Monatsh Chem 139, 1233–1240 (2008)
DOI 10.1007/s00706-007-0839-3
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

A convenient synthesis of pyrrolo[2,3-*b*]pyridines and pyrido-[2′,3′:5,4]pyrrolo[2,3-*d*]pyrimidines

Shawkat A. Abdel-Mohsen, Ahmed A. Geies

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

Received 1 September 2007; Accepted 25 October 2007; Published online 24 July 2008

Abstract 2-Chloro-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile was taken as versatile building block that allows the synthesis of 1*H*-pyrrolo[2,3-*b*]pyridine, thieno[2,3-*b*]pyridine and pyrido[2′,3′:5,4]-pyrrolo[2,3-*b*]pyrimidine systems. Some of the synthesized compounds were screened as antibacterial agents.

Keywords Heterocycles; Antibacterial agents.

Introduction

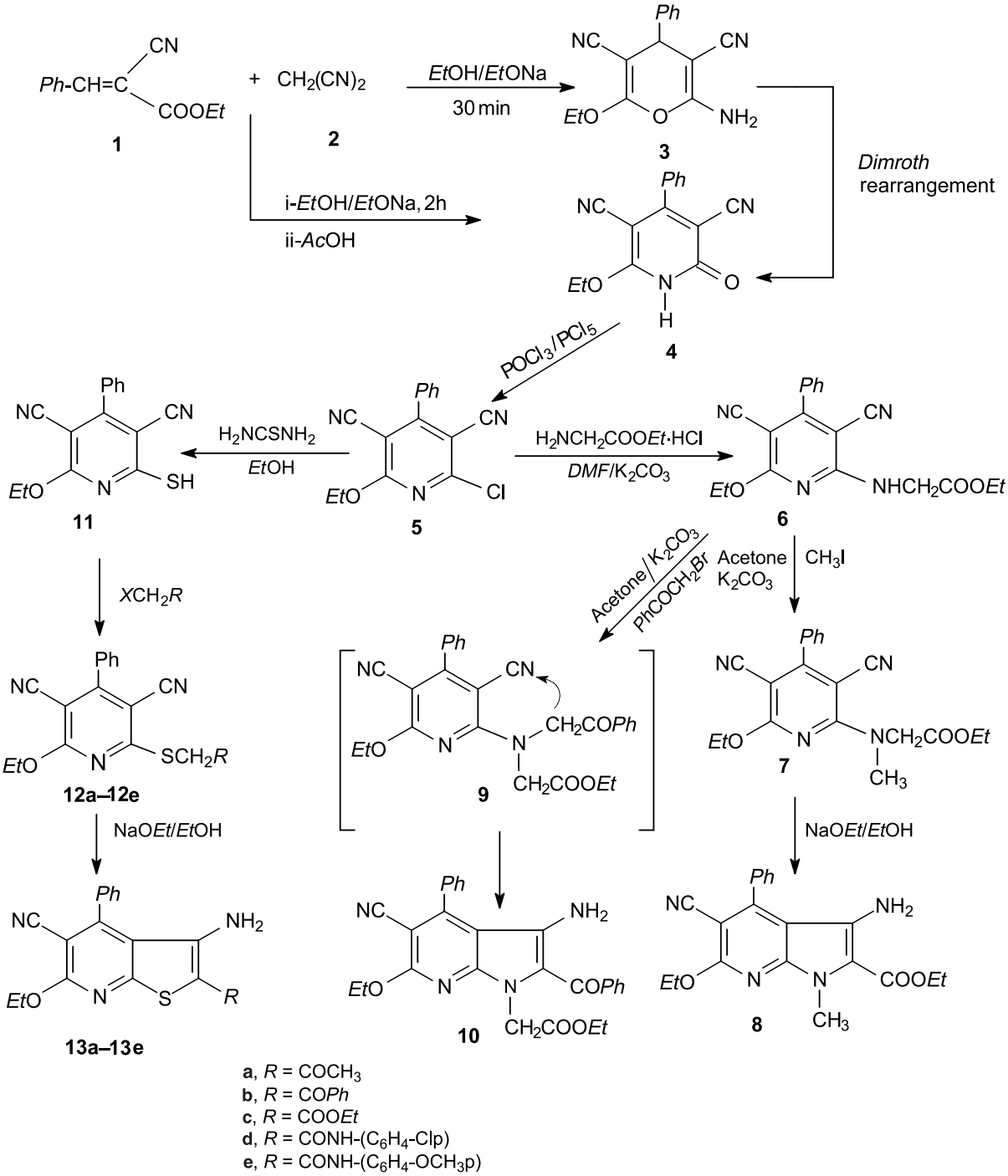
Pyrrolopyridines have attracted considerable attention as an analog of indole nucleus because of their interesting biological activities [1–6]. There are only a few pyrrolopyridine derivatives in nature, so many pyrrolopyridine derivatives are synthetically prepared for the development of pharmaceutical agents. Also, pyridopyrrolopyrimidines *e.g.*, Variolins, isolated by *Munro et al.* [7] from the antartic red sponge *Kirckpatrickia varialosa*, are alkaloids that exhibit antitumor and antiviral properties, Variolin B, the most active molecule of the group, has attracted considerable interest. In our research program devoted to the synthesis of different heterocyclic systems incorporated pyrrole moiety [8–12], we planned to prepare new pyrrolo[2,3-*b*]pyridine derivatives based on the 7-azaindole framework.

Correspondence: Shawkat A. Abdel-Mohsen, Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt. E-mail: shawk662001@yahoo.com

Results and discussion

To reach this target, we started with 3,5-dicyano-6-ethoxypyridine-2(1*H*)-one **4** which was synthesized by *Otto et al.* [13] through the reaction of ethyl benzylidenecyanoacetate and malononitrile in ethanolic sodium ethoxide solution, they suggested that the reaction should be proceeded *via* the intermediate **3**. Fortunately, we succeeded in separation of the aminopyrane **3**, which underwent *Dimroth* rearrangement to give finally the pyridinone derivative **4**. Compound **4** was used as a key intermediate to synthesize some new pyrrolo-, thieno-, pyrazolopyridines, and other fused tri- and/or tetracyclic derivatives. Thus, refluxing of **4** with a mixture of $POCl_3$/PCl_5 yielded the corresponding 2-chloropyridine derivative **5**. The ring system pyrrolo[2,3-*b*]pyridine was obtained *via* the following steps: Treatment of **5** with an equimolar ratio of ethyl glycinate hydrochloride in *DMF* in the presence of K_2CO_3 resulted in the formation of ethyl (3,5-dicyano-6-ethoxy-4-phenylpyridine-2-yl)glycinate (**6**). The latter was easily methylated by its reaction with methyl iodide to give *N*-methyl derivative **7**. Upon treatment with ethanolic sodium ethoxide, **7** underwent cyclization to afford ethyl 3-amino-5-cyano-6-ethoxy-1-methyl-4-phenylpyrrolo[2,3-b]pyridine-2-carboxylate (**8**). The structure of **8** was established using microanalyses and spectral data. Thus, the IR spectrum revealed the strong absorption bands for CO (ester) at 1695 cm^{-1} and for NH_2 at 3480 and 3380 cm^{-1}. The ^1H NMR spectrum revealed the presence of

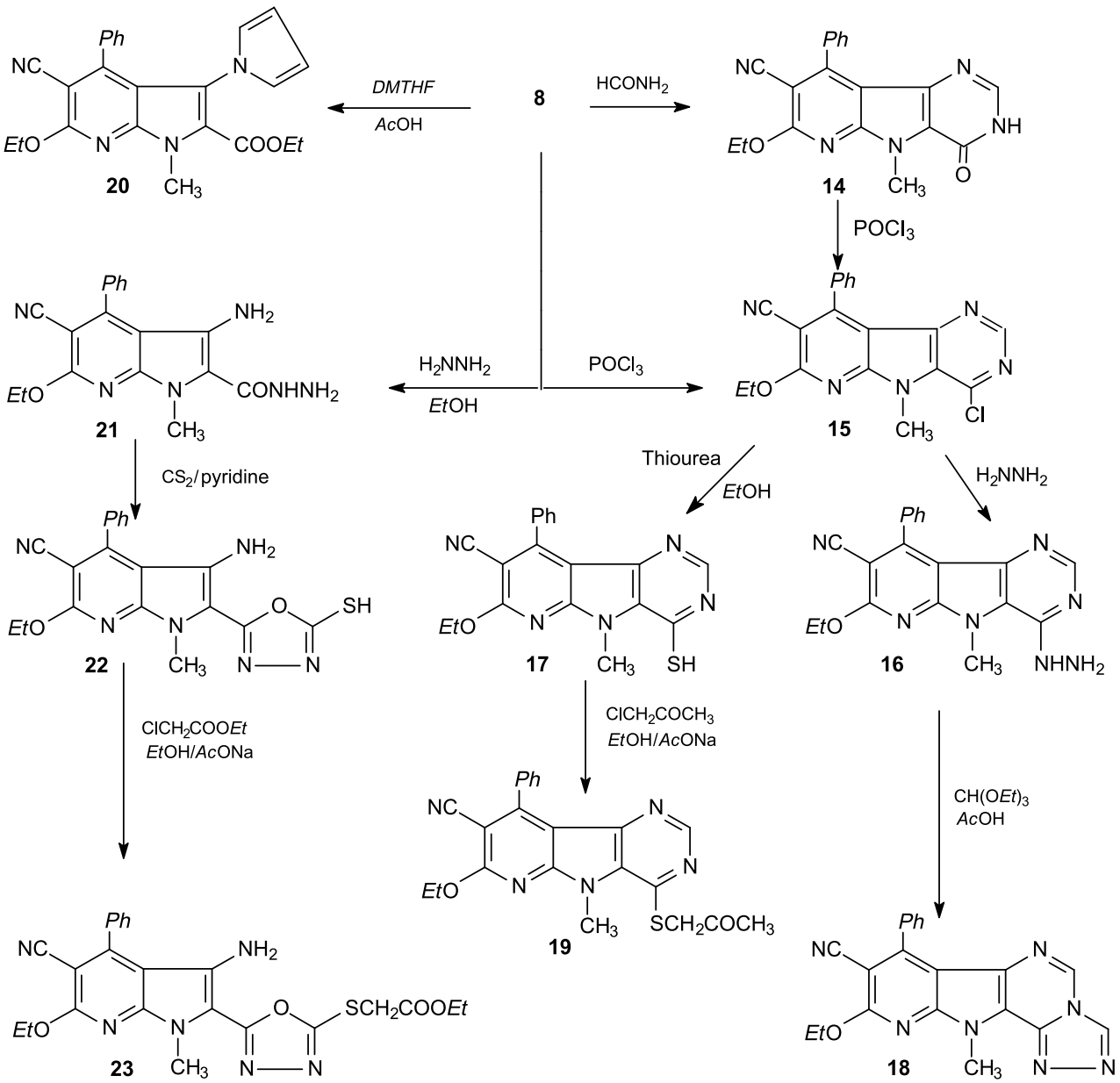
two triplets at $\delta = 1.30$, 1.45 ppm for 2 CH_3, a singlet at $\delta = 3.9$ ppm for N–CH_3, two quartets at $\delta = 4.30$, 4.40 ppm for 2 CH_2, a singlet at $\delta = 4.85$ ppm for NH_2 (exchangeable with D_2O) in addition to the signals for aromatic protons. The mass spectrum showed M^+ peak at 363.99 which was in agreement with molecular formula $C_{20}H_{20}N_4O_3$ ($m/z = 364$). Another pyrrolopyridine derivative **9** was achieved *via* the reaction of **6** with phenacyl bromide in acetone/K_2CO_3 to give 3-amino-2-benzoyl-5-cyano-6-ethoxy-1-ethoxycarbonylmethyl-4-phenylpyrrolo[2,3-*b*]pyridine (**10**). The formation of **10** rather than its



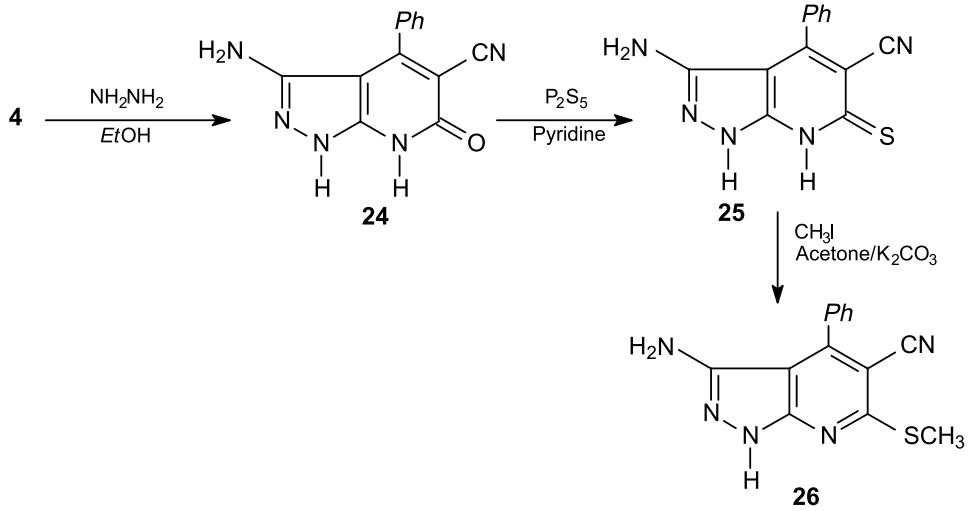
Scheme 1

isomer *N*-benzoylmethyl was assumed to proceed *via* intermediate **9** followed by its subsequent intracyclization of the $CH_2(COPh)$ to the neighboring pyridine C-3 CN function. Structure of **10** was established by spectral analysis. Thus, its IR spectrum showed band for the C=O (ester) that was shifted to longer wavelength ($\bar{\nu} = 1735\,cm^{-1}$) rather than the C=O (ester) attached directly to the pyrrole ring. On the other hand, thieno[2,3-*b*]pyridine derivatives **12a**–**12e** were obtained *via* the reaction of thione derivative **11** with α-halo compounds. By a similar way, **12a**–**12e** underwent cyclization using ethanolic sodium ethoxide solution to furnish 2-substituted 3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-*b*]pyridines **13a**–**13e** (Scheme 1).

The *o*-aminoester **8** was condensed with formamide to yield 8-cyano-7-ethoxy-5-methyl-9-phenylpyrido[2′,3′:5,4]pyrrolo[2,3-*b*]pyrimidine-4(3*H*)-one (**14**). Chlorination at the C-4 position was performed on **14** to afford the chloropyridopyrrolopyrimidine derivative **15** in 66% yield. Compound **15** in turn could be transformed to the 4-hydrazino or the



Scheme 2



Scheme 3

4-mercapto compounds **16**, **17** by its reaction with hydrazine hydrate or thiourea in ethanol (Scheme 2).

The hydrazine **16** was used to build a new triazolopyridopyrrolopyrimidine **18** *via* the condensation with triethyl orthoformate in ethanol in the presence of catalytic amounts of acetic acid. The formation of **18** from **16** was supported by elemental analyses and by the absence of absorption bands at $\bar{\nu} = 3450$, 3350, and 3150 cm^{-1} for the respective stretching vibration of $NHNH_2$ in its IR spectrum. The thione derivative **17** was allowed to react with α-chloroacetone in ethanol containing anhydrous sodium acetate to give the corresponding 4-acetylmethylthio derivative **19** in a good yield.

Other derivatives of *o*-aminoester **8** were synthesized *via* its reaction with *DMTHF* or hydrazine hydrate to furnish 3-pyrrolyl and the corresponding carbohydrazide **20** and **21**. The latter was further reacted with carbon disulfide in pyridine to give 2-(oxadiazolyl)pyrrolopyridine **22**, which was easily S-alkylated with ethyl chloroacetate in ethanol containing anhydrous sodium acetate to give the thioester derivative **23** (Scheme 2).

The pyridinone **4** was also used to synthesize 3-amino-5-cyano-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-7(6*H*)-one **24** by its reaction with hydrazine hydrate. Finally, the pyrazolopyridinone derivative **24** was converted into the corresponding thione **25** by refluxing with P_2S_5 in dry pyridine, which when treated with methyl iodide afforded the 6-methylthio derivative **26** in a good yield (Scheme 3).

Antibacterial activity

Twelve compounds were selected and screened *in vitro* for their antibacterial activity against five strains of bacteria (*Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Staphylococcus aureus*) using the filter paper disc method [14]. The biological activity, as expressed by the growth of the inhibition zones of the tested microorganism are summarized in Table 1. From Table 1, it was observed that all of the tested compounds have a moderate activity against *E. coli* and *S. marcescens*. Among the derivatives of pyridopyr-

Table 1 Antibacterial activities for most of synthesized compounds (diameter of inhibition zones, mm)

Compd. no.	*B. cereus*	*E. coli*	*S. aureus*	*P. aeruginosa*	*S. marcescens*
7	−ve	12	−ve	−ve	15
8	−ve	15	−ve	−ve	19
13c	−ve	13	−ve	−ve	15
13d	−ve	18	−ve	−ve	14
14	−ve	12	−ve	−ve	15
15	−ve	11	27	−ve	22
17	−ve	10	−ve	−ve	14
18	−ve	12	21	−ve	13
19	−ve	11	13	−ve	11
20	−ve	14	−ve	−ve	13
24	−ve	12	−ve	−ve	15
25	−ve	10	10	−ve	14
Sutrim	42	25	20	20	30

−*ve* No inhibition zone

rolopyrimidines compounds **14**, **17**, **15**, **18**, and **19**, only 4-chloropyrimidine derivative **15** and the triazolopyridopyrrolopyrimidine **18** exhibited a remarkable antimicrobial activity against *S. aureus*. None of the investigated compounds possessed any antibacterial activity towards the rest of the bacteria species *B. cereus* and *P. aeruginosa*.

Experimental

All melting points were determined on a Gallenkamp apparatus. IR spectra were recorded on a Pye-Unicam spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were obtained on a *Bruker* 250 MHz NMR spectrometer. MS on a Jeol JMS-600 mass spectrometer. Elemental analyses were determined using *Perkin-Elmer* 240C Microanalyzer and all results were within the acceptable range.

2-Amino-3,5-dicyano-4-phenyl-6-ethoxypyrane (**3**, $C_{15}H_{13}N_3O_2$)
To a mixture of 2.01 g ethyl benzylidenecyanoacetate (**1**) (0.01 mol) and 0.66 g malononitrile **2** (0.01 mol) in 30 cm^3 absolute ethanol, 0.1 g sodium ethoxide in 10 cm^3 ethanol were added. The mixture was heated for 30 min. The solid product that precipitated during the reflux was filtered off, dried, and recrystallized from ethanol to give 1.89 g (71%) pale yellow crystals of **3**; mp 160–162°C; IR (KBr): $\bar{\nu}$ = 3450, 3350 (NH_2), 2220 (CN) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.4$ (t, $J = 7.1$ Hz, CH_3), 4.50 (q, $J = 6.8$ Hz, CH_2), 4.75 (s, CH pyran), 5.80 (s, NH_2), 7.20–7.70 (m, 5*Ar*–H) ppm.

3,5-Dicyano-6-ethoxy 4-phenylpyridine-2-(1H)-one (**4**)
This compound was synthesized according to Ref. [13].

2-Chloro-3,5-dicyano-4-phenyl-6-ethoxypyridine
(**5**, $C_{15}H_{10}N_3OCl$)
A mixture of 2.65 g **4** (0.01 mol), 10 cm^3 phosphorus oxychloride and 10 g phosphorus pentachloride was heated on a water bath for 5 h, allowed to cool, and poured into ice cold water. The solid product was collected and recrystallized from ethanol to yield 1.83 g (65%) white crystals of **5**; mp 140–142°C; IR (KBr): $\bar{\nu} = 2220$ (CN) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.35$ (t, $J = 7.3$ Hz, CH_3), 4.45 (q, $J = 6.5$ Hz, CH_2), 7.20–7.60 (m, 5*Ar*–H) ppm.

Ethyl (3,5-dicyano-4-phenyl-6-ethoxypyridine-2-yl) glycinate (**6**, $C_{19}H_{18}N_4O_3$)
A mixture of 2.8 g **5** (0.01 mol), 1.4 g ethyl glycinate hydrochloride (0.01 mol), and 0.2 g anhydrous potassium carbonate in 20 cm^3 *DMF* was heated at 70°C with stirring for 9 h, allowed to cool, and poured into cold water. The solid product was collected and recrystallized from ethanol to give 2.6 g (75%) white crystals of **6**; mp 137–138°C; IR (KBr): $\bar{\nu} = 3390$ (NH), 2220 (CN), 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (t, $J = 7.4$ Hz, CH_3 ethoxy), 1.45 (t, $J = 7.4$ Hz, CH_3 ester), 4.25 (q, $J = 6.6$ Hz, CH_2 ethoxy), 4.4 (d, N–CH_2), 4.45 (q, $J = 6.7$ Hz, CH_2 ester), 6.25 (s, NH), 7.50–7.80 (m, 5*Ar*–H) ppm.

Ethyl (3,5-dicyano-6-ethoxy-4-phenylpyridine-2-yl)-N-methyl glycinate (**7**, $C_{20}H_{20}N_4O_3$)
A mixture of 1.75 g **6** (0.005 mol), 0.24 g methyl iodide (0.005 mol), and 0.5 g anhydrous potassium carbonate in 30 cm^3 acetone was refluxed for 3 h, then allowed to cool, and poured into cold water. The solid product was collected, washed thoroughly with water, dried, and recrystallized from ethanol to give 1.43 g (79%) white crystals of **7**; mp 165–167°C; IR (KBr): $\bar{\nu} = 2220$ (CN), 1710 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (t, $J = 7.4$ Hz, CH_3 ethoxy), 1.40 (t, $J = 7.4$ Hz, CH_3 ester), 3.85 (s, N–CH_3), 4.25 (q, $J =$ 6.8 Hz, CH_2 ethoxy), 4.40 (q, $J = 6.5$ Hz, CH_2 ester), 4.7 (s, N–CH_2), 7.55–7.80 (m, 5*Ar*–H) ppm.

Ethyl 3-amino-5-cyano-6-ethoxy-1-methyl-4-phenylpyrrolo-[2,3-b]pyridine-2-carboxylate (**8**, $C_{20}H_{20}N_4O_3$)
To a solution of 0.364 g **7** (0.001 mol) in 30 cm^3 absolute ethanol was added a few drops of ethanolic sodium ethoxide solution, and the mixture was refluxed for 30 min. The solid product was collected and recrystallized from ethanol to give 0.29 g (82%) yellow crystals of **8**; mp 225–225°C; IR (KBr): $\bar{\nu} = 3450$, 3350 (NH_2), 2220 (CN), 1660 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (t, $J = 7.4$ Hz, CH_3 ethoxy), 1.45 (t, $J = 7.3$ Hz, CH_3 ester), 3.90 (s, N–CH_3), 4.30 (q, $J = 6.7$ Hz, CH_2 ethoxy), 4.40 (q, $J = 6.7$ Hz, CH_2 ester), 4.85 (s, NH_2), 7.40–7.80 (m, 5*Ar*–H) ppm; MS: $m/z =$ 363.99 [M^+].

3-Amino-2-benzoyl-5-cyano-6-ethoxy-1-ethoxycarbonyl-methyl-4-phenylpyrrolo[2,3-b]pyridine (**10**, $C_{27}H_{24}N_4O_4$)
A mixture of 1.75 g **6** (0.005 mol), 0.99 g phenacyl bromide (0.005 mol), and 0.5 g anhydrous potassium carbonate in 30 cm^3 acetone was refluxed for 6 h, and then allowed to cool. The solid product was collected, washed thoroughly with water, dried and recrystallized from ethanol to give 1.66 g (71%) orange plates of **10**; mp 215–216°C; IR (KBr): $\bar{\nu} =$ 3450, 3390 (NH_2), 2220 (CN), 1735 (C=O), 1665 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (t, $J = 7.2$ Hz, CH_3 ethoxy), 1.40 (t, $J = 7.2$ Hz, CH_3 ester), 4.20 (q, $J = 6.6$ Hz, CH_2 ethoxy), 4.40 (q, $J = 6.4$ Hz, CH_2 ester), 4.65 (s, N–CH_2), 6.15 (s, NH_2), 6.95–7.90 (m, 10*Ar*–H) ppm.

3,5-Dicyano-6-ethoxy-4-phenylpyridine-2-(1H)-thione (**11**)
This compound was synthesized according to Ref. [15].

5-Substituted 3,5-dicyano-6-ethoxy-4-phenyl-2-pyridinethiols ***12a–12e****. General procedure*
A mixture of 1.15 g **11** (0.005 mol), (0.005 mol) halo compounds and 2 g sodium acetate in 30 cm^3 ethanol was refluxed for 1 h, and then allowed to cool. The solid product was collected, washed with water several times, dried, and recrystallized from ethanol.

2-(Acetylthio)-3,5-dicyano-6-ethoxy-4-phenylpyridine
(**12a**, $C_{18}H_{15}N_3O_2S$)
Yield 1.44 g (86%); mp 210–211°C; IR (KBr): $\bar{\nu} = 2220$ (CN), 1700 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.40$ (t, 3H,

$J = 6.8$ Hz, CH_3), 2.45 (s, 3H, CH_3), 4.30 (q, 2H, $J = 6.05$ Hz, CH_2), 4.55 (s, 2H, CH_2), 7.20–7.70 (m, 5H, *Ar*–H) ppm.

3,5-Dicyano-6-ethoxy-4-phenyl-2-(phenylcarbonylthio)-pyridine (**12b**, $C_{23}H_{17}N_3O_2S$)
Yield 1.53 g (77%); mp 199–200°C; IR (KBr): $\bar{\nu} = 2220$ (CN), 1690 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.45$ (t, 3H, $J = 7.3$ Hz, CH_3), 4.15 (q, 2H, $J = 6.1$ Hz, CH_2), 4.60 (s, 2H, CH_2), 6.90–7.70 (m, 10H, *Ar*–H) ppm.

3,5-Dicyano-6-ethoxy-2-(ethoxycarbonylthio)-4-phenylpyridine (**12c**, $C_{19}H_{17}N_3O_3S$)
Yield 1.46 g (80%); mp 145–146°C; IR (KBr): $\bar{\nu} = 2220$ (CN), 1720 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.4$ Hz, CH_3 ethoxy), 1.40 (t, 3H, $J = 7.4$ Hz, CH_3 ester), 4.20 (q, 2H, $J = 6.8$ Hz, CH_2 ethoxy), 4.40 (q, 2H, $J = 6.5$ Hz, CH_2 ester), 4.70 (s, 2H, CH_2), 7.20–7.80 (m, 5H, *Ar*–H) ppm.

2-[(4-Chlorophenyl)aminocarbonylthio]-3,5-dicyano-6-ethoxy-4-phenylpyridine (**12d**, $C_{23}H_{17}ClN_4O_2S$)
Yield 1.79 g (80%); mp 242–243°C; IR (KBr): $\bar{\nu} = 3380$ (NH), 2220 (CN), 1640 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.35$ (t, 3H, $J = 7.2$ Hz, CH_3), 4.20 (q, 2H, $J = 6.6$ Hz, CH_2), 4.4 (s, 2H, CH_2), 6.80–7.90 (m, 9H, *Ar*–H), 8.9 (s, 1H, NH) ppm.

3,5-Dicyano-6-ethoxy-2-[(4-methoxyphenyl)amino-carbonylthio]-4-phenylpyridine (**12e**, $C_{24}H_{20}N_4O_3S$)
Yield 1.72 g (77%); mp 178–180°C; IR (KBr): $\bar{\nu} = 3370$ (NH), 2220 (CN), 1650 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.40$ (t, 3H, $J = 6.8$ Hz, CH_3), 3.65 (s, 3H, CH_3), 4.30 (q, 2H, $J = 6.6$ Hz, CH_2), 4.60 (s, 2H, CH_2), 6.90–8.20 (m, 9H, *Ar*–H), 9.20 (s, 1H, NH) ppm.

*2-Substituted 3-amino-5-cyano-6-ethoxy-4-phenylthieno-[2,3-b]pyridines **13a–13e***
Compounds **13a–13g** were prepared according to the method reported for the synthesis of compound **8**, starting from 0.005 mol **12a–12e**. The precipitate was filtered off and recrystallized from ethanol.

2-Acetyl-3-amino-5-cyano-6-ethoxy-4-phenylthieno[2,3-b]-pyridine (**13a**, $C_{18}H_{15}N_3O_2S$)
Yield 1.41 g (82%); mp 280–282°C; IR (KBr): $\bar{\nu} = 3450$, 3350 (NH_2), 2220 (CN), 1640 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.50 (s, 3H, CH_3), 4.20 (q, 2H, $J = 6.8$ Hz, CH_2), 5.8 (s, 2H, NH_2), 7.40–7.90, (m, 5H, *Ar*–H) ppm.

3-Amino-5-cyano-6-ethoxy-4-phenyl-2-(phenylcarbonyl)-thieno[2,3-b]pyridine (**13b**, $C_{23}H_{17}N_3O_2S$)
Yield 1.50 g (75%); mp 215–217°C; IR (KBr): $\bar{\nu} = 3480$, 3330 (NH_2), 2220 (CN), 1630 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.2$ Hz, CH_3), 4.20 (q, 2H, $J = 6.2$ Hz, CH_2), 6.25 (s, 2H, NH_2), 6.80–7.90 (m, 10H, *Ar*–H) ppm.

3-Amino-5-cyano-6-ethoxy-2-(ethoxycarbonyl)-4-phenylthieno[2,3-b]pyridine (**13c**, $C_{19}H_{17}N_3O_3S$)
Yield 1.49 g (83%); mp 287–288°C; IR (KBr): $\bar{\nu} = 3500$, 3380 (NH_2), 2200 (CN), 1670 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.4$ Hz, CH_3 ethoxy), 1.40 (t, 3H, $J = 7.4$ Hz, CH_3 ester), 4.20 (q, 2H, $J = 6.8$ Hz, CH_2 ethoxy), 4.5 (q, 2H, $J = 6.5$ Hz, CH_2 ester), 5.5 (s, 2H, NH_2), 7.30–7.70 (m, 5H, *Ar*–H) ppm; MS: $m/z = 366.93$ [M^+].

3-Amino-2-[(4-chlorophenyl)aminocarbonyl]-5-cyano-6-ethoxy-4-phenylthieno[2,3-b]pyridine (**13d**, $C_{23}H_{17}N_4O_2ClS$)
Yield 1.81 g (86%); mp 260–262°C; IR (KBr): $\bar{\nu} = 3480$, 3380, 3300 (NH_2, NH), 2200 (CN), 1640 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.40$ (t, 3H, $J = 7.3$ Hz, CH_3), 4.40 (q, 2H, $J = 6.6$ Hz, CH_2), 5.6 (s, 2H, NH_2), 7.3–7.70 (m, 9H, *Ar*–H), 9.6 (s, 1H, NH) ppm.

3-Amino-5-cyano-6-ethoxy-2-[(4-methoxyphenyl)amino-carbonyl]-4-phenylthieno[2,3-b]pyridine (**13e**, $C_{24}H_{20}N_4O_3S$)
Yield 1.39 g (69%); mp 270–272°C; IR (KBr): $\bar{\nu} = 3500$, 3380, 3320 (NH_2, NH), 2220 (CN), 1650 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.3$ Hz, CH_3), 3.50 (s, 3H, CH_3), 4.30 (q, 2H, $J = 6.6$ Hz, CH_2), 5.60 (s, 2H, NH_2), 6.5–7.6 (m, 9H, *Ar*–H), 8.7 (s, 1H, NH) ppm.

8-Cyano-7-ethoxy-5-methyl-9-phenylpyrido[2′,3′:5,4]-pyrrolo[2,3-d]pyrimidine-4(3H)-one (**14**, $C_{19}H_{15}N_5O_2$)
A sample of 1.82 g **8** (0.005 mol) in 10 cm^3 formamide was refluxed for 3 h. The solid product which separated from the hot mixture was filtered off and recrystallized from dioxane to give 1.35 g (78%) pale yellow crystals of **14**; mp 275–277°C; IR (KBr): $\bar{\nu} = 3300$ (NH), 2220 (CN), 1660 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.30$ Hz, CH_3), 3.90 (s, 3H, N–CH_3), 4.40 (q, 2H, $J = 6.5$ Hz, CH_2), 7.45–7.85 (m, 5H, *Ar*–H), 8.6 (s, 1H, CH pyrimidine), 9.2 (s, 1H, NH) ppm; MS: $m/z = 345.02$ [M^+].

4-Chloro-8-cyano-7-ethoxy-5-methyl-9-phenylpyrido-[2′,3′:5,4]pyrrolo[2,3-d]pyrimidine (**15**, $C_{19}H_{14}N_5OCl$)
A mixture of 1.73 g **14** (0.01 mol) and 30 cm^3 phosphorus oxychloride was heated under reflux for 5 h, then allowed to cool and poured into ice cold water. The solid product was collected and recrystallized from ethanol to give 1.19 g (66%) white crystals of **15**; mp 184–186°C; IR (KBr): $\bar{\nu} = 2200$ (CN) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 6.8$ Hz, CH_3), 3.85 (s, 3H, N–CH_3), 4.40 (q, 2H, $J = 6.4$ Hz, CH_2), 7.40–7.8 (m, 5H, *Ar*–H), 8.80 (s, 1H, CH pyrimidine) ppm.

8-Cyano-7-ethoxy-4-hydrazino-5-methyl-9-phenylpyrido-[2′,3′:5,4]pyrrolo[2,3-d]pyrimidine (**16**, $C_{19}H_{17}N_7O$)
A mixture of 1.82 g **15** (0.005 mol) and 0.25 g hydrazine hydrate (0.005 mol) in 30 cm^3 ethanol was refluxed for 3 h and then left to cool. The precipitate solid was collected and recrystallized from dioxane to give 1.12 g (66%) yellow crystals of **16**; mp 225–227°C; IR (KBr): $\bar{\nu} = 3450$, 3350, 3150 (NH_2, NH), 2220 (CN) cm^{-1};

^{1}H NMR (*DMSO*-d_6): $\delta = 1.40$ (t, 3H, $J = 7.05$ Hz, CH_3), 3.90 (s, 3H, N–CH_3), 4.55 (q, 2H, $J = 6.8$ Hz, CH_2), 4.8 (br, s, 2H, NH_2), 7.50–7.80 (m, 5H, *Ar*–H), 8.70 (s, 1H, CH pyrimidine), 10.7 (s, 1H, NH) ppm.

8-Cyano-7-ethoxy-5-methyl-9-phenylpyrido[2′,3′:5,4]-pyrrolo[2,3-d]pyrimidin-4(3H)-thione (**17**, $C_{19}H_{15}N_5OS$)
A mixture of 1.82 g **15** (0.005 mol) and 0.76 g thiourea (0.01 mol) in 30 cm^3 ethanol was refluxed for 8 h and then left to cool. The precipitate solid was collected and recrystallized from acetic acid to give 1.20 g (65%) orange crystals of **17**; mp >300°C; IR (KBr): $\bar{\nu} = 2220$ (CN) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.40$ (t, 3H, $J = 7.25$ Hz, CH_3), 3.90 (s, 3H, N–CH_3), 4.20 (q, 2H, $J = 6.6$ Hz, CH_2), 7.40–7.90 (m, 5H, *Ar*–H), 8.60 (s, 1H, CH pyrimidine), 10.8 (s, 1H, NH) ppm.

3-Cyano-2-ethoxy-11-methyl-4-phenylpyrido[2′,3′:5,4]-pyrrolo[2,3-d]triazolo[3,4-f]pyrimidine (**18**, $C_{20}H_{15}N_7O$)
To a mixture of 1.79 g **16** (0.005 mol) and 2 cm^3 triethyl orthoformate, in 20 cm^3 ethanol a few drops of acetic acid were added as a catalyst. The mixture was heated under reflux for 2 h. The solid product separated from the hot mixture was filtered off and recrystallized from dioxane to give 1.20 g (65%) yellow crystals of **18**; mp >300°C; IR (KBr): $\bar{\nu} = 222$ (CN) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.20$ (t, 3H, $J = 6.4$ Hz, CH_3), 3.80 (s, 3H, N–CH_3), 4.20 (q, 2H, $J = 6.6$ Hz, CH_2), 7.32–7.90 (m, 5H, *Ar*–H), 8.80, 9.20 (2s, 2H, 2CH); MS: $m/z = 369.52$ [M^+] ppm.

4-Acetylmethylthio-8-cyano-7-ethoxy-5-methyl-9-phenyl-pyrido[2′,3′:5,4]pyrrolo[2,3-b]pyrimidine (**19**, $C_{22}H_{19}N_5O_2S$)
Compound **19** was prepared in a similar procedure to that described for compounds **12a**–**12e**, starting from the mixture of 361 mg **17** (0.001 mol) and 93 mg α-chloroacetone (0.001 mol). The solid product was collected and recrystallized from ethanol to give 0.29 g (70%) yellow crystals of **19**; mp 195–196°C; IR (KBr): $\bar{\nu} = 2220$ (CN), 1690 (CO) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 6.4$ Hz, CH_3), 2.45 (s, 3H, CH_3), 3.80 (s, 3H, N–CH_3), 4.40 (q, 2H, $J = 6.7$ Hz, CH_2), 4.8 (s, 2H, CH_2), 7.50–7.80 (m, 5H, *Ar*–H), 8.90 (s, 1H, CH pyrimidine) ppm.

Ethyl 5-cyano-6-ethoxy-1-methyl-3-(1-pyrrolyl)-4-phenyl-pyrrolo[2,3-b]pyridine-2-carboxylate (**20**, $C_{24}H_{22}N_4O_3$)
A mixture of 1.82 g **8** (0.005 mol) and 1.32 mg 2,5-dimethoxytetrahydrofurane (0.01 mol) in 20 cm^3 glacial acetic acid was refluxed for 3 h, the solvent was reduced to one third of its volume under reduced pressure, and then cooled, the solid separated was collected and recrystallized from ethanol to give 1.45 g (70%) white crystals of **20**; mp 135–137°C; IR (KBr): $\bar{\nu} = 2220$ (CN), cm^{-1}, 1700 (CO); ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (t, 3H, $J = 7.3$ Hz, CH_3 ethoxy), 1.40 (t, 3H, $J = 7.2$ Hz, CH_3 ester), 3.80 (s, 3H, N–CH_3), 4.20 (q, 2H, $J = 6.6$ Hz, CH_2 ethoxy), 4.40 (q, 2H, $J = 6.8$ Hz, CH_2 ester), 5.80 (t, 2H, $J = 2.0$ Hz, 2CH pyrrolyl), 6.30 (t, 2H, $J = 2.4$ Hz, 2CH pyrrolyl), 7.5–7.70 (m, 5H, *Ar*–H) ppm.

3-Amino-5-cyano-6-ethoxy-1-methyl-4-phenylpyrrolo[2,3-b]-pyridine-2-carbohydrazide (**21**, $C_{18}H_{18}N_6O_2$)
A mixture of 1.82 g **8** (0.005 mol) and 2 cm^3 hydrazine hydrate was refluxed in 20 cm^3 ethanol for 4 h. The solid separated from the hot mixture was filtered off and recrystallized from dioxane to give 1.20 g (70%) yellow crystals of **21**; mp 287°C; IR (KBr): $\bar{\nu} = 3400$, 3350, 3200 (NH_2, $NHNH_2$), 2220 (CN), 1660 (CO) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.15$ Hz, CH_3), 3.70 (s, 3H, N–CH_3), 4.30 (s, 2H, NH_2), 4.40 (q, 2H, $J = 6.8$ Hz, CH_2), 5.7 (s, 2H, NH_2), 7.50–7.8 (m, 5H, *Ar*–H), 9.20 (s, 1H, NH) ppm.

3-Amino-5-cyano-6-ethoxy-2-(5-mercapto-1,3,4-oxadiazol-2-yl)-1-methyl-4-phenylpyrrolo[2,3-b]pyridine (**22**, $C_{19}H_{16}N_6O_2S$)
A mixture of 1.75 g **21** (0.005 mol) and 5 cm^3 carbon disulfide in 20 cm^3 pyridine was heated on a water bath for 24 h, and then cooled. The precipitated product was filtered off and washed several times with ethanol and recrystallized from dioxane to give 1.37 g (70%) orange crystals of **22**; mp 285–287°C; IR (KBr): $\bar{\nu} = 3400$, 3350, (NH_2), 2600 (SH), 2220 (CN) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.30$ Hz, CH_3), 3.70 (s, 3H, N–CH_3), 3.90 (br. s, 1H, SH), 4.50 (q, 2H, $J = 6.7$ Hz, CH_2), 5.8 (s, 2H, NH_2), 7.40–7.90 (m, 5H, *Ar*–H) ppm.

3-Amino-5-cyano-6-ethoxy-2-(5-ethoxycarbonylmethylthio-1,3,4-oxadiazol-2-yl)-1-methyl-4-phenylpyrrolo[2,3-b]-pyridine (**23**, $C_{23}H_{22}N_6O_4S$)
A mixture of 0.78 g **22** (0.002 mol) and 0.245 g ethyl chloroacetate (0.002 mol) in 20 cm^3 ethanol containing 2 g anhydrous sodium acetate was refluxed for 2 h. After cooling, the crude product was filtered off, washed with water, and air dried. Recrystallisation from ethanol yielded 0.70 g (75%) yellow crystals of **23**; mp 190–192°C; IR (KBr): $\bar{\nu} = 3450$, 3350, (NH_2), 2220 (CN), 1730 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (t, 3H, $J = 7.11$ Hz, CH_3 ethoxy),1.50 (t, 3H, $J = 7.2$ Hz, CH_3 ester), 3.90 (s, 3H, N–CH_3), 4.20 (s, 2H, CH_2), 4.30 (q, 2H, $J = 6.8$ Hz, CH_2 ethoxy), 4.50 (q, 2H, $J = 6.8$ Hz, CH_2 ester), 6.20 (s, 2H, NH_2), 7.50–7.90 (m, 5H, *Ar*–H) ppm.

5-Amino-3-cyano-4-phenyl-7(H)-pyrazolo[3,4-b]pyridine-2(1H)-one (**24**, $C_{13}H_9N_5O$)
A mixture of 0.53 g **4** (0.002 mol) and 5 cm^3 hydrazine hydrate was fused together for 30 min, and then 20 cm^3 ethanol were added. The mixture was refluxed for 3 h and then left to cool. The precipitated solid was collected and recrystallized from dioxane to give 0.4 g (80%) yellow crystals of **24**; mp >300°C; IR (KBr): $\bar{\nu} = 3450$, 3350, 3200 (NH, NH_2), 2220 (CN),1630 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 5.60$ (s, 2H, NH_2), 6.5 (s, 1H, NH pyrazole), 7.50–8.0 (m, 5H, *Ar*–H), 10.9 (S, 1H, NH) ppm.

5-Amino-3-cyano-4-phenyl-7(H)-pyrazolo[3,4-b]pyridine-2(1H)-thione (**25**, $C_{13}H_9N_5S$)
A mixture of 0.5 g **24** (0.002 mol) and 385 mg phosphorus pentasulfide (0.002 mol) in 30 cm^3 pyridine was refluxed for 6 h, allowed to cool, and poured into an acetic acid/water

mixture. The precipitated solid was collected and recrystallized from acetic acid to give 0.43 g (82%) orange crystals of **25**; mp 292–293°C; IR (KBr): $\bar{\nu} = 3450$, 3300, 3250 (NH, NH_2), 2220 (CN) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 5.60$ (s, 2H, NH_2), 6.40 (s, 1H, NH pyrazole), 7.40–7.9 (m, 5H, *Ar*–H), 11.5 (s, 1H, NH) ppm.

5-Amino-3-cyano-2-methythio-4-phenyl-7(H)-pyrazolo[3,4-b]-pyridine (**26**, $C_{14}H_{11}N_5S$)

Compound **25** was prepared in a similar procedure to that described for compounds **12a**–**12e**. The solid product was collected and recrystallized from dioxane to give 0.45 g (82%) yellow crystals of **26**; mp 221–222°C; IR (KBr): $\bar{\nu} =$ 3450, 3300, 3250 (NH, NH_2), 2220 (CN) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.20$ (s, 3H, CH_3), 5.40 (s, 2H, NH_2), 6.30 (s, 1H, NH pyrazole), 7.50–7.9 (m, 5H, *Ar*–H) ppm.

Biological screening

The screened compounds were dissolved in *DMSO* to get a solution of 1% concentration. Filter paper discs (*Whatman* No. 1, 5 mm diameter) were saturated with this solution. The discs were placed on the surface of solidified nutrient agar dishes seeded by the tested bacteria. The inhibition zones were measured at the end of an incubation period of 48 h (at 37°C for bacteria). Sutrim was used as the reference substance.

References

1. Merour JY, Joseph B (2001) Curr Org Chem 5:471
2. Florence Popowycz A, Sylvain Routier B, Joseph B, Merour JY (2007) Tetrahedron 63:1031
3. Allen JR, Amegadzie AK, Gardinier KM, Gregory GS, Hitchcock SA, Hoogestraat PJ, Jones WD, Smith DL (2005) Appl Int WO 066126 CA 143:133274
4. Bennabi S, Heckroth H, Schirok H, Mittendorf J, Kast R, Stasch JP, Gnoth MJ, Muenter K, Lang D, Perez SF, Bauser M, Feurer A, Ehmke H (2005) Appl Int WO 058891 CA 143:97339
5. Dillon MP, Lin CJJ, Moore AG, O'Yang C, Zhai YUS (2004) Patent Appl 224,973, 2004 CA 141:410926
6. Graczyk P, Khan A, Bhatia G, Iimura Y (2004) Appl Int WO 078756 CA 141:277498
7. a) Perry NB, Ettouati L, Litaudon M, Blunt JW, Munro MHG, Parkin S, Hope H (1994) Tetrahedron 50:3987; b) Trimurtulu G, Faulkner DJ, Perry NB, Ettouati L, Litaudon M, Blunt JW, Munro MHG, Jameson GB (1994) Tetrahedron 50:3993
8. Abdel-Mohsen SA, Abdel-Hafez SH, Geies AA (2006) J Chin Chem Soc 53(4):909
9. Kamal El-Dean AM, Geies AA, El-Kashef HS, Rault S, D'Allemagne P, Lancelot JC (2000) J Heterocyclic Chem 37(6):1520
10. Kamal El-Dean AM, Geies AA, Radwan SM (1999) Bull Polish Acad Sci Chem 47(2):135
11. Geies AA, Bakhite EA, El-Kashef HS (1998) Pharmazie 53:686
12. Geies AA, Kamal El-Dean AM, Moustafa OS (1996) Monatsh Chem 127:1263
13. Otto HH, Rinus O, Schmetz H (1978) Synthesis:681
14. Kalyoncuoglu N, Rollas S, Sur-Altiner D, Yegenoglu Z, Ang O (1992) Pharmazie 47:769
15. Peinador C, Ojea V, Quintela JM (1992) J Heterocycl Chem 29(7):1693