Synthesis of novel thieno[2,3-*b*][1,6]naphthyridine and thieno [2',3': 2,3]pyrido[4,5-*d*]pyrimidine derivatives

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Derivatives of novel thieno[2,3-*b*][1,6]naphthyridines and thieno[2',3': 2,3]pyrido[4,5-*d*]pyrimidines containing an attached benzotriazole ring have been synthesised.

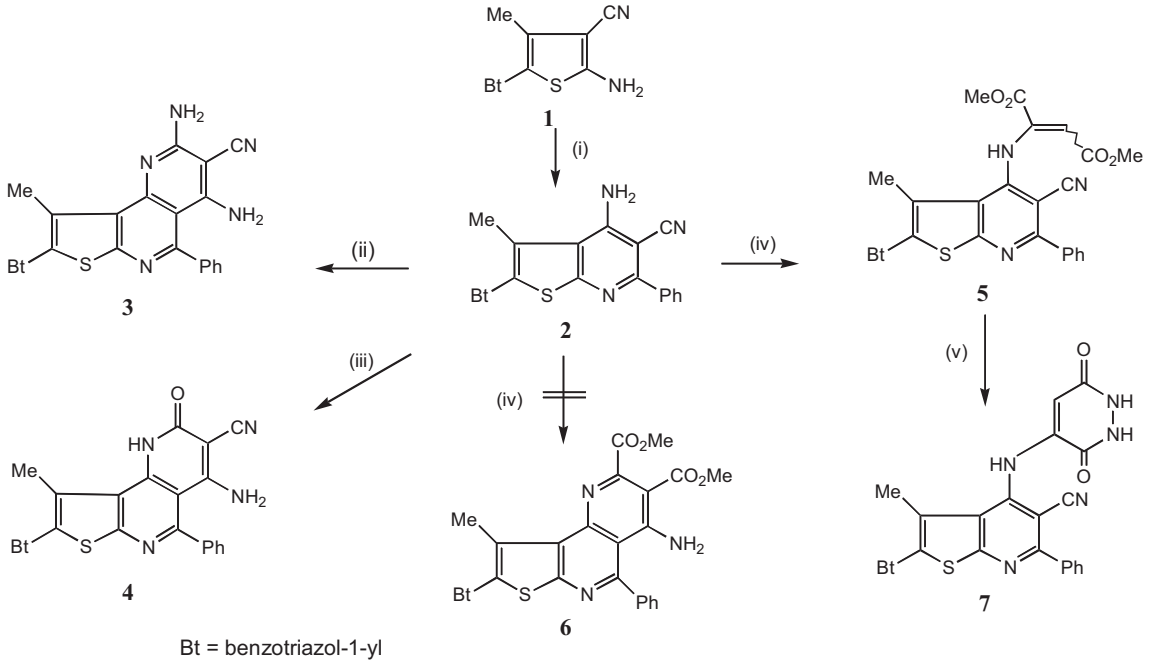
Keywords: *o*-aminonitriles, fused thiophenes, pyridines, pyrimidines, 1,6-naphthyridines, benzotriazoles

Naphthyridine derivatives represent a heterocyclic system of remarkable pharmacological efficiency. They are used for diagnostics and therapy of diseases of humans including AIDS.[1] Several pharmacological studies have also pointed out the value of pyrimidine derivatives as sedatives, antibacterials, and antimalarials.[2,3] Some of them have proved to possess antitumor,[4] analgesic,[5] anti-inflammatory[6,7] and herbicidal[8] activities. Encouraged by all these facts and as a continuation of our research programme dealing with the synthesis of heterocyclic systems, particularly those containing a thiophene moiety,[9,10] we undertook the synthesis of the title compounds which may show good biological and medical applications.

Results and discussion

We envisaged that the amino-nitrile **2** may prove a useful intermediate for synthesis of a broad range of biologically active condensed naphthyridines and pyrimidines, particularly those fused to the thiophene moiety. The key intermediate **2** used in our experiments was readily prepared according to a recently described procedure[9] by the treatment of 2-aminothiophene-3-carbonitrile derivative **1** with benzylidenemalononitrile. The reactivity of the nitrile **2** toward active methylene carbonitriles was investigated. Thus, treatment of compound **2** with malononitrile in refluxing glacial acetic acid afforded the thieno[2,3-*b*][1,6]naphthyridine derivative **3** in good yield (Scheme 1). The structure of the latter compound was established on the basis of analytical and spectral data. The ^{1}H NMR spectrum of **3** revealed, in addition to an aromatic multiplet, two broad signals at δ_H 7.94 and 8.56 ppm attributed to the two NH_2 protons. These signals underwent ready H/D exchange upon addition of deuterium oxide. In a similar manner, derivative **2** reacted with ethyl cyanoacetate in refluxing dioxan in the presence of a catalytic amount of piperidine gave the fused 1,6-naphthyridinone **4**. The IR spectrum of **4** revealed NH and NH_2 stretching bands at ν_{max} 3444-3245 cm^{-1} in addition to the two strong bands at ν_{max} 2206 and 1622 cm^{-1} assigned to the stretching modes of the nitrile and amide carbonyl groups, respectively. Moreover, ^{13}C NMR spectrum revealed highest frequency signal at δ_C 165.9 ppm, assignable to the amide carbonyl carbon.

On the other hand, treatment of **2** with dimethyl acetylenedicarboxylate (DMAD) in refluxing pyridine afforded a product which could have been either the aminoethylene-1,2-dicarboxylate derivative **5** or the thieno[2,3-*b*][1,6]naphthyridine-2,3-dicarboxylate derivative **6**. However, the presence of a cyano absorption band in the IR spectrum indicates that the CN group was not involved in the reaction, excluding the possibility of structure **6**. Moreover, the ^{1}H NMR spectrum revealed the presence of one D_2O-



Scheme 1 Reagents: (i) $PhCH{=}C(CN)_2$/pyridine, reflux; (ii) $CH_2(CN)_2$/AcOH, reflux, H_2O; (iii) $CNCH_2COOEt$/dioxan, pip., reflux, H_2O; (iv) DMAD/pyridine, reflux, H_2O/HCl; (v) $N_2H_4.H_2O$/EtOH:DMF, reflux.

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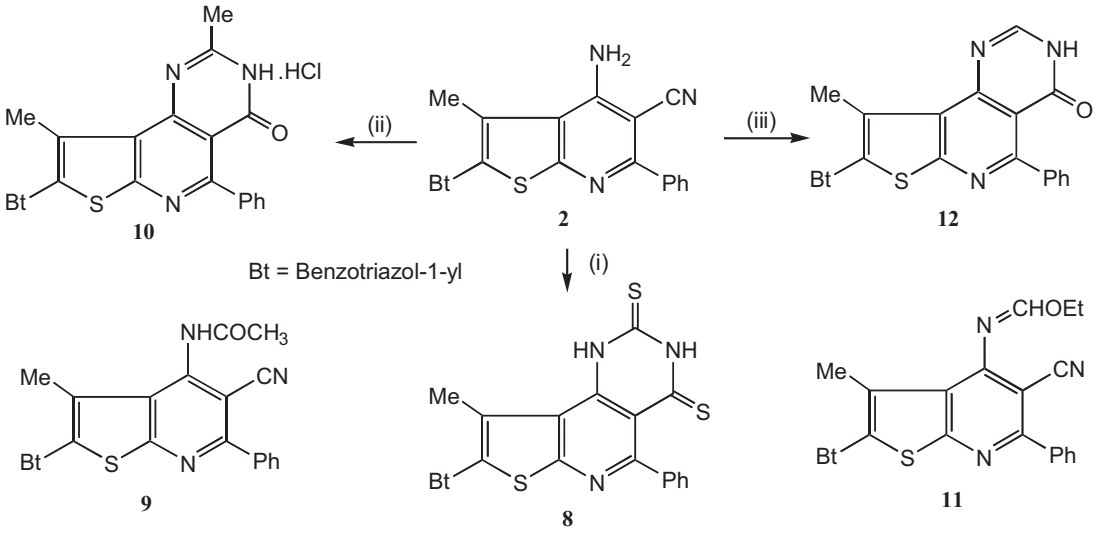
exchangeable proton attributed to an NH function at δ 8.71 ppm. When **5** was allowed to react with an excess of hydrazine hydrate in a mixture of ethanol and *N,N*-dimethylformamide under reflux, the dihydropyridazine-3,6-dione derivative[11] **7** was obtained in 81% yield (Scheme 1). The structure of **7** was confirmed by analytical and spectral data. The absence of the two ester carbonyl groups in the IR and NMR spectra and the presence of two broad singlets at δ_H 7.15 and 8.15 ppm attributed to the three NH groups, in addition to a singlet for the 5-CH proton at δ_H 8.11 ppm in the ^{1}H NMR spectrum was consistent with 4-aminopyridazine ring. Moreover, ^{13}C NMR spectrum revealed two highest frequency signals at δ_C 162.9 and 164.4 ppm, ascribable to two amide carbons.

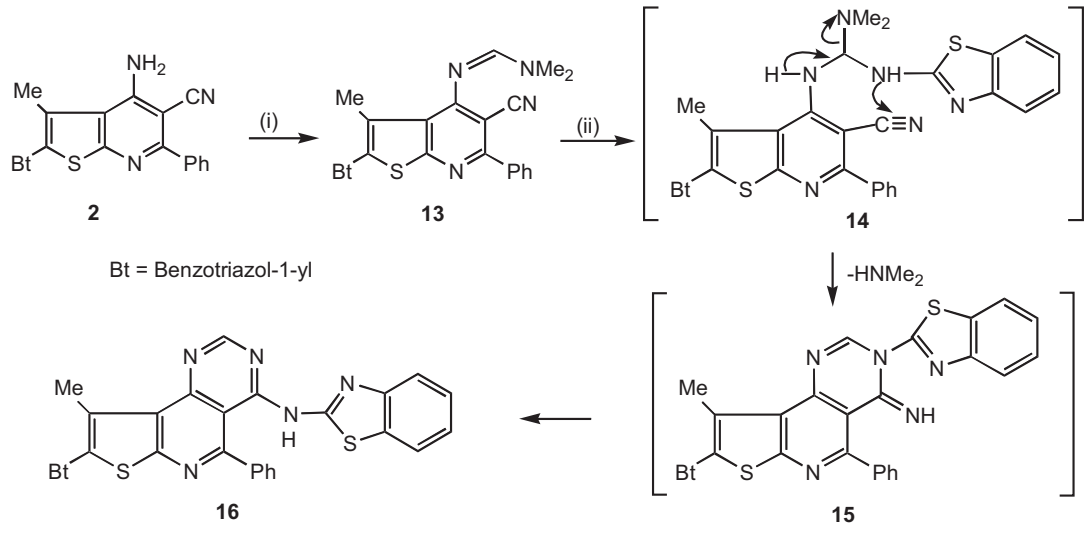
The treatment of **2** with carbon disulfide in pyridine under reflux afforded the fused pyrimidine-2,4-(*1H,3H*)-dithione derivative **8** in 81% yield. The spectral data of **8** were in complete agreement with this proposed structure. The reaction with carbon disulfide proceeded through the addition of CS_2 on the amino group of **2** followed by cyclisation *via* nucleophilic attack of sulfur atom on the cyano group, followed by rearrangement[12,13] to give thieno[2',3':2,3]pyrido[4,5-*d*] pyrimidine-2,4-(*1H*,*3H*)-dithione derivative **8** (Scheme 2). Heating compound **2** with acetic anhydride under reflux afforded a product with the possible structures of the *N*-acetamido derivative **9** or the thieno[2',3':2,3]pyrido[4,5-*d*]pyrimidine **10**. However, the absence of cyano absorption band in the IR spectrum of the reaction product excluded the structure **9**.

Treatment of compound **2** with triethyl orthoformate in the presence of a glacial acetic acid at refluxed temperature afforded **12** and not **11**. The structure of **12** was confirmed by analytical and spectral data. The absence of the nitrile group and the presence of amide carbonyl group at ν_{max} 1623 cm^{-1} in the IR spectrum indicated the formation of a pyrimidinone ring. Moreover, the absence of signals from the ethoxy group in the ^{1}H NMR spectrum ruled out the structure **11** (Scheme 2).

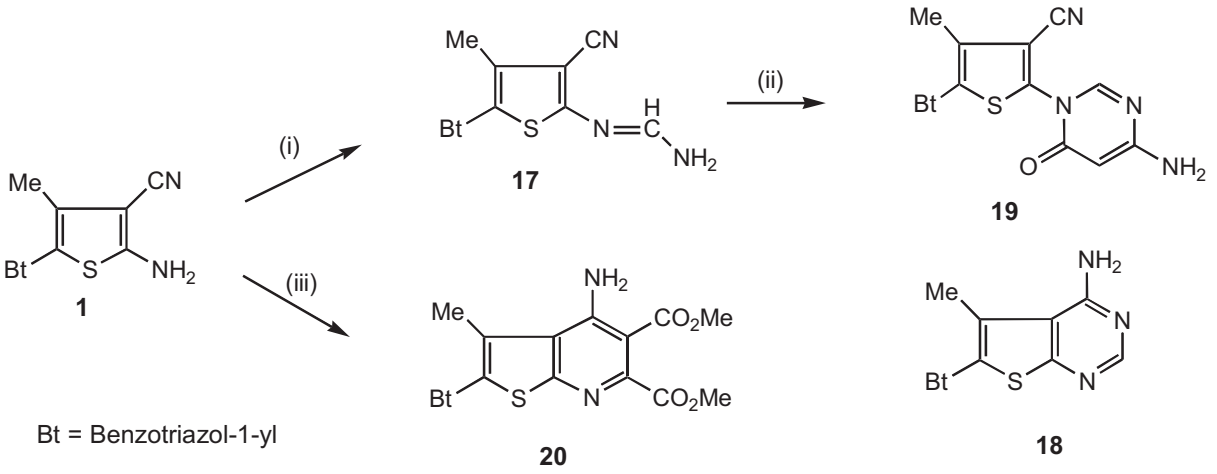
In contrast, compound **2** reacted with dimethylformamide dimethylacetal (DMFDMA) in dioxan under reflux to give 2-benzotriazol-1-yl-4-*N*-(*N′*,*N′*-dimethylaminomethylene) imino-3-methyl-6-phenylthieno[2,3-*b*]pyridine-5-carbonitrile **13** in good yield. The absence of an amino group in the IR spectrum and the presence of three singlet signals at δ_H 3.07, 3.17 and 7.05 ppm corresponding to *N*,*N*-dimethylamino and methylenic protons, respectively, in the ^{1}H NMR spectrum indicated the formation of the amidine derivative **13** (Scheme 3).



Scheme 2 Reagents: (i) CS_2, pyridine, reflux H_2O/HCl; (ii) Ac_2O, reflux; H_2O/HCl; (iii) $HC(OEt)_3/Ac_2O$, reflux.



Scheme 3 Reagents: (i) DMFDMA, dioxan, reflux; (ii) 2-aminobenzothiazole, fused, DMF: EtOH.



Scheme 4 Reagents: (i) $HCONH_2$, DMF: reflux; (ii) $CH_2(CN)_2$, aq.EtOH, pip., reflux; (iii) DMAD, K_2CO_3, DMSO, reflux, HCl.

Fusion of compound **13** with 2-aminobenzothiazole gave the thieno[2',3' : 2,3]pyrido[4,5-*d*]pyrimidine derivative **16** in good yield. The mass spectrum of **16** revealed a molecular ion peak [M^+] at *m/z* 542. The ^{1}H NMR spectrum showed, in addition to an aromatic multiplet, singlet signals for methyl and NH at δ_H 2.01 and 8.19 ppm respectively. The latter signal underwent ready H/D exchange upon addition of deuterium oxide. The formation of **16** we assume to take place *via* initial addition of exocyclic amino group of aminobenzothiazole moiety to the double bond of **13** to give the nonisolable intermediate **14** followed by cyclisation and elimination of *N*,*N*-dimethylamine, affording **15**, followed by a Dimroth type rearrangement[14,15] to **16** under the reaction conditions (Scheme 3). A literature survey revealed that pyridopyrimidine derivatives exhibit a broad spectrum of biologically interesting activity.[16,17]

On the other hand, when compound **1** was refluxed with formamide in *N,N*-dimethylformamide afforded a product which may be either **17** or **18**. The structural assignment for **17** is based on spectral and analytical data. The presence of the cyano group absorption in the IR spectrum indicates that the cyano group is not involved in the reaction, which excludes the possibility of **18**. Moreover, the ^{13}C NMR of the reaction product revealed the highest frequency signal at δ_C 154.4 ppm which corresponds to the imine carbon (Scheme 4).

Treatment of compound **17** with malononitrile in refluxing ethanol in the presence of a catalytic amount of piperidine gave the aminopyrimidone **19**. The IR spectrum of **19** shows stretching bands at ν_{max} 3309 and 3185 cm^{-1} attributed to NH_2 group in addition to strong stretching bands at ν_{max} 2206 and 1629 cm^{-1} assigned to nitrile and amide carbonyl groups respectively. The ^{1}H NMR spectrum showed two downfield singlet signals at δ 8.18 and 8.58 ppm corresponding to H-5 and H-2 pyrimidine ring protons, respectively. Moreover ^{13}C NMR spectrum of reaction product revealed highest frequency signal at δ_C 163 ppm corresponding to amide carbonyl group.

The reaction **1** with dimethyl acetylenedicarboxylate (DMAD) in DMSO and the presence of potassium carbonate gave dimethyl 4-amino-2-benzotriazolyl-3-methylthieno[2,3-b]pyridine-5,6-dicarboxylate (**20**) in good yield (Scheme 4). The absence of nitrile group in the IR spectrum of **20**, and the presence of amino in addition to ester carbonyl stretching bands at ν_{max} 3435, 3378 and 1704 cm^{-1} respectively, were in agreement with this. The ^{1}H NMR spectrum revealed two singlets at δ 3.72 and 3.88 ppm characteristic of the methoxy protons of the ester function.

Experimental

The IR spectra (KBr) were recorded on a Shimadzu 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 400 MHz spectrometer with *DMSO*-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are reported as δ unit (ppm). Mass spectra were measured on GC/MS VG Autospec Q instrument. Microanalyses were performed on a CHNS-LECO 932 analyser. Compounds **1** and **2** were prepared according to a recent report.[4]

2,4-Diamino-8-(benzotriazol-1-yl)-9-methyl-5-phenylthieno[2,3-b][1,6]naphthyridine-3-carbonitrile (**3**): A mixture of **2** (3.82 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in glacial acetic acid was refluxed for 5 h., then left to cool at room temperature and poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallised from a mixture of EtOH/DMF (2 : 1) as brown crystals (3.06 g, 68%), m.p. 124–126°C. IR: ν_{max} 3439–3358 ($2NH_2$), 2213 cm^{-1} (CN). ^{1}H NMR (DMSO-d_6): δ_H 1.95 (s, 3H, CH_3), 6.83–7.67 (m, 9H, Ar–H), 7.94 (br.s, 2H, NH_2, D_2O exchangeable), 8.56 ppm (br.s, 2H, NH_2, D_2O exchangeable). Found: C, 64.37; H, 3.67; N, 24.97. $C_{24}H_{16}N_8S$ (448.50) requires C, 64.27; H, 3.59; N, 24.98%.

4-Amino-8-(benzotriazol-1-yl)-9-methyl-2-oxo-5-phenyl-1,2-dihydrothieno[2,3-b][1,6]naphthyridine-3-carbonitrile (**4**): A suspension of **2** (3.82 g, 10 mmol) in dioxan (20 ml) containing a few drops of piperidine was treated with ethyl cyanoacetate (1.13 g, 10 mmol). The reaction was refluxed for 8 h, then left to cool at room temperature and poured onto ice-cold water. The solid product so formed was collected by filtration and recrystallised from a mixture of EtOH: DMF (2 : 1) as brown crystals (3.28 g, 73%), m.p. 248–250°C. IR: ν_{max} 3444–3245 (NH, NH_2), 2206 (CN), 1622 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d_6): δ_H 1.91(s,3H,CH_3), 7.06–8.16 (m, 9H, Ar–H), 8.25 ppm (br.s, 1H, NH D_2O exchangeable), 8.42 (br.s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 15.33 (CH_3), 103.2, 106.4, 110.4, 111.4, 111.7, 111.8, 111.9, 118.5, 120.2, 120.8, 124.9, 125.8, 128.2, 130.0, 134.0, 135.4, 135.6, 135.7, 145.6, 164.6 (aromatic carbons and CN) 165.9 ppm (amide CO). Found: C, 63.84; H, 3.66; N, 21.68. $C_{24}H_{15}N_7OS$ (449.49) requires C, 64.13; H, 3.36; N, 21.82%.

Dimethyl 1-N-[2'-benzotriazol-1-yl-5'-cyano-3'-methyl-6'-phenylthieno[2',3'-b]pyrido-4'-yl]aminoethylene-1,2-dicarboxylate (**5**): A stirred solution of **2** (3.82 g,10 mmol), in pyridine (20 ml) was treated with dimethyl acetylenedicarboxylate (DMAD) (1.23 g, 10 mmol). The reaction mixture was refluxed for 4 h., then poured onto ice-water and neutralised with hydrochloric acid (10%). The solid product, so formed was collected by filtration and recrystallised from a mixture of DMF: EtOH (2 : 1) as brown crystals (3.77 g, 72%), m.p. 138–140°C. IR: ν_{max} 3195–3325 (NH), 2202 (CN), 1731 cm^{-1} (2 ester CO). ^{1}H NMR (DMSO-d_6): δ_H 1.89 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.05 (s, 1H, vinyl-H), 7.38–8.55 (m, 9H, Ar–H); 8.71 ppm (br.s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ_C 15.2 (CH_3), 50.6 and 52.9 ($2OCH_3$), 111.4, 111.6, 116.5, 118.4, 120.8, 125.9, 126.2, 128.9, 129.9, 130.1, 130.2, 130.5, 131.5, 134.6, 135.6, 140.9, 145.5, 147.9, 162.6, 163.2 (aromatic, vinylic carbon and CN), 164.6 and 167.1 ppm (2 ester CO). Found: C, 61.92; H, 3.84; N, 16.30. $C_{27}H_{20}N_6O_4S$ (524.55) requires C, 61.82; H, 3.84; N, 16.02%.

4-[[2'-(Benzotriazol-1-yl)-5'-cyano-3'-methyl-6'-phenylthieno[2',3'-b]pyridin-4'-yl]amino]-1,2-dihydropyridazin-3,6-dione (**7**): A suspension of **5** (5.24 g, 10 mmol) in EtOH/DMF (2 : 1. 30 ml) was treated with hydrazine hydrate (0.5 g, 10 mmol). The reaction mixture was refluxed for 3 h. and left to cool to room temperature. The product so formed was collected by filtration and recrystallised from a mixture of EtOH: DMF (2 : 1) as brown crystals (3.98 g, 81%), m.p. 188–190°C. IR: ν_{max} 3198–3323 (3NH), 2204 (CN), 1626 cm^{-1} (2 amide CO); ^{1}H NMR (DMSO-d$_6$): δ_H 1.90 (s, 3H, CH_3), 7.15 (br.s, 1H, NH, D_2O exchangeable), 7.27–7.93 (m, 9H, Ar–H), 8.11 (s, 1H, H-5 pyradizine-H), 8.16 ppm (br.s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (DMSO-d$_6$): δ 14.9 (CH_3), 110.9, 111.4, 116.5, 118.2, 120.2, 120.7, 125.6, 126.2, 128.4, 128.9, 129.1, 129.9, 130.1, 130.4, 134.7, 135.2, 144.6, 144.6, 145.4, 150.1 (aromatic carbons and CN), 162.9, 164.4 ppm (2 amide CO). Found: C, 60.88; H, 3.07; N, 22.99. $C_{25}H_{16}N_8O_2S$ (492.51) requires C, 60.97; H, 3.27; N, 22.75%.

8-(Benzotriazol-1-yl)-9-methyl-5-phenylthieno[2',3': 2,3]pyrido[4,5-d]pyrimidine-2,4(1H,3H)-dithione (**8**): A solution of **2** (3.82 g, 10 mmol) in pyridine (30 ml) was treated with carbon disulfide (2.24 g, 10 mmol). The reaction mixture was refluxed for 8 h., then poured onto ice-water and neutralised with hydrochloric acid (10%). The product so formed was collected by filtration and recrystallised from EtOH as brown crystals (3.16 g, 69%), m.p. 195–197°C. IR: ν_{max} 3444–3348 (2NH),1550 cm^{-1} (2CS). ^{1}H NMR (DMSO-d$_6$): δ 2.07 (s, 3H, CH_3); 7.02–7.74 (m, 9H, Ar–H), 8.14 ppm (br.s, 2H, 2NH, D_2O exchangeable). Found: C, 57.62; H, 3.33; N, 18.47. $C_{22}H_{14}N_6S_3$ (458.35) requires C, 57.62; H, 3.07; N, 18.32%.

8-(Benzotriazol-1-yl)-2,9-dimethyl-5-phenylthieno[2',3': 2,3]pyrido[4,5-d]pyrimidin-4(3H)-one hydrochloride (**10**): A solution of **2** (3.82 g, 10 mmol) in acetic anhydride (20 ml) was refluxed for 3 h., then left to cool to room temperature. The reaction mixture was poured onto ice-cold water and neutralised with HCl (10%). The solid product so formed was collected by filtration and recrystallised from EtOH as brown crystals (2.89 g, 63%), m.p. 242–244°C. IR: ν_{max} 3382–3435 (NH), 1614 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d$_6$): δ_H 1.91 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 7.45–7.94 (m, 9H, Ar–H), 8.21 ppm (br.s, 1H, NH, D_2O exchangeable). Found: C, 60.02; H, 3.72; N, 18.20. $C_{23}H_{17}ClN_6OS$ (460.94) requires C, 59.93; H, 3.71; N, 18.23%.

8-(Benzotriazol-1-yl)-9-methyl-5-phenylthieno-[2',3':2,3]pyrido[4,5-d]pyrimidin-4(3H)-one (**12**): To a stirred solution of **2** (3.82 g, 10 mmol) in acetic anhydride (20 ml), triethyl orthoformate (1.6 g, 10 mmol) was added. The reaction mixture was refluxed for 5 h, then left to cool to room temperature. The solid product so formed was collected by filtration and recrystallised from a mixture of DMF: EtOH (2 : 1) as brown crystals (3.23 g, 79%), m.p. 116–118°C. IR: ν_{max} 3383-3435 (NH), 1623 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d$_6$): δ_H 1.94 (s, 3H, CH_3), 7.27–8.10 (m, 9H, Ar–H), 8.22 (br.s, 1H, NH, D_2O exchangeable), 8.56 ppm (s, 1H, H-2 pyrimidine-H). Found: C, 64.08; H, 3.45; N, 20.36. $C_{22}H_{14}N_6OS$ (410.45) requires C, 64.37; H, 3.43; N, 20.47%.

2-(Benzotriazol-1-yl)-4-N-(N,N-dimethylaminomethylene)imino-3-methyl-6-phenylthieno[2,3-b]pyridine-5-carbonitrile (**13**): A mixture of **2** (3.82 g, 10 mmol) and DMFDMA (1.33 g, 10 mmol) in dioxan (20 ml) was refluxed for 4 h. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallised from dioxan as brown crystals (3.53 g, 81%), m.p. 175–177°C. IR: ν_{max} 2209 cm^{-1} (CN). ^{1}H NMR (DMSO-d$_6$): δ_H 2.00 (s, 3H, CH_3), 3.07 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 7.50 (s, 1H, methylenic-H), 7.52–8.20 ppm (m, 9H, Ar–H). ^{13}C NMR (DMSO-d$_6$): δ_C 15.1 (CH_3), 35.9 (NCH_3), 41.37 (NCH_3), 111.5, 116.4, 118.6, 120.4, 120.9, 125.3, 126.0, 127.8, 128.9, 129.7, 129.9, 130.6, 131.5, 133.9, 134.4, 135.0, 145.6, 157.6, 166.7 ppm (aromatic, methylenic carbons and CN). Found: C, 65.90; H, 4.33; N, 22.15. $C_{24}H_{19}N_7S$ (437.52) requires C, 65.88; H, 4.37; N, 22.40%.

8-(Benzotriazol-1-yl)-4-(benzothiazol-2-ylamino)-9-methyl-5-phenylthieno[2',3': 2,3]pyrido[4,5-d]pyrimidine (**16**): A mixture of **13** (4.37 g, 10 mmol) and 2-aminobenzothiazole (1.50 g, 10 mmol) was fused for 10 minutes in an oil bath. The reaction mixture was left to cool, then triturated with a mixture of DMF (20 ml) and EtOH (10 ml). The solid product, so formed, was collected by filtration and recrystallised from a mixture of DMF: EtOH (2 : 1) as brown crystals (3.84 g, (71%), m.p. 210–212°C. IR: ν_{max} 3321 cm^{-1} (NH). ^{1}H NMR (DMSO-d$_6$): δ_H 2.01 (s, 3H, CH_3), 7.00–8.13 (m, 14H, Ar–H), 8.19 cm^{-1} (br.s, 1H, NH, D_2O exchangeable); MS (EI): *m/z* 542 [M$^+$]. Found: C, 64.08, H, 3.37; N, 20.59. $C_{29}H_{18}N_8S_2$ (542.64) requires C, 64.18; H, 3.34; N, 20.64%.

2-N-(Aminomethylene)imino-5-(benzotriazol-1-yl)-4-methylthiophene-3-carbonitrile (**17**): A solution of **1** (2.56 g, 10 mmol) and formamide (0.39 g, 10 mmol) in dimethylformamide (DMF) was refluxed for 10 h. The reaction was left to cool at room temperature. The solid product so formed was collected by filtration and recrystallised from a mixture of DMF: EtOH (2: 1) as pale brown crystals (2.23 g, 79%), m.p. 147–149°C. IR: ν_{max} 3310, 3192 (NH_2), 2207 cm^{-1} (CN). ^{1}H NMR (DMSO-d$_6$): δ_H 1.90 (s, 3H, CH_3), 7.43–8.15 (m, 5H, Ar–H and methylenic-H), 8.17 ppm (br.s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (DMSO-d$_6$): δ_C 15.2 (CH_3), 110.9, 116.6, 118.7, 120.9, 125.0, 126.1, 128.3, 130.2, 134.2, 135.4, 144.7 (aromatic and CN), 154.4 ppm (imine carbon). Found: C, 55.15; H, 3.45; N, 29.90. $C_{13}H_{10}N_6S$ (282.32) requires C, 55.33; H, 3.57; N, 29.76%.

2-(4-Amino-6-oxo-1,6-dihydropyrimidin-1-yl)-5-(benzotriazol-1-yl)-4-methylthiophene-3-carbonitrile (**19**): A mixture of **17** (3.06 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in aqueous EtOH (20 ml), containing few drops of piperidine was refluxed for 2 h. The solid product so formed was collected by filtration and recrystallised from a mixture of EtOH: DMF (2: 1) as pale brown crystals (2.48 g, 71%), m.p. 178–180°C. IR: ν_{max} 3309, 3185 (NH_2), 2206 (CN), 1629 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d$_6$): δ_H 2.01 (s, 3H, CH_3), 7.46–7.95 (m, 6H, Ar–H and NH_2 protons), 8.18 (s, 1H, H-5 pyrimidine-H), 8.58 ppm (s, 1H, H-2, pyrimidine-H). ^{13}C NMR (DMSO-d$_6$): δ_C 15.2 (CH_3), 111.6, 116.5, 118.5, 120.2, 120.3, 125.5, 128.3, 130.2, 134.6, 135.3, 145.0, 144.7, 149.0, 161.1 (aromatic carbons), 163.2 ppm (amide CO). Found: C, 55.03; H, 3.28; N, 28.21. $C_{16}H_{11}N_7OS$ (349.37) requires C, 55.00; H, 3.17; 28.06%.

Dimethyl 4-amino-2-(benzotriazol-1-yl)-3-methylthieno[2,3-b]pyridine-5,6-dicarboxylate (**20**): A mixture of **1** (2.56 g, 10 mmol), dimethyl acetylenedicarboxylate (DMAD), (1.23 g, 10 mmol) and potassium carbonate (1.38 g, 10 mmol) in DMSO (20 ml) was refluxed for 8 h. The reaction mixture was allowed to cool at room temperature and neutralised with hydrochloric acid (10%). The solid product so formed was collected by filtration and recrystallised from DMF as brown crystals, yield: 2.89 g (73%), m.p. 118–120°C. IR: ν_{max} 3435,3378 (NH_2), 1704 cm^{-1} (2 ester CO). ^{1}H NMR (DMSO-d$_6$), δ_H 2.04 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 7.46–8.16 (m, 4H, Ar–H), 8.18 ppm (br.s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (DMSO-d$_6$); δ_C 15.2 (CH_3), 50.5 (OCH_3), 52.7 (OCH_3), 116.5, 118.4, 120.4, 120.9, 125.9, 127.5, 128.3, 128.9, 130.2, 135.4, 135.4, 145.4, 149.9 (aromatic carbons), 163.2 and 164.6 ppm (2 ester CO). Found: C, 54.29; H, 3.77; N, 17.43. $C_{18}H_{15}N_5O_4S$ (397.41) requires C, 54.40; H, 3.80; N, 17.62%.

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