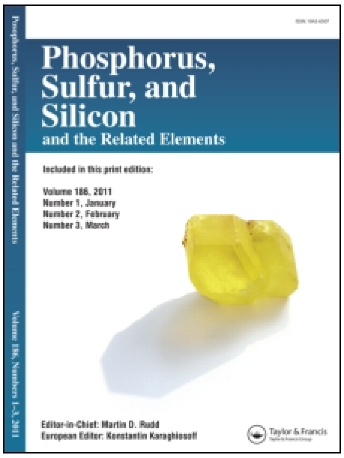

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ANTI-ALZHEIMER AND ANTI-COX-2 ACTIVITIES OF THE NEWLY SYNTHESIZED 2,3′-BIPYRIDINE DERIVATIVES (II)

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3-Amino-4-aryl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carbohydrazides 3a,b were used as the starting materials in the present study. Our targets here were represented by the synthesis of several 3-amino-*N*′-4-arylmethylenes 5a,b, *N*-formamides 8a,b, ethyl imidoformate 10b, *N,N*-dimethyl-*N*′-imidoformamides 12a,b, *N*-acetyl-*N*-acetamides 14a,b, 1,3,4-oxadiazole-2-thiol 16a,b, pyrazolothienopyridines 20a,b, 2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-aryl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-3-amines 22a,b, 2-carbonyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-ones 24a,b, and 2-carbonyl-pyrazolidine-3,5-diones 26a,b. The newly synthesized heterocyclic compounds were tested as anti-Alzheimer and anti-COX-2 agents, and their structures were elucidated by considering the data of IR, ^{1}H NMR, mass spectra, and elemental analyses.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords *N*-Acetyl-*N*-acetamides; ethyl imidoformates; 1,3,4-oxadiazole-2-thiol; 3*H*-pyrazol-3-ones; pyrazolidine-3,5-diones; pyrazolothieno-pyridines

INTRODUCTION

The biological activities of thienopyridines have been reported as antimicrobial,[1–3] anti-inflammatory,[4] and ganadotropin-releasing hormone antagonizing activities,[5] and they also have neurotropic activity.[6] Furthermore, pyridothienopyrimidines were reported to have antiallergic,[7] antiparasitic,[8] antianaphylactic,[9,10] and antimicrobial[1] activity. The previously mentioned findings have stimulated the interest for the synthesis of the title compounds. In our previous recent work,[11–21] we have reported several syntheses, characterizations, reactions, and biological evaluations of 2-thioxo-hydropyridine-3-carbonitrile derivatives. In this work, our goal is to use ethyl [(5-cyano-4-aryl-2,3′-bipyridin-6-yl)thio]acetates **1a**,**b**[15] and ethyl 3-amino-4-aryl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carboxylates **2a**,**b**[15] as synthons required for several chemical transformations as well as our medicinal chemistry programs.

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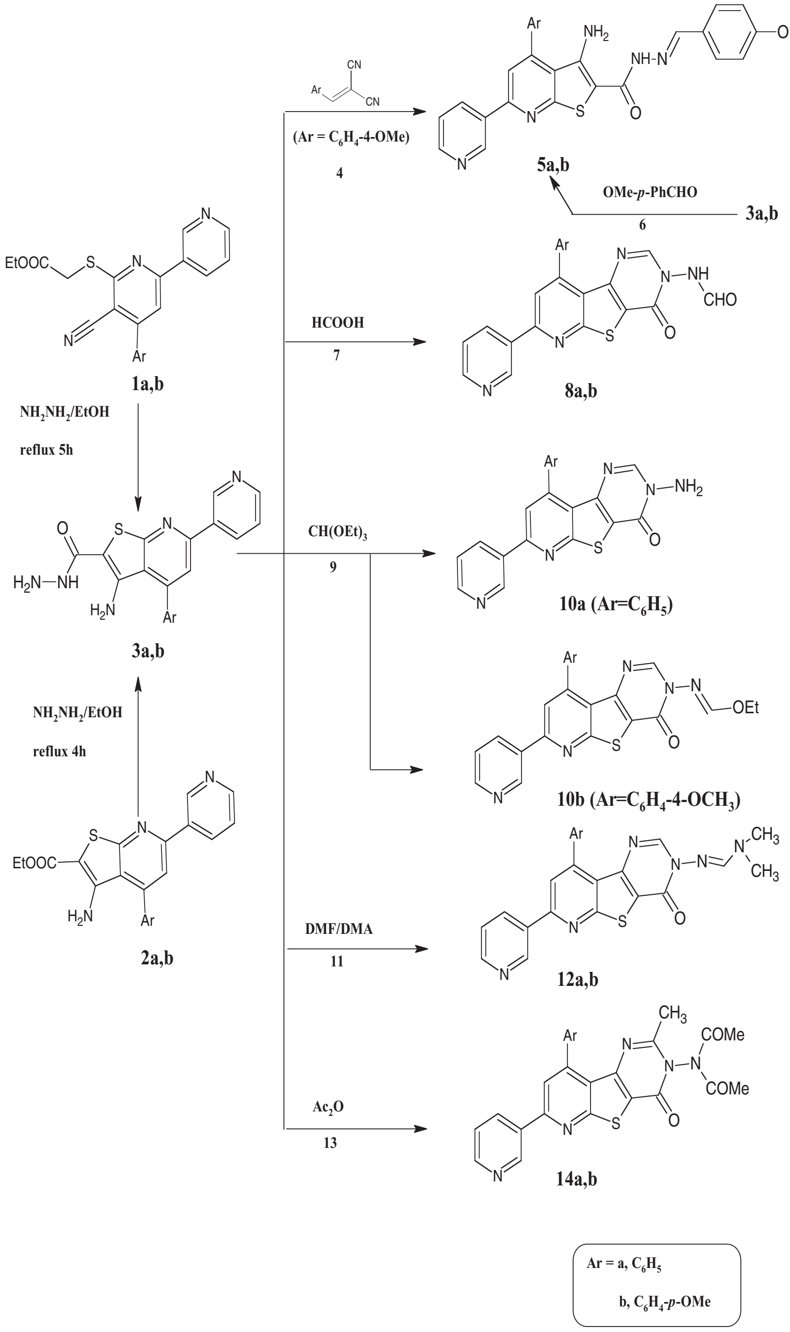
RESULTS AND DISCUSSION

3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carbohydrazide **(3a)** was synthesized via the reaction of ethyl [(5-cyano-4-phenyl-2,3′-bipyridin-6-yl)thio]acetates **1a**[15] with hydrazine hydrate under reflux for 3–5 h. The IR of this reaction product showed no bands for CN and ester CO functions, while the newly formed $NHNH_2$ functions were detected (see the Experimental section). Thus, we concluded that the reaction most probably proceeded via the cyclization of **1a** giving **2a** as an intermediate followed by the reaction with hydrazine hydrate to give the carbohdrazide derivative **3a**. The structure of **3a** was further confirmed chemically by its preparation authentically via the reaction of ethyl 3-amino-4-aryl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carboxylate (**2a**) with hydrazine hydrate. The mass spectrum of **3a** gave peaks at $m/z = 361$ (30.4%) corresponding to the molecular formula $C_{19}H_{15}N_5OS$ of the assigned structure; $m/z = 330$ (100%, $M^+{-}NHNH_2$); 302 (19.9%, $M^+{-}CONHNH_2$).

Similarly, 3-amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]-pyridine-2-carbohydrazide (**3b**) was obtained by the reaction of either **1b** or **2b** with hydrazine hydrate, and its structure was established by considering the data of IR and mass spectrum, as well as elemental analyses (see the Experimental section).

The chemical reactivity and synthetic potentiality of both **3a**,**b** were investigated via their chemical reactions with several reagents. Thus, it has been found that **3a**,**b** reacted with (4-methoxybenzylidene)malononitrile (**4**) or anisaldehyde (**6**) in a pyridine/ethanol mixture under reflux to afford the reaction product formulated as **5a**,**b**, respectively, whose chemical structures were confirmed by considering the data of IR and elemental analyses (see the Experimental section). Moreover, the mass spectra of **5a**,**b** gave $m/z = 479$ and 509, respectively, which corresponded to the molecular formulas $C_{27}H_{21}N_5O_2S$ and $C_{28}H_{23}N_5O_3S$ of the assigned structures, in addition to several peaks corresponding to fragments that confirm their structures.

In a further investigation of the chemical reactivity and synthetic potentiality of $-NHNH_2$ group in each of **3a**,**b**, several reactions with each of formic acid **7**, triethyl orthoformate **9**, dimethylformamide-dimethylacetal **11**, and acetic anhydride **13** in a respective manner to afford the corresponding pyridothienopyrimidines **8a**,**b–14a**,**b**, respectively. The IR and elemental analyses data was considered to elucidate the structure of these structures. Moreover, the mass spectral data was considered as a good physical tool to establish the structures **8–14** as follows: For compounds **8a**,**b**, it gave $m/z = 399$ (61.2%) and 429 (13.1%), which corresponded to the molecular formula $C_{21}H_{13}N_5O_2S$ and $C_{22}H_{15}N_5O_3S$ of the assigned structures. Also, peaks at $m/z = 370$ (M^+ $-CHO$, 53.1%), 355 (M^+ $-NHCHO$, 100%) for **8a** and 400 (35.5%), 385 (100%) for **8b** confirm the presence of the $-NH{-}CHO$ group at the pyrimidine ring **N** atom. In addition to other peaks observed in mass spectra and the data of IR and elemental analyses, the structural formula of each of **8a**,**b** was confirmed (see Scheme 1 and the Experimental section). For compound **10a**, it gave $m/z = 371$ (100%), which corresponded to the molecular formula $C_{20}H_{13}N_5OS$ of the assigned structure; 370 (50%, $M^+{-}H$); 355 (17.1%, $M^+{-}NH_2$), 343 (11.3%, $M^+{-}CO$), 342 (58.3%, 370$-$CO); 328 (5.5%, $M^+{-}CO{-}NH$); 313 (5%, 328$-$NH). These peaks confirm the presence of NH_2 on the pyrimidine **N** atom. The presence of $-N{=}CH{-}OEt$ on pyrimidine **N** atom of **10b** was confirmed by the detection of peaks at $M^+{-}CHNMe_2$ and $M^+{-}N{=}CHNMe_2$. For compounds **14a**,**b** in each case, it gave $m/z = 469$ and 499, which corresponded to the molecular formula $C_{25}H_{19}N_5O_3S$ and $C_{26}H_{21}N_5O_4S$, respectively; $M^+{-}COCH_3$; $M^+{-}2COCH_3$; $M^+{-}N(COCH_3)_2$ in addition to several peaks that further confirm **14a**,**b** structure (see Scheme 1 and the Experimental section).

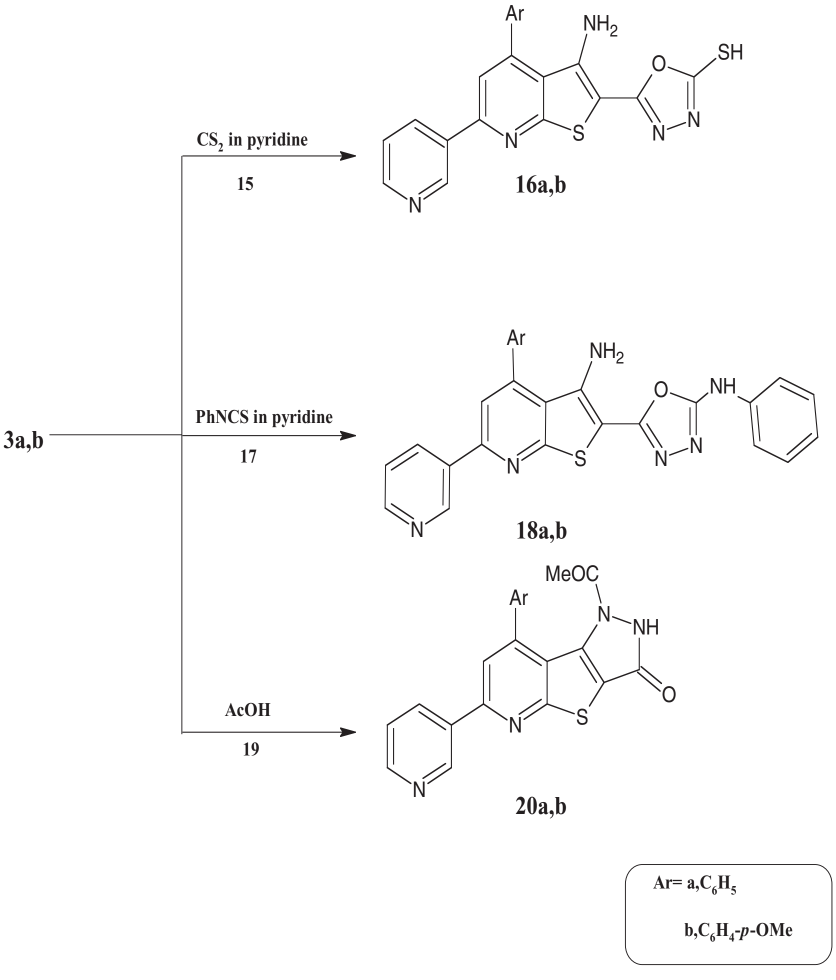


Scheme 1

The nucleophilic character of the **N** atom of $NHNH_2$ group at the 3-position of each of **3a**,**b** was further investigated via their reaction with carbon disulfide (CS_2) in pyridine under reflux for 3–5 h. This reaction most probably proceeded through the attacking of nucleophilic **N** at each of **3a**,**b** and electrophilic **C** of carbon disulfide followed by hydrogen disulfide removal in each case afforded **16a**,**b**, respectively. The elemental analyses and IR spectral data were considered to elucidate the structure of **16a**,**b** and their mass spectra to confirm their structure further, it gave m/z = 403 (100%) and 433 (100%), which corresponded to the molecular formulas $C_{20}H_{13}N_5OS_2$ and $C_{21}H_{15}N_5O_2S_2$ of the assigned structures; M^+—H; M^+—oxadiazole-2-thiol in each case and other peaks that corresponded to several fragments, which confirm the assigned structures

Further investigation for such nucleophilic character was performed via the reaction of each of **3a**,**b** with each of phenylisothiocyanate (**17**) and acetic acid (**19**) to afford **18a**,**b** and **20a**,**b**, respectively, whose structures were elucidated by considering data of the elemental analyses, IR, and mass spectra (Scheme 2).

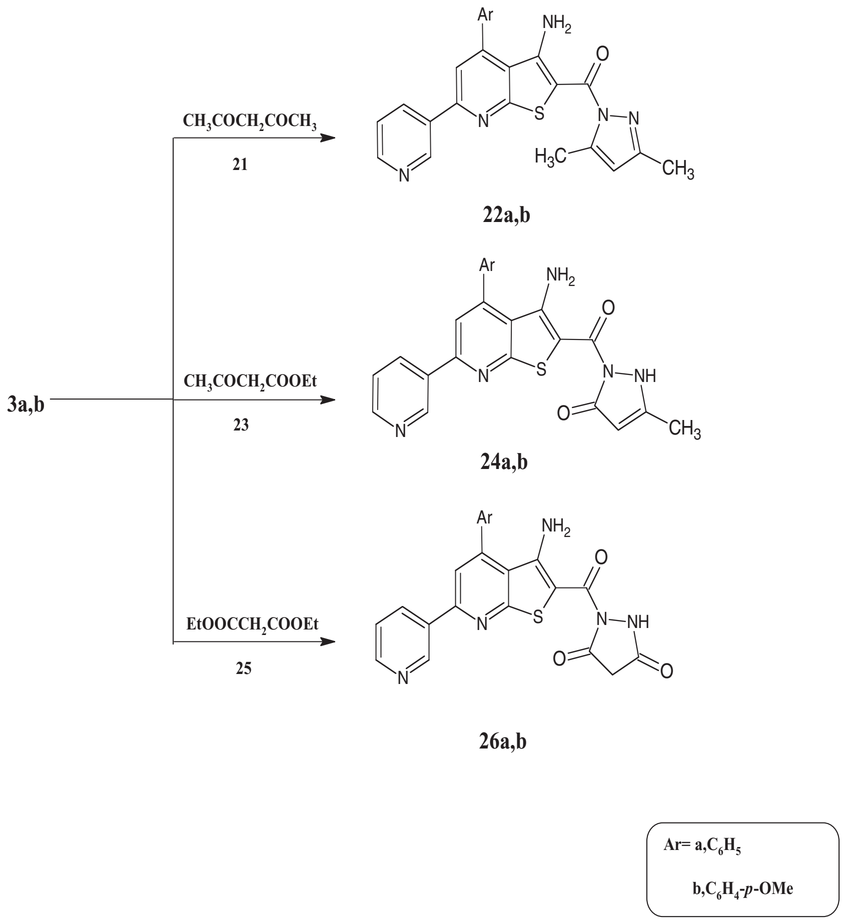
The work was extended to shed more light on both the synthetic potentiality and position of –CONHNH$_2$ in each of **3a**,**b**. This target was obtained through their reactions with each of pentan-2,4-dione (**21**), ethyl 3-oxobutanoate (**23**), and diethyl malonate (**25**)



Scheme 2

to build an additional pyrazole ring along —NH—NH_2 group. Thus, it has been found that **3a** reacted with **21**, **23**, and **25** in acetic acid under reflux for 3–5 h to afford the reaction products **22a**, **24a**, and **26a**, respectively. The IR of these reaction products showed the bands of CO and NH_2 functions, and their mass spectra gave m/z = 425, 427, and 429, respectively, in addition to several fragments that elucidate the assigned structures further. Considering all previously mentioned data in addition to that of elemental analyses, these reaction products were formulated as 2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-3-amine (**22a**), 2-[(3-amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)carbonyl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**24a**), and 1-{[3-amino-4-(4-phenyl)-6-pyridin-3-ylthieno[2,3-*b*]-pyridin-2-yl]carbonyl}-pyrazolidine-3,5-dione (**26a**), respectively.

Similarly, compounds **22b**, **24b**, and **26b** were obtained under the same above-mentioned experimental conditions through the reaction of each **3a**,**b** with each of **21**, **23**, and **25**, respectively (see Scheme 3).



Scheme 3

Biological Evaluation: Anti-Alzheimer Activity

Compounds **5a**,**b**, **8a**,**b**, **10a**,**b**, **12a**,**b**, **14a**,**b**, **16a**,**b**, **18a**,**b**, **20a**,**b**, **22a**,**b**, **24a**,**b**, and **26a**,**b** with potency as anti-Alzheimer agents relative to Flurbiprofen are arranged in descending order as follows: **3a**, **26a**, **8a**, **22a**, **5a**, **20a**, **18a**, **16a**, **14a**, **10a**, **12a**, **18b**, **16b**, **20b**, **5b**, **12b**, **10b**, **3b**, **24b**, **8b**, **14b**, **22b**, **26b**. (For further details on the biological activities of these compounds, see the Supplemental Materials and Figures S1–S5, available online.)

EXPERIMENTAL

All melting points were uncorrected. IR (KBr discs) spectra were recorded on a Shimadzu FTIR-8201PC Spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz and a Varian Gemini 200 MHz spectrometers using TMS as an internal standard and $CDCl_3$, DMSO-d_6, and $(CD_3)_2CO$ as solvents. Chemical shifts were expressed as δ (ppm) units. Mass spectra were recorded on Shimadzu GCMS-QP1000EX using an inlet type at 70 eV. The Microanalytical Center of Cairo University performed the microanalyses.

Synthesis of 3a,b

Method A. A solution of each of **1a**,**b** (1 g, 1 g; 0.0027 mol, 0.0025 mol) in hydrazine hydrate (15 mL) and ethanol (20 mL) was heated under reflux for 5 h; the excess solvents were evaporated. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **3a**,**b**, respectively.

Method B. A solution of each of **2a**,**b** (1 g, 1 g; 0.0027 mol, 0.0025 mol) in hydrazine hydrate (15 mL) and ethanol (20 mL) was heated under reflux for 4 h; the excess solvent was evaporated. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **3a**,**b**, respectively.

3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carbohydrazide (3a) as yellow crystals (76%), mp = 270°C; **IR** (ν cm^{-1}): 3461, 3319, 3251 (NH & NH_2), 3018 (aromatic-CH); **MS**: 361 (M^+, 30.4% corresponding to the molecular formula $C_{19}H_{15}N_5OS$ of the assigned structure), 330 ($M^+{-}NHNH_2$, 100%), 302 ($M^+{-}CONHNH_2$, 19.9%); **^{1}H NMR** (DMSO-D_6) (δppm): 4.46 (br, 2H, NH_2); 5.83 (br, 2H, NH_2); 7.51–8.67 (m, 9H′s, Aryl and pyridinyl H′s); 9.19 (br, 1H, NH) and 9.37 (s, 1H, C_5 H); Anal., Calcd./Found(%): C(63.14/63.16) H(4.18/4.20) N(19.38/19.42) S(8.86/8.90).

3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*] pyridine-2-carbohydrazide (3b) as yellow crystals (92%), mp = 252°C; **IR** (ν cm^{-1}): 3479, 3331, 3214 (NH & NH_2), 3040 (aromatic-CH); **MS**: 391 (M^+, 51.1% corresponding to the molecular formula $C_{20}H_{17}N_5O_2S$ of the assigned structure), 360 ($M^+{-}NHNH_2$, 100%); Anal., Calcd./Found(%): C(61.37/61.40) H(4.38/4.42) N(17.89/17.91) S(8.18/8.22).

Synthesis of 5a,b

Method A. A solution of each of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and (4-methoxybenzylidene)malononitrile **4** (0.10g, 0.00055 mol) in pyridine (15 mL) and ethanol (20 mL) was heated under reflux for 2 h; the excess solvent was evaporated. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **5a**,**b**, respectively.

Method B. A solution of each of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and 4-methoxybenzaldehyde **6** (0.075 g, 0.00055 mol) in pyridine (15 mL) and ethanol (20 mL) was heated under reflux for 2 h. Excess solvent was evaporated. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **5a**,**b**, respectively.

3-Amino-*N*′-[(4-methoxyphenyl)methylene]-4-methoxyphenyl-6-pyridin-3-yl-thieno[2,3-*b*]pyridine-2-carbohydrazide (5a) as yellow crystals (96%), mp = 299°C; **IR** (ν cm^{-1}): 3477, 3290 (NH$_2$), 3149 (NH), 3048 (aromatic-CH) and 1629 (CO); **MS**: 479 (M$^+$, 68.3% corresponding to the molecular formula $C_{27}H_{21}N_5O_2S$ of the assigned structure), 330 (M$^+$—NHN=CH—C$_6$H$_4$—*p*—OMe, 100%); Anal., Calcd./Found(%): C(67.62/67.65) H(4.41/4.44) N(14.60/14.63) S(6.69/6.71).

3-Amino-*N*′-[(4-methoxyphenyl)methylene]-4-methoxyphenyl-6-pyridin-3-yl-thieno[2,3-*b*]pyridine-2-carbohydrazide (5b) as yellow crystals (90%), mp = 298°C; **IR** (ν cm^{-1}): 3472, 3281 (NH$_2$), 3150 (NH), 3032 (aromatic-CH) and 1627 (CO); **MS**: 508 (M$^+$, 21% which corresponds to the molecular formula $C_{28}H_{22}N_5O_3S$ of the assigned structure), 333 (M$^+$ —CONHN=CH—C$_6$H$_4$-*p*-OMe, 100%), 360 (M$^+$ —NHN=CH—C$_6$H$_4$-*p*-OMe, 42.8%); Anal., Calcd./Found(%): C(66.00/66.03) H(4.55/4.58) N(13.74/13.77) S(6.29/6.31).

Synthesis of 8a,b

A solution of each of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and formic acid (15 mL) was heated under reflux for 6 h. The excess formic acid was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the ethanol to give **8a**,**b**, respectively.

***N*-[9-(4-Phenyl)-4-oxo-7-pyridin-3-ylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyra-midin-3(4*H*)-yl]formamide (8a)** as white crystals (87%), mp = 300–302°C; **IR** (ν cm^{-1}): 3222 (NH), 3055 (aromatic-CH) and 1715–1683 (twoCO); **MS**: 399 (M$^+$, 61.2% corresponding to the molecular formula $C_{21}H_{13}N_5O_2S$ of the assigned structure), 370 (M$^+$ —CHO, 53.1%), 356 (M$^+$ —NCHO, 72.9%), 355 (M$^+$ —NHCHO, 100%), 300 (M$^+$ —CON(CH)NHCHO, 77.7%); Anal., Calcd./Found(%): C(63.15/63.18) H(3.28/3.30) N(17.53/17.57) S(8.03/8.06).

***N*-[9-(4-Methoxyphenyl)-4-oxo-7-pyridin-3-ylpyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidin-3(4*H*)-yl]formamide (8b)** as yellow crystals (83%), mp = 292°C; **IR** (ν cm^{-1}): 3427 (NH), 3063 (aromatic-CH) and 1681 (CO); **MS**: 429 (M$^+$, 13.1% corresponding to the molecular formula $C_{22}H_{15}N_5O_3S$ of the assigned structure), 400 (M$^+$ —CHO, 35.5%), 386 (M$^+$ —NCHO, 31.8%), 385 (M$^+$ —NHCHO, 100%), 331 (M$^+$ —CON(C)NHCHO, 90.7%); Anal., Calcd./Found(%): C(61.53/61.55) H(3.52/3.56) N(16.31/16.34) S(7.47/7.50).

Synthesis of 10a,b

A solution of each of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and triethylorthoformate (10 mL) was heated under reflux for 4 h; the excess triethylorthoformate was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from acetic acid to give **10a**,**b**, respectively.

3-Amino-9-phenyl-7-pyridin-3-ylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*) -one (10a) as orange crystals (77%), mp = 318–320°C; **IR** (ν cm^{-1}): 3329, 3254 (NH$_2$), 3050 (aromatic-CH) and 1674 (CO); **MS**: 371 (M$^+$, 100% corresponding to the molecular formula $C_{20}H_{13}N_5OS$ of the assigned structure), 370 (M$^+$ —H, 50.3%), 355 (M$^+$ —NH$_2$, 17.1%), 343 (M^+ −CO, 11.3%), 342 (M^+ −NNH, 58.3%); **^{1}H NMR** (DMSO-D_6) (δ ppm): 6.038 (s, 2H, NH_2); 7.51–9.45 (m, 11H, phenyl, pyridinyl, and C_2(H)); Anal., Calcd./Found(%): C(64.68/64.70) H(3.53/3.58) N(18.86/18.70) S(8.63/8.66).

Ethyl(4-oxo-9-(4-methoxyphenyl)-7-pyridin-3-ylpyrido[3′,2′:4,5]thieno-[3,2-*d*] pyrimidin-3(4*H*)-yl)imidoformate (10b) as yellow crystals (78%), mp = 242°C; **IR** (ν cm^{-1}): 3040 (aromatic-CH) and 1665 (CO); **MS**: 457 (M^+, 100% corresponding to the molecular formula $C_{24}H_{19}N_5O_3S$ of the assigned structure), 455 (M^+ −2H, 72.6%), 400 (M^+ −COEt, 52.1%); **^{1}H NMR** (DMSO-D_6) (δ ppm): 1.35 (t, 3H, $-CH_2\underline{CH_3}$); 3.86 (s, 3H, OCH_3); 4.42 (q, 2H, $-\underline{CH_2}CH_3$); 7.08–7.05 (d, 2H, J = 8.1 Ar H′s); 7.71–7.68 (d, 2H, J = 8.1 Ar H′s); 8.05–9.45 (m, 7H, pyridinyl, C_2(H) and N=$\underline{CH}$−OEt); Anal., Calcd./Found(%): C(63.01/63.05) H(4.19/4.22) N(15.31/15.34) S(7.01/7.05).

Synthesis of 12a,b

A solution of each of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and dimethylformamidedimethylacetal (0.07 g, 0.00055 mol) in dry xylene (15 mL) was heated under reflux for 5 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from dioxane to give **12a**,**b**, respectively.

***N*,*N*-Dimethyl-*N*′-(4-oxo-9-phenyl-7-pyridin-3-ylpyrido[3′,2′:4,5]thieno-[3,2-*d*] pyrimidin-3(4*H*)-yl)imidoformamide (12a)** as pale yellow crystals (70%), mp = 284°C; **IR** (ν cm^{-1}): 3038 (aromatic-CH) and 1655. (CO); **MS**: 426 (M^+, 14.1% corresponding to the molecular formula $C_{23}H_{18}N_6OS$ of the assigned structure), 355 (M^+ −N=CHN$(CH_3)_2$, 100%); **^{1}H NMR** (DMSO-D_6) (δ ppm): 2.94 (s, 3H, N$(CH_3)_2$); 3.00 (s, 3H, N$(CH_3)_2$); 7.50–9.44 (m, 12H, Ar, pyridinyl H′s, C_2(H), C_8(H) and N=$\underline{CH}$NMe$_2$); Anal., Calcd./Found(%): C(64.77/64.80) H(4.25/4.29) N(19.70/19.73) S(7.52/7.55).

***N*,*N*-Dimethyl-*N*′-(4-oxo-9-methoxyphenyl-7-pyridin-3-ylpyrido[3′,2′:4,5]thieno [3,2-*d*]pyrimidin-3(4*H*)-yl)imidoformamide (12b)** as pale yellow crystals (72%), mp = 264°C; **IR** (ν cm^{-1}): 3048 (aromatic-CH) and 1662 (CO); **MS**: 456 (M^+, 61.4% corresponding to the molecular formula $C_{24}H_{20}N_6O_2S$ of the assigned structure), 399 (M^+ −CHN$(CH_3)_2$, 90.9%), 358 (M^+ −CHNN=CHN$(CH_3)_2$, 31.8%); **^{1}H NMR** (DMSO-D_6) (δ ppm): 2.987 (s, 6H, N$(CH_3)_2$); 3.869 (s, 3H, $O\underline{CH_3}$); 7.073 (d, 2H, J = 8.4 Hz Ar H′s); 7.702 (d, 2H, J = 8.4 Ar H′s) and 8.029–9.429 (m, 7H, pyridinyl H′s, C_2(H) and C_8(H) and N=$\underline{CH}$NMe$_2$); Anal., Calcd./Found(%): C(63.14/63.16) H(4.42/4.44) N(18.41/18.44) S(7.02/7.05).

Synthesis of 14a,b

A solution of each of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and acetic anhydride (15 mL) was heated under reflux for 6 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the proper acetic acid to give **14a**,**b**, respectively.

***N*-Acetyl-*N*-(9-phenyl-2-methyl-4-oxo-7-pyridin-3-yl-1,4-dihydropyrido-[3′,2′: 4,5]thieno[3,2-*d*]pyrimidin-3(2*H*)-yl)acetamide (14a)** as pale yellow crystals (78%), mp = 270°C; **IR** (ν cm^{-1}): 3023 (aromatic-CH) and 1736, 1690 (CO); **MS**: 469 (M^+, 43.4% corresponding to the molecular formula $C_{25}H_{19}N_5O_3S$ of the assigned structure), 426 (M^+ −$COCH_3$, 26.7%), 383 (M^+ −2$COCH_3$, 100%), 369 (M^+ −N $(COCH_3)_2$, 13.5%); **^{1}H NMR** (DMSO-D_6) (δppm): 1.908 (s, 3H, CH_3); 2.245 (s, 3H, $CO\underline{CH_3}$); 2.488

(s, 3H, CO$\underline{CH_3}$); 7.514–9.488 (m, 10H, Ph and pyridinyl H′s); Anal., Calcd./Found(%): C(63.68/63.70) H(4.49/4.52) N(14.85/14.89) S(6.80/6.86).

***N*-Acetyl-*N*-(9-[4-methoxyphenyl]-2-methyl-4-oxo-7-pyridin-3-yl-1,4-di-hydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-3(2*H*)-yl)acetamide (14b)** as pale yellow crystals (73%), mp = 260°C; **IR** (ν cm^{-1}): 2982 (aromatic-CH) and 1741, 1696 (CO); **MS**: 499 (M$^+$, 39.9% corresponding to the molecular formula $C_{26}H_{21}N_5O_4S$ of the assigned structure), 456 (M$^+$ −COCH$_3$, 9.3%), 413 (M$^+$ −2COCH$_3$, 100%); **^{1}H NMR** (DMSO-D$_6$) (δ ppm): 2.29 (s, 3H, CH$_3$); 2.40 (s, 6H, 2COCH$_3$); 3.86 (s, 3H, OCH$_3$); 7.10–7.07 (d, 2H, J = 8.7, Ar H′s); 7.77–7.74 (d, 2H, J = 8.7, Ar H′s); 8.16–9.46 (m, 5H, pyridinyl and C$_8$(H)); Anal., Calcd./Found(%): C(62.26/62.30) H(4.62/4.65) N(13.96/14.00) S(6.39/6.42).

Synthesis of 16a,b

A solution of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and carbon disulfide (5 mL) in pyridine (15 mL) was heated under reflux for 5 h, cooled, poured onto ice-cold water, and neutralized with drops of acetic acid. The solid was collected by filtration, dried, and crystallized from the ethanol to give **16a**,**b**, respectively.

5-[3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl]-1,3,4-oxa-diazole-2-thiol (16a) as orange crystals (67%), mp = 310–312°C; **IR** (ν cm^{-1}): 3476, 3352 (NH$_2$), 3053 (aromatic-CH); **MS**: 403 (M$^+$, 100% corresponding to the molecular formula $C_{20}H_{13}N_5OS_2$ of the assigned structure), 326 (M$^+$ −C$_6$H$_5$, 15.7%), 302 (M$^+$ −CONNCSH, 13.4%); Anal., Calcd./Found (%): C(59.54/59.58) H(3.25/3.28) N(17.36/17.39) S(15.89/15/92).

5-{3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl}-1,3,4-oxadiazole-2-thiol (16b) as orange crystals (72%), mp = 264°C; **IR** (ν cm^{-1}): 3474, 3362 (NH$_2$), 3047 (aromatic-CH); **MS**: 433 (M$^+$, 100% corresponding to the molecular formula $C_{21}H_{15}N_5O_2S_2$ of the assigned structure), 432 (M$^+$ −H, 15.3%), 417 (M$^+$ −NH$_2$, 16.7%), 332 (M$^+$ −CONNCSH, 17.6%); Anal., Calcd./Found(%): C(58.18/58.20) H(3.49/3.52) N(16.16/16.19) S(14.79/14.82).

Synthesis of 18a,b

A solution of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and phenylisothiocyanate (0.07 g, 0.00055 mol) in pyridine (15 mL) was heated under reflux for 5 h, cooled, poured onto ice-cold water, and neutralized with drops of acetic acid. The solid was collected by filtration, dried, and crystallized from the ethanol to give **18a**,**b**, respectively.

2-(5-Anilino-1,3,4-oxadiazol-2-yl)-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]-pyridin-3-amine (18a) as yellow crystals (78%), mp = >330°C; **IR** (ν cm^{-1}): 3446, 3270 (NH$_2$), 3202 (NH) 3058 (aromatic-CH); **MS**: 462 (M$^+$, 59.0% corresponding to the molecular formula $C_{26}H_{18}N_6OS$ of the assigned structure), 385 (M$^+$ −H,C$_6$H$_5$, 82.1%), 330 (M$^+$ −NN=CNHC$_6$H$_5$, 100%), 301 (M$^+$ −H,CONHN=CNHC$_6$H$_5$, 66.7%); Anal., Calcd./Found(%): C(67.52/67.57) H(3.92/3.96) N(18.17/18.20) S(6.93/6.97).

2-(5-Anilino-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl-6-pyridin-3-ylthieno-[2,3-*b*]pyridin-3-amine (18b) as orange crystals (70%), mp = 190°C; **IR** (ν cm^{-1}): 3473, 3359 (NH$_2$), 3219 (NH), 3054 (aromatic-CH); **MS**: 492 (M$^+$, 10.9% corresponding to the molecular formula $C_{27}H_{20}N_6O_2S$ of the assigned structure), 360 (M$^+$ −NN=CNHC$_6$H$_5$, 63.8%), 358 (360–2H, 100%), 330 (M^{+}—NH_2, CONN=$CNHC_6H_5$, 65.5%); Anal., Calcd./Found(%): C(65.84/65.87) H(4.09/4.12) N(17.06/17.09) S(6.51/6.55).

Synthesis of 20a,b

A solution of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) in acetic acid (15 mL) was heated under reflux for 5 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from acetic acid to give **20a**,**b**, respectively.

1-Acetyl-8-(4-phenyl)-6-pyridin-3-yl-1,2-dihydro-3*H*-pyrazolo[3′,4′:4,5]-thieno [2,3-*b*]pyridin-3-one (20a) as pale yellow crystals (69%), mp = 322°C; **IR** (ν cm^{-1}): 3311 (NH), 3055 (aromatic-CH), 1710, 1667 (acetyl and amidic CO); **MS**: 386 (M^{+}, 26.8% corresponding to the molecular formula $C_{21}H_{14}N_4O_2S$ of the assigned structure), 385 (M^{+} —H, 100%), 328 (M^{+} —H, $NCOCH_3$, 11.0%); Anal., Calcd./Found(%): C(65.27/65.30) H(3.65/3.70) N(14.50/14.54) S(8.30/8.33).

1-Acetyl-8-(4-methoxyphenyl)-6-pyridin-3-yl-1,2-dihydro-3*H*-pyrazolo-[3′,4′:4,5]thieno[2,3-*b*]pyridin-3-one (20b) as yellow crystals (79%), mp = >330°C; **IR** (ν cm^{-1}): 3313 (NH), 3006 (aromatic-CH), 1708, 1662 (CO); **MS**: 416 (M^{+}, 29% corresponding to the molecular formula $C_{22}H_{16}N_4O_3S$ of the assigned structure), 415 (M^{+} —H, 41.9%), 399 (M^{+} —H, $NH_2$11.3%), 386 (M^{+} —OCH_3, 21%); Anal., Calcd./Found(%): C(63.45/63.48) H(3.87/3.90) N(13.45/13.49) S(7.70/7.73).

Synthesis of 22a,b

A solution of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) in acetylacetone (10 mL) was heated under reflux for 6 h. The reaction mixture was triturated with ethanol (5 mL) and then left to cool. The solid was collected by filtration, dried, and crystallized from the ethanol to give **22a**,**b**, respectively.

2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-3-amine (22a) as yellow crystals (87%), mp = 200°C; **IR** (ν cm^{-1}): 3480, 3326 (NH_2), 3031 (aromatic-CH), 1640 (CO); **MS**: 425 (M^{+}, 64.3% corresponding to the molecular formula $C_{24}H_{19}N_5OS$ of the assigned structure), 330 (M^{+} —$NC(CH_3)CHC(CH_3)N$, 33.3%); Anal., Calcd./Found(%): C(67.74/67.77) H(4.50/4.54) N(16.46/16.50) S(7.54/7.59).

2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-methoxyphenyl-6-pyridin-3-yl thieno[2,3-*b*]pyridin-3-amine (22b) as yellow crystals (90%), mp = 242°C; **IR** (ν cm^{-1}): 3476, 3313 (NH_2), 2957 (aromatic-CH), 1681 (CO); **MS**: 455 (M^{+}, 55.8% corresponding to the molecular formula $C_{25}H_{21}N_5O_2S$ of the assigned structure), 360 (M^{+} -pyrazolyl ring, 25.8%), 358 (360 -2H, 100%); **^{1}H NMR** (DMSO-D_6) (δppm): 2.26 (s, 3H, CH_3); 2.50 (s, 3H, CH_3) 3.86 (s, 3H, OCH_3); 6.22 (s, 2H, NH_2); 7.05–9.45 (m, 10H, Ar H′s, pyridinyl H′s and C_4(H)); Anal., Calcd./Found(%): C(65.92/65.97) H(4.65/4.69) N(15.37/15.40) S(7.04/7.07).

Synthesis of 24a,b

A solution of **3a**,**b** (0.20 g, 0.21 g; 0.00055 mol) and ethyl acetoacetate (0.07 g, 0.00055 mol) in acetic acid (15 mL) was heated under reflux for 5 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **24a**,**b**, respectively.

2-[(3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)carbonyl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (24a) as yellow crystals (86%), mp = >330°C; **IR** (ν cm^{-1}): 3386 (NH_2), 3148 (NH), 3058 (aromatic-CH), 1681 (CO); **MS**: 427 (M^+, 15.3% corresponding to the molecular formula $C_{23}H_{17}N_5O_2S$ of the assigned structure), 386 (M^+ −COCH, 24.0%), 385 (M^+ −CH_3CNH, 92.9%); Anal., Calcd./Found(%): C(64.62/64.66) H(4.01/4.05) N(16.38/16.40) S(7.50/7.54).

2-[(3-Amino-4-methoxyphenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)-carbonyl]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (24b) as yellow crystals (70%), mp = >330°C; **IR** (ν cm^{-1}): 3422, 3363 (NH_2), 3068 (aromatic-CH), 1682, 1662 (two CO); **MS**: 441 (M^+ −NH_2 54.2%), 440 (M^+ −NH_2, H,), 439 (M^+ −NH_2, 2H, 100%); Anal., Calcd./Found(%): C(63.01/63.06) H(4.19/4.22) N(15.31/15.35) S(7.01/7.07).

Synthesis of 26a,b

A solution of **3a**,**b** (0.20 g, 0.21 g, 0.00055 mol) and diethyl malonate (0.09 g, 0.00055 mol) in acetic acid (15 mL) was heated under reflux for 5 h. The excess solvent was evaporated and cooled. The solid was collected by filtration, dried, and crystallized from the acetic acid to give **24a**,**b**, respectively.

1-{[3-Amino-4-(4-phenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl]carbonyl}pyrazolidine-3,5-dione (26a) as pale yellow crystals (77%), mp = 280°C; **IR** (ν cm^{-1}): 3262, 3203 (NH_2), 3052 (aromatic-CH), 1673, 1634 (two CO); **MS**: 428 (M^+ −H, 5.1%), 427 (M^+ −2H, 12.6%), 314 (M^+ −NH_2, $NCOCH_2CONH$, 10.0%); **^{1}H NMR** (DMSO-D_6) (δ ppm): 2.50 (s, 2H, CH_2); 6.01 (s, 2H, NH_2); 7.49–9.40 (m, 11H, Phenyl, pyridinyl H′s and NH); Anal., Calcd./Found(%): C(61.53/61.56) H(3.52/3.55) N(16.31/16.35) S(7.47/7.52).

1-{[3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl]carbonyl}pyrazolidine-3,5-dione (26b) as yellow crystals (67%), mp = 300–302°C; **IR** (ν cm^{-1}): 3485, 3362 (NH_2), 3246 (NH), 2958 (aromatic-CH), 1716, 1671. (two CO); **MS**: 458 (M^+ −H, 21.7%), 457 (M^+ −2H, 43%), 415 (M^+ −H, CONH, 85.7%), 360 (M^+ −$NCOCH_2CONH$, 100%), 332 (M^+ −$CONCOCH_2CONH$, 9.2%), 316 (M^+ −NH_2, −$CONCOCH_2CONH$, 15.0%); Anal., Calcd./Found(%): C(60.12/60/.16) H(3.73/3.78) N(15.24/15.27) S(6.98/7.01).

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