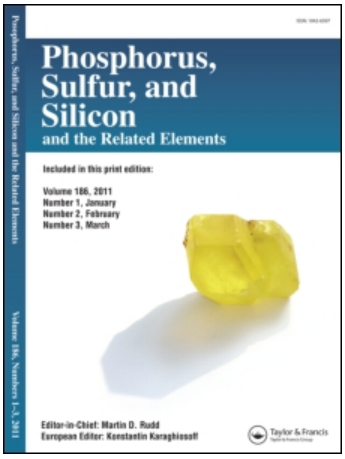

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF NEW RING SYSTEMS: ISOMERIC 1,2,4-TRIAZOLOPYRIMIDO [4",5":4',5']THIENO[3',2':5,6]PYRIDO[3,2C]CINNOLINES AND OTHER RELATED SYSTEMS

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Online publication date: 16 August 2010

To cite this Article Badr, M. Z. A. , Geies, A. A. , Abbady, M. S. and Dahy, A. A.(2004) 'SYNTHESIS OF NEW RING SYSTEMS: ISOMERIC 1,2,4-TRIAZOLOPYRIMIDO [4",5":4',5']THIENO[3',2':5,6]PYRIDO[3,2C]CINNOLINES AND OTHER RELATED SYSTEMS', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 12, 2581 — 2593
To link to this Article: DOI: 10.1080/10426500490494642
URL: http://dx.doi.org/10.1080/10426500490494642

Phosphorus, Sulfur, and Silicon, 179:2581–2593, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490494642

Taylor & Francis
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SYNTHESIS OF NEW RING SYSTEMS: ISOMERIC 1,2,4-TRIAZOLOPYRIMIDO [4″,5″:4′,5′]THIENO[3′,2′:5,6]PYRIDO[3,2-C]CINNOLINES AND OTHER RELATED SYSTEMS

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(Received October 29, 2002; accepted May 21, 2004)

*3-Amino-2-Cyano-4-(*p*-tolyl)thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline* ***1*** *underwent ring closures with formamide and carbon disulphide to afford pyrimidothienopyridocinnaline* ***2*** *and its pyrimido-9,11-thione derivative* ***3****, respectively. Treatment of* ***1*** *with triethylorthoformate followed by hydrazine hydrate produced 10-amino-11-imino-pyrimido system* ***5****, which in turn reacted with triethylorthoformate, acetic acid, carbon disulphide, and acetylacetone to cyclize into the systems, 1,2,4-triazolo, 2-methyltriazolo, triazolo-2-thione, and 1,2,4-triazepinopyrimido thienopyridocinnolines* ***6–8****,* ***11****, respectively. Similarly, 3-amino-2-carboxamido-thienopyridocinnoline* ***12*** *was reacted with triethylorthoformate to give pyrimidothienopyridocinnoline-11-one* ***13****, which was treated with phosphorous oxychloride and then hydrazine hydrate to produce 11-hydrazinopyrimido system* ***16****. Treatment of* ***16*** *with triethylorthoformate, acetic anhydride, carbon disulphide, and ethyl chloroformate afforded the systems, 1,2,4-triazolopyrimidothienopyrido-cinnoline derivatives* ***16–18****,* ***20****, respectively.*

INTRODUCTION

During last few years many cinnoline derivatives have attracted considerable attention because of their various pharmacological activities such as antihypertensive,[1] antithrombotic,[2] anti-inflammatory,[3] bronchodilators,[4] immunostimulants,[5] cardiovascular agents,[6]

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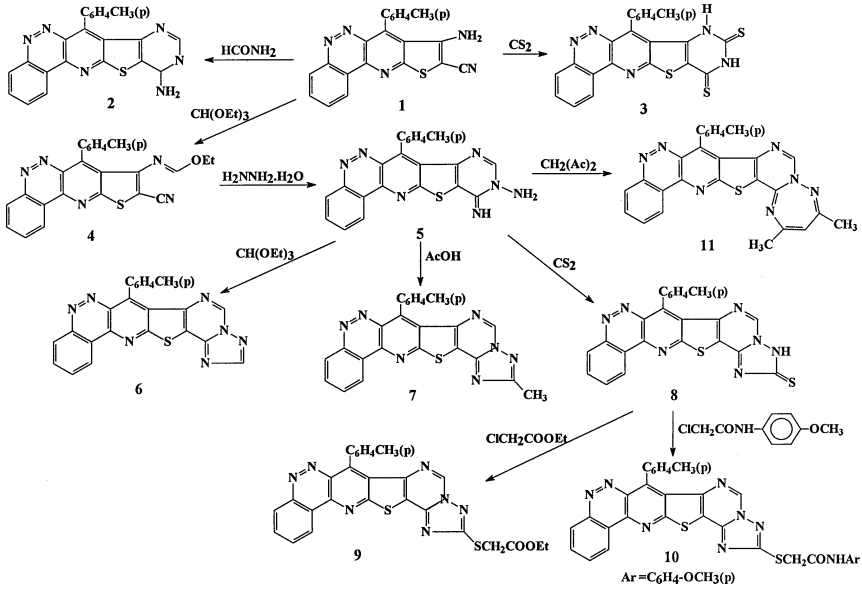
anxiolytics to activate brain functions,[7] and antileukemic activity.[8] Similarly, they showed antibacterial, antifungal, and microbicidal activities,[9] as well as some other activities. We have reported several research programs concerning the synthesis of novel fused S, N-heterocycles.[10] The present article deals with methods leading to a new series of linear and angular tetra-, penta-, and hexaheterocyclic systems of promising biological properties derived from the parent system thienopyridocinnolines.

RESULTS AND DISCUSSION

An approach to ring closure reactions leading to target compounds started from treatment of 3-cyano-4-(*p*-tolyl) pyrido [3,2-*c*] cinnolin-2(1*H*) thione[11] with chloroacetonitrile in ethanolic sodium ethoxide solution to produce 3-amino-2-cyano-4-(*p*-tolyl) thieno [3′,2′:5,6] pyrido[3,2-*c*] cinnoline **1**. The latter was successfully used as a strategic starting material for synthesis of novel target polyheterocyclic systems. Ring closure reactions of **1** by heating with formamide gave the pentacyclic product 11-amino-7-(*p*-tolyl) pyrimido [4″,5″,:4′,5′] thieno [3′,2′, -5,6] pyrido [3,2-*c*] cinnoline **2**. Refluxing **1** with carbon disulphide in dry pyridine produced the corresponding pyrimidothienopyridocinnoline-9(8*H*), 11(10*H*)-dithione **3**. Treatment of **1** with triethylorthoformate in acetic acid produced the corresponding 3-ethoxymethyleneamino derivative **4**, which underwent ring closure on refluxing with hydrazine hydrate to produce 10-amino-7-(*p*-tolyl) pyrimido[4″,5″:4′,5]thieno [3′,2′:5,6]pyrido[3,2-*c*]cinnoline-11-imine **5**. Treatment of **5** with triethylorthoformate in acetic acid produced 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 **6**, while refluxing **5** with acetic acid produced the corresponding 2-methyl-1,2,4-triazolo derivative **7**. Interaction of **5** with carbon disulphide in pyridine produced 1,2,4-triazolopyrimidothienopyridocinnolin-2(*3H*)-thione **8**. The latter compound was interacted separately with ethyl chloroacetate and chloroacetaniside with anhydrous sodium acetate in ethanol to give 2-ethoxycarbonylmethylthio derivative **9** and 2-*p*-anisilidomethylthio derivative **10**, respectively. Condensation of **5** with acetylacetone in ethanol produced 12,14-dimethyl-7(*p*-tolyl)-1,2,4-triazepino[6‴,7‴:1″,6″]pyrimido[4″,5″:4′,5′]thieno [3′,2′:5,6] pyrido[3,2-*c*]cinnoline **11** (Scheme 1).

On the other hand, treatment of 3-cyano-4-(*p*-tolyl) pyrido [3,2-*c*] cinnolin-2(1*H*)-thione[11] with chloroacetamide in ethanolic sodium ethoxide solution produced 3-amino-4-(*p*-tolyl) thieno[3′,2′:5,6]pyrido [3,2-*c*] cinnolin-2-carboxamide **12**, which was successfully used as



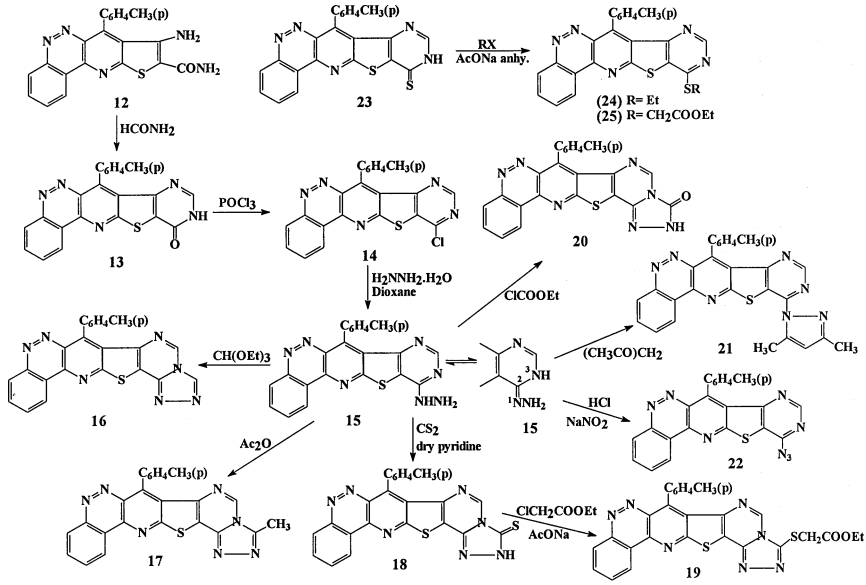
SCHEME 1

starting material for synthesis of other new heterocyclic ring systems. Ring closure reaction of **12** by heating with triethylorthoformate in glacial acetic acid gave 7-(*p*-tolyl) pyrimido [4″,5″:4′,5′] thieno[3′,2′:5,6]pyrido[3,2-*c*] cinnolin-11(10*H*)-one **13**, which on treatment with phosphorus oxychloride gave the corresponding 11-chloropyrimidine derivative **14**. The chlorine group of **14** underwent nucleophilic displacement by refluxing with hydrazine hydrate in dioxane to produce the corresponding product 11-hydrazinopyrimidothienopyridocinnoline **15**.

The hydrazino compound **15**, containing an active nitrogen nucleophile, was used as a strategic starting material that on treatment with carbonyl, thionyl, and other electrophilic reagents resulted in ring closure reactions to form the target novel series of hexaheterocyclic systems. Annelation of **15** into an *s*-triazolo moiety points to high nucleophilicity of the *N*-3 atom of the hydrazone tautomer **15′** as observed with other comparable systems.[12]

Thus, treatment of **15** with triethylorthoformate in acetic acid afforded 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 **16**. The reaction of **15** with acetic anhydride produced the corresponding 3-methyltriazolo derivative **17**. Interaction of **15** with carbon disulphide in dry pyridine produced

triazolopyrimidothieno-pyridocinnolin-3(2*H*)-thione **18**, which in turn interacted with ethyl chloroacetate to give the corresponding 3-ethoxycarbonylmethylthio derivative **19**. Condensation of **15** with ethyl chloroformate led to the formation of the corresponding triazolo-3(2*H*)-one **20**. On the other hand, heating **15** with acetylacetone produced 11-(3,5-dimethylpyrazolyl) pyrimido derivative **21**, while treatment of **15** with nitrous acid produced only the 11-azidopyrimido derivative **22**. On the other hand, thionation of **13** on treatment with phosphorus pentasulphide produced pyrimidothienopyridocinnolin-11(10*H*)-thioine **23**, which in turn was alkylated with ethyl iodide and ethyl chloroacetate to produce 11-ethylthio derivative **24** and 11-ethoxycarbonylmethylthio derivative **25**, respectively (Scheme 2).



SCHEME 2

BIOLOGICAL ACTIVITY

Twelve compounds were selected and screened in vitro for their antimicrobial activity against three strains of bacteria (*Serratia marcescens, Staphyococcus aureus, Bacillus cereus*) using filter paper disc method.[13] The biological activity, as expressed by the growth of the inhibition zones of the tested microorganism, are summarized in Table I.

TABLE I The Antimicrobial Activity of Selected Compounds

Compd. no	*S. marcescens*	*S. aureus*	*B. cereus*
2	—	—	11
3	12	13	—
6	9	—	—
8	10	—	15
9	12	—	13
10	11	9	—
11	—	9	—
14	—	12	—
18	12	—	15
19	14	—	13
24	12	—	9
25	15	—	14

EXPERIMENTAL

All melting points are uncorrected and were determined on an electric melting point (GallenKamp) apparatus. IR spectra were 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 appropiate solvent [$CDCl_3$, dimethylsulfoxide (DMSO)-d_6 and deuterated trifluoroacetic acid (TFA-d) using tetramethylsilane (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 GCMS-QP 1000 EX spectrometer at an ionizing potential of 70 ev. Elemental analyses were carried out using a 240 C Perkin Elmer analyzer.

3-Amino-2-cyano-4-(*p*-tolyl)thieno[3′,2′:5,6]pyrido[3,2-*c*]-cinnoline (1)

A mixture of 3-cyano-4(*p*-tolyl)pyrido[3,2-*c*]cinnolin-2(1*H*)-thione[11] (0.01 mol) and α-chloroacetonitrile (0.01 mol) in ethanol (50 ml) and anhydrous sodium acetate (2 g) was refluxed for 1 h. The solid product was separated while hot and was filtered, washed with water, and recrystallized from acetic acid as red crystals, m.p. 250°C, yield (80%). IR, 3450,3300 (NH_2), 2200 (CN) cm^{-1}. ^{1}H NMR (DMSO-d_6) $\delta = 2.50$ (s, 3H, *p*-CH_3), 5.80 (s, 2H, NH_2), 7.5–9.1 (m, 8H, ArH). Anal. Calcd for $C_{21}C_{13}N_5S$: C, 68.65; H, 3.57, N, 19.06; S, 8.73. Found: C, 68.46; H, 3.78; N, 18.94; S, 8.85.

11-Amino-7-(*p*-tolyl)pyrido[4″,5″,4′,5′]thieno[3′,2′:5,6]-pyrido[3,2-*c*]cinnoline (2)

A mixture of **1** (0.001 mol) and formamide (10 ml) was refluxed for 2 h. The solid, which separated on cooling, was filtered and recrystallized from ethanol as green crystals, m.p. > 360°C, yield (75%). IR, 3450, 3350 (NH_2) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.70$ (s, 3H, *p*-CH_3), 7.6–9.9 (m, 9H, ArH). Anal. Calcd. for $C_{22}H_{14}N_6S$: C, 66.99; H, 3.58; N, 21,31; S,8.13. Found: C, 67.12; H, 3.70; N, 21.26; S, 8.32.

7-(p-Tolyl)pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-9(8*H*), 11(10*H*)-dithione (3)

A mixture of **1** (0.001 mol) and carbon disulphide (4 ml) in dry pyridine (20 ml) was refluxed on a water bath for 10 h. The solid product was filtered and recrystallized from dioxane as orange crystals, m.p. > 360°C, yield (90%). IR, 3350 (NH), 1260 (CS), 1210 (CS) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.70$ (s, 3H, *p*-CH_3), 7.5–9.85 (m, 8H, ArH). MS; m/z (%), 445 (28.3), 444 (100), 443 (M^+, 92.2), 442 (22.9), 429 (39.4), 428 (43.4), 376 (15.3), 213 (18.6). Anal. Calcd. for $C_{22}H_{13}N_5S_3$: C, 59.57; H, 2.95; N, 15.79; S, 21.69. Found: C, 59.71; H, 3.08; N, 15.64; S, 21.86.

2-Cyano-3-(ethoxymethyleneamino)thieno[3′,2′:5,6]-pyrido[3,2,-*c*]cinnoline (4)

A mixture of **1** (0.001 mol) and triethylorthoformate (10 ml) in acetic acid (2 ml) was refluxed for 2 h. The solid product was filtered and recrystallized from ethanol as brown crystals, m.p. 205°C, yield (90%). IR, 2200 (CN), 1623 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) $\delta = 1.20$ (t, 3H, CH_3), 2.60 (s, 3H, *p*-CH_3), 3.65 (q, 2H, CH_2), 7.4–9.2 (m, 8H, ArH), 8.05 (s, 1H, =CH–O). Anal. Calcd. for $C_{24}H_{17}N_5OS$; C, 68.06; H, 4.05; N, 16.54; S, 7.57. Found: C, 68.20; H, 4.22; N, 16.39; S, 7.66.

10-Amino-7-(*p*-tolyl)pyrimido[4′,5′:4′,5′]thieno[3′,2′:5,6]-pyrido[3,2-*c*]cinnoline-11-imine (5)

Hydrazine hydrate (0.5 ml, 0.01 mol) was added dropwise to a solution of **4** (0.001 mol) in dioxane (40 ml) and stirred for 1 h. The precipitate was filtered and recrystallized from dioxane as yellow crystals, m.p. 340°C, yield (80%). IR, 3300 (NH_2), 3190 (NH), 1630 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.50$ (s, 3H, *p*-CH_3), 8.70 (s, 1H, CH, pyrimido), 7.3–9.8 (m, 8H, ArH). Anal. Calcd. for $C_{22}H_{15}N_7S$; C, 64.53; H, 3.69; N, 23.95; S, 7.83. Found: C, 64.62; H, 3.76; 23.86; S, 7.90.

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

A mixture of **5** (0.001 mol) and triethylorthoformate (10 ml) in acetic acid (20 ml) was refluxed for 5 h. The precipitate was filtered and recrystallized from acetic acid as yellow crystals, m.p. > 360°C, yield (70%). IR, 1605 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.65$ (s, 3H, *p*-CH_3), 7.0–9.9 (m, 8H, ArH), 9.25 (s, 1H, CH, triazolo), 9.70 (s, 1H, CH, pyrimido). Anal. Calcd. for $C_{23}H_{13}N_7S$: C, 65.86; H, 3.12; N 23.38; S, 7.64. Found: C, 65, 78; H, 3.25; N, 23.30; S, 7.72.

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

A mixture of **5** (0.001 mol) and acetic acid (20 ml) was refluxed for 5 h. The precipitate was filtered and recrystallized from acetic acid as green crystals, m.p. > 360°C, yield (76%), IR, 1610 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.65$ (s, 3H, *p*-CH_3), 3.00 (s, 3H, CH_3, triazolo), 7.5–9.9 (m, 8H, ArH), 9.60 (s, 1H, CH, pyrimido). Anal. Calcd. for $C_{24}H_{15}N_7S$: C, 66.50; H, 3.49; N, 22.62; S, 7.40. Found: C, 66.58; H, 3.59; N, 22.68; S, 7.49.

7-(*p*-Tolyl)-1,2,4-triazolo[2‴,3‴:1″,6″]pyrimido[4″,5″:4′,5′]-thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-2(3*H*)-thione (8)

A mixture of **5** (0.001 mol), carbon disulphide (3 ml) and dry pyridine (20 ml) was refluxed for 8 h. The precipitate was filtered and recrystallized from pyridine as yellow crystals, m.p. > 360°C, yield (65%). IR, 3250 (NH), 1250 (CS), 1635 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.68$ (s, 3H, *p*-CH_3), 7.5–9.85 (m, 9H, 8H, ArH + 1H, CH, pyrimido). Anal. Calcd. for $C_{23}H_{13}N_7S_2$: C, 61.18; H, 2.90; N, 21.72; S, 14.20. Found: C, 61.26; H, 3.03; N, 21.66; S, 14.32.

7-(*p*-Tolyl)-2-(ethoxycarbonylmethylthio)-1,2,4-triazolo-[2‴,3‴:1″,6″]pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido-[3,2-*c*]cinnoline (9)

A mixture of **8** (0.001 mol) and ethyl chloroformate (0.5 ml) in ethanol (40 ml) and anhydrous sodium acetate (2 g) was refluxed for 1 h and concentrated. The precipitate was filtered and recrystallized from ethanol as yellow crystals, m.p. 255°C, yield (67%). IR, 1720 (CO), 1605 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) $\delta = 1.25$ (t, 3H, CH_3), 2.35 (s, 3H, *p*-CH_3), 4.10 (s, 2H, SCH_2), 4.20 (q, 2H, CH_2), 7.1–9.2 (m, 8H, ArH), 7.70 (s, 1H, CH,

pyrimido). Anal. Calcd. for $C_{27}H_{19}N_7O_2S_2$: C, 60.32; H, 3.56; N, 18.24; S, 11.93. Found; C, 60.39; H, 3.68; N, 18.38; S, 12.04.

7-(*p*-Tolyl)-1,2,4-triazolo[2‴,3‴:1″,6″]pyrimido[4″,5″:4′,5′]-thieno[3′,2′:5,6]pyrido 3,2-*c*]cinnolin-2-*N*-(*p*-methoxyphenyl)thioacetamide (10)

A mixture of **8** (0.001 mol) and *p*-methoxychloroacetanilide (0.002 mol) in ethanol (40 ml) and anhydrous sodium acetate (2 g) was refluxed for 1 h. The precipitate was filtered and recrystallized from ethanol as yellow crystals, m.p. 340°C, yield (70%). IR, 3200 (NH), 1685 (CO), 1618 (C=N), 1030 (—OCH_3) cm^{-1}. ^{1}H NMR (TFA-d) $\delta = 2.52$ (s, 3H, *p*-CH_3), 2.82 (s, 3H, *p*-OCH_3), 4.38 (s, 2H, SCH_2), 7.3–9.7 (m, 13H, 12H, ArH + 1H, CH, pyrimido). Anal. Calcd. for $C_{32}H_{22}N_8O_2S_2$: C, 62.52; H, 3.61; N, 18.23; S, 10.43. Found: C, 62.63; H, 3.73; N, 18.30; S, 10.36.

12,14-Dimethyl-7-(*p*-tolyl)-1,2,4-triazepino[3‴,2‴:1″,6″]-pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]-cinnoline (11)

A mixture of **5** (0.001 mol) and acetylacetone (0.5 ml) in ethanol (30 ml) was refluxed for 8 h. The precipitate was filtered and recrystallized from ethanol as brown crystals, m.p. 350°C, yield (65%). IR, 1605 (C=N), 1540 (C=N) cm^{-1}. ^{1}H NMR (TFA-d) $\delta = 2.55$ and 2.90 (2d, 6H, $2CH_3$), 2.60 (s, 3H, *p*-CH_3), 6.50 (s, 1H, CH, triazepino), 7.5–9.9 (m, 8H, ArH), 9.55 (s, 1H, CH, pyrimido). MS; m/z (%), 475 (32.3), 474 (100), 473 (M^+, 90.4), 472 (19.4), 460 (20), 459 (50.7), 458 (47.8), 434 (44.6), 433 (46.8), 432 (24.7), 420 (27.2), 419 (82.4), 418 (82.5), 213 (18.6). Anal. Calcd. for $C_{27}H_{19}H_7S$: C, 68.48; H, 4.04; N, 20.71; S, 6.77. Found: C, 68.56; H, 4.18; N, 20.66; S, 6.82.

3-Amino-4-(*p*-tolyl)thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-2-carboxamide (12)

Compound 12 was prepared by heating 3-cyano-4-(*p*-tolyl) pyrido[3,2-*c*] cinnolin-2-thioacetamide (0.01 mol) in ethanol (50 ml) and sodium ethoxide (2 ml) at reflux for 1 h. The solid product was filtered and recrystallized from ethanol as red crystals, m.p. 270°C, yield (75%). IR, 3450, 3300 (NH_2),1650 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6) $\delta = 3.30$ (s, 3H, *p*-CH_3), 6.10 (s, 2H, NH_2), 7.40 (s, 2H, NH_2), 7.4–9.1 (m, 8H, ArH). MS; m/z(%), 386 (58.4), 385 (M^+, 69.7), 384 (11.2), 369 (19.7), 368 (29.7), 367 (27.9), 353 (35.8), 352 (17.5), 342 (24.3), 341 (70.2), 340 (100), 339 (34.1), 328 (21.5), 327 (23), 326 (35.3), 325 (45), 296 (16.1), 295 (21.5). Anal.

Calcd. for $C_{21}H_{15}N_5OS$: C, 65.42; H, 3.95; N, 18.17; S, 8.32. Found: C, 65.50; H, 4.03; N, 18.23; S, 8.26.

7-(*p*-Tolyl)pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-11(10*H*)-one (13)

A mixture of **12** (0.01 mol), triethylorthoformate (20 ml) and glacial acetic acid (2 ml) was refluxed for 2 h. The precipitate was filtered and recrystallized from dioxane as green crystals, m.p. > 360°C, yield (75%). IR, 3300 (NH), 1680 (CO) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.60$ (s, 3H, *p*-CH_3), 7.6–9.85 (m, 8H, ArH), 9.30 (s, 1H, CH, pyrimido). MS; m/z(%), 397(32.2), 396 (82.3), 395 (M^+, 72.3), 394(39), 382(27), 381(62.3), 380 (100). Anal. Calcd. for $C_{22}H_{13}N_5OS$: C, 66.82; H, 3.31; N, 17.71; S, 8.11. Found: C, 66.90; H, 3.45; N, 17.66; S, 8.20.

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

A mixture of **13** (0.001 mol) and phosphorous oxychloride (40 ml) was refluxed for 4 h. The precipitate from ice/water was filtered, washed with water, and recrystallized from dioxane as brown crystals, m.p. 295°C, yield (83%). IR, 1580 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.80$ (s, 3H, *p*-CH_3), 7.6–9.80 (m, 8H, ArH), 9.32 (s, 1H, CH, pyrimido). Anal. Calcd. for $C_{22}H_{12}N_5SCl$: C, 63.84; H, 2.92; N 16.92; S, 7.75; Cl, 8.57. Found: C, 63.95; H, 3.03; N, 16.85; S, 7.81; Cl, 8.65.

11-Hydrazino-7-(*p*-tolyl)pyrimido[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (15)

A mixture of **14** (0.01 mol) and hydrazine hydrate (0.01 mol) in dioxane (30 ml) was refluxed for 30 min. The precipitate was filtered and recrystallized from dioxane as greenish-yellow crystals, m.p. 328°C, yield (87%). IR, 3350, 3220 (NH_2), 3200 (NH) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.65$ (s, 3H, *p*-CH_3), 7.6–9.9 (m, 9H, 8H, ArH+1H,CH, pyrimido). Anal. Calcd. for $C_{23}H_{13}N_7S$: C, 65.86; H, 3.12; N, 23.83; S, 7.64. Found: C, 65.92; H, 3,25; N, 23.76; S, 7.72.

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 (16)

A mixture of hydrazino compound **15** (0.001 mol), triethylorthoformate (5 ml) and acetic acid (0.01 mol) was refluxed for 6 h. The precipitate was filtered and recrystallized from acetic acid as greenish-yellow-crystals,

m.p. > 360°C, yield (80%). IR, 1595 (C=N) cm^{-1}. ^1H NMR (TFA-d) δ = 2.50 (s, 3H, *p*-CH_3), 8.70 (s, 1H, CH, triazolo), 7.5–9.95 (m, 8H, ArH), 9.66 (s, 1H, CH, pyrimido). MS; m/z(%), 421 (27.5), 420 (75.2), 419 (M^+, 45.6), 418 (47.7), 406 (45.6), 405 (100), 404 (81.2), 183 (20.1), 182 (16.1), 67 (20.8). Anal. Calcd. for $C_{23}H_{13}N_7S$: C, 65.86; H, 3.12; N, 23.38; S, 7.64. Found: C, 65.94; H, 3.25; N, 23.29; S, 7.71.

3-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 (17)

A mixture of **15** (0.001 mol) and acetic anhydride (20 ml) was refluxed for 6 h. The solid product was filtered and recrystallized from acetic acid as greenish-yellow crystals, m.p. > 360°C, yield (78%). IR, 1600(C=N) cm^{-1}. ^1H NMR (TFA-d) δ = 2.65 (s, 3H, *p*-CH_3), 3.22 (s, 3H, CH_3), 9.35 (s, 1H, CH, pyrimido), 7.47–9.9 (m, 8H, ArH). Anal. Calcd. for $C_{24}H_{15}N_7S$: C, 66.50; H, 3.49; N, 22.62; S, 7.40. Found: C, 66.57; H, 3.56; N, 22.54; S, 7.46.

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(2H)-thione (18)

A mixture of **15** (0.001 mol), carbon disulphide (2 ml) and dry pyridine (20 ml) was refluxed on water bath for 8 h. The precipitate was filtered and recrystallized from pyridine as golden crystals, m.p. > 360°C, yield (80%). IR, 3500 (NH), 2700(SH), 1280 (CS) cm^{-1}. ^1H NMR (TFA-d) δ = 2.70 (s, 3H, *p*-CH_3), 7.5–9.85 (m, 9H, 8H, ArH + 1H, CH, pyrimido). Anal. Calcd. for $C_{23}H_{13}N_7S_2$: C, 61.18; H, 2.90; N, 21.72; S, 14.20. Found: C, 61.23; H, 2.98; N, 21.66; S, 14.28.

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 (19)

A mixture of **18** (0.001 mol), ethyl chloroacetate (0.5 ml) in ethanol (30 ml) and anhydrous sodium acetate (2 g) was refluxed for 30 min. The solid product was filtered and recrystallized from ethanol as yellow crystals, m.p. 300°C, yield (85%). IR, 1720 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ = 1.25 (t, 3H, CH_3), 2.35 (s, 3H, *p*-CH_3), 4.28 (s, 2H, SCH_2), 4.42 (q, 2H, CH_2), 7.2–9.3 (m, 8H, ArH), 7.60 (s, 1H, CH, pyrimido). MS; m/z(%), 538 (18); 537 (M^+, 45.8), 522(29.5), 420 (35.2), 419 (100), 418(87), 405(19.7), 404(23.1), 403 (20.3) 365 (19.1). Anal. Calcd. for $C_{27}H_{19}N_7O_2S_2$: C,

60.32; H, 3.56; N, 18.24; S, 11.93. Found: C, 60.39; H, 3.64; N, 18.19; S, 11.98.

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)

A mixture of **15** (0.001 mol), ethyl chloroformate (0.002 mol) and dry pyridine (20 ml) was refluxed for 30 min. The precipitate was filtered and recrystallized from acetic acid as yellow crystals, m.p. > 360°C, yield (70%). IR, 3200 (NH), 1700 (CO) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.50$ (s, 3H, *p*-CH_3), 7.5–9.9 (m, 8H, ArH), 8.90 (s, 1H, CH, pyrimido). Anal. Calcd. for $C_{23}H_{13}N_7OS$: C, 63.44; H, 3.01; N, 22.52; S, 7.36. Found: C, 63.50; H, 3.10; N, 22.46; S, 7.41.

7-(*p*-Tolyl)-11-(3,5-dimethylpyrazolyl)pyrimido-[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido [3,2-*c*]cinnoline (21)

A mixture of **15** (0.001 mol) and acetylacetone (0.005 mol) in ethanol (40 ml) was refluxed for 6 h. The precipitate was filtered while hot and recrystallized from ethanol as orange crystals, m.p. 327°C, yield (82%). IR, 1590 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.40$ (s, 3H, CH_3), 2.70 (s, 3H, CH_3) 2.89 (s, 3H, *p*-CH_3), 6.50 (s, 1H, CH, pyrazolo), 7.7–9.9 (m, 8H, ArH), 9.20 (s, 1H, CH, pyrimido). MS; m/z (%), 475 (20.6), 474 (47.5), 473 (M^+, 100), 472 (46), 459 (33.8), 458 (54.4), 437 (22.4), 436 (17.5), 77 (14.1). Anal. Calcd. for $C_{27}H_{19}N_7S$: C, 68.48; H, 4.04; N, 20.71; S, 6.77. Found: C, 68.54; H, 4.11; N, 20.66; S, 6.85.

11-Azido-7-(*p*-tolyl)pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]-pyrido[3,2-*c*]cinnoline (22)

Sodium nitrite solution (7 ml, 10%, 0.01 mol) was added dropwize to a solution of hydrazino compound **15** (0.002 mol) in dilute HCl (10 ml, 50%) at 0°C during 10 min with stirring. The precipitate was filtered and recrystallized from ethanol as green crystals, m.p. 280°C (dec), yield (70%). IR, 2130(N_3)cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.67$ (s, 3H, *p*-CH_3), 7.55–9.0 (m, 8H, ArH), 9.20 (s, 1H, CH, pyrimido). Anal. Calcd. for $C_{22}H_{12}N_8S$: C, 62.84; H, 2.88; N, 26.65; S, 7.63. Found: C, 62.79; H, 2.97; N, 26.59; S, 7.69.

7-(*p*-Tolyl)pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnolin-11(10*H*)-thione (23)

A mixture of pyrimidone **13** (0.001 mol) and phosphorous pentasulphide (0.0012 mol) in dry pyridine (15 ml) was refluxed for 4 h and poured on

ice/water. The precipitate was filtered, washed with water, and recrystallized from acetic acid as brown crystals, m.p. > 360°C, yield (80%). IR, 3200 (NH), 1280 (CS), 1630 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 2.61$ (s, 3H, *p*-CH_3), 9.40 (s, 1H, CH, pyrimido), 7.68–9.86 (m, 8H, ArH). Anal. Calcd for, $C_{22}H_{13}N_5S_2$: C, 64.21; H, 3.18; N, 17.02; S, 15.58. Found: C, 64.27; H, 3.26; N, 17.08; S, 15.63.

7-(*p*-Tolyl)-11-(ethylthio)pyrimido[4″,5″:4′,5′]thieno-[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (24)

A mixture of **23** (0.001 mol), iodoethane (0.05 ml) in ethanol (20 ml) and anhydrous sodium acetate (1.5 g) was refluxed for 1 h. The precipitate was filtered and recrystallized from ethanol as yellow crystals, m.p. 280°C, yield (70%). IR, 1520 (C=N) cm^{-1}. ^1H NMR (TFA-d) $\delta = 1.65$ (t, 3H, CH_3), 2.50 (s, 3H, *p*-CH_3), 3.80 (q, 2H, CH_2), 7.7–9.8 (m, 8H, ArH), 9.10 (s, 1H, CH, pyrimido). Anal. Calcd. for $C_{24}H_{17}N_5S_2$: 65.58, H, 3.90; N, 15.93; S, 14.59. Found: C, 65.63; H, 3.98; N, 15.88; S, 14.66.

7-(*p*-Tolyl)-11-(ethoxycarbonylmethylthio)pyrimido-[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[3,2-*c*]cinnoline (25)

A mixture of **23** (0.001 mol), ethyl chloroacetate (0.25 ml) in ethanol (20 ml), and anhydrous sodium acetate (2 g) was refluxed for 1 h. The precipitate was filtered and recrystallized from ethanol as yellow crystals, m.p. 185°C, yield (85%). IR, 1720 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) $\delta = 1.35$ (t, 3H, CH_3), 2.50 (s, 3H, *p*-CH_3), 4.19 (q, 2H, CH_2), 4.20 (s, 2H, SCH_2), 7.2–9.25 (m, 9H, 8H, ArH + 1H, CH, pyrimido). Anal. Calcd. for, $C_{26}H_{19}N_5O_2S_2$: C, 62.76; H, 3.85; N, 14.08; S, 12.89. Found: C, 62.82; H, 3.92; N, 14.13; S, 12.83.

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