno[3′,2′:5,6]pyrido[3,2-*c*]-cinnolinyl)carboxylic acid (7)

A mixture of **6c** (0.01 mol) and alcoholic sodium ethoxide (30 mL, 25%) was refluxed for 3 h. Sodium salt precipitated and was filtered and acidified in water (200 mL) with dilute HCl. The solid free acid was filtered and recrystallized from acetic acid as yellow crystals, mp 330°C, yield 70%. IR: 3400, 3300 (NH_2) cm^{-1}. ^1H NMR (DMSO) δ: 2.48 (s, 3H, CH_3), 6.55 (s, 2H, NH_2), 10.20 (s, 1H, OH), both of them exchangeable with D_2O, and 7.1–9.2 (m, 8H, ArH). Anal. calcd. for $C_{21}H_{14}N_4O_2S$: C 65.27, H 3.65, N 14.50, S 8.30; found: C 65.31, H 3.87, N 14.06, S 7.97%.

9-Methyl-7-(*p*-tolyl)oxazino[4″,5″:4′,5′]thieno[3′,2′:5,6]-pyrido[3,2-*c*]cinnolin-11-one (8)

A mixture of **7** (0.01 mol) and acetic anhydride (20 mL) was refluxed for 2 h. The solid separated on cooling was filtered and recrystallized from dioxane as yellow crystals, mp 320°C, yield 74%. IR: 1750 (CO) cm^{-1}. ^1H NMR (TFA-*d*) δ: 2.58 (s, 3H, *p*-CH_3), 2.70 (s, 3H, CH_3), 7.4–9.85 (m, 8H, ArH). MS, *m*/*z* (%): 411 (M + 1, 29), 410 (M^+, 100). Anal. calcd. for $C_{23}H_{14}N_4O_2S$: C 67.3, H 3.44, N 13.65, S 7.81; found: C 66.96, H 3.89, N 13.60, S 8.00%.

10-Amino-9-methyl-7-(*p*-tolyl)pyrimido[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]-cinnolin-11(10*H*)-one (9)

A mixture of the oxazino compound **8** (0.01 mol) and hydrazine hydrate (0.01 mol) in dry pyridine (30 mL) was refluxed for 1 h. The solid separated on cooling was filtered and recrystallized from dioxane into yellow crystals, mp >360°C, yield 82%. IR: 3402, 3300 (NH_2), 1660 (CO) cm^{-1}. ^1H NMR (TFA-*d*) δ: 2.90 (s, 3H, *p*-CH_3), 3.18 (s, 3H, CH_3), 7.65–9.95 (m, 8H, ArH). Anal. calcd. for $C_{23}H_{16}N_6OS$: C 65.08, H 3.80, N 19.80, S 7.55; found: C 64.90, H 4.00, N 19.32, S 7.23%.

10-Arylidene amine derivatives of 9 (10a and 10b)

These were prepared by refluxing **9** (0.01 mol) with each of (*a*) benzaldehyde and (*b*) *p*-anisaldehyde (0.01 mol) in glacial acetic acid (20 mL) for 30 min. The solid product in each case

Table 2. Analytical, spectral, and physical data of compounds, **5b**–**5h**.

Comp. no.	mp, °C	Color	Yield%	Mol. formula	Analysis calcd./found (%) C	H	N	S	Spectral data IR (KBr) cm^{-1}	^1H NMR δ (ppm), and MS, *m/z* (%)
5b	230°C	Yellow	75	$C_{27}H_{18}N_4OS$	72.63 72.78	4.03 3.89	12.55 12.32	7.18 7.32	(CN) 2200, (CO) 1670	^1H NMR (DMSO) δ: 2.85 (s, 3H, *p*-CH_3), 5.00 (s, 2H, SCH_2), 7.3–8.9 (m, 13H,ArH)
5c	221°C	Yellow	79	$C_{23}H_{18}N_4O_2S$	66.65 66.85	4.38 4.36	13.52 13.29	7.74 7.48	(CN) 2200, (CO) 1720	^1H NMR ($CDCl_3$) δ: 1.20 (t, 3H, CH_2 CH_3), 2.40 (s, 3H, *p*-CH_3), 4.20 (q, 2H, CH_2), 7.2–9.2 (m, 8H, ArH)
5d	286–287°C	Yellow	76	$C_{21}H_{15}N_5OS$	65.43 65.21	3.90 3.88	18.17 18.34	8.37 8.16	(NH_2) 3800, 3600, (CN) 2200, (CO) 1670	^1H NMR (TFA-*d*) δ: 2.50 (s, 3H, *p*-CH_3), 4.55 (s, 2H, CH_2), 7.2–9.5 (m, 8H, ArH)
5e	289–290°C	Green-yellow	76	$C_{27}H_{19}N_5OS$	70.26 70.06	4.15 4.10	15.17 14.98	6.95 6.82	(NH) 3300, (CN) 2200, (CO) 1660	^1H NMR ($CDCl_3$ + drop TFA-*d*) δ: 2.50 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 6.9–9.4 (m, 13H, ArH) MS, *m/z* (%): 461 (M^+, 51%)
5f	300°C	Green-yellow	70	$C_{28}H_{21}N_5OS$	70.72 70.53	4.45 4.28	14.73 14.64	6.74 6.48	(NH) 3300, (CN) 2200, (CO) 1655	^1H NMR (DMSO) δ: 2.20 (s, 3H, *p*-CH_3), 2.50 (s, 3H, *p*-CH_3), 4.40 (s, 2H, CH_2), 6.95–9.2 (m, 12H, ArH), 10.55 (s, 1H, NH)
5g	300–302°C	Green-yellow	81	$C_{28}H_{21}N_5OS$	68.42 68.66	4.31 4.45	14.25 14.14	6.52 6.51	(NH) 3300, (CN) 2200, (CO) 1650	^1H NMR (DMSO) δ: 2.20 (s, 3H, *p*-CH_3), 3.20 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2), 6.5–8.95 (m, 12H, ArH), 10.30 (1H, NH)
5h[a]	325°C	Green-yellow	84	$C_{27}H_{18}ClN_4OS$	65.38 65.28	3.66 3.76	14.12 14.00	6.47 6.35	(NH) 3300, (CN) 2200, (CO) 1660	^1H NMR (DMSO) δ: 2.50 (s, 3H, *p*-CH_3), 4.50 (s, 2H, CH_2), 7.2–9.2 (m, 12H, ArH), 7.85 (s, 1H, NH)

[a] Chlorine analysis for **5h**, calcd.: 7.15; found: 7.34%.

was filtered and recrystallized from ethanol. The analytical, spectral, and physical data are summarized in Table 4.

9-Methyl-7-(*p*-tolyl)pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]-pyrido[3,2-*c*]cinnolin-11(10*H*)-one (11)

Refluxing the oxazino compound **8** (0.01 mol) and ammonium acetate in acetic acid (30 mL) for 30 min precipitated a solid that was filtered and recrystallized from acetic acid as yellow crystals, mp 320°C, yield 80%. IR: 3600 br (NH), 1650 (CO) cm^{-1}; ^1H NMR (TFA-*d*) δ: 2.70 (s, 3H, *p*-CH_3), 2.92 (s, 3H, CH_3), 7.7–9.9 (m, 8H, ArH). Anal. calcd. for $C_{23}H_{15}N_5OS$: C 67.47, H 3.69, N 17.10, S 7.83; found: C 65.7, H 4.00, N 16.95, S 7.69%.

11-Chloro-9-methyl-7-(*p*-tolyl)pyrimido[4″,5″:4′,5′]thieno-[3′,2′:5,6] pyrido[3,2-*c*]-cinnoline (12)

The pyrimidinone **11** (0.01 mol) in phosphorus oxychloide (40 mL) was refluxed for 4 h. The cooled mixture was stirred in ice-water for 30 min. The solid product was filtered, washed with water, and recrystallized from dioxane as yellow crystals, mp 283°C, yield 68%. IR: both NH and CO absorptions disappeared. ^1H NMR (TFA-*d*) δ: 2.60 (s, 3H, *p*-CH_3), 2.85 (s, 3H, CH_3), 7.55–9.8 (m, 8H, ArH). Anal. calcd. for $C_{23}H_{14}N_5SCl$: C 64.56, H 3.30, N 16.37, S 7.49, Cl 8.29; found: C 64.50, H 3.60, N 16.02, S 7.60, Cl 8.58%.

11-Hydrazino-9-methyl-7-(*p*-tolyl)pyrimido[4″,5″:4′,5′]-thieno[3′,2′:5.6]pyrido[3.2-*c*]-cinnoline (13)

The chloro compound **12** (0.01 mol) and hydrazine hydrate (0.01 mol) in dioxane (30 mL) were refluxed for 30 min. The separated solid was filtered and recrystallized from dioxane as yellow crystals, mp 300°C, yield 85%. IR: 3350 (NH_2), 3200 (NH) cm^{-1}; ^1H NMR (TFA-*d*) δ: 2.69 (s, 3H, *p*-CH_3), 2.73 (s, 3H, CH_3), 7.6–9.9 (m, 8H, ArH). Anal. calcd. for $C_{23}H_{17}N_7S$: C 65.23, H 4.05, N 23.15, S 7.57; found: C 64.92, H 4.25, N 23.25, S 7.87%.

9-Methyl-11-(3,5-dimethylpyrazolyl)-7-(*p*-tolyl)pyrimido-[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (14)

The hydrazino compound **13** (0.001 mol) and acetylacetone (0.005 mol) in ethanol (40 mL) were refluxed for 6 h. The separated solid was filtered and recrystallized from ethanol as pale brown crystals, mp 320°C, yield 77%. IR: NH and NH_2 absorptions disappeared. ^1H NMR (TFA-*d*) δ: 2.45 (s, 3H, *p*-CH_3), 2.60 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 6.40 (s,,1H, ═CH), 7.6–9.8 (m, 8H, ArH). MS, *m/z* (%): 488 (M + 1, 35), 487(M^+, 100), 486(M – 1, 16). Anal. calcd. for $C_{28}H_{21}N_7S$: C 68.97, H 4.34, N 20.11, S 6.58; found: C 64.10, H 4.62, N 19.90, S 6.82%.

5-Methyl-7-(*p*-tolyl)-1,2,4-triazolo[4‴,3‴:1″,6″]pyrimido-[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnoline(15).

The hydrazino compound **13** (0.001 mol), triethylorthoformate

Table 3. Analytical, spectral, and physical data of compounds, **6a**–**6h**.

Comp. no. [a]	mp, °C	Color	Yield %	Mol. formula	Analysis calcd./found (%) C	H	N	S	Spectral data IR (KBr) cm^{-1}	^1H NMR δ (ppm), and MS, *m/z* (%)
6a	310°C	Orange	69	$C_{22}H_{16}N_4OS$	68.73 68.46	4.19 4.35	14.57 14.55	8.34 8.11	(NH_2) 3500, 3300(CO), 1610	^1H NMR ($CDCl_3$) δ: 2.55 (s, 3H, *p*-CH_3), 2.90 (s, 3H, $COCH_3$), 6.20 (s, 2H, NH_2), 7.2–9.1 (m, 8H, ArH)
6b	265°C	Red	78	$C_{27}H_{18}N_4OS$	72.63 72.70	4.06 4.12	12.55 12.36	7.18 7.31	(NH_2) 3400, 3300, (CO) 1560	^1H NMR ($CDCl_3$)δ: 2.60 (s, 3H, *p*-CH_3), 7.12 (s, 2H, NH_2), 7.2–9.3 (m, 13H, ArH); MS, *m/z* (%): 446 (M^+, 100%)
6c	290°C	Orange	82	$C_{23}H_{18}N_4O_2C$	66.65 66.82	4.38 4.31	13.52 13.30	7.74 7.52	(NH_2) 3470, 3350, (CO) 1670	^1H NMR ($CDCl_3$) δ: 1.50 (t, 3H, CH_3 ester), 2.60 (s, 3H, *p*-CH_3), 4.10 (q, 2H, CH_2), 5.90 (s, 2H, NH_2), 7.2–9.3 (m, 8H, ArH); MS, *m/z* (%): 414(M^+, 100%)
6d	270°C	Red	75	$C_{21}H_{15}N_5OS$	65.43 65.60	3.90 3.98	18.17 17.94	8.32 8.16	(NH_2) 3450, 3300, (CO) 1630	^1H NMR (DMSO) δ: 3.30 (s, 3H, *p*-CH_3), 6.00 (s, 2H, NH_2), 7.35 (s, 2H, $CONH_2$), 7.35–9.1 (m, 8H, ArH); MS, *m/z* (%); 385 (M^+, 69%)
6e	297°C	Orange	69	$C_{28}H_{19}N_5OS$	70.26 70.36	4.15 4.28	15.17 15.32	6.95 6.80	(NH_2) 3450, 3400, (NH) 3300, (CO) 1640	^1H NMR ($CDCl_3$) δ: 3.00 (s, 3H, *p*-CH_3),6.05 (s, 2H, NH_2), 7.73 (s, 1H, NH), 7–9.2 (m, 13H, ArH)
6f	194°C	Red	70	$C_{28}H_{21}N_5OS$	70.72 70.53	4.45 4.25	14.73 14.50	6.74 6.81	(NH_2) 3460–3400, (NH) 3300, (CN) 2200, (CO) 1622	^1H NMR (DMSO) δ: 2.25 (s, 3H, *p*-CH_3), 2.52 (s, 3H, *p*-CH_3), 6.03 (s, 2H, NH_2), 7.52 (s, 1H, NH), 7–9.1 (m, 12H, ArH)
6g	257°C	Red	72	$C_{28}H_{21}N_5O_2S$	69.17 68.94	4.20 4.06	13.91 13.72	6.37 6.57	(NH_2) 3500, 3450, (NH) 3300, (CO) 1630	^1H NMR ($CDCl_3$) δ: 2.60 (s, 3H, *p*-CH_3), 2.80 (s, 3H, *p*-OCH_3), 6.15 (s, 2H, NH_2), 7.80 (s, 1H, NH), 6.8–9 (m, 12H, ArH)
6h[b]	285°C	Red	74	$C_{27}H_{18}ClN_5OS$	65.38 65.20	3.66 3.71	14.12 13.92	6.47 6.32	(NH_2) 3450, (NH) 3300, (CO) 1620	^1H NMR ($CDCl_3$) δ: 2.60 (s, 3H, CH_3), 6.20 (s, 2H, NH_2), 8.90 (s, 1H, NH), 7.15–9.3 (m, 12H, ArH)

[a] All products were recrystallized from ethanol except **6a** from acetic acid.
[b] Chlorine analysis for **6h**, calcd.: 7.15; found: 7.23%.

(5 mL) and five drops of acetic acid were refluxed for 6 h. The separated product was filtered and recrystallized from acetic acid as yellow crystals, mp >360 °C, yield 75%. IR: NH and NH_2 absorptions disappeared. ^1H NMR (TFA-*d*) δ: 2.40 (s, 3H, *p*-CH_3), 2.96 (s, 3H, CH_3), 7.35–9.9 (m, 8H, ArH), 9.65 (s, 1H, =CH). MS, *m/z* (%); 434 (M + 1, 48), 433 (M^+, 60), 432 (M – 1, 32). Anal. calcd. for $C_{24}H_{15}N_7S$: C 66.50, H 3.49, N 22.62, S 7.40; found: C 66.26, H 3.86, N 22.81, S 7.73%.

5-Methyl-7-(*p*-tolyl)1,2,4-triazolo[4‴,3‴:1″,6″]pyrimido-[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-3(2*H*)-thione (16)

The hydrazino compound **13** (0.001 mol) and carbon disulphide (2 mL) in dry pyridine (20 mL) were refluxed for 8 h. The separated solid was filtered and recrystallized from ethanol as brown crystals, mp >360°C. IR: 3450 (NH), 1280 (C=S) cm^{-1}. ^1H NMR (TFA-*d*) δ: 2.70 (s, 3H, *p*-CH_3), 3.30 (s, 3H, CH_3), 7.5–9.82 (m, 8H, ArH). Anal. calcd. for $C_{24}H_{15}N_7S_2$: C 61.92, H 3.25, N 21.06, S 13.78; found: C 62.06, H 3.57, N 20.89, S 13.56%.

5-Methyl-7-(*p*-tolyl)-3-(ethoxycarbonylmethylthio)1,2,4-triazolo-[4‴,3‴:1″,6″]pyrimido[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (17)

The triazolo compound **16** (0.001 mol) and ethyl chloroacetate (0.5 mL) in ethanol (30 mL) were refluxed for 30 min. The separated solid was filtered and recrystallized from ethanol as greenish yellow crystals, mp 275°C, yield 77%. IR: 1720 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.17 (t, 3H, CH_3 ester), 2.50 (s, 3H, *p*-CH_3), 2.77 (s, 3H, CH_3), 4.08 (s, 2H, SCH_2), 4.17 (q, 2H, CH_2 ester), 7.2–9 (m, 8H, ArH). Anal. calcd. for $C_{28}H_{21}N_7O_2S_2$: C 60.96, H 3.84, N 17.77, S 11.63; found: C 59.51, H 3.89, N 17.56, S 11.80%.

Table 4. Analytical, spectral, and physical data of compounds **10a**, **10b** and **18a**, **18b**.

Comp. no.	mp, °C[a]	Color	Yield %	Mol. formula	Analysis calcd./found (%) C	H	N	S	Spectral data IR (K Br) cm^{-1}	^{1}H NMR δ (ppm) and MS, *m/z* (%)
10a	325°C	Pale yellow	74	$C_{30}H_{20}N_6OS$	70.30 70.04	3.93 4.20	16.40 13.21	6.26 6.40	(CO) 1650	^{1}H NMR (TFA-*d*) δ: 2.70 (s, 3H, *p*-CH_3), 2.90 (s, 3H, CH_3), 8.98 (s, 1H, =CH), 7.4–9.9 (m, 14H, ArH)
10b	315°C	Yellow	78	$C_{31}H_{22}N_6O_2S$	68.62 68.39	4.09 4.10	15.49 15.67	5.91 6.08	(CO) 1660	^{1}H NMR (TFA-*d*) δ: 2.70 (s, 3H, *p*-CH_3), 2.93 (s, 3H, CH_3), 4.20 (s, 3H, *p*-OCH_3), 7.1–9.8(m, 13H, ArH+ 1H, =CH)
18a	320°C	Yellow	81	$C_{31}H_{23}N_7OC$	68.74 68.48	4.28 4.40	18.10 17.89	5.92 5.78	(NH) 3250	^{1}H NMR (TFA-*d*) δ: 2.30 (s, 3H, *p*-CH_3), 2.63 (s, 3H,CH_3), 4.15 (s, 3H, *p*-OCH_3), 8.50 (s, 1H, =CH), 7.1–9.9 (m, 12H, ArH)
18b	330°C	Pale yellow	74	$C_{30}H_{20}N_8O_2S$	64.50 64.69	3.61 3.81	20.06 19.91	5.74 5.48	(NH) 3210	^{1}H NMR (TFA-*d*) δ: 2.20 (s, 3H, *p*-CH_3), 2.64 (s, 3H, CH_3), 7.7–9.8 (m, 13H, ArH + H, = CH)

[a] All products were recrystallized from ethanol.

11-(Arylidenehydrazono)-9-methyl-7-(*p*-tolyl)pyrimido-[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (18a and 18b)

The hydrazino compound **13** and each of (*a*) *p*-anisaldehyde and (*b*) *p*-nitrobenzalehyde (0.001 mol) in acetic acid (20 mL) were refluxed for 30 min. The solid product was filtered and recrystallized from ethanol. The analytical, spectral, and physical data are reported in Table 4.

5-Methyl-7-(*p*-tolyl)tetrazolo[4‴,3‴:1″,6″]pyrimido-[4″,5″:4′,5′]thieno- [3′,2′:5,6]pyrido[3,2-*c*]cinnoline (19)

Sodium nitrite (7 mL, 10%, 0.01 mol) was added dropwise to a solution of the hydrazino derivative **13** (0.002 mol) in dilute hydrochloric acid (10 mL, 50%) at 0°C and stirred for 10 min. The solid product separated and recrystallized from ethanol as pale yellow crystals, mp >360°C, yield 70%. IR: NH and NH_2 absorptions disappeared. ^{1}H NMR (TFA-*d*) δ: 2.65 (s, 3H, *p*-CH_3), 3.30 (s, 3H, CH_3), 7.4–9.95 (m, 8H, ArH). Anal. calcd. for $C_{23}H_{14}N_8S$: C 63.58, H 3,25, N 25.79, S 7.38; found: C 63.30, H 3.40, N 25.37, S 7.19%.

5-Methyl-7-(*p*-tolyl)-1,2,4-triazolo[4‴,3‴:1″,6″]pyrimido-[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-3(2*H*)-one (20)

The hydrazino compound **13** (0.001 mol) and ethyl chloroformate (0.002 mol) in acetic acid (20 mL) were refluxed for 30 min. The solid product was recrystallized from acetic acid as yellow crystals, mp 300°C, yield 66%. IR: 1725 (CO), 3400 (NH) cm^{-1}. ^{1}H NMR (TFA-*d*) δ: 2.60 (s, 3H, *p*-CH_3), 2.95 (s, 3H, CH_3), 7.45–9.8 (m, 8H, ArH). MS, *m/z* (%): 449 (M^+, 4). Anal. calcd. for $C_{24}H_{16}N_7OS$: C 24.0, H 3.28, N 21.76, S 7.12; found: C 64.20, H 3.76, N 21.58, S 6.96%.

3,5-Dimethyl-7-(*p*-tolyl)-1,2,4-triazolo[4‴,3‴:1″,6″]pyrimido-[4″,5″:4′,5′]- thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (21)

The hydrazino compound **13** (0.001 mol) and acetic anhydride (20 mL) were refluxed for 6 h. The solid product was recrystallized from acetic acid as greenish yellow crystals, mp >360°C, yield 71%. IR: NH and NH_2 absorptions disappeared. ^{1}H NMR (TFA-*d*) δ: 2.50 (s, 3H, *p*-CH_3), 2.95 (s, 3H, CH_3), 3.20 (s, 3H, CH_3 triazol), 7.2–9.7 (m, 8H, ArH). Anal. calcd. for $C_{25}H_{17}N_7S$: C 67.10, H 3.83, N 21.91, S 7.17; found: C 63.70, H 4.05, N 22.10, S 6.98%.

References

1. S. Kneubuehler, V. Carta, A. Vincengo, C. Altomare, A. Carotti, and B. Testa. Helv. Chim. Acta, **76**, 1956(1993); T. Nakao, M. Kawakami, M. Hisadome, and T. Tahara. PCT Int. Appl. WO 89 04,306, 18 May, 1989; JP Appl. 87/278,009, 2 Nov. 1987; Chem. Abstr. **111**, 214498 (1989).
2. S. Inoue, A. Yazaki, H. Mochizuki, H. Tsutsumi, M. Murata, and K. Sakane. Jpn. Kokai Tokkyo Koho, JP 06 228, 138[94, 228, 138]; Chem. Abstr. **123**, 9452 (1995); S. Inoe, J. Yoshida, M. Yokomoto, A. Yazaki, N. Hayashi, and H. Amano. Jpn. Kokai Tokkyo Koho, JP 06, 228, 138 [94, 228, 138], JP Appl. 92/22, 407; Chem. Abstr. **121**, 179602 (1994); M. Yokomoto, A. Yazaki, N. Hayashi, S. Hatono, S. Inoue, and Y. Kuramato. Eur. Pat. Appl. Ep 470, 578; JP Appl 90/211, 190; Chem. Abstr. **117**, 7943(1992); R. Fusco, L.F. Piselli, and P.M. Boschi. Eur. Pat. Appl. Ep 287, 853 IT Appl. 87/20,230; Chem. Abstr. **110**, 75540 (1989); T. Miyamoto and J. Matsumoto. Chem. Pharm. Bull. **37**, 93 (1989); **36**, 1321 (1988).
3. M. Mizutani, M. Shiroshita, M. Sasaki, H. Okuda, and N. Mito. Eur. Pat. Appl. EP 273, 325; JP Appl. 86/309, 981; Chem. Abstr. **110**, 75532 (1989).
4. G.A. Pinna, M.M. Curzu, G. Cignarella, D. Barlocco, M. D'Amico, A. Filippelli, V. DeNovellis, and F. Rossi. Eur. J. Med. Chem. **29**, 447 (1994); G. Cignarella, D. Barrlocco, S. Villa, M.M. Curzu, G.A. Pinna, A. Lavezzo, and A. Bestetti. **27**, 819 (1992); G. Cignarella, D. Barlocco, M.M. Curzu, G.A. Pinna, P. Cazzulani, M. Cassin, and B. Lumachi. Eur. J. Med. Chem. **25**, 749,(1990); G. Cignarella, D. Barlocco, G.A. Pinna, M. Loriga, M.M. Curzu, O. Toffametti, M. Germini, P. Cazzulani, and E. Cavelletti. J. Med. Chem. **32**, 2277 (1989).
5. N. Garcia-Dominguez, E. Ravina, L. Santana, C. Teran, G. Garcia-Mera, F. Orallo, M. Crespo, and J.A. Fontenla. Arch. Pharm. **321**, 735 (1988).
6. J.F. Patoiseau, J.M. Autin, J.L. Maurel, and D. Bigg. PCT Int. Appl. Wo 93/09, 098, FR Appl. 91/13,571; Chem. Abstr. **119**,

225963 (1993); E. Ravina, J. Fueyo, C. Teran, J. Cid, G. Garcia-Mera, F. Orallo, and B. Bardan. Pharmazie, **47**, 574(1992).
7. J.F. Resch. Ger. (East) DD 249, 011, Appl. 291, 515, 86; Chem. Abstr. **108**, 186758 (1988).
8. G. Doria, A.M. Isetta, M. Ferrari, and D. Trizio. Eur. Pat. Appl. Ep 277, 791, IB Appl. 87/2,288; Chem. Abstr. **109**, 231043 (1988); L.V.G. Nargund, V.V. Badiger, and S.M. Yarnal. J. Pharm. Sci. **81**, 365 (1992).
9. G. Dattolo, G. Cirrincione, A.M. Almerico, E. Aiello, and I. D'Asdia. J. Heterocycl. Chem. **23**, 1371 (1986); S. Radl, J. Moural, and R. Bendova. Collect. Czech. Chem. Commun. **55**, 1311 (1989); S.J. Bakewell, W.J. Coates, M.B. Comer, M.L. Reeves, and B.H. Warrington. Eur. J. Med. Chem. **25**, 765 (1990); G.A. Pinna, M.M. Curzu, G. Cignarella, D. Barlocco, M. Cassin, and B. Lumachi. Eur. J. Med. Chem. **25**,249 (1990); H. Sasaki, H. Tsutsumi, M. Murata, T. Terasawa, and K. Sakane. J. Org. Chem. **60**, 3928 (1995).
10. M.Z.A. Badr, G.M. El-Naggar, H.A. El-Sherief, and S.A. Mahgoub. Bull. Chem. Soc. Jpn. **57**, 1653 (1984); M.Z.A. Badr, S.A. Mahgoub, O.S. Moustafa, and F.F.A. Latif. J. Indian Chem. Soc. **67**, 216 (1990); M.Z.A.Badr, S.A. Mahgoub, F.M. Atta, and O.S. Moustafa. J. Indian Chem. Soc. **74**, 30 (1997); M.Z.A. Badr, S.A. Mahgoub, O.S. Moustafa, and A.A. Geies. Phosphorus, Sulfur Silicon Relat. Elem. **73**, 27, (1992); M.Z.A..Badr, S.A. Mahgoub, O.S. Moustafa, and A.A. Geies. Phosphorus, Sulfur Silicon Relat. Elem. **79**, 77 (1993); M.Z.A. Badr and O.S. Moustafa. Phosphorus, Sulfur Silicon Relat. Elem. **1**,127(1996).
11. K. Gewald, O. Calderon, H. Schafer, and U Hain. Liebigs Ann. Chem. 1390 (1983), and ref. 5 cited therein.
12. M.Z.A. Badr, H.A. El-Sherief, G.M. El-Naggar, and S.A. Mahgoub. J. Heterocycl. Chem. **21**, 471 (1984); K.T. Potts and C. Lovelette. J. Org. Chem. **34**, 3221 (1969); A. Amer, K. Weisz, and H. Zimmer. Heterocycles, **26**, 1853 (1987); H.Zimmer, J. McManus, T. Novinson, E.V. Hess, and A. Litwin. Arzneim.-Forsch. **20**, 1586 (1970).