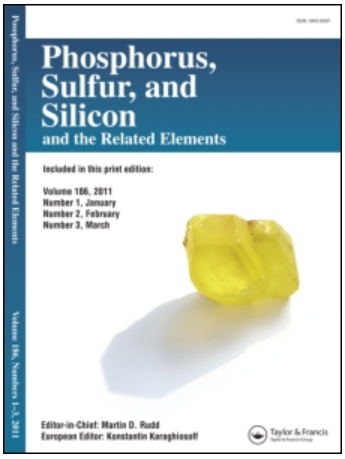

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Fawzy A. Attaby[a]; Azza M. Abdel-Fattah[a]; Labeeb M. Shaif[a]; Mohamed M. Elsayed[b]
[a] Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt [b] Research Units, Hi-Care Pharmaceutical Co., Cairo, Egypt

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

Fawzy A. Attaby,[1] Azza M. Abdel-Fattah,[1] Labeeb M. Shaif,[1] and Mohamed M. Elsayed[2]

[1]*Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt*
[2]*Research Units, Hi-Care Pharmaceutical Co., Cairo, Egypt*

3-Aryl-1-pyridin-3-ylprop-2-en-1-ones 1a,b reacted with 2-cyanoethane-thioamide (2) to afford the corresponding 4-aryl-6-thioxo-1,6-dihydro-2,3′-bipyridine-5-carbonitriles 6a,b. The synthetic potentiality of compounds 6a,b were investigated in the present study via their reactions with several active-hydrogen containing compounds 8a–g aiming to synthesize 4-aryl-6-pyridin-3-ylthieno[2,3-b]pyridin-3-amines 10a–n via 6-(alkylthio)-4-aryl-2,3′-bipyridine-5-carbonitriles 9a–n. The structures of all newly synthesized heterocyclic compounds were elucidated by considering the data of IR, ^{1}H NMR, and mass spectra, as well as that of elemental analyses. Anti-Alzheimer and anti-COX-2 activities for all newly synthesized heterocyclic compounds were investigated.

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 6-(Alkylthio)-4-aryl-2, 3′-bipyridine-5-carbonitriles; 3-aryl-1-pyridin-3-ylprop-2-en-1-ones; 2-cyanoethanethioamide; 6-pyridin-3-ylthieno-[2,3-*b*]pyridin-3-amines; 6-thioxo-1, 6-dihydro-2,3′-bipyridine-5-carbonitrile

INTRODUCTION

In conjunction with our previous recent work,[1–19] and with the aim to investigate and evaluate the biological activities of the newly synthesized heterocyclic compounds, we here interested to use 3-aryl-1-pyridin-3-ylprop-2-en-1-ones as key compounds to synthesize 2,3′-bipyridine-5-carbonitriles required for several chemical transformations, as well as our medicinal chemistry programs.

RESULTS AND DISCUSSION

3-Phenyl-1-pyridin-3-ylprop-2-en-1-one[20] (**1a**) reacted with 2-cyanoethane-thioamide (**2**) in absolute ethanol containing a catalytic amount of piperidine under reflux to afford a reaction product. The reaction product formed via a Michael addition of $-CH_2-$

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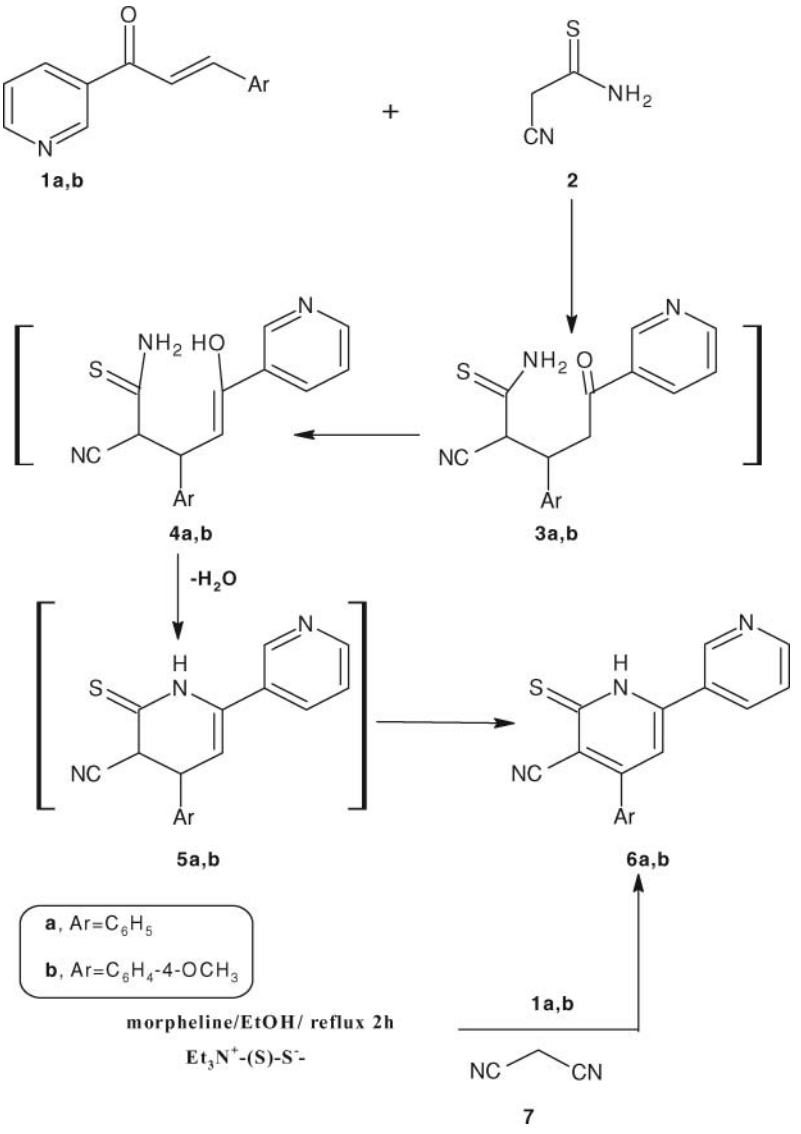
Address correspondence to Fawzy A. Attaby, Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt. E-mail: Fattaby@hotmail.com

in **2** on −CH=CH− of **1a** to give the non-isolable products **3a**, **4a**, and **5a** followed by cyclization via dehydration and dehydrogenation to give **6a**. The IR (cm^{-1}) of this reaction product showed the bands of NH (3169) and CN (2220) groups. Its mass spectrum gave m/z = 289 (100%), which corresponded to the molecular weight of the formula $C_{17}H_{11}N_3S$ of the assigned structure, as well as m/z = 256 (12.5%), which corresponded to (M^+ - SH).

In a similar manner, 3-(4-methoxyphenyl)-1-pyridin-3-ylprop-2-en-1-one (**1b**) reacted with 2-cyanoethanethioamide (**2**) under the same above-mentioned experimental conditions to give the finally isolated **6b** via the non-isolable intermediates **3b**, **4b**, and **5b**. The chemical structure of **6b** was elucidated by considering the data of IR, ^{1}H NMR, and mass spectra, as well as that of elemental analyses (see the Experimental section). A further confirmation of **6a**,**b** arose from their synthesis through another pathway via the reaction of each of **1a,b** and malononitrile (**7**) in a dispersed sulfur, morpholine, and ethanol under reflux for 2 h (Scheme 1).[21] It important to note here that **6a**,**b** obtained by the two pathways are identical in all physical and chemical properties.

The synthetic potentiality of each of **6a**,**b** was investigated through electrophilic substitution reactions using several electrophilic C-species. Thus, it has been found that **1a** reacted with ethyl chloroacetate (**8a**) in stirred methanolic solution of sodium methoxide at room temperature for 15 min to give a reaction product. The IR (cm^{-1}) of this reaction product showed the bands of CN (2220) and CO (1734) of the newly introduced COOEt group. Its ^{1}H NMR (δ ppm) spectrum revealed the signals of $-S\underline{CH_2}-$, $-COO\underline{CH_2}CH_3$, and $-COOCH_2\underline{CH_3}$ protons, and this confirm the good nucleophilicity of S in **6a** that facilitates the electrophilic attack of **8a** to afford **9a** in a very pure form and in a good yield. Furthermore, the structure of **9a** was elucidated through its cyclization in ethanolic sodium ethoxide under reflux for 30 min to give a reaction product whose IR spectrum showed no bands of CN group, but instead bands of the newly formed NH_2 group were detected. Also, the ^{1}H NMR spectrum of this reaction product revealed signals of $-NH_2$ protons and did not reveal the signals of $-CH_2-$ protons. Considering the data of both IR and ^{1}H NMR, we concluded that both $-SCH_2-$ and CN functional groups in **9a** involved in the cyclization step to give the finally isolated **10a**. A further confirmation of the structure of **10a** was obtained through its preparation authentically via the reaction of **6a** with **8a** in ethanolic sodium ethoxide under reflux for 2 h (see the Experimental section). Similarly, **6a** reacted with each of **8c**, **8e**, and **8g** in stirred methanolic solution of sodium methoxide at room temperature to give the corresponding 2-alkylthio derivatives **9c**, **9e**, and **9g**, whose structures were elucidated by considering the data of IR and elemental analyses. Also, **9c** and **9e** cyclized in ethanolic sodium ethoxide under reflux for 30 min and gave the corresponding thieno[2,3-b]pyridine derivatives **10c** and **10e** respectively, which were also obtained via refluxing of **6a** with each of **8c** and **8e** in ethanolic sodium ethoxide for 2 h. Unexpectedly, **9g** did not undergo a cyclization reaction under a variety of experimental conditions to give the corresponding thieno[2,3-b]pyridine derivative **10g**.

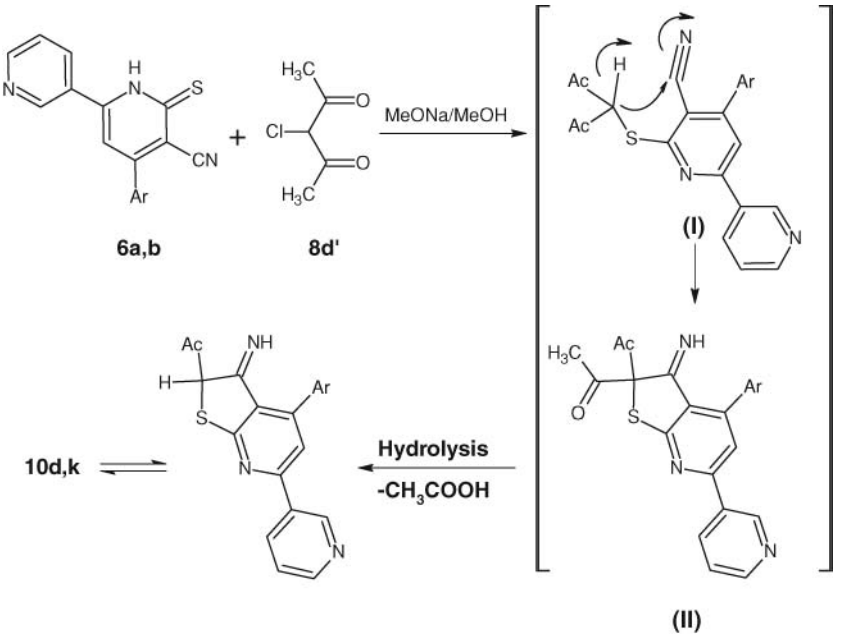
In contrast to the behavior of **6a** towards each of **8a**, **8c**, **8e**, and **8g**, it has been found that **6a** reacted with each of **8b**, **8d**, and **8f** either in stirred methanolic sodium methoxide at room temperature or under reflux in ethanolic sodium ethoxide to give the corresponding thieno[2,3-b]pyridine derivatives **10b**, **10d**, and **10f**, respectively, whose structures were elucidated by considering the data of IR, ^{1}H NMR, and mass spectra, as well as that of elemental analyses. It is important to report here that all trials aimed at isolating compounds **9b**, **9d**, and **9f** failed under a variety of experimental



Scheme 1

conditions. The structure of **10d** was confirmed via its preparation through another route by reaction of **6a** with or 3-chloropentan-2,4-dione (**8d′**) in methanolic solution of sodium methoxide either under stirring at room temperature or under reflux for 2 h. The reaction appears to proceed via the intermediates **I** and **II** through removal of the acetic acid molecule to give 2-acetyl-3-amino-4-phenyl-6-(3-pyridyl)thieno[2,3-b]pyridine (**10d**) (see Equation 1).

In continuation to our effort to investigate the electrophilic substitution reaction along the SH group in each of **6a**,**b**, compound **6b** is a key structure for that goal. Thus, it has been found that **6b** reacted with each of **8a**, **8b**, **8c**, **8e**, **8f**, and **8g** in a stirred methanolic solution of sodium methoxide for 15 min to afford the corresponding 2-alkylthio derivatives **9h**, **9i**,



Equation 1

9j, **9l**, **9m**, and **8n** (Scheme 2). The structures of these reaction products were elucidated by considering the data of their elemental analyses, IR, and ^{1}H NMR (see the Experimental section). A further elucidation for these structures arose from their cyclization in methanolic solution of sodium methoxide under reflux for 30 min to give the corresponding thieno[2,3-b]pyridine derivatives **10h**, **10i**, **10j**, **10l**, **10m**, and **10n**, respectively. An authentic sample of each of **10h**, **10i**, **10j**, **10l**, **10m**, and **10n** obtained via a reflux mixture of **6b** and each of **8a**, **8b**, **8c**, **8e**, **8f**, and **8g** in ethanolic solution of sodium ethoxide for 2 h. In contrast to this behavior, **6b** reacted with 1-chloroacetone (**8d**) or 3-chloropentan-2,4-dione (**8d′**) either in a methanolic solution of sodium methoxide at room temperature for 15 min under stirring or under reflux for 2 h in an ethanolic solution of sodium ethoxide to give directly the corresponding thieno[2,3-b]pyridine derivative **10k** (see Equation 1). The structure of **10n** was confirmed further via its preparation authentically through the hydrolysis of **10h** in ethanolic 10% KOH under reflux (see the Experimental section).

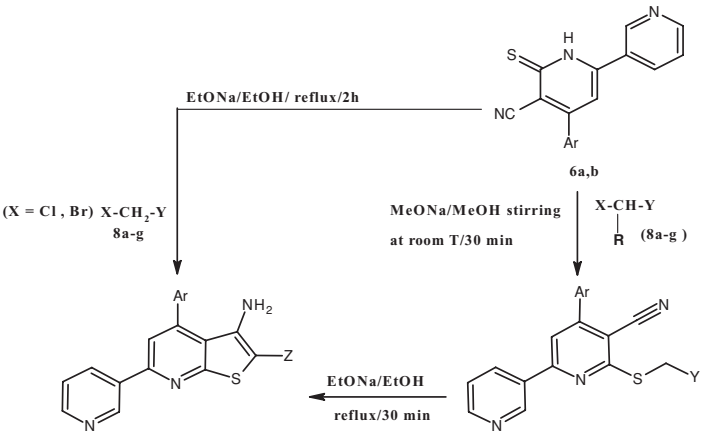
Biological Evaluation

Anti-Alzheimer activity. For compounds **1a**,**b**, their potency as anti-Alzheimer agents relative to Flurbiprofen is high enough, while after their reactions to afford the corresponding bipyridine-5-carbonitriles **6a**,**b**, their relative potency decreased. (See the Supplemental Materials online).

Structural activity relationship of anti-Alzheimer activity. Generally for compounds **9**, we note that the phenyl moiety provides the highest anti-Alzheimer activity compared with phenyl-*p*-methoxy. Thus, we can conclude that the *p*-methoxy group has no effect. The potency as anti-Alzheimer agents for S-substitution in all compounds **9** with

phenyl moiety relative to Flurbiprofen is arranged in descending order as follows: acid > ketone > ester > amide.

Anti-COX-2 activity. For the substituted pyridine derivatives **9**, their potency as anti-COX-2 activities is arranged in descending order as follows: **9h**, **9n**, **9e**, **9i**, **9m**, **9a**, (**9c**, **6b**), **9j**, (**9l**, **9g**). (See Figure 6 in the Supplemental Materials online).



10a, b, c, d, e, f, g, h, i, j, k, l, m, n **9a, [b], c, [d], e, [f], g, h, i, j, l, m, n**

10	Ar	z	9	Ar	Y
a	C_6H_5	COOEt	**a**	C_6H_5	COOEt
b	C_6H_5	CN	**c**	C_6H_5	$CONH_2$
c	C_6H_5	$CONH_2$	**e**	C_6H_5	COPh
d	C_6H_5	COMe	**g**	C_6H_5	COOH
e	C_6H_5	COPh	**h**	C_6H_4-4-OCH_3	COOEt
f	C_6H_5	COPh-p-Cl	**i**	C_6H_4-4-OCH_3	CN
h	C_6H_4-4-OCH_3	COOEt	**j**	C_6H_4-4-OCH_3	$CONH_2$
i	C_6H_4-4-OCH_3	CN	**l**	C_6H_4-4-OCH_3	COPh
j	C_6H_4-4-OCH_3	$CONH_2$	**m**	C_6H_4-4-OCH_3	COPh-p-Cl
k	C_6H_4-4-OCH_3	COMe	**n**	C_6H_4-4-OCH_3	COOH
l	C_6H_4-4-OCH_3	COPh			
m	C_6H_4-4-OCH_3	COPh-p-Cl			
n	C_6H_4-4-OCH_3	COOH			

8	X	Y	R
a	Cl	COOEt	H
b	Cl	CN	H
c	Cl	$CONH_2$	H
d	Cl	COMe	H
d′	Cl	COMe	COMe
e	Br	COPh	H
f	Br	COPh-p-Cl	H
g	Cl	COOH	H

Scheme 2

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 6a,b (General Method)

Method A. A solution of each of **2** (2.60 g, 2.6 mmol) and each of **1a**,**b** (5.43 g and 5.8 g, 2.6 mmol) in absolute ethanol (30 mL) containing a catalytic amount of piperidine (0.4 mL) was heated under reflux for 5 h. The reaction mixture was evaporated, cooled, and triturated with ethanol. The products were formed collected by filtration, washed with cold ethanol, and then crystallized from the proper solvent to give the corresponding **6a**,**b**, respectively.

Method B. A mixture of dispersed sulfur (0.67 g, 1.9 mmol) and morpholine (1.7 mL, 1.9 mmol) in ethanol (50 mL) was refluxed for 20 min. Malononitrile (**7**) (1.30 g, 1.9 mmol) was added followed by **1a**,**b** (3.97 g and 4.54 g, 1.9 mmol), and the mixture was refluxed for 2 h. The mixture was cooled to ~20 °C, and 10% HCl was added to reach pH 5–6. The precipitates that formed were filtered off and washed with water and cooled ethanol, then crystallized from dioxane to give the corresponding **6a**,**b** respectively.

4-Phenyl-6-thioxo-1,6-dihydro-2,3′-bipyridine-5-carbonitrile (6a): As orange crystals, yielded by 71%, mp 240 °C, **IR** (ν cm^{-1}): 3169 (NH), 3053 (aromatic—CH) and 2220 (CN); **MS**: 289 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{17}H_{11}N_3S$ of the assigned structure), 287 (M^+—2H, 84%); 256 (M^+—SH, 12.5%); **^{1}H NMR** (DMSO-D_6) (δppm): 7.22–7.82(m, 5H, Ph, protons), 8.19–9.01 (m, 5H, pyridine H·s) and 14.10 (s, br, 1H, SH); Anal. for $C_{17}H_{11}N_3S$ (289) Calcd./Found (%): C(70.56/70.60), H(3.83/3.90), N(14.52/14.58), S(11.08/11.16%).

4-(4-Methoxyphenyl)-6-thioxo-1,6-dihydro-2,3′-bipyridine-5-carbonitrile (6b): As orange crystals, yielded by 76%, mp 272 °C; **IR** (ν cm^{-1}): 3174 (NH), 3020 (aromatic-CH) and 2216 (CN); **MS**: 319 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{18}H_{13}N_3OS$ of the assigned structure), 318 (M^+-H, 30.6%), 287 (M^+—S, 4.6%); **^{1}H NMR** (DMSO-D_6) (δ ppm): 3.85 (s, 3H, OCH_3), 7.11–7.84(m, 4H, Ar), 8.17–9.22 (m, 5H, pyridine H·s) and 14.2 (s, br, 1H, SH); Anal, for $C_{18}H_{13}N_3OS$ (319) Calcd./Found(%): C(67.69/67.72), H(4.10/4.14), N(13.16/13.19), and S (10.04/10.11%).

Synthesis of 9a, 9c, 9e, 9g–i, 9j, 9l–n: General Procedure

A solution of each of **6a**,**b** (0.29 g and 0.32 g, 1 mmol) and ethyl chloroacetate (**8a**), chloroacetonitrile (**8b**), 2-chloroacetamide (**8c**), 1-chloroacetone (**8d**), 3-chloropentane-2,4-dione (**8d′**), 2-bromo-1-phenyl-ethanone (**8e**), 2-bromo-1-*p*-chlorophenylethanone (**8f**), chloroacetic acid (**8g**) (0.12 g, 0.08 g, 0.09 g, 0.09 g, 0.13 g, 0.2 g, 0.23 g and 0.09 g 1 mmol, respectively) in sodium methoxide (prepared from 0.14 g of sodium and methanol 25 mL) was stirred at room temperature for 15 min. The formed precipitate was collected by filtration, washed with water, and crystallized from the proper solvent to give **9a**, **9c**, **9e**, **9g**, **9h**, **9i**, **9j**, **9l**, **9m**, and **9n**, respectively.

Ethyl [(5-cyano-4-phenyl-2,3′-bipyridin-6-yl)thio]acetate (9a): As pale yellow crystals (87%), mp 196 °C; **IR** $\upsilon(cm^{-1})$: 3066 (C—H, aromatic), 2220 (CN), 1734 (ester CO); **^{1}H NMR** (DMSO-D_6) (δppm): 1.16 (t, 3H, $CH_2\underline{CH_3}$), 2.49 (s, 2H, $S\underline{CH_2}$), 4.30 (q, 2H, $\underline{CH_2}CH_3$), 7.56–7.79(m, 5H, phenyl H·s), 8.07–9.40 (m, 5H, pyridine H·s); Anal., for $C_{21}H_{17}N_3O_2S$ (375), Calcd./Found (%): C(67.18/67.23), H(4.56/4.61), N(11.19/11.23), S(8.54/8.61%).

2-[(5-Cyano-4-phenyl-2,3′-bipyridin-6-yl)thio]acetamide (9c): As pale yellow crystals (84%), mp 265 °C; **IR** $\upsilon(cm^{-1})$: 3432, 3128 (NH_2), 2215 (CN), 1684 (CO amide); Anal., for $C_{19}H_{14}N_4OS$ (346), Calcd./Found (%): C(65.88/65.90%), H(4.07/4.11%), N(16.17/16.22%), S(9.26/9.30%).

6-[(2-Oxo-2-phenylethyl)thio]-4-phenyl-2,3′-bipyridine-5-carbonitrile (9e): As orange crystals (91%); mp 210 °C; **IR** $\upsilon(cm^{-1})$: 3058 (C—H, aromatic), 2213 (CN), 1690 (CO); Anal. for $C_{25}H_{17}N_3OS$ (407), Calcd./Found(%): C(73.69/73.72), H(4.21/4.26), N(10.31/10.40), S(7.87/7.90%).

[(5-Cyano-4-phenyl-2,3′-bipyridin-6-yl)thio]acetic acid (9g): As orange crystals (80%); mp = 300–302 °C; **IR** $\upsilon(cm^{-1})$: 2927–3387 acid (OH), 3062 (CH, aromatic), 2214 (CN); Anal. for $C_{19}H_{13}N_3O_2S$ (347), Calcd./Found (%): C(65.69/65.73), H(3.77/3.85), N(12.10/1219), S(9.23/9.30).

Ethyl{[5-cyano-4-(4-methoxyphenyl)-2,3′-bipyridin-6-yl]thio}acetate (9h): As pale yellow crystals (80%); mp 182 °C; **IR** $\upsilon(cm^{-1})$: 3045 (C—H aromatic), 2214 (CN), 1736 (ester CO). **^{1}H NMR** (DMSO-D_6) (δppm): 2.50 (s, 2H, $-SCH_2$), 3.18–3.18 (overlapped, 3H, $-CH_2\underline{CH_3}$), 3.86 (s, 3H, OCH_3), 4.28 (overlapped q, 2H, $-\underline{CH_2}CH_3$), 7.79 (m, 4H, Ar—H·s), 8.03–9.39 (m, 5H, pyridine); Anal. for $C_{22}H_{19}N_3O_3S$ (405), Calcd./Found (%): C(65.17/65.21), H(4.72/4.80), N(10.36/10.43), S(7.91/8.00).

6-[(Cyanomethyl)thio]-4-(4-methoxyphenyl)-2,3′-bipyridine-5-carbonitrile (9i): As yellow crystals (84%); mp 185–157 °C; **IR** $\upsilon(cm^{-1})$: 3051 (C—H aromatic), 2214 (CN); Anal. for $C_{20}H_{14}N_4OS$ (358) Calcd./Found (%): C(67.02/67.10), H(3.94/4.03), N(15.63/15.70), S(8.95/9.06).

2-{[5-Cyano-4-(4-methoxyphenyl)-2,3′-bipyridin-6-yl]thio}acetamide (9j): As yellow crystals (84%); mp 212 °C; **IR** $\upsilon(cm^{-1})$: 3391, 3204 (NH_2), 3079 (C—H aromatic), 2216 (CN), 1666 (CO); Anal. for $C_{20}H_{16}N_4O_2S$ (376) Calcd./Found(%):C(63.81/63.90), H(4.28/4.33), N(14.88/14.95), S(8.52/8.61).

6-[(2-Oxo-2-phenylethyl)thio]-4-(4-methoxyphenyl)-2,3′-bipyridine-5-carbonitrile (9l): As orange crystals (91%); mp 182 °C; **IR** $\upsilon(cm^{-1})$: 3046 (C—H aromatic), 2213 (CN); Anal. for $C_{26}H_{19}N_3O_2S$ (437), Calcd./Found (%): C(71.38/71.42), H(4.38/4.44), N(9.60/9.64), S(7.33/7.41).

6-{[2-(4-Chlorophenyl)-2-oxoethyl]thio}-4-(4-methoxyphenyl)-2,3′-bipyrid-ine-5-carbonitrile (9m): As yellow crystals (89%); mp 225 °C; **IR** $\upsilon(cm^{-1})$: 3064 (C—H aromatic), 2206 (CN), 1697 (CO); Anal. for $C_{26}H_{18}ClN_3O_2S$ (471), Calcd./Found (%): C(66.17/66.22), H(3.84/3.90), Cl(7.51/7.60), N(8.90/9.00), S(6.79/6.85).

{[5-Cyano-4-(4-methoxyphenyl)-2,3′-bipyridin-6-yl]thio}acetic acid (9n): As orange crystals (80%); mp 278 °C; **IR** $\upsilon(cm^{-1})$: 3336–3529 (acidic OH), 3040 (C—H aromatic), 2209 (CN), 1653 (CO); **^{1}H NMR** (DMSO-D_6) (δ ppm): 2.49 (s, 3H, $-SCH_2-$), 3.85 (s, 3H, OCH_3), 7.11–7.83 (m, 4H, Ar H·s), 8.16–9.21 (m, 5H, pyridine H·s) and 14.3 (s, br., 1H, COOH); Anal. for $C_{20}H_{15}N_3O_3S$ (377) Calcd./Found (%): C(63.65/63.70), H(4.01/4.10), N(11.13/11.20), S(8.50/8.58).

The Synthesis of 10a–n

Method A. A solution of each of **9a**, **9c**, **9e**, **9g**, **9h**, **9i**, **9j**, **9l**, **9m**, and **9n** (0.38 g, 0.35 g, 0.41 g, 0.35 g, 0.41 g, 0.36 g, 0.38 g, 0.44 g, 0.47 g, and 0.38 g, respectively 1 mmol) in sodium ethoxide solution (prepared from 0.10 g of sodium and 25 mL ethanol) was heated under reflux for 30 min. The solid that formed after cooling was collected by filtration, washed with water and ethanol, then crystallized from the proper solvent to afford **10a–n**, respectively.

Method B. A solution of each of **6a**,**b** (0.29 g and 0.32 g, respectively, 1 mmole) and ethyl-chloroacetate (**8a**), chloroacetonitrile (**8b**), 2-chloroacetamide (**8c**), 1-chloroacetone (**8d**), 3-chloropentane-2,4-dione (**8d′**), 2-bromo-1-phenylethanone (**8e**), 2-bromo-1-(4-chlorophenyl)ethanone (**8f**), and chloroacetic acid (**8g**) (0.12 g, 0.08 g, 0.09 g, 0.09 g, 0.13 g, 0.20 g, 0.23 g, and 0.09 g, respectively, 1 mmole) in sodium methoxide (prepared from 0.10 g of sodium and 25 mL ethanol) heated under reflux for 2 h. The solid products so formed after cooling, collected by filtration, washed with water and ethanol, and dried, then crystallized from the proper solvent to afford **10a–n**, respectively.

Ethyl 3-amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carboxylate (10a): As yellow crystals crystallized from ethanol (90%); mp 180 °C; **IR** $\upsilon(cm^{-1})$: 3478, 3333 (NH_2), 3057 (C—H aromatic), 1666 (CO); **^{1}H NMR** (DMSO-D_6) (δppm): 1.05 (t, 2H, $CH_2\underline{CH_3}$), 3.44 (q, 2H, $\underline{CH_2}CH_3$), 6.46 (s, 2H, NH_2), 7.48–7.89 (m, 5H, phenyl H's) and 8.57–9.38 (m, 5H, pyridine H's); Anal, for $C_{21}H_{17}N_3O_2S$ (375), Calcd./Found (%): C(67.18/67.23), H(4.56/4.61), N(11.19/11.23), and S (8.54/8.60).

3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carbonitrile (10b): As yellow crystals crystallized from ethanol (85%); mp 274 °C; **IR** $\upsilon(cm^{-1})$: 3448, 3298, 3180 (NH_2), 3052(C–H aromatic), 2183 (CN); **MS** (m/z): 328 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{19}H_{12}N_4S$ of the assigned structure), 254 (M^+—Pyridyl, 17%), 166 (Pyridine—CN, CN—C=C—NH_2, 5.3%), 140 (Pyridine, CN—C=C—NH_2, 7.0%), 100 (Pyridine—CN, 5.3%) and 66 (CN—C=C—NH_2, 10.5%); Anal. for $C_{19}H_{12}N_4S$ (328), Calcd./Found (%): C(69.49/69.52), H(3.68/3.72), N(17.06/17.12), S(9.76/9.82).

3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carboxamide (10c): As orange crystals crystallized from dioxane (80%); mp 225 °C; **IR** $\upsilon(cm^{-1})$: 3475, 3433, 3300, 3119 (NH_2 and amidic NH_2), 1645 (amidic CO); **MS** (m/z): 346 (M^+, 100% which corresponds the molecular weight of the molecular formula $C_{19}H_{14}N_4OS$ of the assigned structure), 330 (M^+—NH_2, 7.5%), 329 (M^+—NH_2—H, 50.7%), 328 (M^+—NH_2—2H, 11.0%), 300 (M^+—$CONH_2$–2H, 84.9%), 256 (M^+—PhCN—NH_2, 35.6%), 228 (M^+—PhCN—$CONH_2$, 26.0%); Anal. for $C_{19}H_{14}N_4OS$ (346), Calcd./Found (%): C(65.88/65.94), H(4.07/4.11), N(16.17/16.21), S(9.26/9.31%).

1-(3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)ethanone (10d): As orange crystals crystallized from acetic acid (83%); mp 183 °C; **IR** $\upsilon(cm^{-1})$: 3485, 3310 (NH_2), 3054 (C—H aromatic), 1620 (CO); **MS** (m/z): 345 (M+, 100% which corresponds to the molecular weight of the molecular formula $C_{20}H_{15}N_3OS$ of the assigned structure), 344 (M^+—H, 43.4%), 330 (M^+—CH_3, 56.2%), 302 (M^+—$COCH_3$, 36.9%);**^{1}H NMR** (DMSO-D_6) (δppm): 2.39 (s, 3H, $COCH_3$), 6.50 (s, br., 2H, NH_2) 7.48–7.92 (m, 5H, phenyl H's) and 8.57–9.39 (m, 5H, pyridine H's); Anal. for $C_{20}H_{15}N_3OS$ (345), Calcd./Found (%): C(69.54/69.62), H(4.38/4.42), N(12.17/12.22), S(9.28/9.30).

(3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)(phenyl)-methanone (10e): As orange crystals crystallized from dioxane (79%); mp = 210 °C; **IR** $\upsilon(cm^{-1})$:

3469, 3382, 3305 (NH_2), 3057 (C—H aromatic), 1678 (CO); **MS** (m/z): 407 (M+, 84.3% which corresponds to the molecular weight of the molecular formula $C_{25}H_{17}N_3OS$ of the assigned structure), 406 (M^+—H, 100%), 302 (M^+—COPh, 28.2%), 105 (PhCO, 68.8%); Anal. for $C_{25}H_{17}N_3OS$ (407), Calcd./Found (%): C(73.69/73.75), H(4.21/428), N(10.31/10.38), S(7.87/7.94).

(3-Amino-4-phenyl-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)(4-chlorophenyl)-ethanone (10f): As yellow crystals crystallized from dioxane (86%); mp 226 °C; **IR** $\upsilon(cm^{-1})$: 3461, 3284 (NH_2), 3053 (C—H aromatic), 1685 (CO); **MS** (m/z): 442 (M^+, 60.6% which corresponds to the molecular weight of the molecular formula $C_{25}H_{16}ClN_3OS$ of the assigned structure), 443 (M+1, 29.9%), 440 (M^+—2H, 100%), 301 (M^+—COC_6H_4—p—Cl, 10.3%); Anal. for $C_{25}H_{16}ClN_3OS$ (441.5), Calcd./Found (%): C(67.94/67.99), H(3.65/3.71), Cl(8.02/8.11), N(9.51/9.59), S(7.26/7.33).

Ethyl 3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyrid-ine-2-carboxylate (10h): As yellow crystals crystallized from ethanol (88%); mp 219 °C; **IR** $\upsilon(cm^{-1})$: 3497, 3379 (NH_2), 3062 (C—H aromatic), 1665 (CO); **MS** (m/z): 405 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{22}H_{19}N_3O_3S$ of the assigned structure), 358 (M^+—C_2H_5, —H, 66.4%), 332 (M^+—COOEt, 4.3%), 330 (M^+—COOEt, —2H, 27.6%), 139 (—COC_6H_4Cl 31%); **^{1}H NMR** (DMSO-D_6) (δppm): 1.28 (t, 3H, $CH_2\underline{CH_3}$), 3.86 (s, 3H, OCH_3), 4.27 (q, 2H, $\underline{CH_2}CH_3$), 5.90 (s, 2H, NH_2), 7.14–7.48 (m, 4H, Ar H·s) and 8.53–9.35 (m, 5H, pyridine H·s); Anal. for $C_{22}H_{19}N_3O_3S$ (405) Calcd./Found (%): C(65.17/65.22), H(4.72/4.80), N(10.36/10.41), S(7.91/7.99).

3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carbonitrile (10i): As orange crystals crystallized from dioxane (90%); mp 210 °C; **IR** $\upsilon(cm^{-1})$: 3460, 3382, 3296 (NH_2), 3065 (C—H aromatic), 2188 (CN); **MS** (m/z): 358 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{20}H_{14}N_4OS$ of the assigned structure), 357 (M^+—H, 34.6%), 327 (M^+—OCH_3, 17.4%), 316 (M^+—CN—NH_2, 5.3%), 313 (M^+—NH_2,—CN,—3H 19%); Anal. for $C_{20}H_{14}N_4OS$ (358), Calcd./Found (%): C(67.02/6711), H(3.94/4.00), N(15.63/15.70), S(8.95/9.02).

3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carboxamide (10j): As yellow crystals crystallized from acetic acid (81%); mp 268 °C; **IR** $\upsilon(cm^{-1})$: 1656 (CO), 3467, 3289 (NH_2), 3407, 3126 (NH_2); **MS** (m/z): 376 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{20}H_{16}N_4O_2S$ of the assigned structure), 360 (M^+—NH_2, 12%), 358 (M^+—NH_2, —2H, 80.8%), 332 (M^+—$CONH_2$, 5.2%), 330 (M^+—$CONH_2$, —2H, 44.3%); Anal. for $C_{20}H_{16}N_4O_2S$ (376), Calcd./Found (%): C(63.81/63.90), H(4.28/4.33), N(14.88/1494), S(8.52/8.60).

1-[3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl]ethanone (10k): As yellow crystals crystallized from acetic acid (86%); mp = 233–236 °C; **IR** $\upsilon(cm^{-1})$: 3445, 3288 (NH_2), 3033 (C—H aromatic), 1620 (CO); **MS** (m/z): 375 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{21}H_{17}N_3O_2S$ of the assigned structure), 374 (M^+—H, 61.7%), 360 (M^+—CH_3 40.5%), 332 (M^+—$COCH_3$ 18.8%); Anal. for $C_{21}H_{17}N_3O_2S$ (375), Calcd./Found (%): C(67.18/67.22), H(4.56/4.62), N(11.19/11.23), S(8.54/8.62).

(3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)(phenyl)methanone (10l): As orange crystals crystallized from dioxane (72%); mp 206 °C; **IR** $\upsilon(cm^{-1})$: 3481, 3301 (NH_2), 3045 (C—H aromatic), 1656 (CO); **MS** (m/z): 437 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{26}H_{19}N_3O_2S$ of the assigned structure), 436 (M^+—H, 93%), 105 (COPh, 20.9%); Anal. for $C_{26}H_{19}N_3O_2S$ (437), Calcd./Found (%): C(71.38//71.42), H(4.38/4.42), N(9.60/9.68), S(7.33/7.42).

(3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridin-2-yl)-(4-chlorophenyl)methanone (10m): As orange crystals crystallized from dioxane (90%); mp 205 °C; **IR** $\upsilon(cm^{-1})$: 3479, 3306 (NH_2), 3040 (C—H aromatic), 1654 (CO); **MS** (m/z): 471 (M^+, 100% which corresponds to the molecular weight of the molecular formula $C_{26}H_{18}ClN_3O_2S$ of the assigned structure), 473 (M^+2, 37.0%), 472 (M^+1, 50.3%), 470 (M^+-H, 99.2%), 469 (M^+—2H, 11.7%), 139 (—COC_6H_4Cl, 31%); Anal. for $C_{26}H_{18}ClN_3O_2S$ (471), Calcd./Found (%): C(66.17/66.22), H(3.84/3.90), Cl(7.51/7.60), N(8.90/8.98), S(6.79/6.82).

3-Amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carboxylic acid (10n): As orange crystals crystallized from acetic acid (71%), mp 320–322 °C; **IR** $\upsilon(cm^{-1})$: 3467 (NH_2), 3230–3467 (acid OH); **MS** (m/z): 332 (M^+-COOH, 64.5%), 316 (M^+—COOH—NH_2, 43.5%), 303 (M^+—pyridyl, 9.7%), 289 (M^+—CO_2—CS, 64.5%); **^{1}H NMR** (DMSO-D_6) (δppm): 3.85 (s, 3H, OCH_3), 5.57 (s, 2H, NH_2), 7.10–7.68 (m, 4H, Ar H's), 8.50–932 (m, 5H, pyridine H's) and 14.3 (s, br., 1H, COOH); Anal. for $C_{20}H_{15}N_3O_3S$ (377), Calcd./Found (%): C(63.65/63.71), H(4.01/4.11), N(11.13/11.19), S(8.50/8.59).

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