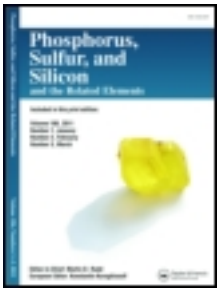

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Utility of Nitriles in Synthesis of Pyrido[2,3-d]pyrimidines, Thiazolo[3,2-a]pyridines, Pyrano[2,3-b]benzopyrrole, and Pyrido[2,3-d]benzopyrroles

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Version of record first published: 25 Sep 2007.

To cite this article: M. R. Mahmoud , E. A. A. El-Bordany , N. F. Hassan & F. S. M. Abu El-Azm (2007): Utility of Nitriles in Synthesis of Pyrido[2,3-d]pyrimidines, Thiazolo[3,2-a]pyridines, Pyrano[2,3-b]benzopyrrole, and Pyrido[2,3-d]benzopyrroles, Phosphorus, Sulfur, and Silicon and the Related Elements, 182:11, 2507-2521

To link to this article: http://dx.doi.org/10.1080/10426500701506465

Phosphorus, Sulfur, and Silicon, 182:2507–2521, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701506465

Utility of Nitriles in Synthesis of Pyrido[2,3-d]pyrimidines, Thiazolo[3,2-a]pyridines, Pyrano[2,3-b]benzopyrrole, and Pyrido[2,3-d]benzopyrroles

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*3-Aryl-2-cyanoacrylonitriles (**1a**,**b**) reacted with 6-aminothiouracil, 2-ethoxy carbonylmethyl-4-oxo-Δ^2-thiazoline, 2-cyanomethyl-4-oxo-Δ^2-thiazoline and indan-2-one to give pyrido[2,3-d]pyrimidines, thiazolo[3,2-a]pyridines, pyrano [2,3-b]benzopyrrole and pyrido[2,3-b]benzopyrrole, respectively. The IR, MS and ^{1}H-NMR of the synthesized compounds were discussed. The antimicrobial activity of some of the synthesized compounds was tested.*

Keywords Pyrido[2,3-d]pyrimidines; thiazolopyridines; pyrano-; pyridobenzopyrroles; antimicrobial activity

INTRODUCTION

Pyrido[2,3-d]pyrimidines standout for their antitumer,[1] anticonvulsive,[2] antiasthmatic, antiallergic,[3] anthihypertensive,[4] and useful as diuretic compound.[5–9] Previously, we have reported several new synthesis of fused heterocyclic compounds utilizing laboratory available activated nitrile derivatives as starting materials.[10–20] In the present article, we report on the utility of the substituted acrylonitriles for synthesis of several pyrido[2,3-d]pyrimidine, thiazolo[3,2-a]pyridines with the aim of finding new chemotherapeutic agents.

RESULTS AND DISCUSSION

The reaction of 3-aryl-2-cyanoacrylonitrile **1a**,**b** with 6-aminothiouracil **2** in ethanol in the presence of catalytic amount of piperidine

Received February 10, 2007; accepted March 4, 2007.
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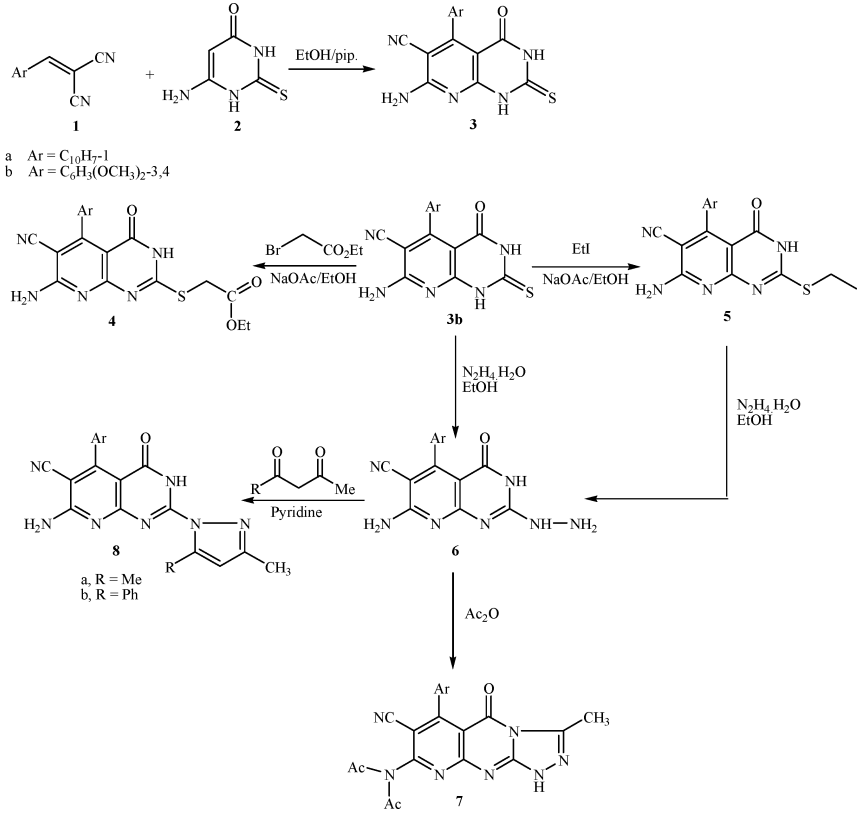
afforded the 1:1 adduct, the structure of the adduct was established as pyrido[2,3-d]pyrimidine derivative **3** rather than pyrano[2,3-d]pyrimidine or thiazino[3,2-a]pyrimidine on the basis of spectroscopic data which revealed a pattern completely in accord with structure **3**. Thus, the IR spectrum shows the stretching absorption bands characteristic for NH_2, C=N, C=O and C=S groups at 3378, 3220, 3113, 2206, 1687, 1640, and 1128 cm^{-1}, respectively, which in accord with the proposed structure **3**. Furthermore, ^{1}H-NMR spectrum of **3b** revealed two signals at δ 12.7 (s, 1H, NH, exchangeable with D_2O) and 12.2 (s, 1H, NH, exchangeable with D_2O) characteristic for -NH-CS-NH- group **(c.f. Exp.)**. Alkylation of **3b** using ethylbromoacetate or ethyl iodide in ethanol containing anhydrous sodium acetate gave the S-alkylated products **4** and **5**, respectively. The reaction of **3b** with hydrazine hydrate in boiling ethanol yielded the Sulfur-free compound **6** which also obtained upon treatment of the S-alkylated product **5** with hydrazine hydrate. The hydrazino derivative **6** was used as the key intermediate for the synthesis of polyheterocyclic compounds. Treatment of compound **6** with freshly distilled acetic anhydride afforded the pyridotriazolopyrimidine derivative **7**. When a solution of **6** in dilute hydrochloric acid was refluxed with 2,4-pentadione and/or 1-phenylbut-1,3-dione in pyridine afforded pyrazol-1-ylpyridopyrimidine derivatives **8a** and **8b**, respectively (Scheme 1).

The reaction of **1a** with 2-ethoxy carbonylmethyl-4-oxo-Δ^2-thiazoline **9a** in absolute ethanol in the presence of piperidine afforded the adduct thiazolo[3,2-a]pyridine **10a**. Treatment of **10a** with triethylorthoformate yielded thiazolo[3,2-a]pyridine derivative **11**. The reaction of **11** with benzylamine results in the formation of the thiazolopyridine derivative **12**. The reaction of 2-cyanomethyl-4-oxo-Δ^2-thiazoline **9b** with **1a** in ethanol in the presence of catalytic amount of piperidine resulted in the formation of thiazolo[3,2-a]pyridine derivative **10b** (Scheme 2).

The carbanion derived from indan-2-one in absolute ethanol upon treatment with piperidine reacts with **1a** to afford 3-arylidene indan-2-one **13a** (ethanol insoluble fraction) and pyrano[2,3-b]benzopyrrole **14** (ethanol soluble fraction). It is worthy to mention that **13a** could be obtained from the reaction of indan-2-one with 1-naphthaldehyde in boiling ethanol and pyrano benzopyrrole **14** prepared upon treatment of **13a** with malononitrile in refluxing ethanol in the presence of piperidine. Similarly, the reaction of 2-bromobenzaldehyde with indanone under the same conditions yielded the 3-(2-bromobenzylidene)indan-2-one **13b**. Compound **13b** when fused with malononitrile in the presence of ammonium acetate at 190–200°C afforded pyrido[2,3-b]benzopyrrole **15**. Hydrazinolysis of **13a** in refluxing ethanol afforded the azine **16** not



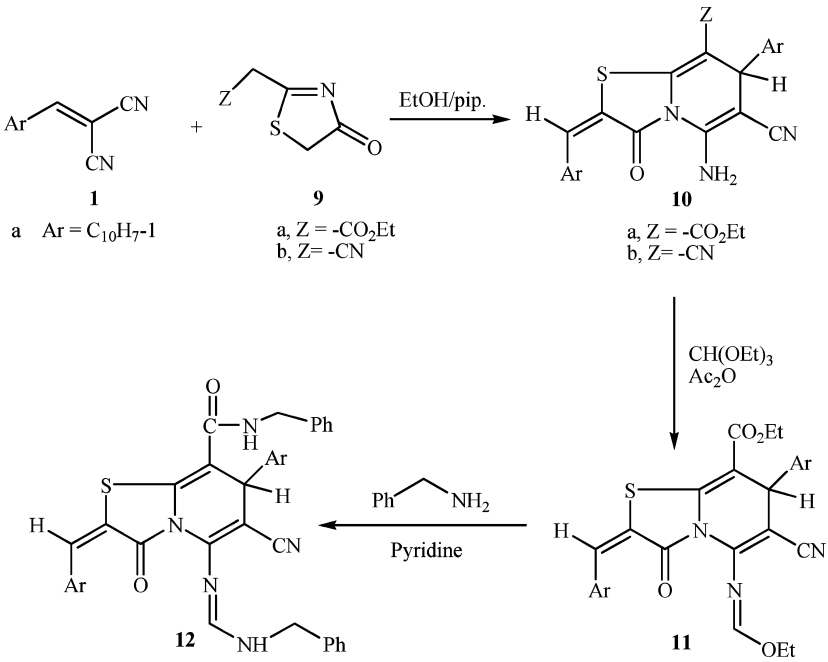
SCHEME 1

pyrazolobenzopyrrole derivative **17**. Treatment of compound **13a**,**b** with freshly distilled acetic anhydride yielded the N-acyl derivative **18a**,**b**. The reaction of the N-acyl derivative **18b** with β-cyanoethylhydrazine in ethanol yielded pyrazolo[3,4-b]indole **19** (Scheme 3).

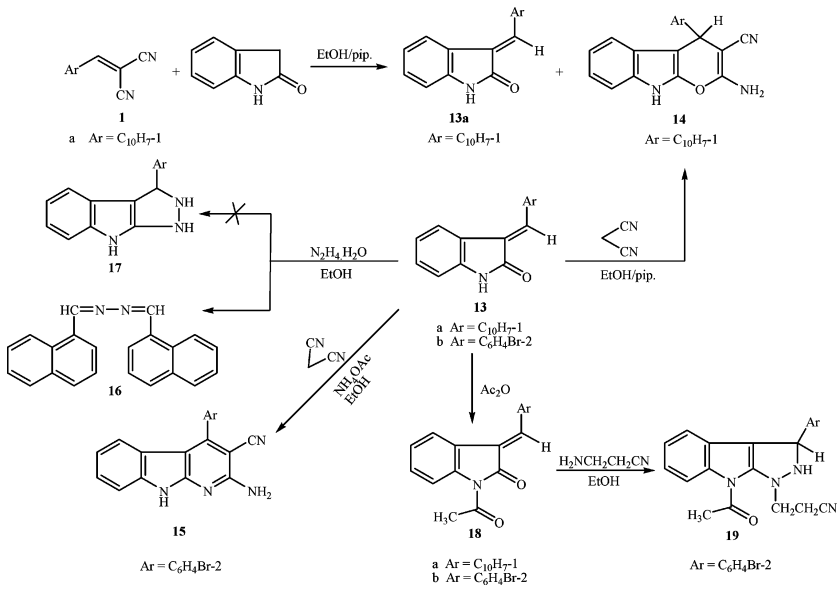
Biological Investigation

Antimicrobial Activity

The antimicrobial screening of some of the synthesized compounds was done using the agar diffusion assay. This screening was performed against the Gram-negative bacteria, Escherichia coli ATCC 10536 and Gram-positive bacteria, Staphylococcus aurous ATCC 06538 in addition to the pathogenic fungi Candida albicans ATCC 1023 and Aspergilus flavus. A moderate activity was observed with compounds **7**, **10a**, **14**,



SCHEME 2



SCHEME 3

TABLE I Antimicrobial Screening Results of the Tested Compounds at 1000 μg/ml

Compd. no.	*E. coli*	*S. aurous*	*C. albicans*
3b	00	00	00
4	00	00	00
5	00	00	00
7	13	12	12
8a	00	00	00
8b	00	00	00
10a	12	12	11
10b	00	00	00
11	00	00	00
12	00	00	00
13a	00	00	00
14	17	15	15
15	16	15	15
18a	10	11	11
18b	12	13	12
19	11	11	9
Ampicillin	00	22	00
Streptomycin	20	21	00
Nystatin	00	00	22

00, no activity (inhibition zone < 7 mm); weak activity (7–10 mm); moderate activity (11–15 mm); strong activity (>15 mm). Solvent: DMSO (6 mm).

15, **18a**, **18b**, and **19**, which proved to possess marked activity against E. coli, S. aurous, and C. albicans. The inhibitory concentration was determined for each of the active compounds along with Ampicillin, Streptomycin, and Nystatin as positive controlled. No activity was detected for all the synthesized compounds towards Aspergilus flavus. Results are shown in Table I.

CONCLUSION

The results of this article indicates that activated nitriles are used as the key starting materials for synthesis of biologically active fused heterocyclic compounds such as Pyrido[2,3-d]pyrimidines, Thiazolo[3,2-a]pyridines, Pyrano[2,3-b]benzopyrrole, and Pyrido[2,3-d]benzopyrroles.

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra were recorded on FTIR Maltson (infinity series) spectrometers as KBr discs. The

^{1}H-NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS. Mass spectra were recorded on Shimaduzu GC-MS, QP 1000 EX instrument operating at 70 eV. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was runned using TLC aluminum sheets silica gel F_{254} (Merck).

7-Amino-6-cyano-5-aryl-4-oxo-1H,3H-pyrido[2,3-d]pyrimidin-2-thione 3a,b

A mixture of 3-aryl-2-cyanoacrylonitrile **1a**,**b** (10 mmol) and 6-aminothiouracil (1.43 g, 10 mmol) in ethanol (50 ml) containing 1 ml piperidine was heated under reflux for 2 h (TLC). The pale yellow product that deposited during reflux, was collected by suction, washed with ethanol, dried, and then recrystallized from the proper solvent to give **3a** and/or **3b**.

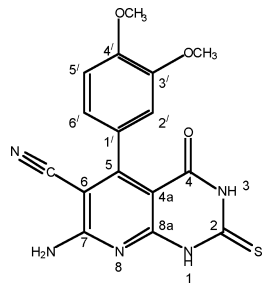
7-Amino-6-cyano-5-[1′-naphthyl]-4-oxo-1H,3H-pyrido-[2,3-d]pyrimidin-2(H)-thione 3a

Recrystallized from ethanol as pale yellow crystals, m.p.: 326–328°C, yield 46%. IR (KBr): 3378, 3220, 3113 cm^{-1} (NH_2), 2206 cm^{-1} (C≡N), 1687 cm^{-1} (C=O), 1640 cm^{-1} (C=N) and 1128 cm^{-1} (C=S).^{1}H-NMR (DMSO-d_6)δ (ppm): 12.08 (s, 1H, NH, exchangeable with D_2O), 11.7 (s, 1H, NH, exchangeable with D_2O), 7.1 (br.s, 2H, NH_2, exchangeable with D_2O) and 8.0–7.5 (m, $7H_{arom.}$). ^{13}C-NMR (DMSO-d_6)δ (ppm): 173.8 (CS), 160.2 (CO), 114 (CN), 102 (C_{4a}), 153.8 (C_5), 80.1 (C_6), 156 (C_7), 160.7 (N=C-N), 124.8-138.2 (naphthyl carbons). MS m/z (%): 345 ($M^{+\cdot}$, 98.2), 344 (M-1, 100), 343 (40.3), 285 (11.6), 215 (17.9). Anal. calcd. for $C_{18}H_{11}N_5OS$ (345): C, 62.6%; H, 3.19%; N, 20.28%; S, 9.27%. Found: C, 62.48%; H, 3.32%; N, 19.77%; S, 9.30%.

7-Amino-6-cyano-5-(3′,4′-dimethoxyphenyl)-4-oxo-1H,3H-pyrido[2,3-d] pyrimidin-2(H)-thione 3b

Recrystallized from ethanol as yellow crystals, m.p.: 344–346°C, yield 48%. IR (KBr): 3377, 3299, 3216 cm^{-1} (NH_2), 2206 cm^{-1} (C≡N), 1696 cm^{-1} (C=O), 1640 cm^{-1} (C=N), and 1128 cm^{-1} (C=S). ^{1}H-NMR (DMSO-d_6)δ (ppm): 12.7 (s, 1H, NH, exchangeable with D_2O), 12.2 (s, 1H, NH, exchangeable with D_2O), 7.7 (br.s, 2H, NH_2, exchangeable with D_2O), 7.04-6.8 (m, $3H_{arom.}$), 3.84 (s, 3H, OMe) and 3.74 (s, 3H, OMe).

^{13}C-NMR (DMSO-d_6)δ (ppm): 174.7 (CS), 161.3 (CO), 158.4 (C_5), 82.4 (C_6), 112.6 (CN), 160.1 (C_7), 102 (C_{4a}), 155.3 (N=C-N), 132 (C_{8a}), 158.9



(C-OMe), 160.2 (C-OMe), 56.1 (OMe), 55.7 (OMe), 121.8, 122.9, 126.3 ($C_{arom.}$). MS m/z (%): 355 ($M^{+\cdot}$, 100). Anal. calcd. for $C_{16}H_{13}N_5O_3S$ (355): C, 54.08%; H, 3.6%; N, 19.7%; S, 9.0%. Found: C, 52.86%; H, 4.0%; N, 20.09%; S, 8.66%.

7-Amino-6-cyano-5-(3′,4′-dimethoxyphenyl)-2-ethoxycarbonylmethylthiopyrido[2,3-d]pyrimidin-4(3H)-one 4

A mixture of **3b** (3.5 g, 10 mmol), ethylbromoacetate (1.67 ml, 10 mmol), and anhydrous sodium acetate (5 g, 160 mmol) in absolute ethanol (50 ml) was refluxed for 6 h (TLC). Most of the solvent was distilled and the reaction mixture was poured onto water to afford a white substance which was filtered off, washed several times with hot water, dried and recrystallized from dioxane to give **4**. m.p.: 321–323°C, yield 85%. IR (KBr): 3478, 3389, 3214, 3144 cm^{-1} (NH_2, NH), 2212, 2182 cm^{-1} (C≡N), 1737 cm^{-1} (C=O ester), 1669 cm^{-1} (C=O pyrimidone), and 1630 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.5 (s, 1H, NH, exchangeable with D_2O), 7.6 (br.s, 2H, NH_2, exchangeable with D_2O), 7.03–6.8 (m, 3$H_{arom.}$), 4.2 (q, 2H, $COO\underline{CH_2}CH_3$), 3.8 (s, 2H, $S\underline{CH_2}COOEt$), 3.7 (s, 6H, 2OMe) and 1.2 (t, 3H, $COOCH_2\underline{CH_3}$). ^{13}C-NMR (DMSO-d_6) δ (ppm): 158.7 (C_2), 162.1 (C_4), 99.3 (C_{4a}), 155.2 (C_5), 89.7 (C_6), 161.7 (C_7), 158.1 (C_{8a}), 114.9 (CN), 132.4 (C'_1), 126.3 (C'_2), 156 (C'_3), 150.9 (C'_4), 120.3 (C'_5), 124.3 (C'_6), 55.8 (OMe), 55.7 (OMe), 32.4 (SCH_2), 171.3 (CO_{ester}), 57.7 (OCH_2), 14.8 (Me). MS m/z (%): 441 ($M^{+\cdot}$, 73.8), 396 (33.6), 368 (87.9), 355 (100), 323 (17.4). Anal. calcd. for $C_{20}H_{19}N_5O_5S$ (441): C, 54.4%; H, 4.3%; N, 15.8%; S, 7.2%. Found: C, 54.43%; H, 4.52%; N, 16.31%; S, 6.99%.

7-Amino-6-cyano-5-(3′,4′-dimethoxyphenyl)-2-ethylthiopyrido[2,3-d]pyrimidin-4(3H)-one 5

A mixture of **3b** (3.5 g, 10 mmol), ethyl iodide (1.5 ml, 10 mmol) and anhydrous sodium acetate (5 g, 160 mmol) in absolute ethanol (50 ml)

was heated under reflux for 3 h (TLC). Most of the solvent was distilled and the reaction mixture was stirred with hot water to give a white substance which was filtered off, dried and recrystallized from dioxane to give **5**. m.p.: 361–363°C, yield 90%. IR (KBr): 3449, 3301, 3217 cm^{-1} (NH_2,NH), 2215 cm^{-1} (C≡N), 1697 cm^{-1} (C=O), 1622 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6)δ (ppm): 12.2 (s, 1H, NH, exchangeable with D_2O), 7.7 (br.s, 2H, NH_2, exchangeable with D_2O), 7.0-6.8 (m, $3H_{arom.}$), 3.84 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.2 (q, 2H, $S\underline{CH_2}CH_3$) and 1.3 (t, 3H, $SCH_2\underline{CH_3}$). MS m/z (%): 383 ($M^{+\cdot}$, 48), 355 (100), 340 (28.1). Anal. calcd. for $C_{18}H_{17}N_5O_3S$ (383): C, 56.3%; H, 4.4%; N, 18.2%; S, 8.3%. Found: C, 56.1%; H, 4.8%; N, 17.68%; S, 8.0%.

7-Amino-6-cyano-2-hydrazino-5-(3′,4′-dimethoxphenyl)-pyrido[2,3-d]pyri-midin-4(3H)-one 6

Method 1

A mixture of **3b** (3.5 g, 10 mmol) and hydrazine hydrate 80% (0.5 ml, 10 mmol) in absolute ethanol (50 ml) was heated under reflux for 3 h. The yellowish white product that deposited during reflux, was collected by suction and washed with ethanol to give **6**. m.p.: >360°C, yield 20%. IR (KBr): 3451, 3303, 3208 cm^{-1} (NH_2), 2215 cm^{-1} (C≡N), 1691 cm^{-1} (C=O).^{1}H-NMR (DMSO-d_6)δ (ppm): 10.9 (s, 1H, NH, exchangeable with D_2O), 8.4 (br.s, 2H, NH_2, exchangeable with D_2O), 8.1 (br.s, 2H, NH_2, exchangeable with D_2O), 7.3 (s, 2H, NH_2, exchangeable with D_2O), 7.2–6.9 (m, $3H_{arom.}$), 3.83 (s, 3H, OMe), and 3.79 (s, 3H, OMe). MS m/z (%): 353 ($M^{+\cdot}$, 100), 323 (40), 308 (31.2), 280 (23.1). Anal. calcd. for $C_{16}H_{15}N_7O_3$ (353): C, 54.3%; H, 4.2%; N, 27.7%. Found: C, 54.71%; H, 3.93%; N, 28.21%.

Method 2

A mixture of **5** (3.83 g, 10 mmol) and hydrazine hydrate 80% (0.5 ml, 10 mmol) in absolute ethanol (50 ml) was heated under reflux for 3 h. The excess solvent was removed by suction. The deposited solid was filtered off and washed by ethanol to give **6** (yield 80%).

8-Diacetylamino-7-cyano-6-(3′,4′-dimethoxyphenyl)-3-methyl-5-oxo-1H,1, 2,4-triazolo[4,5-a]pyrido[2,3-d]pyrimidine 7

A solution of **6** (1 g, 2.8 mmol) in freshly distilled acetic anhydride (10 ml) was heated under reflux for 6 h, left to cool, and diluted with cold water. The crude pale green solid that separated out was collected, washed with cold water, dried and then recrystallized from ethanol to give **7**. m.p.: 195–196°C, yield 82%. IR (KBr): 2229 cm^{-1} (C≡N), 1740,

1704, 1691 cm^{-1} (C=O).^{1}H-NMR ($CDCl_3$)δ (ppm): 8.9 (s, 1H, NH, exchangeable with D_2O), 6.9–6.8 (m, $3H_{arom.}$), 3.95 (s, 3H, OMe), 3.88 (s, 3H, OMe), 2.5 (s, 3H, $COCH_3$), 2.4 (s, 3H, $COCH_3$) and 2.2 (s, 3H, N=C–CH_3). MS m/z (%): 461 ($M^{+\cdot}$, 21.3), 419 (100), 404 (41.5), 377 (78.1), 362 (33.6). Anal. calcd. for $C_{22}H_{19}N_7O_5$ (461): C, 57.2%; H, 4.1%; N, 21.2%. Found: C, 56.76%; H, 3.81%; N, 21.7%.

7-Amino-6-cyano-5-(3′,4′-dimethoxyphenyl)-2-(3″,5″-dimethylpyrazolo-1-yl)-3H-pyrido[2,3-d]pyrimidin-4(3H)-one 8a and 7-Amino-6-cyano-5-(3′, 4′-dimethoxyphenyl)-2-(3″-methyl-1-phenylpyrazolo-2″-yl)-3H-pyrido-[2,3-d]pyrimidin-4(3H)-one 8b

A solution of **6** (1 g, 2.8 mmol) in dilute hydrochloric acid (10 ml, 50%) was heated under reflux with 2,4-pentadione (0.28 ml, 2.8 mmol) or 1-phenylbut-1,3-dione (0.45 g, 2.8 mmol) in pyridine (10 ml) for 0.5 h. The pale yellow product deposited on hot, was collected by suction, dried and then recrystallized from dioxane to give **8a** and **8b**, respectively.

8a. m.p.: 342–344°C, yield 76%. IR (KBr): 3459, 3301, 3211 cm^{-1} (NH_2), 2213 cm^{-1} (C≡N), 1682 cm^{-1} (C=O).^{1}H-NMR (DMSO-d_6)δ (ppm): 11.45 (s, 1H, NH, exchangeable with D_2O), 7.68 (br.s, 2H, NH_2, exchangeable with D_2O), 7.0–6.8 (m, $3H_{arom.}$), 6.3 (s, 1H, =CH), 3.86 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.6 (s, 3H, C′$_5$-CH_3), and 2.25 (s, 3H, C′$_3$-CH_3). MS m/z (%): 417 ($M^{+\cdot}$, 100), 402 (50.7), 95 (18.2). Anal. calcd. for $C_{21}H_{19}N_7O_3$ (417): C, 60.4%; H, 4.5%; N, 23.5%. Found: C, 59.33%; H, 4.5%; N, 23.9%.

8b. m.p.: 311–313°C, yield 80%. IR (KBr): 3484, 3336, 3289 cm^{-1} (NH_2), 2208 cm^{-1} (C≡N), 1698 cm^{-1} (C=O).^{1}H-NMR (DMSO-d_6)δ (ppm): 12.03 (s, 1H, NH, exchangeable with D_2O), 7.74(br.s, 2H, NH_2, exchangeable with D_2O), 7.5–7.0 (m, $8H_{arom.}$), 6.7 (s, 1H), 3.87 (s, 3H, OMe), 3.77 (s, 3H, OMe), and 2.52 (s, 3H, C′$_3$-Me). MS m/z (%): 479 ($M^{+\cdot}$, 100), 464 (28.2), 157 (6.9). Anal. calcd. for $C_{26}H_{21}N_7O_3$ (479): C, 65.1%; H, 4.38%; N, 20.4%. Found: C, 64.77%; H, 4.41%; N, 20.91%.

5-Amino-7-aryl-2-arylidene-6-cyano-8-substituted-3-oxo-2H,3H,7H-thiazolo-[3,2-a]-pyridine 10a,b

A mixture of **1a** (4.08 g, 20 mmol) and 2-ethoxycarbonylmethyl-4-oxo-Δ^2-thiazoline **9a** and/or 2-cyanomethyl-4-oxo-Δ^2-thiazoline **9b** (10 mmol) in absolute ethanol (50 ml) containing 1 ml piperidine was heated under reflux for 1 h. The yellow product that deposited during reflux,

was collected by suction, washed by ethanol, dried and recrystallized from the proper solvent to give **10a** and **10b**, respectively.

5-Amino-6-cyano-8-ethoxycarbonyl-3-oxo-2-[1-naphthylidene]-7-[1-naphth-yl]-2H,3H, 7H-thiazolo[3,2-a]pyridine 10a

Recrystallized from dioxane to give a yellow crystals, m.p.: 265–266°C, yield 63%. IR (KBr): 3457, 3347 cm^{-1} (NH_2), 2196 cm^{-1} (C≡N), 1691 cm^{-1} (C=O unsaturated ester), 1643 cm^{-1} (C=O unsaturated cyclic imide).^{1}H-NMR ($CDCl_3$)δ (ppm): 8.6–7.6 (m, $14H_{arom.}$), 7.3 (br.s, 2H, NH_2 exchangeable with D_2O), 6.6 (s, 1H, olefinic proton), 4.8 (s, 1H, C_7-H), 3.89 (q, 2H, $COO\underline{CH_2}CH_3$), and 0.98 (t, 3H, $COOCH_2\underline{CH_3}$). MS m/z (%): 529 ($M^{+\cdot}$, 10.3), 402 (24), 403 (100), 152 (12.8). Anal. calcd. for $C_{32}H_{23}N_3O_3S$ (529): C, 72.5%; H, 4.3%; N, 7.9%; S, 6.0%. Found: C, 73.06%; H, 4.09%; N, 8.32%; S, 5.49%.

5-Amino-6,8-dicyano-3-oxo-2-(1-naphthylidene)-7-(1-naphthyl)-2H,3H,7H-thiazolo[3,2-d]pyridine 10b

Recrystallized from dioxane as yellow crystals, m.p.: 290–291°C, yield 70%. IR (KBr): 3387, 3331, 3287 cm^{-1} (NH_2), 2196 cm^{-1} (C≡N), 1717 cm^{-1} (C=O), 1653 cm^{-1} (C=N).^{1}H-NMR (DMSO-d_6)δ (ppm): 8.81–7.4 (m, $14H_{arom.}$), 7.1 (s, 1H, olefinic proton), 6.5 (br.s, 2H, NH_2 exchangeable with D_2O) and 4.6 (s, 1H, C_7-H). MS m/z (%): 355 ($M^{+\cdot}$-$C_{10}H_7$, 19.4), 301 (100), 184 (62.2). Anal. calcd. for $C_{30}H_{18}N_4OS$ (482): C, 74.6%; H, 3.7%; N, 11.6%; S, 6.6%. Found: C, 74.26%; H, 3.63%; N, 11.24%; S, 6.72%.

6-Cyano-5-ethoxymethyleneamino-8-ethoxycarbonyl-3-oxo-2-(1-naphthyl-idene)-7-(1-naphthyl)-2H,3H,7H-thiazolo-[3,2-a]pyridine 11

A mixture of **10a** (1 g, 1.9 mmol) and triethylorthoformate (10 ml, 67 mmol) in freshly distilled acetic anhydride (10 ml) was heated under reflux for 8 h. The pale green solid deposited during reflux, was collected by filtration, washed with light-petroleum ether (b.p. 80–100) and, then, recrystallized from benzene to give **11**. m.p.: 236–238C, yield 57%. IR (KBr): devoid ν_{NH2}, 2205 cm^{-1} (C≡N), 1723 cm^{-1} (C=O ester), 1690 cm^{-1} (C=O $\alpha\beta$-unsaturated ketone), 1626 cm^{-1} (C=N).^{1}H-NMR ($CDCl_3$)δ (ppm): 8.5–7.3 (m, $15H_{arom.}$ + N=CH), 7.2 (s, 1H, =CH), 5.7 (s, 1H, C_7-H), 4.4 (q, 2H, $CH_3\underline{CH_2}$–OCO), 3.9 (q, 2H, $CH_3\underline{CH_2}$–O), 1.5 (t, 3H, $\underline{CH_3}CH_2$-O-CO) and 0.7 (t, 3H, $\underline{CH_3}CH_2O$). MS m/z (%): 585 ($M^{+\cdot}$,

12.1), 458 (100), 312 (10.1), 184 (16). Anal. calcd. for $C_{35}H_{27}N_3O_4S$ (585): C, 71.79%; H, 4.6%; N, 7.17%; S, 5.47%. Found: C, 71.56%; H, 4.23%; N, 7.62%; S, 5.81%.

Formation of the Thiazolo Pyridine Derivative 12

A mixture of **12** (5.85 g, 10 mmol) and benzylamine (1 ml, 10 mmol) in dry pyridine (30 ml) was heated under reflux for 6 h. The reaction mixture was cooled and acidified with cold dilute acetic acid. The solid deposited was filtered off, washed several times with water and dried, then recrystallized from dioxane to give **12**. m.p.: 257–259°C, yield 80%. IR (KBr): 3450, 3341 cm^{-1} (NH), 2194 cm^{-1} (C≡N), 1694 cm^{-1} (C=O), 1643 cm-1 (C=O).^{1}H-NMR ($CDCl_3$)δ (ppm): 9.1 (br.s, 2H, NH_2, exchangeable with D_2O), 8.5–7.4 (m, 24$H_{arom.}$), 7.0 (s, 1H, olefinic proton), 6.93 (s, 1H, N=CH), 4.9 (s, 1H, C_7-H), and 4.34 (d,d, 4H, benzylic protons). MS m/z (%): 590 [$M^{+\cdot}$-($PhCH_2$, CN), 2.6], 402 (15.5), 184 (15.5), 152 (20.38), 127 (100). Anal. calcd. for $C_{45}H_{33}N_5O_2S$ (707): C, 76.37%; H, 4.6%; N, 9.9%; S, 4. %5. Found: C, 76.71%; H, 4.3%6; N, 10.21%; S, 4.32%.

Reaction of 1a with 2-indanone: Formation of 13a and 14

A mixture of **1a** (2.04 g, 10 mmol) and indan-2-one (1.33 g, 10 mmol) in absolute ethanol (50 ml) containing 1 ml piperidine was heated under reflux for 2 h (TLC). The reaction mixture was cooled and the solid deposited was collected by suction, washed by ethanol and recrystallized from benzene to give **13a**. Most of the solvent of the mother liquor was distilled off and then acidified with cold dilute hydrochloric acid. The green solid that separated out was collected by filtration, washed by cold water, dried and recrystallized from ethanol to give **14**.

13a. m.p.: 190–192°C, yield 50%. IR (KBr): 3179, 3151 cm^{-1} (NH), 1710 cm^{-1} (C=O), 1616 cm^{-1} (C=C).^{1}H-NMR ($CDCl_3$)δ (ppm): 8.3 (s, 1H, NH), 8.0–7.2 (m, 11$H_{arom.}$), and 6.7 (s, 1H, CH=). MS m/z (%): 271 ($M^{+\cdot}$, 79.3), 270 (100), 144 (11.2), 120 (9). Anal. calcd. for $C_{19}H_{13}NO$ (271): C, 84.1%; H, 4.79%; N, 5.1%. Found: C, 83.75%; H, 5.0%; N, 4.77%.

Authentic Sample

A solution of indan-2-one (1.33 g, 10 mmol) in absolute ethanol (30 ml) was stirred with 1-naphthaldehyde (1.56 ml, 10 mmol) for ½ h and then refluxed for 1 h. The excess solvent was removed and left a crude

product which recrystallized from benzene to give **13a** (identity by m.p., mixed m.p. and TLC).

14. m.p.: 327–329°C, yield 20%. IR (KBr): 3429, 3317, 3211 cm^{-1} (NH_2), 2210 cm^{-1} (C≡N), 1645 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$)δ (ppm): 10.4 (s, 1H, NH, exchangeable with D_2O), 8.18-7.0 (m, $11H_{arom.}$), 6.7 (br.s, 2H, NH_2, exchangeable with D_2O), and 4.86 (s, 1H). MS m/z (%): 337 ($M^{+\cdot}$, 37.6), 334 (100), 307 (17.8). Anal. calcd. for $C_{22}H_{15}N_3O$ (337): C, 78.3%; H, 4.45%; N, 12.46%. Found: C, 78.0%; H, 4.61%; N, 12.09%.

Reaction of 13a with Malononitrile

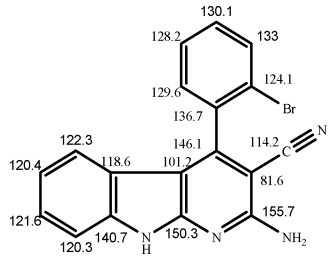
A mixture of **13a** (2.71 g, 10 mmol) and malononitrile (0.99 g, 15 mmol) in absolute ethanol (50 ml) and 1 ml piperidine was refluxed for 3 h. The excess solvent was collected by distillation and the residual acidified with cold dilute acetic acid to give **14** (yield 28.7%) (identity by m.p., mixed m.p., IR, and TLC).

Formation of 13b

A mixture of indan-2-one (1.33 g, 10 mmol) and 2-bromobenz-aldehyde (1.85 ml, 10 mmol) in absolute ethanol (50 ml) was refluxed for 4 h. The resulting yellow product (one spot in TLC) was collected by filtration and then recrystallized from benzene to give **13b**. m.p.: 166–167°C, yield 80%. IR (KBr): 3143 cm^{-1} (NH), 1713 cm^{-1} (C=O). MS m/z (%): 300 ($M^{+\cdot}$, 100), 301 (9.6), 302 (30). Anal. calcd. For $C_{15}H_{10}NOBr$ (300): C, 60.0%; H, 3.3%; N, 4.6%; Br, 26.6%. Found: C, 59.4%; H, 3.4%; N, 4.4%; Br, 27.0%.

2-Amino-3-cyano-4-(2-bromophenyl)-pyrido-[2,3-b]benzopyrrole 15

A mixture of **13b** (1 g, 3.3 mmol), malononitrile (0.22 g, 3.3 mmol) and ammonium acetate (3 g, 40 mmol) was firstly fused for 2 min, then heated under reflux in absolute ethanol (25 ml) for 6 h. Most of the solvent was distilled off and the reaction mixture was poured onto water. The pale green solid that separated out was collected by filtration, dried and then, recrystallized from benzene to give **15**. m.p.: 165–167°C, yield 30%. IR (KBr): 3475, 3331, 3217 cm^{-1} (NH_2), 2196 cm^{-1} (C≡N), and no band for C=O group.^{1}H-NMR ($CDCl_3$)δ (ppm): 10.3 (s, 1H, NH, exchangeable with D_2O), 8.1-7.3 (m, $8H_{arom.}$), and 6.88 (br.s, 2H, NH_2, exchangeable with D_2O).^{13}C-NMR ($CDCl_3$)δ (ppm):



MS m/z (%): 363 ($M^{+\cdot}$, 22.5), 364 (9.2), M+2 (9.2), 283 (100). Anal. calcd. for $C_{18}H_{11}N_4Br$ (363): C, 59.5%; H, 3.0%; N, 15.4%; Br, 22.0%. Found: C, 59.28%; H, 3.01%; N, 15.63%; Br, 22.46%.

Reaction of 13a with Hydrazine Hydrate; Formation of the Azine 16

A mixture of **13a** (10 mmol) and hydrazine hydrate (1.5 mmol) in ethanol (25 ml) was heated under reflux for 2 h . The solid deposited after evaporation of the solvent, was filtered off, dried, and recrystallized from light petroleum ether (b.p. 80–100°C) to give **16**. m.p.: 63–65°C, yield 43%. MS m/z (%): 308 ($M^{+\cdot}$, 32.9), 280 (100), 181 (59), 154 (71.1), 127 (87.3). Identity (m.p, mixed m.p, TLC) with authentic sample resulted from the reaction of 1-naphthaldehyde with hydrazine hydrate in ethanol.

Acetylation of 13a,b; Formation of 18a,b

A solution of **13a** or **13b** (1 g) in freshly distilled acetic anhydride (10 ml) was heated under reflux on water bath for 2 h. The solid deposited on hot was collected by suction, washed several times with light petroleum ether and recrystallized from the proper solvent to give **18a** and/or **18b**.

18a. Recrystallized from light petroleum ether (b.p. 80–100°C), m.p.: 112–114°C, yield 65%. IR (KBr): 1733, 1704 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$)δ (ppm) : 8.4–7.2 (m, $11H_{arom.}$), 6.9 (d, 1H, C=CH), and 2.8 (s, 3H, COMe). MS m/z (%): 313 ($M^{+\cdot}$, 32.2), 271 (95.3), 270 (95.3), 270 (100), 242 (19.5), 144 (12.6). Anal. calcd. for $C_{21}H_{15}NO_2$ (313): C, 80.5%; H, 4.79%; N, 4.47%. Found : C, 80.23%; H, 4.72%; N, 4.39%.

18b. Recrystallized from benzene, m.p.: 138–139°C, yield 90%. IR (KBr): 1734, 1708 cm^{-1} (C=O).^{1}H-NMR ($CDCl_3$)δ (ppm) : 8.8–7.6 (m, $8H_{arom.}$), 7.2 (s, 1H, C=CH) and 2.45 (s, 3H, COMe). MS m/z (%): 342 ($M^{+\cdot}$, 3.1), 262 (17.4), 220 (100). Anal. calcd. for $C_{17}H_{12}NO_2Br$ (342): C,

59.6%; H, 3.5%; N, 4.1%; Br, 23.39%. Found : C, 59.1%; H, 3.84%; N, 4.44%; Br, 23.69%.

8-Acetyl-1-(2′-cyanoethyl)-3-(2′-bromophenyl)-2,3-dihydropyrazolo [3,4-b]indole 19

A solution of compound **18b** (3.42 g, 10 mmol) in pyridine (50 ml) was stirred with β-cyanoethylhydrazine (0.7 ml, 10 mmol) for 1 h and then refluxed for 3 h on water bath. The reaction mixture was concentrated and acidified with cold dilute acetic acid. The deposited solid was filtered off, dried and then recrystallized from ethanol to give **19** as yellow crystals. m.p.: 177–178°C, yield 40%. IR (KBr): 3242, 3183 cm^{-1} (NH), 2253 cm^{-1} (C≡N), 1695 cm^{-1} (C=O), 1647 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$)δ (ppm) : 8.3–7.3 (m, $8H_{arom.}$), 5.3 (d, 1H), 4.2 (d, 1H, NH, exchangeable with D_2O), 3.4 (t, 2H, N-CH_2-CH_2-), 3.1 (t, 2H, CH_2CN) and 2.45 (s, 3H, COMe). MS m/z (%): 383 (M–$CN^{\cdot}$, 11.1), 220 (100). Anal. calcd. for $C_{20}H_{17}N_4OBr$ (409): C, 58.6%; H, 4.1%; N, 13.69%; Br, 19.5%. Found C, 58.32%; H, 3.81%; N, 14.02%; Br, 20.0%.

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