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Studies on heterocyclic β-enaminonitriles: Synthesis of new condensed thieno[2,3-*b*]pyridines containing *N*-heterocyclic moieties

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New versatile enaminonitrile-type building blocks, 3-aminothieno[2,3-*b*]pyridine-2-carbonitriles **3a,b**, were synthesized from 3-cyanopyridine-2-(1*H*)-thiones **1a,b**. Interaction of **3a,b** with triethyl orthoformate furnished the corresponding ethoxymethylideneamino derivatives **6a,b**. Derivatives of heterocyclic systems having the pyrazole, pyrimidine, and pyridine rings were obtained from the key precursors **3a,b** and **6a**, respectively.

Keywords: Enaminonitriles; Thienopyridines; Pyridothienopyrimidines; 1,2,4-Triazoles; Hydrazinolysis; Michael adducts

1. Introduction

Substituted 3-cyanopyridine-2-(1*H*)-thiones are versatile reagents and their chemistry has recently received considerable interest [1–3]. Derivatives of this ring system are interesting because of their diverse biological properties. Historically, a wide range of biological activities has been attributed to thienopyridine derivatives. Of particular interest, thieno[2,3-*b*]pyridines have been found to possess antibacterial [4–6], anticancer [7], and anti-inflammatory [8, 9] activities. Furthermore, fused heterocyclic derivatives of this ring system are also of great biological importance. For instance, derivatives of the pyridothienopyrimidine nucleus have been of recent interest owing to their ability to act as biologically active compounds. They show antimicrobial [10–12], antihyperlipaemic [13], anti-inflammatory [14], antiallergic [15], and antipyretic [16] properties, and were found to be useful as intercalating nucleic acids (INA) [17] and as antiprotozoals [18]. Prompted by the above considerations, and within the framework of our medicinal chemistry program [19–22], we have synthesized a variety of novel arylazo derivatives of tri- and tetracyclic heterocycles bearing thieno[2,3-*b*]pyridine moiety, with the

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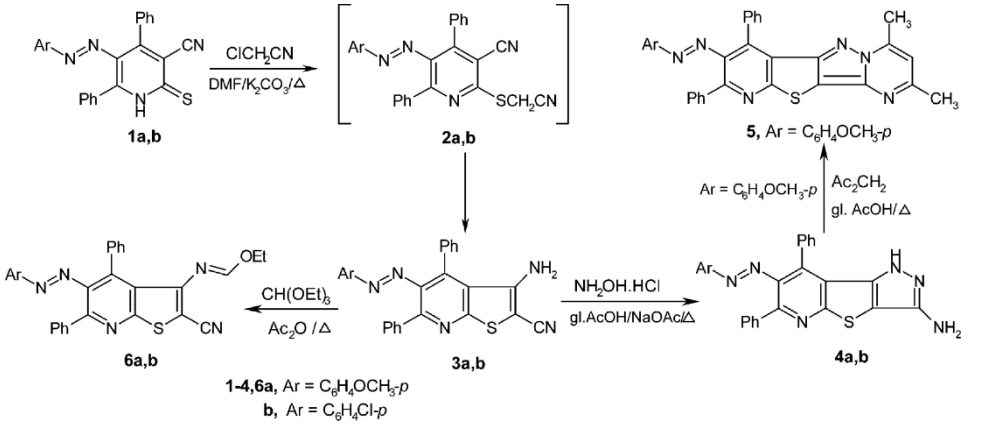
aim of obtaining compounds with potentially useful biological activities attractive to a wide circle of investigators.

2. Results and discussion

The starting materials 5-arylazo-3-cyano-4,6-diphenylpyridine-2-(1*H*)-thiones (**1a,b**) required for the synthesis of the title compounds were obtained from reaction of the arylhydrazones of dibenzoylmethane with cyanothioacetamide in refluxing ethanolic sodium ethoxide solutions as described earlier [23]. They were reacted with chloroacetonitrile, in dry dimethylforamide in the presence of excess anhydrous potassium carbonate, to give the non-isolable *S*-alkylated intermediates **2a,b**, which in turn underwent intramolecular heterocyclization affording the corresponding thieno[2,3-*b*]pyridine derivatives **3a,b** (Scheme 1). Elemental analyses and spectral data studies were used to establish both structures. As an example, the IR spectrum of **3a** indicated the presence of NH_2 group stretching at 3405-3300 cm^{-1} and CN group stretching at 2223 cm^{-1}. Its ^1H NMR spectrum exhibited a singlet at δ3.90 (3H) ppm corresponding to methoxy protons, as well as a singlet at δ5.72 (2H) ppm assigned to the NH_2 protons, besides the expected multiplet signal for the aromatic protons. Additionally, its mass spectrum revealed a molecular ion (M^+) peak at $M/z = 461$ with 20% relative abundance corresponding to the molecular formula $C_{27}H_{19}N_5OS$.

The 3-aminothieno[2,3-*b*]pyridine-2-carbonitriles **3a,b** could be cyclized under different conditions to form a variety of polycyclic compounds. Thus, treatment of those enaminonitriles **3a,b** with hydroxylamine hydrochloride in glacial acetic acid in the presence of anhydrous sodium acetate produced the corresponding aminopyrazoles **4a,b** via loss of a water molecule. When **4a** was allowed to react with acetylacetone, the tetracyclic compound **5** was formed. On the other hand, interaction of the nucleophilic 3-amino function of **3a,b** with triethyl orthoformate in acetic anhydride yielded the corresponding ethoxymethylideneamino derivatives **6a,b** (Scheme 1).

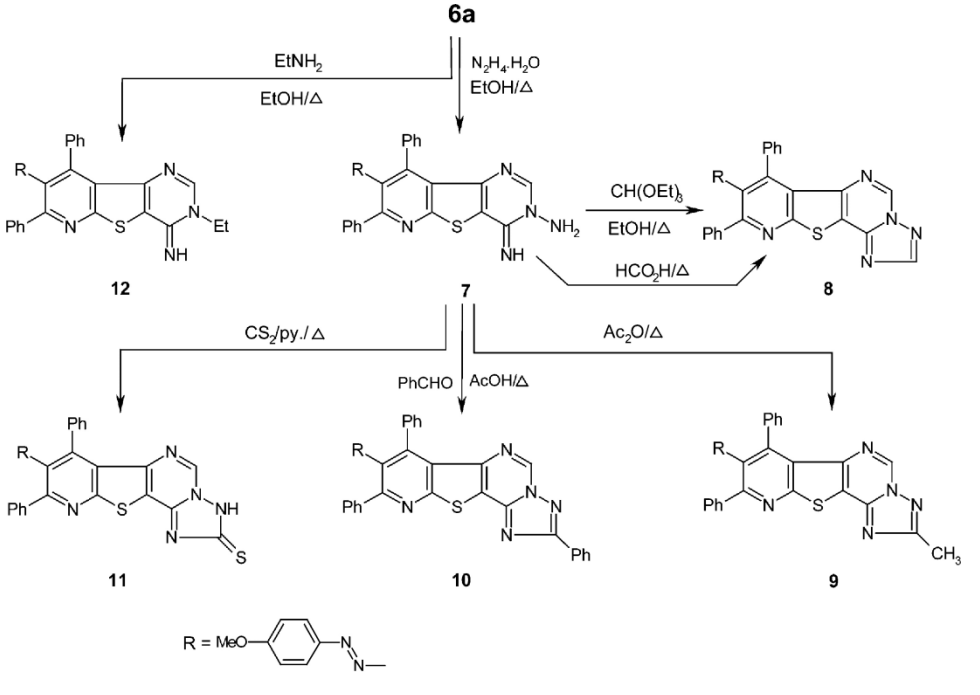
Interestingly, compound **6a** seemed to be a useful candidate for further chemical transformations. Thus, hydrazinolysis of **6a** in ethanol gave the imino compound **7**. Incorporation of various functionally-substituted triazole moieties into pyridothienopyrimidine structure was achieved by treating **7** with different reagents. Thus, compound **7** underwent further cyclization upon treatment with triethyl orthoformate affording the tetracyclic 1,2,4-triazole derivative **8**, which was also available from reaction of the imino derivative **7** with formic acid. Assignment



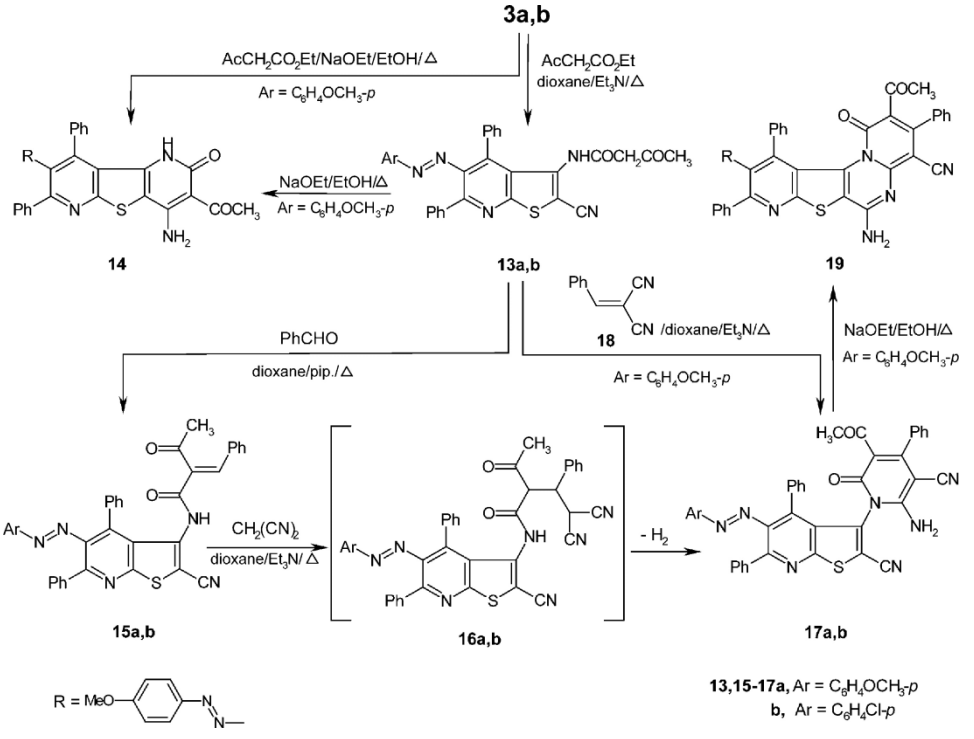
SCHEME 1

of structure **8** was established on the basis of analytical and spectral data. Thus, its IR spectrum showed the absence of the NH_2 and NH absorption bands, indicating the formation of a cyclic structure. Also, its ^{1}H NMR spectrum revealed, besides the expected signals, three singlet signals at δ3.94 (3H), δ9.01 (1H) and δ9.60 (1H) ppm attributed to the methoxy, triazole-CH and pyrimidine-CH protons, respectively. Another new triazolo derivative **9** was synthesized from the imino compound **7** by reaction with acetic anhydride. In addition, treatment of **7** with benzaldehyde gave the respective 2-phenyl derivative **10**. Formation of **10** was believed to proceed *via* loss of a water molecule and subsequent autoxidation involving elimination of a hydrogen molecule. Similar autoxidations, under comparable conditions, have been reported by Manhas *et al.* [24] and by others [25–27]. Finally, 2-thione derivative **11** was obtained by treating **7** with carbon disulfide in pyridine. Elucidation of the proposed structure of the latter products was established on the basis of elemental analyses and spectral background in each case (c.f. Experimental section). By analogy with hydrazine, compound **6a** also reacted with ethylamine to produce the desired *N*-ethyl derivative **12** (Scheme 2).

On the other hand, interaction of the enaminonitriles **3a,b** with ethyl acetoacetate, in 1,4-dioxane containing a catalytic amount of triethylamine, gave the corresponding amide derivatives **13a,b**. The analytical and spectral data for **13a,b** were in agreement with the assigned structures. Bands of NH, CN and two CO groups appeared in their IR spectra, while their ^{1}H NMR spectra confirmed the presence of CH_3, CH_2 and NH functionalities, in addition of the aromatic protons, in their proper positions (c.f. Experimental section). Cyclization of **13a** upon refluxing in ethanolic sodium ethoxide solution afforded the tricyclic derivative **14**, which was obtained directly from thienopyridine derivative **3a** upon refluxing in ethanolic sodium ethoxide solution. Both elemental and spectral data of **14** were consistent with the assigned structure. Thus, its IR spectrum revealed the disappearance of the absorption band characteritic for CN group. Also, its ^{1}H NMR spectrum exhibited, besides the expected signals, a singlet signal at δ6.03 (2H) ppm assigned to the NH_2 protons. The acyclic amide



SCHEME 2



SCHEME 3

derivatives **13a,b** were also found to be versatile intermediates in the synthetic realizations of heterocyclic systems (Scheme 3). The reaction of **13a,b** with benzaldehyde yielded the condensation products **15a,b**, which were subjected to ring closure by reacting them with malononitrile, affording the corresponding pyridines **17a,b**. Formation of **17a,b**, as illustrated in Scheme 3, may be explained through the intermediacy of the non-isolable adducts **16a,b** and a subsequent intramolecular nucleophilic attack took place, accompanied by aromatization *via* loss of a hydrogen molecule forming the final isolable products **17a,b**. Alternatively, compound **17a** could be obtained *via* an independent one-pot route involving the reaction of **13a** with benzylidenemalononitrile (**18**) to produce a reaction product that was identical in all respects (mp, mixed mp and IR data) to **17a**. Formation of latter product, in this case, could be also assumed to proceed through the intermediacy of the non-isolable acyclic *Michael* adduct **16a**, which spontaneously cyclized and aromatized to the final isolable product **17a**. Compound **17a** underwent further cyclization upon refluxing in ethanolic sodium ethoxide solution, affording the desired tetracyclic derivative **19** (Scheme 3). Elucidation of the proposed structure of the latter products was established on the basis of elemental analyses and spectral background in each case (c.f. Experimental section). Work along the expansion of such synthetic approach is now in progress. A discussion of the biological results as well as the industrial applications will be the subject of a future publication.

3. Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer in

DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. EI mass spectra were recorded on a Finnigan MAT SSQ 710 at 70 eV. Compounds **1a,b** were prepared according to the literature procedure [23].

3.1 *General procedure for the synthesis of 5-(arylazo)-3-amino-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonitriles (3a,b)*

To a solution of either pyridinethione **1a** or **1b** (0.005 mol) in dry dimethylformamide (25 ml), anhydrous potassium carbonate (0.01 mol) and chloroacetonitrile (5 mmol) were added. The reaction mixture heated at reflux for 45 min. and then allowed to stand at room temperature overnight under stirring. The reaction mixture was then diluted with cold water whereby the resulting precipitate, in each case, was filtered off, dried and recrystallized from the proper solvent to give the enaminonitriles **3a** (0.97 g; 42%) and **3b** (1.19 g; 51%), respectively.

3.2 *3-Amino-4,6-diphenyl-5-(*p*-methoxyphenylazo)thieno[2,3-*b*]pyridine-2-carbonitrile (3a)*

Mp 178–179 °C (1,4-dioxane); IR (ν/cm^{-1}) = 3405–3300 (NH_2), 3040 (CH aromatic), 2223 (CN), 1625 (C=N); ^{1}H NMR δ = 3.90 (s, 3H, OCH_3), 5.72 (s, 2H, NH_2), 7.29–7.88 (m, 14H, $2C_6H_5$, C_6H_4); MS: m/z (%) = 461 (M^+, 20%); $C_{27}H_{19}N_5OS$ (461.542): Calcd: C, 70.26; H, 4.15; N, 15.17; S, 6.95; Found: C, 70.03; H, 4.02; N, 14.89; S, 6.75.

3.3 *3-Amino-5-(*p*-chlorophenylazo)-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonitrile (3b)*

Mp 223–225 °C (DMF-H_2O); IR (ν/cm^{-1}) = 3412–3302 (NH_2), 3042 (CH aromatic), 2220 (CN), 1625 (C=N); ^{1}H NMR δ = 5.93 (s, 2H, NH_2), 7.35–7.83 (m, 14H, $2C_6H_5$, C_6H_4); $C_{26}H_{16}ClN_5S$ (465.961): Calcd: C, 67.02; H, 3.46; Cl, 7.61; N, 15.03; S, 6.88; Found: C, 66.84; H, 3.30; Cl, 7.36; N, 14.79; S, 6.69.

3.4 *General procedure for the synthesis of 7-(arylazo)-3-amino-6,8-diphenyl-1*H*-pyrazolo[3′,4′:4,5]thieno[2,3-*b*]pyridines (4a,b)*

A mixture of either enaminonitrile **3a** or **3b** (0.003 mol) and hydroxylamine hydrochloride (0.0035 mol), in glacial acetic acid (20 ml) containing anhydrous sodium acetate (1 g) was boiled under reflux for 5 h. The reaction mixture was left overnight at room temperature and then poured over iced water. The resulting solid products were collected by filtration, washed with water and recrystallized from the proper solvents to give the fused aminopyrazole derivatives **4a** (1.00 g; 70%) and **4b** (0.85 g; 59%), respectively.

3.5 *3-Amino-6,8-diphenyl-7-(*p*-methoxyphenylazo)-1*H*-pyrazolo[3′,4′:4,5]-thieno[2,3-*b*]pyridine (4a)*

Mp 228–230 °C (1,4-dioxane); IR (ν/cm^{-1}) = 3460–3230 (NH, NH_2), 3036 (CH aromatic), 1628 (C=N); ^{1}H NMR δ = 3.88 (s, 3H, OCH_3), 5.09 (s, 2H, NH_2), 7.25–7.80 (m, 14H, $2C_6H_5$, C_6H_4), 8.49 (s, 1H, NH); $C_{27}H_{20}N_6OS$ (476.556): Calcd: C, 68.05; H, 4.23; N, 17.63; S, 6.73; Found: C, 67.82; H, 4.11; N, 17.49; S, 6.55.

3.6 *3-Amino-7-(*p*-chlorophenylazo)-6,8-diphenyl-1*H*-pyrazolo[3′,4′:4,5]-thieno[2,3-*b*]pyridine (4b)*

Mp 248–250°C (DMF); IR (ν/cm^{-1}) = 3662–3225 (NH, NH_2), 3039 (CH aromatic), 1627 (C=N); ^{1}H NMR δ = 4.96 (s, 2H, NH_2), 7.33–7.78 (m, 14H, $2C_6H_5$, C_6H_4), 8.81 (s, 1H, NH); $C_{26}H_{17}ClN_6S$ (480.975): Calcd: C, 64.93; H, 3.56; Cl, 7.37; N, 17.47; S, 6.67; Found: C, 64.81; H, 3.38; Cl, 7.15; N, 17.21; S, 6.40.

3.7 *Synthesis of 7,9-dimethyl-2,4-diphenyl-3-(*p*-methoxyphenylazo)pyrido[3″,2″:4′,5′]-thieno[3′,2′:3,4]pyrazolo[1,5-*a*]pyrimidine (5)*

Acetylacetone (0.002 mol) was added to a solution of **4a** (0.002 mol) in glacial acetic acid (25 ml). After refluxing for 10 h, the solvent was removed *in vacuo* and the residue was triturated with water. The solid formed was filtered off, dried and recrystallized from AcOH to give **5** (0.58 g; 54%). Mp 263-264 °C; IR (ν/cm^{-1}) = 3045 (CH aromatic), 1630 (C=N); ^{1}H NMR δ = 2.53 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.30–7.81 (m, 14H, $2C_6H_5$, C_6H_4), 8.94 (s, 1H, CH pyrimidine); MS: m/z (%) = 540 (M^+, 16%); $C_{32}H_{24}N_6OS$ (540.642): Calcd: C, 71.09; H, 4.47; N, 15.54; S, 5.93; Found: C, 70.83; H, 4.25; N, 15.29; S, 5.81.

3.8 *General procedure for the synthesis of 5-(arylazo)-4,6-diphenyl-3-(ethoxymethylideneamino)thieno[2,3-*b*]pyridine-2-carbonitriles (6a,b)*

A mixture of either **3a** or **3b** (0.003 mol) and triethyl orthoformate (12 ml), was heated at reflux in acetic anhydride (8 ml) for 12 h, cooled at room temperature and then diluted with cold water. The resulting solid products were collected by filtration and recrystallized from the appropriate solvents to give **6a** (1.20 g; 77%) and **6b** (0.80 g; 51%), respectively.

3.9 *4,6-Diphenyl-3-(ethoxymethylideneamino)-5-(*p*-methoxyphenylazo)-thieno[2,3-*b*]pyridine-2-carbonitrile (6a)*

Mp 156–158 °C (EtOH); IR (ν/cm^{-1}) = 3038 (CH aromatic), 2224 (CN), 1626 (C=N); ^{1}H NMR δ = 1.23 (t, 3H, J = 7.1 Hz, CH_3 ethoxy), 3.84 (s, 3H, OCH_3), 4.31 (q, 2H, J = 7.1 Hz, OCH_2), 7.39–7.90 (m, 14H, $2C_6H_5$, C_6H_4), 8.27 (s, 1H, N=CH); $C_{30}H_{23}N_5O_2S$ (517.606): Calcd: C, 69.61; H, 4.48; N, 13.53; S, 6.20; Found: C, 69.46; H, 4.19; N, 13.23; S, 6.02.

3.10 *5-(*p*-Chlorophenylazo)-4,6-diphenyl-3-(ethoxymethylideneamino)-thieno[2,3-*b*]pyridine-2-carbonitrile (6b)*

Mp 189–190 °C (AcOH-H_2O); IR (ν/cm^{-1}) = 3041 (CH aromatic), 2223 (CN), 1624 (C=N); ^{1}H NMR δ = 1.27 (t, 3H, J = 7.0 Hz, CH_3 ethoxy), 4.24 (q, 2H, J = 7.0 Hz, OCH_2), 7.42–7.86 (m, 14H, $2C_6H_5$, C_6H_4) 8.22 (s, 1H, N=CH); $C_{29}H_{20}ClN_5OS$ (522.025): Calcd: C, 66.72; H, 3.86; Cl, 6.79; N, 13.42; S, 6.14; Found: C, 66.46; H, 3.72; Cl, 6.60; N, 13.16; S, 6.01.

3.11 *Synthesis of 3-amino-7,9-diphenyl-4-imino-8-(*p*-methoxyphenylazo)-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (7)*

Compound **6a** (0.002 mol) was mixed with hydrazine hydrate (2 ml, 0.04 mol), in ethanol (10 ml). The mixture was heated at reflux for 10 h, allowed to cool and then diluted with cold

water. The solid that separated was filtered off, washed with water, dried and recrystallized from AcOH to give the imino derivative **7** (0.90 g; 89%). Mp 218–219 °C; IR (ν/cm^{-1}) = 3365–3200 (NH, NH_2), 3035 (CH aromatic), 1629 (C=N); ^{1}H NMR δ = 3.91 (s, 3H, OCH_3), 5.78 (s, 2H, NH_2) 7.23–7.88 (m, 14H, $2C_6H_5$, C_6H_4), 8.89 (s, 1H, pyrimidine H-2), 10.05 (s, 1H, NH); MS: m/z (%) = 503 (M^+, 19%); $C_{28}H_{21}N_7OS$ (503.581): Calcd: C, 66.78; H, 4.20; N, 19.47; S, 6.37; Found: C, 66.56; H, 4.04; N, 19.31; S, 6.19.

3.12 *Synthesis of 7,9-diphenyl-8-(*p*-methoxyphenylazo)pyrido[3′,2′:4,5]thieno-[2,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8)*

3.12.1 Method A. To a solution of the imino derivative **7** (0.002 mol) in ethanol (20 ml), triethyl orthoformate (0.008 mol) was added. The reaction mixture was refluxed for 12 h. After cooling, the precipitate was filtered off, dried and recrystallized from DMF to give the triazolo compound **8** (0.60 g; 58%). Mp 243–244 ∘C; IR (ν/cm^{-1}) = 3037 (CH aromatic), 1630 (C=N); ^{1}H NMR δ = 3.94 (s, 3H, OCH_3), 7.27–7.98 (m, 14H, $2C_6H_5$, C_6H_4), 9.01 (s, 1H, CH triazole), 9.60 (s, 1H, CH pyrimidine); $C_{29}H_{19}N_7OS$ (513.576): Calcd: C, 67.82; H, 3.73; N, 19.09; S, 6.24; Found: C, 67.56; H, 3.54; N, 18.87; S, 6.09.

3.12.2 Method B. To formic acid (85%, 15 ml) was added compound **7** (0.002 mol) and the resulting mixture was refluxed for 7 h. After cooling to room temperature, the reaction mixture was poured with vigrous stirring over iced water. The obtained solid was collected by filtration and recrystallized from DMF to give a solid product (0.52 g; 51%) that was found to be identical in all aspects (mp, mixed mp, and IR data) to **8** obtained by method A.

3.13 *Synthesis of 7,9-diphenyl-8-(*p*-methoxyphenylazo)-2-methylpyrido-[3′,2′:4,5]thieno[2,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (9)*

A sample of compound **7** (0.002 mol), in acetic anhydride (15 ml), was heated at reflux for 5 h and then allowed to cool. Under stirring, the reaction mixture was poured over iced water. The separated solid product was collected by filtration, washed with water, dried and recrystallized from 1,4-dioxane to give **9** (0.65 g; 62%). Mp 255–257 °C; IR (ν/cm^{-1}) = 3034 (CH aromatic), 1628 (C=N); ^{1}H NMR δ = 2.78 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 7.28–7.95 (m, 14H, $2C_6H_5$, C_6H_4), 9.81 (s, 1H, CH pyrimidine); $C_{30}H_{21}N_7OS$ (527.603): Calcd: C, 68.30; H, 4.01; N, 18.58; S, 6.08; Found: C, 68.02; H, 3.84; N, 18.41; S, 5.92.

3.14 *Synthesis of 7,9-diphenyl-8-(*p*-methoxyphenylazo)-2-phenylpyrido-[3′,2′:4,5]thieno[2,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (10)*

A mixture of equimolar amounts (0.002 mol) of compound **7** and benzaldehyde was heated at reflux in glacial acetic acid (20 ml) for 6 h and then left aside to cool at room temperature overnight under stirring. The reaction mixture was then diluted with cold water, whereby the resulting solid product was collected by filtration and recrystallized from DMF to give **10** (0.78 g; 66%). Mp 275–276 °C; IR (ν/cm^{-1}) = 3041 (CH aromatic), 1628 (C=N); ^{1}H NMR δ = 3.95 (s, 3H, OCH_3), 7.25–8.02 (m, 19H, $3C_6H_5$, C_6H_4), 9.77 (s, 1H, CH pyrimidine); MS: m/z (%) = 589 (M^+, 24%); $C_{35}H_{23}N_7OS$ (589.673): Calcd: C, 71.29; H, 3.93; N, 16.63; S, 5.44; Found: C, 71.06; H, 3.77; N, 16.35; S, 5.26.

3.15 *General procedure for the synthesis of 7,9-diphenyl-8-(*p*-methoxyphenylazo)-pyrido[3′,2′:4,5]thieno[2,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine-2-(3*H*)-thione (11)*

A mixture of compound **7** (0.0025 mol) and carbon disulfide (1 ml), in dry pyridine (15 ml), was heated at reflux on a steam bath for 12 h and then allowed to cool. The excess of carbon disulfide was removed, and the remaining solid product was filtered off, dried and recrystallized from DMF to give **11** (0.75 g; 55%). Mp > 300 °C; IR (ν/cm^{-1}) = 3170 (NH), 3029 (CH aromatic), 1623 (C=N), 1235 (C=S); ^{1}H NMR δ = 3.92 (s, 3H, OCH_3), 7.22–8.00 (m, 14H, $2C_6H_5$, C_6H_4), 9.49 (s, 1H, CH pyrimidine), 10.02 (s, 1H, NH); $C_{29}H_{19}N_7OS_2$ (545.642): Calcd: C, 63.84; H, 3.51; N, 17.97; S, 11.75; Found: C, 63.57; H, 3.38; N, 18.03; S, 11.64.

3.16 *Synthesis of 7,9-diphenyl-3-ethyl-4-imino-8-(*p*-methoxyphenylazo)-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (12)*

To a mixture of compound **6a** (0.002 mol) in ethanol (20 ml), ethylamine (3 ml) was added. The mixture was heated at reflux for 3 h. After cooling, the precipitate was collected by filtration and recrystallized from AcOH to give **12** (0.55 g; 53%). Mp 204 °C; IR (ν/cm^{-1}) = 3300 (NH), 3035 (CH aromatic), 1620 (C=N); ^{1}H NMR δ = 1.40 (t, 3H, J = 7.0 Hz, CH_3), 3.42 (q, 2H, J = 7.0 Hz, CH_2), 3.94 (s, 3H, OCH_3), 7.24–7.91 (m, 14H, $2C_6H_5$, C_6H_4), 8.40 (s, 1H, pyrimidine H-2), 9.73 (s, 1H, NH); $C_{30}H_{24}N_6OS$ (516.620): Calcd: C, 69.75; H, 4.68; N, 16.27; S, 6.21; Found: C, 69.50; H, 4.51; N, 16.12; S, 6.06.

3.17 *General procedure for the synthesis of 5-(arylazo)-3-(acetoacetamido)-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonitriles (13a,b)*

Equivalent amounts (0.005 mol) of either **3a** or **3b** and ethyl acetoacetate, in 1,4-dioxane (30 ml) containing a catalytic amount of triethylamine (0.5 ml), were heated at reflux for 2 h and then left aside to cool at room temperature. The reaction mixture was poured onto cold water containing a few drops of dilute hydrochloric acid, whereby the resulting solid product, in each case, was collected by filtration and recrystallized from the proper solvent to give **13a** (1.64 g; 60%) and **13b** (1.13 g; 41%), respectively.

3.18 *3-(Acetoacetamido)-4,6-diphenyl-5-(*p*-methoxyphenylazo)thieno-[2,3-*b*]pyridine-2-carbonitrile (13a)*

Mp 195–197 °C (AcOH-H_2O); IR (ν/cm^{-1}) = 3291 (NH), 3031 (CH aromatic), 2219 (CN), 1683, 1670 (2C=O), 1622 (C=N); ^{1}H NMR δ = 2.62 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 7.24–7.86 (m, 14H, $2C_6H_5$, C_6H_4), 9.07 (s, 1H, NH); ^{13}C NMR δ = 30.9 (CH_3), 51.2 (CH_2), 56.0 (OCH_3), 114.1 (CN), 116.8, 117.3, 123.1, 125.2, 126.7, 127.5, 128.1, 129.7, 130.6, 132.6, 135.8, 139.1, 140.3, 142.5, 143.4, 144.2, 145.4, 148.7 (aromatic-C), 172.6 (C-OCH_3), 171.3, 179.8 (2C=O); $C_{31}H_{23}N_5O_3S$ (545.616): Calcd: C, 68.24; H, 4.25; N, 12.84; S, 5.88; Found: C, 67.99; H, 4.13; N, 12.64; S, 5.67.

3.19 *3-(Acetoacetamido)-5-(*p*-chlorophenylazo)-4,6-diphenylthieno-[2,3-*b*]pyridine-2-carbonitrile (13b)*

Mp 239–240 °C (AcOH); IR (ν/cm^{-1}) = 3305 (NH), 3031 (CH aromatic), 2220 (CN), 1685, 1670 (2C=O), 1622 (C=N); ^{1}H NMR δ = 2.59 (s, 3H, $COCH_3$), 4.09 (s, 2H, CH_2), 7.46–7.83

(m, 14H, $2C_6H_5$, C_6H_4), 8.85 (s, 1H, NH); $C_{30}H_{20}ClN_5O_2S$ (550.035): Calcd: C, 65.51; H, 3.66; Cl, 6.45; N, 12.73; S, 5.83; Found: C, 65.24; H, 3.42; Cl, 6.21; N, 12.48; S, 5.75.

3.20 *Synthesis of 3-acetyl-4-amino-7,9-diphenyl-8-(*p*-methoxyphenylazo)-2-oxo-1,2-dihydrothieno[2,3-*b*:4,5-*b*′]dipyridine (14)*

Either **13a** or **3a** (0.002 mol) was added portionwise with stirring to ethanolic sodium ethoxide solution [obtained from 0.046 g (0.002 mol) metallic sodium and 20 ml absolute ethanol]. The reaction mixture was refluxed with stirring on a water bath for 8 h. The reaction mixture was poured onto iced water containing a few drops of dilute hydrochloric acid, whereby the resulting precipitate, in each case, was filtered off, dried and recrystallized from DMF to give **14** (50–60%). Mp > 300 °C; IR (ν/cm^{-1}) = 3450–3321 (NH, NH_2), 3030 (CH aromatic), 1695, 1680 (2C=O), 1625 (C=N); ^{1}H NMR δ = 2.96 (s, 3H, $COCH_3$), 3.95 (s, 3H, OCH_3), 6.03 (s, 2H, NH_2), 7.22–7.90 (m, 14H, $2C_6H_5$, C_6H_4), 10.91 (s, 1H, NH); $C_{31}H_{23}N_5O_3S$ (545.616): Calcd: C, 68.24; H, 4.25; N, 12.84; S, 5.88; Found: C, 68.07; H, 4.01; N, 12.58; S, 5.71.

3.21 *General procedure for the synthesis of 5-(arylazo)-3-(α-benzylidene-β-oxobutyramido)-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonitriles (15a,b)*

To a mixture of either **13a** or **13b** (0.003 mol), in 1,4-dioxane (30 ml) containing a catalytic amount of piperidine (0.5 ml), benzaldehyde (0.003 mol) was added. The reaction mixture was heated at reflux for 3 h and then concentrated *in vacuo*. The remaining solid products were triturated with ethanol. The resulting solid products were filtered off, dried and recrystallized from the appropriate solvents to give **15a** (1.10 g; 58%) and **15b** (1.23 g; 64%), respectively.

3.22 *3-(α-Benzylidene-β-oxobutyramido)-4,6-diphenyl-5-(*p*-methoxyphenylazo)-thieno[2,3-*b*]pyridine-2-carbonitrile (15a)*

Mp 211–213 °C (1,4-dioxane); IR (ν/cm^{-1}) = 3296 (NH), 3027 (CH aromatic), 2218 (CN), 1682, 1671 (2C=O), 1623 (C=N); ^{1}H NMR δ = 2.76 (s, 3H, $COCH_3$), 3.89 (s, 3H, OCH_3), 6.72 (s, 1H, C=CH), 7.30–7.93 (m, 19H, $3C_6H_5$, C_6H_4), 9.18 (s, 1H, NH); $C_{38}H_{27}N_5O_3S$ (633.724): Calcd: C, 72.02; H, 4.29; N, 11.05; S, 5.06; Found: C, 71.76; H, 4.04; N, 10.83; S, 4.88.

3.23 *3-(α-Benzylidene-β-oxobutyramido)-5-(*p*-chlorophenylazo)-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonitrile (15b)*

Mp 261–262 °C (DMF); IR (ν/cm^{-1}) = 3301 (NH), 3030 (CH aromatic), 2216 (CN), 1681, 1669 (2C=O), 1623 (C=N); ^{1}H NMR δ = 2.80 (s, 3H, $COCH_3$), 6.61 (s, 1H, C=CH), 7.45–7.79 (m, 19H, $3C_6H_5$, C_6H_4), 8.66 (s, 1H, NH); $C_{37}H_{24}ClN_5O_2S$ (638.143): Calcd: C, 69.64; H, 3.79; Cl, 5.56; N, 10.97; S, 5.02; Found: C, 69.36; H, 3.62; Cl, 5.37; N, 10.68; S, 4.79.

3.24 *General procedure for the synthesis of 5-(arylazo)-3-(5-acetyl-2-amino-3-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-1-yl)-4,6-diphenylthieno[2,3-*b*]-pyridine-2-carbonitriles (17a,b)*

3.24.1 Method A. To a solution of **15a** or **15b** (0.002 mol), in 1,4-dioxane (30 ml) containing a catalytic amount of triethylamine (0.5 ml), malononitrile (0.002 mol) was added. The

reaction mixture was heated, under reflux, for 4 h and then evaporated *in vacuo*. The remaining products were triturated with ethanol, whereby the resulting solid products were filtered off, dried and recrystallized from the proper solvents to give **17a** (0.94 g; 67%) and **17b** (0.74 g; 53%), respectively.

3.25 *3-(5-Acetyl-2-amino-3-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-1-yl)-4,6-diphenyl-5-(*p*-methoxyphenylazo)thieno[2,3-*b*]pyridine-2-carbonitrile (17a)*

Mp 269–270 °C (DMF-H_2O); IR (ν/cm^{-1}) = 3442, 3365 (NH_2), 3047 (CH aromatic), 2225, 2220 (2CN), 1705, 1692 (2C=O), 1627 (C=N); ^{1}H NMR δ = 3.10 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 5.90 (s, 2H, NH_2), 7.21–8.05 (m, 19H, $3C_6H_5$, C_6H_4); $C_{41}H_{27}N_7O_3S$ (697.769): Calcd: C, 70.58; H, 3.90; N, 14.05; S, 4.60; Found: C, 70.36; H, 3.74; N, 13.83; S, 4.48.

3.26 *3-(5-Acetyl-2-amino-3-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-1-yl)-5-(*p*-chlorophenylazo)-4,6-diphenylthieno[2,3-*b*]pyridine-2-carbonitrile (17b)*

Mp > 300 °C (DMF); IR (ν/cm^{-1}) = 3455, 3370 (NH_2), 3047 (CH aromatic), 2225, 2221 (2CN), 1708, 1690 (2C=O), 1630 (C=N); ^{1}H NMR δ = 3.07 (s, 3H, $COCH_3$), 5.78 (s, 2H, NH_2), 7.50–7.99 (m, 19H, $3C_6H_5$, C_6H_4); $C_{40}H_{24}ClN_7O_2S$ (702.188): Calcd: C, 68.42; H, 3.44; Cl, 5.05; N, 13.96; S, 4.57; Found: C, 68.16; H, 3.21; Cl, 4.87; N, 13.66; S, 4.29.

3.26.1 Method B. Equimolar amounts (0.005 mol) of **13a** and benzylidenemalononitrile (**18**), in 1,4-dioxane (30 ml) containing a catalytic amount of triethylamine (0.5 ml), were heated at reflux for 5 h. The reaction mixture was then cooled, poured over iced water and neutralized with dilute hydrochloric acid to precipitate the solid product, which was collected by filtration and recrystallized from DMF-H_2O to give a reaction product (0.74 g; 57%) identical in all respects to that described in method A.

3.27 *Synthesis of 7-acetyl-11-amino-9-cyano-3-(*p*-methoxyphenylazo)-6-oxo-2,4,8-triphenylpyrido[3′,2′:4,5]thieno[2,3-*e*]pyrido[1,2-*a*]pyrimidine (19)*

Compound **17a** (0.002 mol) was added portionwise with stirring to ethanolic sodium ethoxide solution [obtained from 0.046 g (0.002 mol) metallic sodium and 20 ml absolute ethanol]. The reaction mixture was refluxed with stirring on a water bath for 6 h. The solid product formed upon pouring onto ice/water containing a few drops of dilute hydrochloric acid was filtered off, dried and recrystallized from DMF to give **19** (0.88 g; 63%). Mp > 300 °C; IR (ν/cm^{-1}) = 3461, 3375 (NH_2), 3050 (CH aromatic), 2217 (CN), 1706, 1691 (2C=O), 1632 (C=N); ^{1}H NMR δ = 3.21 (s, 3H, $COCH_3$), 3.93 (s, 3H, OCH_3), 6.11 (s, 2H, NH_2), 7.27–8.04 (m, 19H, $3C_6H_5$, C_6H_4); $C_{41}H_{27}N_7O_3S$ (697.769): Calcd: C, 70.58; H, 3.90; N, 14.05; S, 4.60; Found: C, 70.29; H, 3.66; N, 13.90; S, 4.41.

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