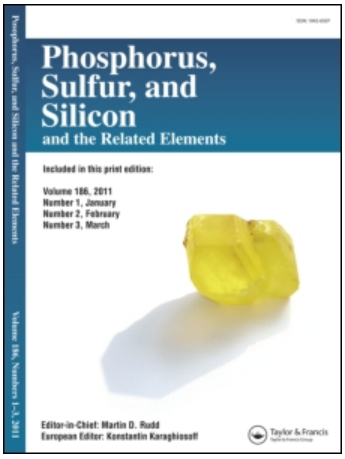

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N-1-Naphthyl-3-oxobutanamide in Heterocyclic Synthesis: A Facile Synthesis of Nicotinamide, Thieno[2,3-*b*]pyridine, and Bi- or Tricyclic Annulated Pyridine Derivatives Containing Naphthyl Moiety

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N-1-Naphthyl-3-oxobutanamide in Heterocyclic Synthesis: A Facile Synthesis of Nicotinamide, Thieno[2,3-*b*]pyridine, and Bi- or Tricyclic Annulated Pyridine Derivatives Containing Naphthyl Moiety

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*N-1-Naphthyl-3-oxobutanamide (**1**) reacts with arylidinecyanothioacetamide **2a–c** in ethanol/piperidine solution under reflux to yield the pyridine-2(1H)-thiones **6a–c**. Compound **6a** reacts with α-haloketones **7a–e** to give the 6-thio-N-1-naphthyl-nicotinamides derivatives **8a–e**, which cyclized to thieno[2,3-b]pyridine derivatives **9a–e**. The reaction of compound **9a** with hydrazine hydrate and formamide gives the thieno[2,3-b]pyridine carbohydrazide derivative **10** and pyridothienopyrimidine derivative **11**, respectively. Reaction of **9a** with benzoyl isothiocyanate gave thiourea derivative **12**. Compound **12**, upon treatment with alcoholic NaOH, gave pyridothienopyrimidine **13**. Saponifications of **9a** gave the amino acid **15**, which affords **16** when refluxed in Ac_2O. Treatment of compound **16** with $AcONH_4$/AcOH gave **17**. Diazotization and self-coupling of **9b** gave the pyridothienotriazine **18**. Also, diazotization of the ortho-aminohydrazide **10** give the corresponding azide **19**, which was subjected to Curtius rearrangement in boiling xylene to give imidazothienopyridine **20**. Reaction of **10** with either formic acid or triethylorthoformate and phenyl isothiocyanate gave the corresponding pyridothienotriazepines **22** and **23**, respectively. The interaction of **10** with acetylacetone furnished the pyrazolyl derivative **24**. The structures of the synthesized compounds were established from their analytical and spectral data.*

Keywords *N*-1-Naphthylnicotinamides; *N*-1-naphthyl-3-oxobutanamides; pyridine-2(1*H*)-thiones; pyridothienopyrididines; pyridothienotriazepines; thieno[2,3-*b*]pyridines

INTRODUCTION

Polyfunctionally substituted pyridines are among the most intensively studied heterocyclic chemistry. Many of the polyfunctionally

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substituted pyridines are biologically active as anti-proliferative,[1] cardiotonic agents,[2,3] and antiviral[4,5] agents.

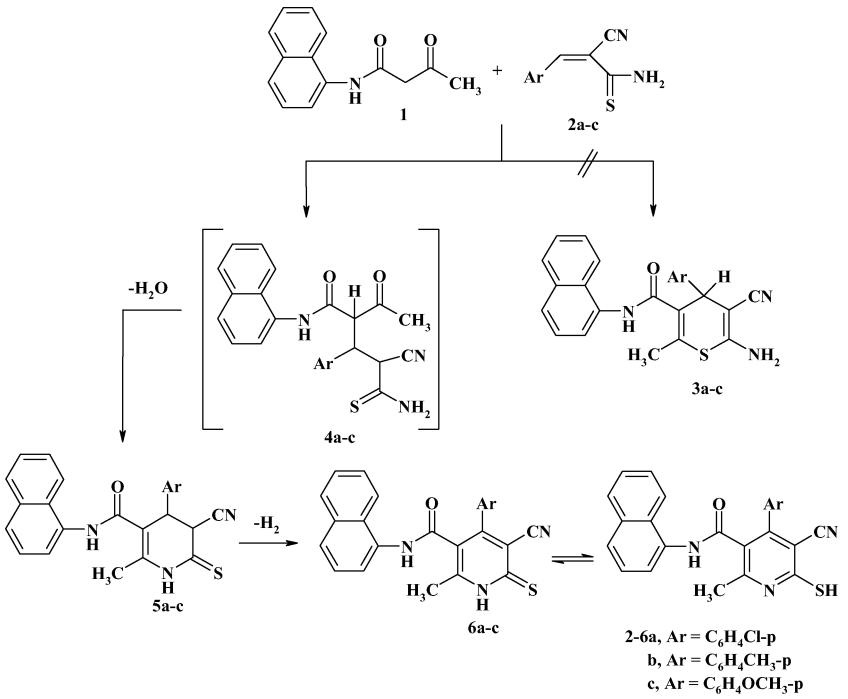
The literature contains a number of syntheses of substituted biheterocyclic and triheterocyclic ring systems containing a pyridine moiety and featuring a variety of pharmacological effects such as antimicrobial,[6,7] antiviral,[4,5,8] anti-inflammatory,[9] antiallergic,[10] antiprotozoa,[11] anti-anaphylactic,[12] antitumor,[13] and antiparasitic,[14] and a few possess significant hypocholesteromic[15] activity.

Recently many chemical structures containing the naphthyl moiety were reported to exhibit diverse biological and pharmaceutical activities such as anticonvulsant,[16] antimicrobial,[16,17] anticancer,[18,19] antiallergic,[20] antiobesity,[21] and antidiabetic[21] activities. In continuation of our research program for the synthesis of bi- or tricyclic annulated pyridine derivatives,[22–31] and in view of the continued interest in the chemistry of these compounds, we report here the results of our investigation on the synthesis of new *N*-1-naphthylnicotinamides, thieno[2,3-*b*]pyridines, pyrido-thienopyrididines, and pyridothienotriazipenes using pyridine-2(1*H*)-thiones.

RESULTS AND DISCUSSION

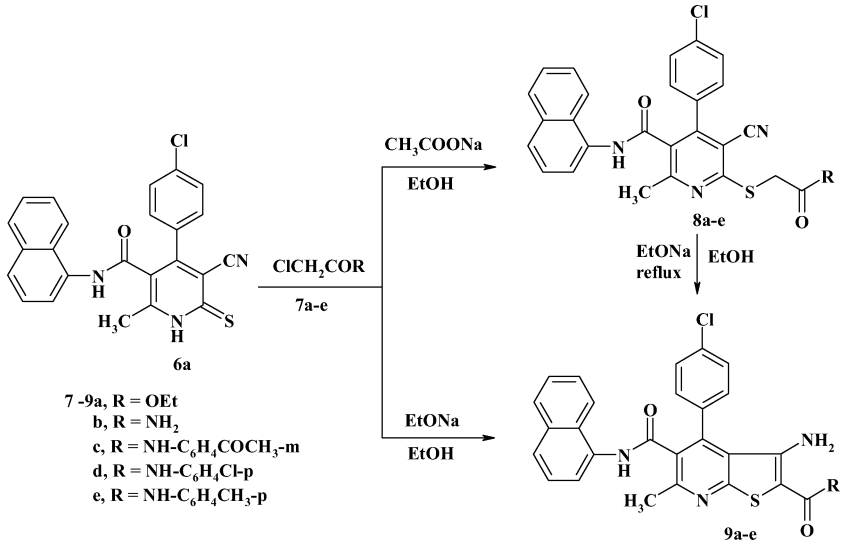
It has been found that *N*-1-naphthyl-3-oxobutanamides **(1)** (prepared by treating 1-naphthylamine with ethyl acetoacetate as described in the literature[32]) easily reacted with arylidine cyanothioacetamide **2a–c** in refluxing ethanol and sodium acetate to yield a product that may be either pyridine-2(1*H*)-thiones **6a–c**[33] or its isomeric thiopyran structure **3**. Establishing the exact structure of the reaction product as structure **6a–c** rather than **3** is based on the spectroscopic data. Thus, the ^{1}H NMR spectrum of compound **6b**, for example, revealed the presence of singlet signals at $\delta = 10.22$ and 14.36 ppm assigned to 2NH groups and no signal assigned for the thiopyrane CH-4. So the pyridine-2(1*H*)-thiones **6a–c** are considered to be the only reaction products. The formation of compound **6** is assumed to proceed via an initial addition of the active methylene moiety in **1** to the active double bond in **2**, thus forming the acyclic Michael adduct **4**, which then cyclized to **5** by a loss of water and aromatized by a loss of hydrogen to the final product[33] **6** (Scheme 1).

The reaction of pyridinethione derivative **6a** with α -haloketones **7a–e** in ethanol containing 1.0 g of sodium acetate afforded the *S*-alkyl-*N*-1-naphthylnicotinamide derivatives **8a–e**. The structure of compounds **8a–e** has been confirmed as the correct one based on its spectral data and elemental analyses. Thus, the IR spectrum of compound **8a**, for



SCHEME 1

example, exhibited the presence of the absorption band of the CN functional group at υ 2221 cm^{-1} and a carbonyl ester at υ 1737 cm^{-1}. The ^1H NMR spectrum of compound **8a** revealed the appearance of CH_3-CH_2-protons at $\delta = 1.26, 4.25$ ppm, SCH_2 protons at $\delta = 5.63$ ppm, in addition to the other protons assigned in compound **6a** and the disappearance of the proton of one NH ($\delta = 14.50$ ppm in compound **6a**). Compound **8a** underwent cyclization into the thieno[2,3-*b*]pyridine derivative **9a** upon treatment with ethanolic sodium ethoxide. The IR spectrum of compound **9a** exhibited the disappearance of the absorption band due to the CN function group and the appearance of absorption bands due to the NH_2 functional group at υ 3450, 3300 cm^{-1}. The ^1H NMR spectrum of compound **9a** revealed the disappearance of the protons assigned to the methylene group at $\delta = 5.63$ ppm and revealed the presence of two protons as a singlet at $\delta = 4.02$ ppm assignable to the NH_2 group beside the other protons in their proper positions. The structure of **9a** has been confirmed as the correct one by its synthesis via the reaction of **6a** with ethyl chloroacetate (**7a**) in boiling ethanolic sodium ethoxide solution. Compound **9a** prepared via this route was found to be completely identical with **9a** as prepared by the first route (Scheme 2).



SCHEME 2

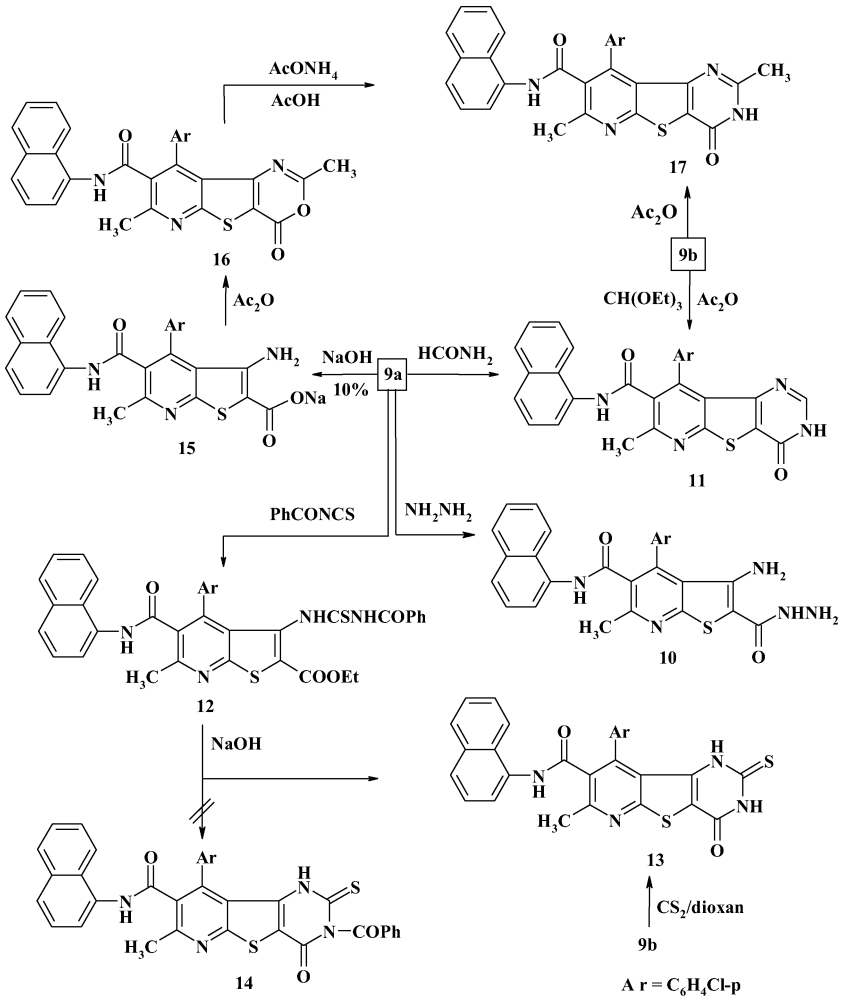
Similarly, compounds **8b–e** underwent reactions into thieno[2,3-*b*]-pyridine derivative **9b–e** upon treatment with ethanolic sodium ethoxide. The structures of **9b–e** were established based on spectral data, elemental analyses, and by their synthesis via the reaction of **6a** with α-haloketones **7b–e** in boiling ethanolic sodium ethoxide solution (Scheme 2).

The reactivity of β-amino ester derivative **9a** toward some electrophilic reagents has been studied. Thus, the reaction of **9a** with hydrazine hydrate afforded 3-aminothieno[2,3-*b*]pyridine carbohydrazide derivative **10**. The structure of hydrazide **10** was compatible with the spectroscopic data (IR and ^{1}H NMR). In contrast to this behavior, when compound **9a** was refluxed in formamide solution, it afforded the expected *N*-1-naphthyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine-8-carboxamide derivative **11**.

Hard evidence of the structure of **11** came from its synthesis via the reaction of **9b** with triethylorthoformate in acetic anhydride.

Alternatively, the thiourea derivative **12** was obtained by the reaction of **9a** with benzoyl isothiocyanate in anhydrous acetone.[34,35] Compound **12**, upon alkaline cyclization with alcoholic sodium hydroxide, gave 1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide derivative **13** instead of 3-benzoyl-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide derivative **14**. The ^{1}H NMR spectrum of compound **13** revealed the presence of 3NH

protons and the absence of benzoyl protons. Compound **13** has been confirmed as the correct one by its synthesis via the reaction of **9b** with carbon disulfide in refluxing dioxane (Scheme 3).

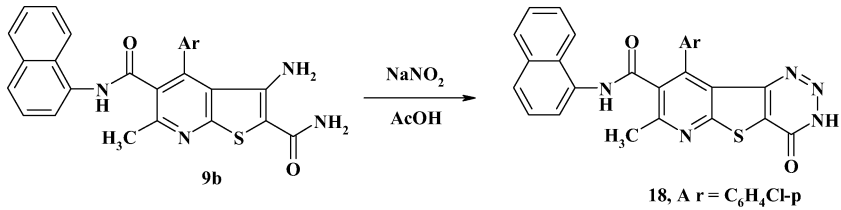


SCHEME 3

Saponification of **9a** using alcoholic sodium hydroxide yielded the sodium salt of the *β*-amino acid **15**, which gave the pyrido[3′,2′:4,5]thieno[3,2-*d*][1,3]-oxazine-8-carboxamide derivative **16** when refluxed in acetic anhydride. Structure **16** was established based on elemental analysis and spectral data. Thus, the IR spectrum of

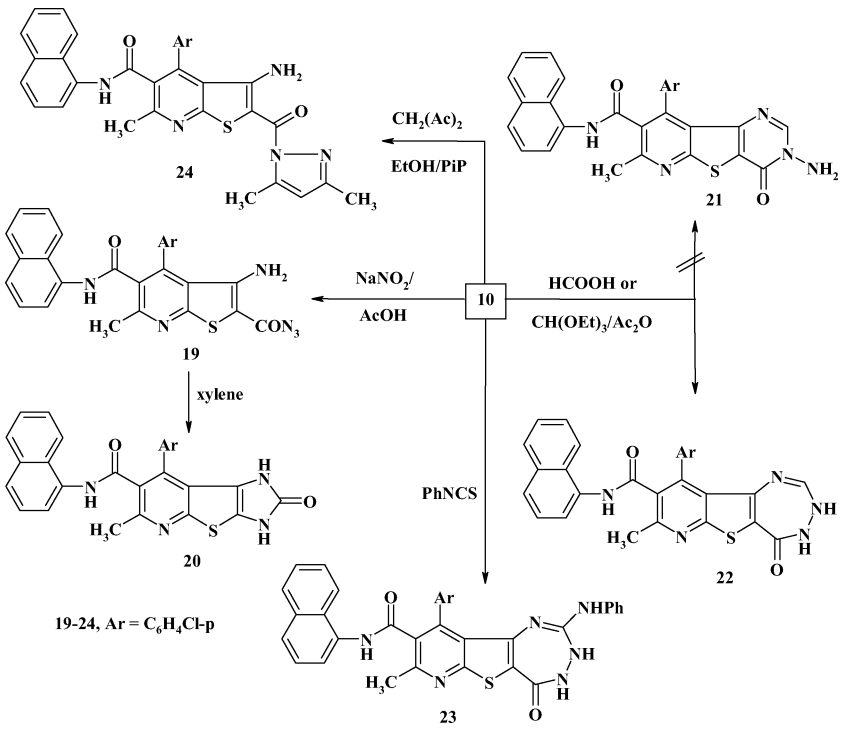
16 showed the absence of any absorption bands that may be attributed to NH_2 function group. Moreover, its ^1H NMR spectrum showed two singlet signals at $\delta = 2.67$ and 2.87 ppm assigned to two CH_3. The treatment of **16** with ammonium acetate in boiling acetic acid led to the formation of pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide derivative **17**. Compound **17** can also be prepared by heating compound **9b** in acetic anhydride under reflux (Scheme 3).

Treatment of 3-amino-N^5-1-naphthylthieno[2,3-*b*]pyridine-2,5-dicarboxamide derivative **9b** with a cold solution of sodium nitrite in acetic acid **9b** gave *N*-1-naphthyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-*d*][1,2,3]triazine-8-carboxamide derivative **18** (Scheme 4).



SCHEME 4

Similarly, diazotization of 3-aminothieno[2,3-*b*]pyridine carbohydrazide derivative **10** gave the corresponding 3-amino-5-[(1-naphthylamino)carbonyl]thieno[2,3-*b*]pyridine-2-carbonyl azide derivative **19**, which was subjected to Curtius rearrangement in refluxing xylene[25,30] to give *N*-1-naphthyl-2-oxo-2,3-dihydro-1*H*-imidazo-[4′,5′:4,5]thieno[2,3-*b*]pyridine-7-carboxamide derivative **20**. Structure **20** was elucidated based on spectral data and elemental analysis (cf. the Experimental section). Also, the reaction of **10** with formic acid or triethyl orthoformate in ethanol gave either the *N*-amino pyrimidine derivative **21** or the triazepine derivative **22**. Structure **21** was ruled out based on ^1H NMR, which revealed the absence of *N*-amino protons. Moreover the ^1H NMR spectrum of the reaction product revealed three protons as singlet signals at $\delta = 7.14$–7.92 with the aromatic protons, 10.46 and 11.57 ppm for three NH protons. So the reaction product was formulated as *N*-1-naphthyl-5-oxo-4,5-dihydro-3*H*-pyrido[3′,2′:4,5]thieno[3,2-*e*][1,2,4]triazepine-9-carboxamide derivative **22**. Also, the reaction, of **10** with phenyl isothiocyanate in anhydrous dioxane gave the triazepine derivative **23**. The structure of triazepines **22** and **23** was confirmed by spectral data, elemental analysis, and reports in the literature.[25] The interaction of **10**



SCHEME 5

with acetyl acetone furnished 3-amino-2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-*N*-1-naphthylthieno[2,3-*b*]pyridine-5-carboxamide derivative **24**. The ^{1}H NMR spectrum of compound **24** showed the presence of three methyl groups at $\delta = 2.02$, 2.52, and 2.76 ppm (cf. Scheme 5 and the Experimental section).

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra in KBr discs were recorded on a Bruker Vector 22 FT-IR spectrophotometer. ^{1}H NMR spectra were determined in DMSO-d_6 and $CDCl_3$ at 300 MHz on Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed as δ ppm. Mass spectra were recorded on GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Compound **1** was prepared according to reports in the literature.[32]

Preparation of Compounds 6a–c: General Procedure

A mixture of compound **1** (0.01 mol) and arylidinecyanothioacetamide **2a–c** (0.01 mol) in ethanol (30 mL) was treated with piperidine (0.5 mL) and heated under reflux for 8 h. The reaction mixture was then cooled by being poured into crushed ice and acidified with HCl. The solid product was collected and recrystallized from ethanol to give compounds **6a–c**.

4-(4-Chlorophenyl)-5-cyano-2-methyl-N-1-naphthyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (6a)

It was obtained as yellow crystals from ethanol, yield 88%; mp 285°C; IR (KBr): υ cm^{-1} 3358, 3200 (2NH), 3055 (CH-arom.), 2973 (CH-aliph.), 2226 (CN) and 1653 (CO). ^{1}H NMR (DMSO-d$_6$): $\delta = 2.60$ (s, 3H, CH_3), 7.15–7.92 (m, 11H, Ar-H), 10.30 (s, 1H, NH) and 14.50 (br, 1H, NH). MS: $m/z = 431$ (28%), 426 (80%), 143 (100%). Elemental analysis for $C_{24}H_{16}N_3OSCl$ (429.5): Calcd., C 67.05, H 3.75, N 9.77, S 7.45, Cl 8.26%. Found, C 67.35, H 3.49, N 9.98, S 7.16, Cl 8.01%.

5-Cyano-2-methyl-4-(4-methylphenyl)-N-1-naphthyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (6b)

It was obtained as yellow crystals from ethanol, yield 86%; mp 298°C. IR (KBr): υ cm^{-1} 3368, 3210 (2NH), 3045 (CH-arom.), 2922 (CH-aliph.), 2209 (CN), 1655(CO).^{1}H NMR (DMSO-d$_6$): $\delta = 2.35$ (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.15–7.89 (m, 11H, Ar-H), 10.22 (s, 1H, NH) and 14.36 (br, 1H, NH). Elemental analysis for $C_{25}H_{19}N_3OS$ (409): Calcd. C 73.33, H 4.65, N 10.27, S 7.82%. Found: C 73.60, H 4.43, N 10.55, S 7.60%.

5-Cyano-4-(4-methoxyphenyl)-2-methyl-N-1-naphthyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (6c)

It was obtained as yellow crystals from ethanol, yield 89%; mp 260°C. IR (KBr): υ cm^{-1} 3226, 3174 (2NH), 3051 (CH-arom.), 2933 (CH-aliph.), 2216 (CN) and 1647 (CO). Elemental analysis for $C_{25}H_{19}N_3O_2S$(425): Calcd. C 70.59, H 4.47, N 9.88, S 7.53%. Found: C 70.33, H, 4.70, N 9.62, S 7.31%.

Preparation of Compounds 8a–e: General Procedure

A mixture of compound **6a** (0.01 mol), halo compounds **7a–e** (0.01 mol), and sodium acetate (0.5 g) in ethanol (30 mL) was heated under reflux for 8 h, then cooled, poured into crushed ice, and acidified with HCl. The precipitates formed were collected and recrystallized from the proper solvent to give **8a–e**.

Ethyl (4-(4-Chlorophenyl)-3-cyano-6-methyl-5-[(1-naphthylamino)carbonyl]pyridin-2-ylthio)acetate (8a)

It was obtained as yellow crystals from ethanol, yield 82%; mp 170°C. IR (KBr): υ cm^{-1} 3245 (NH), 3054 (CH-arom.), 2982 (CH-aliph.), 2221 (CN), 1737, 1654 (2CO). ^{1}H NMR (DMSO-d$_6$): $\delta = 1.26$ (t, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.25 (q, 2H, CH_2), 5.63 (s, 2H, S-CH_2), 7.18–7.91 (m, 11H, Ar-H) and 10.40 (s, 1H, NH). Elemental analysis for $C_{28}H_{22}N_3O_3SCl$ (515.5); Calcd. C 65.18, H 4.27, N 8.15, S 6.21, Cl 6.88%. Found C 665.39, H 4.250, N 8.40, S 60.00, Cl 6.70%.

6-[(2-Amino-2-oxoethyl)thio]-4-(4-chlorophenyl)-5-cyano-2-methyl-N-1-naphthylnicotinamide (8b)

It was obtained as brown crystals from ethanol, yield 71%; mp 145°C. IR (KBr): υ cm^{-1} 3447, 3313 (NH_2), 3238 (NH), 3052 (CH-arom.), 2925 (CH-aliph.), 2217 (CN), 1671, 1655 (2CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.57$ (s, 3H, CH_3), 2.73 (s, 2H, NH_2), 3.99 (s, 2H, S-CH_2) and 7.27–7.81 (m, 12H, Ar-H+NH). Elemental analysis for $C_{26}H_{19}N_4O_2SCl$ (486.5): Calcd. C 64.13, H 3.90, N 11.51, S 6.58, Cl 7.29%. Found C 64.39, H 3.69, N 11.77, S 6.31, Cl 7.56%.

6-(2-[(3-Acetylphenyl)amino]-2-oxoethylthio)-4-(4-chlorophenyl)-5-cyano-2-methyl-N-1-naphthylnicotinamide (8c)

It was obtained as yellow crystals from ethanol, yield 75%; mp 198°C. IR (KBr): υ cm^{-1} 3474, 3241 (2NH), 3056 (CH-arom), 2920 (CH-aliph.), 2217 (CN), 1707, 1665 and 1648 (3CO). Elemental analysis for $C_{34}H_{25}N_4O_3SCl$ (604.5): Calcd. C 67.49, H 4.14, N 9.26, S 5.29, Cl 5.87%. Found C 67.72, H 4.42, N 9.46, S 5.01, Cl 5.62%.

4-(4-Chlorophenyl)-6-[2-(4-chlorophenyl)-2-oxoethyl]thio-5-cyano-2-methyl-N-1-naphthylnicotinamide (8d)

It was obtained as yellow crystals from ethanol, yield 68%; mp 186°C. IR (KBr): υ cm^{-1} 3471, 3238 (2NH), 3056 (CH-arom), 2926 (CH-aliph.), 2221 (CN), 1702, 1648 (2CO). Elemental analysis for $C_{32}H_{22}N_4O_2SCl_2$ (597): Calcd. C 64.32, H 3.68, N 9.38, S 5.36, Cl 11.89%. Found C 64.53, H 3.40, N 9.70, S 5.59, Cl 11.63%.

4-(4-Chlorophenyl)-5-cyano-2-methyl-6-[2-(4-methylphenyl)-2-oxoethyl]-thio-N-1-naphthylnicotinamide (8e)

It was obtained as yellow crystals from ethanol, yield 70%; mp 195°C. IR (KBr): υ cm^{-1} 3445, 3253 (2NH), 3055 (CH-arom), 2923 (CH-aliph.), 2220 (CN), 1716, 1653 (2CO). Elemental analysis for $C_{33}H_{25}N_4O_2SCl$

(576.5): Calcd. C 68.68, H 4.34, N 9.71, S 5.55, Cl 6.16%. Found C 68.89, H 4.59, N 9.50, S 5.78, Cl 6.38%.

Preparation of Compounds 9a–e: General Procedure

Method A

A mixture of compound **6a** (0.01 mol), halo compounds **7a–e** (0.01 mol), and sodium ethoxide (0.01 mol) in ethanol (30 mL) was heated under reflux for 24 h, then left to stand, poured into cold water, and acidified with HCl. The product formed was collected by filtration and recrystallized from the proper solvent to give **9a–e**.

Method B

Solutions of each of **8a–e** (0.01) in ethanol and sodium ethoxide (0.01 mol Na in 10 mL ethanol) were heated under reflux for 24 h, then left to stand, poured into cold water, and acidified with HCl. The product formed was collected by filtration and recrystallized from the proper solvent to afford **9a–e.**

Ethyl 3-Amino-4-(4-chlorophenyl)-6-methyl-5-[(1-naphthylamino)carbonyl]thieno[2,3-b]pyridine-2-carboxylate (9a)

It was obtained as pale yellow crystals from ethanol, yield 79%; mp 194°C. IR (KBr): υ cm^{-1}. 3483, 3398 (NH_2), 3157 (NH), 2982 (CH-aliph.), 1679, 1649 (2CO). ^{1}H NMR ($CDCl_3$): $\delta = 1.32$ (t, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.02 (s, 2H, NH_2), 4.24 (q, 2H, CH_2), 6.83-7.83 (m, 12H, Ar-H + NH). MS: $m/z = 517$ (2.75%), 515 (9.17%), 115 (100%). Elemental analysis for $C_{28}H_{22}N_3O_3SCl$ (515.5): Calcd. C 65.18, H 4.27, N 8.15, S 6.21, Cl 6.88%. Found C 65.00, H 4.01, N 8.39, S 6.50, Cl 6.55%.

3-Amino-4-(4-chlorophenyl)-6-methyl-N^5-1-naphthylthieno[2,3-b]pyridine-2,5-dicarboxamide (9b)

It was obtained as brown crystals from dioxane/ethanol, yield 70%; mp 250°C. IR (KBr): υ cm^{-1} 4485, 4432, 3378, 3286 ($2NH_2$), 3185 (NH), 3053 (CH-arom.), 2926 (CH-aliph.), 1665, 1657 (2CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.49$ (s, 3H, CH_3), 5.21 (s, 2H, NH_2), 7.39-7.88 (m, 13H, Ar-H + NH_2) and 10.59 (s, 1H, NH). MS: $m/z = 488$ (5%), 486 (16%), 143 (100%). Elemental analysis for $C_{26}H_{19}N_4O_2SCl$ (486.5): Calcd. C 64.13, H 3.90, N 11.51, S 6.58, Cl 7.29%. Found C 64.41, H 3.66, N 11.70, S 6.29, Cl 7.60%.

N^2-(3-Acetylphenyl)-3-amino-4-(4-chlorophenyl)-6-methyl-N^5-1-naphthylthieno[2,3-b]pyridine-2,5-dicarboxamide (9c)

It was obtained as green crystals from dioxane/ethanol, yield 65%; mp 248°C. IR (KBr): υ cm^{-1} 3482, 3324 (NH_2), 3245, 3200 (2NH), 3053 (CH-arom.), 2924 (CH-aliph.), 1705, 1675 and 1648 (3CO). ^1H NMR (DMSO-d_6): $\delta = 2.49$ (s, 3H, CH_3), 2.80 (s, 3H, $COCH_3$), 5.89 (s, 2H, NH_2), 7.20-7.92 (m, 14H, Ar-H), 8.27 (s, 1H, Ar-H of acetylphenyl), 9.77 (s, 1H, NH) and 10.41 (s, 1H, NH). Elemental analysis for $C_{34}H_{25}N_4O_3SCl$ (604.5): Calcd. C 67.49, H 4.14, N 9.26, S 5.29, Cl 5.87%. Found C 67.70, H 4.46, N 9.56, S 5.60, Cl 5.60%.

3-Amino-4-(4-chlorophenyl)-N^2-(4-chlorophenyl)-6-methyl-N^5-1-naphthylthieno[2,3-b]pyridine-2,5-dicarboxamide (9d)

It was obtained as pale yellow crystals from ethanol, yield 62%; mp 230°C. IR (KBr): υ cm^{-1} 3472, 3321 (NH_2), 3252, 3210 (2NH), 3054 (CH-arom.), 2923 (CH-aliph.) 1685 and 1643 (2CO). ^1H NMR (DMSO-d_6): $\delta = 2.18$ (s, 3H, CH_3), 7.31–7.76 (m, 17H, Ar-H + NH_2), 10.36 (s, 1H, NH) and 10.53 (s, 1H, NH). Elemental analysis for $C_{32}H_{22}N_4O_2SCl_2$ (597): Calcd. C 64.32, H 3.68, N 9.38, S 5.36, Cl 11.89%. Found C 64.03, H 3.90, N 9.60, S 5.62, Cl 11.60%.

3-Amino-4-(4-chlorophenyl)-6-methyl-N^2-(4-methylphenyl)-N^5-1-naphthylthieno[2,3-b]pyridine-2,5-dicarboxamide (9e)

It was obtained as pale yellow crystals from ethanol, yield 66%; mp 258°C. IR (KBr): υ cm^{-1} 3464, 3336 (NH_2), 3224, 3215 (2NH), 3055 (CH-arom.), 2922 (CH-aliph.) 1683, 1677 (2CO). ^1H NMR (DMSO-d_6): $\delta = 2.25$ (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 5.89 (s, 2H, NH_2), 7.10-7.90 (m, 15H, Ar-H), 9.50 (s, 1H, NH) and 10.37 (s, 1H, NH). Elemental analysis for $C_{33}H_{25}N_4O_2SCl$ (576.5): Calcd. C 68.68, H 4.34, N 9.71, S 5.55, Cl 6.16%. Found C 68.39, H 4.09, N 9.98, S 5.71, Cl 6.42%.

3-Amino-4-(4-chlorophenyl)-2-(hydrazinocarbonyl)-6-methyl-*N*-1-naphthylthieno[2,3-*b*]pyridine-5-carboxamide (10)

To a solution of **9a** (0.01 mol) in ethanol (30 mL), the hydrazine hydrate (2 mL) was added. The reaction mixture was heated under reflux for 15 h. The solid product that formed was collected by filtration and recrystallized from ethanol to give **10** as deep yellow crystals, yield 66%; mp 182°C. IR (KBr): υ cm^{-1} 3480, 3432, 3347, 3285 ($2NH_2$), 3225, 3198 (2NH), 3050 (CH-arom.), 2977 (CH-aliph.), 1651, 1633 (2CO). ^1H NMR ($CDCl_3$): $\delta = 2.32$ (s, 3H, CH_3), 5.42 (s, 2H, NH_2), 6.95 (s, 2H, NH_2), 6.98–7.79 (m, 13H, Ar-H + 2NH). Elemental analysis for

$C_{26}H_{20}N_5O_2SCl$ (501.5): Calcd. C 62.21, H 3.99, N 13.95, S 6.38, Cl 7.08%. Found C 62.44, H 4.31, N 13.71, S 6.15, Cl 7.30%.

9-(4-Chlorophenyl)-7-methyl-4-oxo-*N*-1-naphthyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (11)

Method A

A solution of compound **9a** (0.01 mol) in formamide (10 mL) was heated under reflux for 5 h, then allowed to cool and poured into cold water. The solid product was collected and crystallized from ethanol to give **11**.

Method B

To a solution of compound **9b** (0.01 mol) in acetic anhydride (30 mL), triethyl orthoformate (3 mol) was added. The reaction mixture was refluxed for 8 h, then poured into cold water and left to stand for 12 h. The solid product that formed was filtered off and recrystallized from ethanol to give **11** as green crystals, yield 55%; mp > 320°C. IR (KBr): υ cm^{-1} 3446, 3326 (2NH), 3057 (CH-arom.), 2986 (CH-aliph.), 1686, 1657 (2CO). ^1H NMR (DMSO-d_6): $\delta = 2.78$ (s, 3H, CH_3), 7.18–7.92 (m, 11H, Ar-H), 8.09 (s, 1H, CH-pyrimidine), 10.40 (s, 1H, NH), 12.96 (s, 1H, NH). MS: $m/z = 498$ (20%), 496 (56%), 115 (100%). Elemental analysis for $C_{27}H_{17}N_4O_2SCl$ (496.5): Calcd. C 65.25, H 3.42, N 11.27, S 6.44, Cl 7.15%. Found C 65.353, H 3.76, N 11.55, S, 6.20, Cl 7.38%.

Ethyl 3-[(benzoylamino)carbonothioyl]amino-4-(4-chlorophenyl)-6-methyl-5-[(*N*-1-naphthyl)carbonyl]-thieno[2,3-*b*]pyridine-2-carboxylate (12)

To a solution of compound **9a** (0.01 mol) in anhydrous acetone, benzoyl isothiocyanate [prepared in situ by heating a mixture of benzoyl chloride (0.01 mol) and ammonium thiocyanate (0.01 mol) in anhydrous acetone for 10 min] was added. The reaction mixture was refluxed for 18 h, then poured into cooled water. The precipitate was collected by filtration, washed with cold water, and recrystallized from ethanol to give **12** as pale green crystals, yield 56%; mp 180°C. IR (KBr): υ cm^{-1} 3448, 3378, 3324 (3NH), 3045 (CH-arom.), 2991 (CH-aliph.), 1719, 1682 (2CO).^1H NMR ($CDCLl_3$): $\delta = 1.31$ (t, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.18 (s, 1H, NH), 4.23 (q, 2H, CH_2), 6.82 (s, 1H, NH), 7.25–7.82 (m, 12H, Ar-H + NH). Elemental analysis for $C_{36}H_{27}N_4O_4S_2Cl$ (678.5): Calcd. C

63.66, H 3.98, N 8.25, S 9.43, Cl 5.23%. Found C 63.98, H 4.22, N 8.45, S 9.13, Cl 5.50%.

9-(4-Chlorophenyl)-7-methyl-4-oxo-*N*-1-naphthyl-2-thioxo-1,2,3,4-tetrahydro-pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine-8-carboxamide (13)

Method A

Compound **12** (1 g) was dissolved in ethanol (30 mL) containing 2 mL of 2N NaOH and heated under reflux for 12 h. The reaction mixture was cooled, poured into ice/water, and acidified with 10% HCl. The solid that formed was collected by filtration and recrystallized from dioxane to give **13**.

Method B

Compound **9b** (0.01 mol) and CS_2 (2 mL) in dioxane (20 mL) were heated under reflux for 15 h. The reaction mixture was cooled, poured into ice/water and neutralized with HCl. The solid product that formed was collected by filtration and recrystallized from dioxane to give **13** as brown crystals, yield 40%; mp 200°C. IR (KBr): υ cm^{-1} 3448, 3382, 3324 (3NH), 3056 (CH-arom.), 2964 (CH-aliph.), 1688, 1656 (2CO).^{1}H NMR (DMSO-d_6): $\delta = 2.74$ (s, 3H, CH_3), 4.07 (s, 1H, NH), 7.81–7.92 (m, 12H, Ar-H + NH), 10.46 (s, 1H, NH). Elemental analysis for $C_{27}H_{17}N_4O_2S_2Cl$ (528.5): Calcd. C 61.30, H 3.21, N 10.59, S 12.11, Cl 6.71%. Found C 61.60, H 3.55, N 10.81, S 12.39, Cl 6.46%.

Preparation of Compound 15

The amino ester **9a** was heated under reflux for 8 h in ethanolic NaOH (30 mL 10%). The solid product that was obtained after cooling was collected by filtration, washed with ethanol, and left to dry to give compound **15**. This compound was used as such in the next procedure.

9-(4-Chlorophenyl)-2,7-dimethyl-4-oxo-*N*-1-naphthyl-4*H*-pyrido[3′,2′:4,5]thieno[3,2-*d*][1,3]oxazine-8-carboxamide (16)

The sodium salt **15** (0.5 g) was heated under reflux in acetic anhydride (30 mL) for 4 h. The reaction mixture was left to stand 12 h. The solid product that formed was filtered off and recrystallized from dioxane to give **16** as green crystals, yield 44%; mp 240°C. IR(KBr): υ cm^{-1} 3423 (NH), 3055 (CH-arom.), 2923 (CH-aliph.), 1722, 1692 (2CO).^{1}H NMR

(DMSO-d_6): $\delta = 2.67$ (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 7.17–8.08 (m, 12H, Ar-H+NH). Elemental analysis for $C_{28}H_{18}N_3O_3SCl$ (511.5): Calcd. C 65.69, H 3.52, N 8.21, S 6.25, Cl 6.94%. Found: C 65.95, H 3.79, N 8.43, S 6.53, Cl 6.65%.

9-(4-Chlorophenyl)-2,7-dimethyl-4-oxo-*N*-1-naphthyl-3, 4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide (17)

Method A

A mixture of compound **16** (0.01 mol) and ammonium acetate (0.02 mol) in acetic acid 30 mL was heated under reflux for 12 h. The solid product that formed after cooling was collected by filtration, washed with water, and recrystallized from DMF/EtOH to give **17**.

Method B

A sample of compound **9b** (0.01 mol) in acetic anhydride 30 mL was heated under reflux for 18 h, then cooled and poured into cold water. The solid product was collected and recrystallized from DMF/EtOH to give **17** as green crystals, yield 45%; mp > 300°C. IR (KBr): υ cm^{-1} 3420, 3382 (2NH), 3056 (CH-arom.), 2966 (CH-aliph.), 1698, 1688 (2CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.67$ (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.26–7.92 (m, 12H, Ar-H + NH) and 10.42 (s, 1H, NH). MS: $m/z = 512$ (8.2%), 510 (24%) and 115 (100%). Elemental analysis for $C_{28}H_{19}N_4O_2SCl$ (510.5): Calcd. C 65.81, H 3.72, N 10.97, S 6.17, Cl 6.95%. Found: C 65.55, H 3.93, N 10.68, S 6.50, Cl 6.70%.

9-(4-Chlorophenyl)-7-methyl-4-oxo-*N*-1-naphthyl-3, 4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazine-8-carboxamide (18)

To a cold solution of compound **9b** (0.01 mol) in acetic acid 30 mL, a cold solution of sodium nitrite (1 g in 2 mL water) was added dropwise with stirring for 5 h and left to stand for 2 h. The solid product that formed was collected by filtration and recrystallized from dioxane to give **18** (60%) as green crystals, mp 220°C. IR (KBr): υ cm^{-1} 3424, 3486 (2NH), 3057 (CH-arom.), 2968 (CH-aliph.), 1671, 1657 (2CO).^{1}H NMR (DMSO-d_6): $\delta = 2.74$ (s, 3H, CH_3), 7.11–7.91 (m, 12H, Ar-H + NH), 10.48 (s, 1H, NH). Elemental analysis for $C_{26}H_{16}N_5O_2SCl$ (497.5): Calcd. C 62.71, H 3.21, N 14.07, S 6.43, Cl 7.13%. Found: C 62.48, H 3.55, N 14.31, S 6.15, Cl 7.38%.

3-Amino-4-(4-chlorophenyl)-6-methyl-5-[(1-naphthylamino)carbonyl]thieno[2,3-*b*]pyridine-2-carbonyl azide (19)

To a cold solution of **10** (0.01 mol) in acetic acid 20 mL, a cold solution of sodium nitrite (0.5 g in 2 mL of water) was added dropwise with stirring for 6 h and left to stand for 24 h. The precipitate was collected and recrystallized from ethanol to give **19** (52%) as buff crystals, mp 240°C. IR (KBr): υ cm^{-1} 3486, 3423 (NH_2), 3258 (NH), 3056 (CH-arom.), 2963 (CH-aliph.), 2129 (CON_3) and 1656 (CO).^{1}H NMR ($CDCl_3$) $\delta = 2.72$ (s, 3H, CH_3), 7.02–7.80 (m, 14H, Ar-H + NH + NH_2). Elemental analysis for $C_{26}H_{17}N_6O_2SCl$ (512.5): Calcd. C 60.88, H 3.32, N 16.39, S 6.24, Cl 6.92%. Found: C 60.57, H 3.53, N 16.67, S 6.49, Cl 6.70%.

8-(4-Chlorophenyl)-6-methyl-N-1-naphthyl-2-oxo-2,3-dihydro-1H-imidazo[4′,5′:4,5]thieno[2,3-b]pyridine-7-carboxamide (20)

The carbonyl azide **19** (0.01 mol) was heated under reflux in xylene (20 mL) for 18 h and allowed to cool. The solid product that formed was filtered off, then washed with petroleum ether, dried, and recrystallized from dioxane to give **20** (72%) as brown crystals, mp > 300°C. IR (KBr): υ cm^{-1} 3443, 3395, 3324 (3NH), 2923 (CH-aliph.), 1720 (CO) and 1648 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.68$ (s, 3H, CH_3), 7.21–7.87 (m, 13H, Ar-H + 2NH) and 10.29 (s, 1H, NH). Elemental analysis for $C_{26}H_{17}N_4O_2SCl$ (484.5): Calcd. C 64.39, H 3.51, N 11.55, S 6.60, Cl 7.32%. Found: C 64.11, H 3.75, N 11.83, S 6.38, Cl 7.55%.

10-(4-Chlorophenyl)-8-methyl-*N*-1-naphthyl-5-oxo-4,5-dihydro-3*H*-pyrido-[3′,2′:4,5]thieno[3,2-*e*][1,2,4]triazepine-9-carboxamide (22)

Method A

A suspension of **10** (0.01 mol) and triethyl orthoformate (3 mol) in acetic anhydride 30 mL was heated under reflux for 18 h. The reaction mixture was poured into cold water and left to stand overnight. The solid precipitate was filtered off and recrystallized from ethanol to give **22**.

Method B

A solution of compound **10** (0.01 mol) in formic acid (30 mL) was heated under reflux for 24 h. The solid product that formed was collected by filtration and recrystallized from ethanol to give **22** as green

crystals, yield 81%; mp 192°C. IR (KBr): υ cm^{-1} 3391, 3371, 3220 (3NH), 3049 (CH-arom.), 2968 (CH-aliph.), 1670, 1660 (2CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.60$ (s, 3H, CH_3), 5.63 (s, 1H, CH-triazepine), 7.14–7.92 (m, 12H, Ar-H + NH), 10.46 (s, 1H, NH) and 11.57 (s, 1H, NH). MS m/z = 517 (41%), 515 (100%). Elemental analysis for $C_{27}H_{18}N_5O_2SCl$ (511.5): Calcd. C 63.34, H 3.52, N 13.68, S 6.25, Cl 6.94%. Found: C 63.12, H 3.85, N 13.96, S 6.53, Cl 6.68%.

2-Anilino-10-(4-chlorophenyl)-8-methyl-5-oxo-*N*-1-naphthyl-4,5-dihydro-3*H*-pyrido[3′,2′:4,5]thieno[3,2-*e*][1,2,4]-triazepine-9-carboxamide (23)

To a solution of compound **10** (0.01 mol) in anhydrous dioxane 30 mL, phenyl isothiocyanate (0.01 mol) was added. The mixture was heated under reflux for 24 h. The solid product that formed after cooling was collected by filtration and recrystallized from dioxane to give **23** (64%) as pale yellow crystals, mp 220°C. IR (KBr): υ cm^{-1} 3447, 3396, 3380, 3325 (4NH), 3056 (CH-arom.), 2924 (CH-aliph.), 1665, 1656 (2CO).^{1}H NMR ($CDCl_3$): $\delta = 2.71$ (s, 3H, CH_3), 7.00 (s, 1H, NH), 7.13 (s, 1H, NH), 7.18–7.84 (m, 18H, Ar-H + 2NH). Elemental analysis for $C_{33}H_{23}N_6O_2SCl$ (602.5): Calcd. C 65.72, H 3.81, N 13.94, S 5.31, Cl 5.89%. Found: C 65.97, H 3.58, N 13.68, S 5.60, Cl 5.68%.

3-Amino-4-(4-chlorophenyl)-2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-6-methyl-*N*-1-naphthylthieno[2,3-*b*]-pyridine-5-carboxamide (24)

A mixture of compound **10** (0.01 mol) and acetyl acetone (0.02 mol) in ethanol (30 mL) was treated with piperidine (0.5 mL). The reaction mixture was heated under reflux for 6 h. The solid product that formed after cooling was collected by filtration and recrystallized from ethanol to give **24** (44%) as green crystals, mp 175°C. IR (KBr): υ cm^{-1} 3482, 3380 (NH_2), 3286 (NH), 3051 (CH-arom.), 2964 (CH-aliph.), 1681, 1648 (2CO). ^{1}H NMR ($CDCl_3$): $\delta = 2.02$ (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 5.78 (s, CH-pyrazole), 6.93–7.78 (m, 14H, Ar-H + NH + NH_2). Elemental analysis for $C_{31}H_{24}N_5O_2SCl$ (565.5): Calcd. C 65.78, H 4.24, N 12.37, S 5.65, Cl 6.27%. Found: C 65.52, H 4.61, N 12.64, S 5.41, Cl 6.55%.

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