Utilization of 2-Chloronicotinonitrile in the Syntheses of Novel Fused Bicyclic and Polynuclear Heterocycles of Anticipated Antitumor Activity

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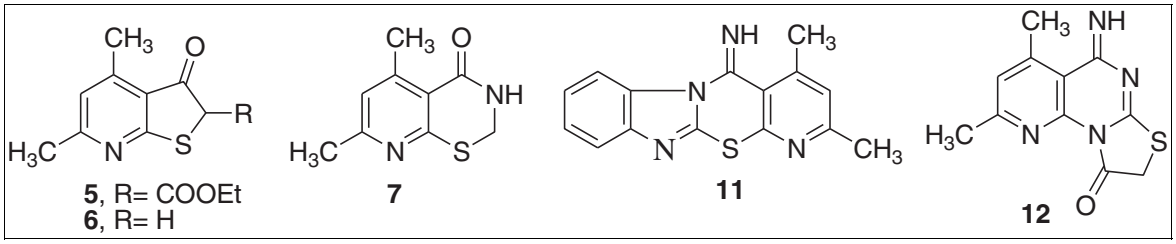

Some of synthetic bicyclic and polynuclear heterocyclic compounds based on pyridine scaffold were tested as *in vitro* antitumor agents, and these compounds found to exhibit interesting activities. Fused heterocycles containing sulfur such as thienopyridine, pyridothiazine, and some related fused heterocycles as new ring systems were achieved. Bicyclic thienopyridine **6** and pyrido[3,2-*e*][1,3]thiazin-4(3*H*)-one **7** exhibited good antitumor activities compared with 5-fluorouracil.

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INTRODUCTION

Several pyridine ring systems "binary and fused" have attracted the attention of several research groups because of their potential biological activities as anti-inflammatory [1–4], anticancer [5–9], and antimicrobial agents [6]. Recently, we have reported a modified synthetic method for the synthesis of 2-chloro-4,6-dimethylnicotinonitrile (**1**) through reaction of acetylacetone with malononitrile. Compound **1** was used as a starting material for the syntheses of fused or binary heterocycles containing nitrogen [10]. It was reported that the fused 5,7-dimethyl-[1,2,4]triazolo [4,3-*a*]pyridine-8-carbonitrile (**2**) have higher affinity than 5-fluorouracil [10]. In this work, our aim is to obtain novel biologically active heterocyclic compounds [11] through building up different fused bicyclic and polynuclear heterocyclic ring systems containing sulfur on the basis of 2-chloropyridine. The reaction of compound **1** with thiourea in refluxing ethanol afforded 2-mercapto-4,6-dimethylnicotinonitrile (**3**) [12] (Fig. 1).

RESULTS AND DISCUSSION

The synthetic procedures adopted to obtain the target compounds were depicted in Schemes 1–3. Synthesis of five fused bicyclic ring systems was achieved via the alkylation of pyridinethiol derivative **3** with ethyl chloroacetate in the presence of sodium carbonate to afford the acetate ester derivative **4** (which is consistent with the published data [12]). Refluxing of a solution of acetate ester **4** with sodium hydride in THF gave ethyl 4,6-dimethyl-3-oxo-2,3-dihydrothieno[2,3-*b*]pyridine-2-carboxylate (**5**), with carefully working up at −20°C. Attempting for working up at 0°C causes the hydrolysis and decarboxylation of the β-ketoester derivative **5** to give the 4,6-dimethylthieno[2,3-*b*]pyridin-3(2*H*)-one (**6**). Compound **6** was obtained in this route through hydrolysis and decarboxylation of compound **5** in a mixture of acetic acid and hydrochloric acid. Another route for the preparation of compound **6** was achieved by direct alkylation of compound **3** with ethyl chloroacetate and cyclization in the presence of sodium hydride as a base in a one-pot synthesis (Scheme 1). The ^{1}H NMR spectrum of **6** revealed the presence of singlet signal at δ 3.8 ppm corresponding to methylene protons of thiophene ring.

The bicyclic fused six-membered ring system was achieved through Schmidt rearrangement for compound **6**. Refluxing of **6** with sodium azide in DMF in the presence of few drops of H_2SO_4 afforded 5,7-dimethyl-2*H*-pyrido[3,2-*e*][1,3]thiazin-4(3*H*)-one (**7**) (Scheme 1). The IR spectrum of **7** showed absorption band at 1684 cm^{-1} corresponding to amide carbonyl group, whereas its ^{1}H NMR spectrum revealed the presence of singlet signal at δ 3.33 ppm because of methylene protons of thiazine ring and a signal at δ 13.8 ppm because of NH proton.

Some newly fused polynuclear heterocycle-incorporated thienopyridine moieties of anticipated antitumor activity were further synthesized. Thus, refluxing of compound **3** with 2-(1*H*-benzo[*d*]imidazol-2-yl)-4-chloro-3-oxobutanenitrile (**8**) [13,14] in DMF containing sodium carbonate afforded benzo[*d*]imidazol-thieno[2,3-*b*:4,5-*b*′]dipyridine derivative

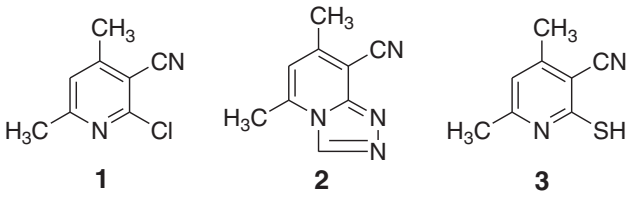
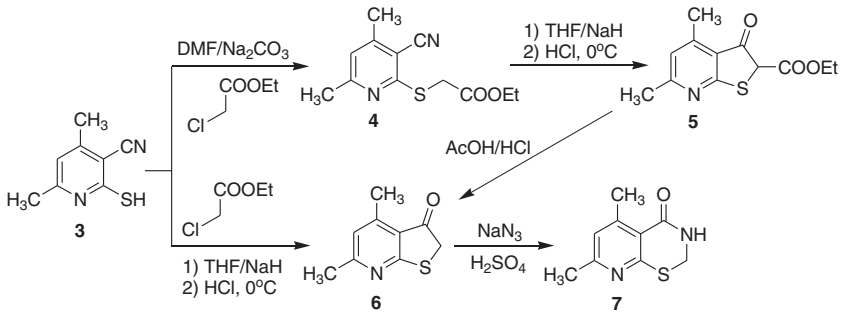


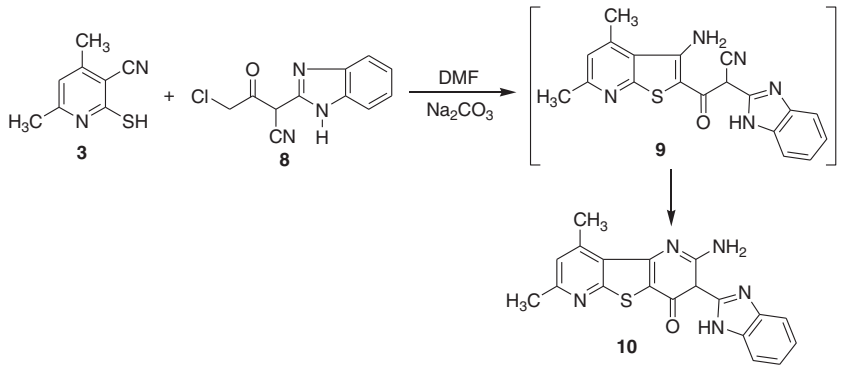
Figure 1. Structures of different heterocycles containing pyridine moiety.

10. Compound **10** was obtained through intramolecular cyclization of the intermediate **9** (Scheme 2). The structure **10** was elucidated by IR spectrum that showed absorption bands at 1660 cm^{-1} because of carbonyl group and bands at 3392, 3327, and 3290 cm^{-1} because of NH_2 and NH groups, respectively, whereas its ^1H NMR spectrum showed signals at δ 4.2 ppm because of NH_2 protons and

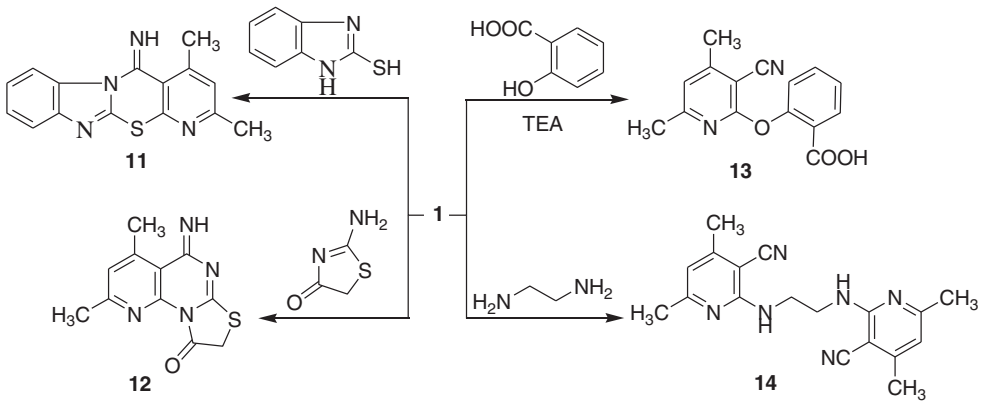
Scheme 1. Synthesis of thieno[2,3-*b*]pyridinone **5** and pyrido[3,2-*e*][1,3]thiazin-4(3*H*)-one **7**.



Scheme 2. Synthesis of benzo[*d*]imidazol-thieno[2,3-*b*:4,5-*b*′]dipyridine derivative **10**.



Scheme 3. Reactions of compound **1** with different nucleophiles.



multiplet signals at δ 7.1–7.5 ppm indicating the presence of aromatic protons.

In addition, refluxing of compound **1** with 1*H*-benzo[*d*] imidazole-2-thiol in DMF catalyzed by triethylamine afforded the corresponding benzo[4,5]imidazo[2,1-*b*]pyrido[3,2-*e*][1,3]thiazine **11** in 66% yield (Scheme 3). Its ^{1}H NMR spectrum showed multiplet signals at δ 7.2–7.9 ppm because of aromatic protons and signals at δ 10.6 ppm because of imino proton.

Also, 5-imino-2,4-dimethyl-9*H*-pyrido[3,2-*e*]thiazolo[3,4-*a*] pyrimidin-9-one (**12**) was obtained by refluxing of **1** with 2-aminothiazol-4(5*H*)-one in the presence of a few drops of triethylamine (Scheme 3). The IR spectrum of **12** showed absorption band at 1663 cm^{-1} as a sharp peak indicated to the presence of lactam group and a band at 3434 cm^{-1} because of imino group. The ^{1}H NMR spectrum of **12** showed signals at δ 3.2 ppm corresponding to methylene protons of thiazole moiety.

On the other hand, compound **1** was allowed to react with salicylic acid in DMF in the presence of sodium carbonate to give 2-(3-cyano-4,6-dimethylpyridin-2-yloxy) benzoic acid **13** (Scheme 3). The structure **13** was elucidated by its correct elemental analysis and spectral data. Its IR spectrum showed absorption band at 2213 cm^{-1} indicated the presence of cyano group, at 3436 cm^{-1} corresponding to hydroxyl group, and at 1680 cm^{-1} for carbonyl group. Its ^{1}H NMR spectrum showed two singlet signals at δ 2.39 and 2.54 ppm because of two methyl groups in pyridine ring and multiplet signals at δ 7.1–7.5 ppm because of aromatic protons.

Moreover, refluxing of **1** with ethylenediamine in acetonitrile containing sodium carbonate afforded dimmeric product **14** (Scheme 3). Its IR spectrum showed absorption band as a sharp peak at 3311 cm^{-1} because of (NH) group, besides the presence of a sharp band at 2203 cm$-^1$ corresponding to two symmetrical cyano groups. Moreover, its ^{1}H NMR spectrum showed signals at δ 5.4 ppm because of two NH protons and at δ 6.3 ppm because of pyridyl proton.

BIOLOGICAL ACTIVITY

Antitumor activity. ***Effect of drugs on the viability of Ehrlich ascites carcinoma cells in vitro.*** To examine whether these substances have a direct cytotoxic effect on Ehrlich ascites cell (EAC) viability, the percentage of viable cells was estimated by the trypan blue [15] exclusion test. Eleven fused bicyclic and polynuclear heterocycles were tested for cytotoxicity against EACs *in vitro*. Results for the ED_{100}, ED_{50}, and ED_{25} values of the active compounds are summarized in Table 1. The data showed clearly that compounds **6** and **7** exhibited more potent activities, whereas the other compounds showed moderate activities compared with 5-fluorouracil.

Table 1

In vitro cytotoxicity of pyridine derivatives using Ehrlich ascites cell assay.

	% Dead		
Compound no.	ED_{100} μL	ED_{50} μL	ED_{25} μL
5-FU	95.2	62.0	38.0
1	46.0	28.9	20.0
3	61.7	31.3	17.2
4	53.2	27.1	20.0
5	54.0	28.2	21.6
6	88.0	49.0	28.0
7	81.2	47.5	26.9
10	56.0	30.0	16.0
11	73.3	41.0	23.0
12	50.3	29.8	13.4
13	62.2	28.1	12.4
14	60.0	29.0	13.3

ED_{100}, ED_{50}, and ED_{25} are the effective doses at 25, 50, and 100 μL, respectively, of the compounds used. The dead % refers to the % of the dead tumor cells, and 5-FU is 5-fluorouracil as a well-known cytotoxic agent.

By comparing the cytotoxicity results in Table 1, the following structure–activity relationships were drawn: (i) fused sulfur heterocyclic ring systems increase the activity of the tested compounds and (ii) the presence of basic skeleton is necessary for the broad spectrum of antitumor activity toward Ehrlich ascites carcinoma cells.

Modification of produced fused bicyclic and polynuclear heterocycle compounds is potential for further development as anticancer agents. With these preliminary screening results, compounds **6** and **7** showed significant activity in certain cancer cells and have been targeted for further studies. Additional research, including mode of action studies, is planned to accurately establish relative activity for structure–activity relationships and rational design.

CONCLUSION

The present investigation offers rapid and effective novel procedures for the syntheses of a new class of fused and ring junction pyridines. It involves reactions of 2-mercapto-4,6-dimethylnicotinonitrile (**3**) with ethyl chloroacetate at different conditions and α-halo ketone to afford thieno[2,3-*b*]pyridinone, pyrido[3,2-*e*][1,3]thiazin-4(3*H*)-one, and benzo[*d*]imidazol-thieno[2,3-*b*:4,5-*b*′] dipyridine ring systems. Moreover, reactions of 2-chloronicotinonitrile (**1**) toward different nucleophiles were investigated. The newly prepared ring systems seem to be interesting for biological studies. It is worth mentioning that fused sulfur heterocyclic ring systems were crucial for the antitumor activity as in the case of compounds **6** and **7**.

EXPERIMENTAL

Melting points (uncorrected) (Electronic Melting Point Apparatus, Great Britain, London) were determined on a Gallenkamp melting point apparatus. The IR spectra were recorded on a Jasco 4100 FTIR spectrophotometer (Microanalytical Unit, Mansoura University, Mansoura, Egypt) in KBr discs (υ_{max} in cm^{-1}). The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 and 75 MHz by using $CDCl_3$ and DMSO-d_6 as solvents, respectively. Chemical shifts were expressed in δ-scale downfield as part per million (ppm) against TMS as an internal standard. Elemental analyses (C, H, N, and S) were recorded on Perkin-Elmer 2400 elemental analyzer. The completion of reaction and the purity of the compounds were controlled by TLC on silica gel-precoated aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany), and spots were exposed to iodine vapor. Ethyl 2-(3-cyano-4,6-dimethylpyridin-2-ylthio)acetate (**4**) [12] and 2-(1*H*-benzo[*d*]imidazol-2-yl)-4-chloro-3-oxobutanenitrile (**8**) [13,14] were prepared according to the previously reported methods.

Ethyl 2-(3-cyano-4,6-dimethylpyridin-2-ylthio)acetate (4). A mixture of **3** (3.28 g, 0.02 mol), ethyl chloroacetate (2.44 g, 0.02 mol), and sodium carbonate (2.1 g, 0.02 mol) in DMF (50 mL) was refluxed with stirring for 4 h. After cooling, it was poured onto ice–cold water, and the solid formed was collected and recrystallized from methanol to give compound **4** (4.4 g, 88% yield), mp 90–92°C, Lit. [12]; IR (KBr) υ (cm^{-1}), 2217 (CN), 1735 (CO, ester).

Ethyl 4,6-dimethyl-3-oxo-2,3-dihydrothieno[2,3-*b*]pyridine-2-carboxylate (5). A solution of **4** (2.5 g, 0.01 mol) in THF (20 mL) added to sodium hydride (0.8 g, 60%, 0.02 mol) under nitrogen in THF (40 mL) was refluxed for 3 h. The reaction mixture was cooled in ice bath at −20°C and then ethanol (10 mL) was added followed by cold water (50 mL) and acidified with dilute HCl. The formed solid product was collected and recrystallized from methanol to give compound **5** (1.83 g, 73%), mp 183–140°C; IR (KBr) υ (cm^{-1}), 1701, 1666 (β-keto ester); ^1H NMR ($CDCl_3$): δ/ppm, 1.31 (t, 3H, CH_3, $J = 7.1$ Hz), 2.42 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.22 (q, 2H, CH_2, $J = 7.1$ Hz), 6.70 (s, 1H, C-2), 7.01 (s, H, C-5); ^{13}C NMR ($CDCl_3$): δ, 197.54, 163.58, 162.45, 159.31, 144.20, 123.92, 118.18, 61.44, 60.37, 20.34, 19.75, 13.95. *Anal*. Calcd for $C_{12}H_{13}NO_3S$ (251.3): C, 57.35; H, 5.12; N, 5.57; S, 12.76%. Found: C, 57.24; H, 5.26; N, 5.66; S, 12.83%.

4,6-Dimethylthieno[2,3-*b*]pyridine-3(2*H*)-one (6).

Method A. A solution of **3** (1.64 g, 0.01 mol) in THF (20 mL) added to sodium hydride (0.8 g, 60%, 0.02 mol) under nitrogen in THF (40 mL) was refluxed for 3 h. The reaction mixture was cooled in ice bath at 0°C and then ethanol (10 mL) was added followed by cold water (50 mL) and acidified with dilute HCl. The formed solid product was collected and recrystallized from methanol to give compound **6**; (85%), mp 198–200°C; IR (KBr) υ (cm^{-1}), 1681 (CO); ^1H NMR ($CDCl_3$): δ/ppm, 2.56 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 3.80 (s, 2H, CH_2), 6.71 (1H, s, C-5). *Anal*. Calcd for C_9H_9NOS (179.24): C, 60.31; H, 5.06; N, 7.81; S, 17.89%. Found: C, 60.38; H, 5.18; N, 7.95; S, 17.71%.

Method B. A solution of β-ketoester **5** (1.25 g, 0.005 mol) in acetic acid (20 mL) and concentrated HCl (10 mL) was refluxed for 4 h. After cooling, the mixture was poured onto cold water, and solid formed was filtered off and recrystallized from methanol to give the same pure product **6** (TLC control, mp), (0.7 g, 77.7%).

5,7-Dimethyl-2*H*-pyrido[3,2-*e*][1,3]thiazin-4(3*H*)-one (7). A mixture of **6** (1.79 g, 0.01 mol) and sodium azide (1.0 g) in DMF (30 mL) in the presence of a few drops of conc. H_2SO_4 was refluxed with stirring for 5 h. After cooling, the reaction mixture was poured onto ice water (50 mL). The precipitated solid was filtered off, dried, and recrystallized from methanol to give compound **7**; (1.0 g, 51.5%), mp 280–282°C. IR (KBr) υ (cm^{-1}), 1684 (CO), 3450 (NH); ^1H NMR ($CDCl_3$): δ/ppm, 2.41 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 6.34 (s, 1H), 13.8 (s, 1H, exchangeable NH). *Anal*. Calcd for $C_9H_{10}N_2OS$ (194.25): C, 55.65; H, 5.19; N, 14.42; S, 16.51%. Found: C, 55.54; H, 5.24; N, 14.54; S, 16.42%.

2-Amino-3-(1*H*-benzo[*d*]imidazol-2-yl)-7,9-dimethylthieno[2,3-*b*:4,5-*b*′]dipyridin-4(3*H*)-one (10). A mixture of **3** (1.64 g, 0.01 mol), 2-(1*H*-benzo[*d*]imidazol-2-yl)-4-chloro-3-oxobutanenitrile (**8**) (2.2 g, 0.01 mol), and sodium carbonate (1.05 g, 0.01 mol) in DMF (50 mL) was refluxed with stirring for 4 h. The reaction mixture was then poured onto ice–cold water (50 mL), and the formed solid product was filtered off, dried, and recrystallized from DMF to give compound **10** (2.5 g, 69.44%), mp 131–133°C. IR (KBr) υ (cm^{-1}), 1660 (CO); 3392, 3327 (NH_2), 3290 (NH); ^1H NMR ($CDCl_3$): δ/ppm, 2.31 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 6.1 (s, 1H, CH-CO), 6.3 (s, 1H, pyridyl), 7.5 (m, 4H, phenyl). *Anal*. Calcd for $C_{19}H_{15}N_5OS$ (361.42): C, 63.14; H, 4.18; N, 19.38; O, 4.43; S, 8.87%. Found: C, 63.22; H, 4.07; N, 19.51; O, 4.34; S, 8.81%.

2,4-Dimethyl-5*H*-benzo[4,5]imidazo[2,1-*b*]pyrido[3,2-*e*][1,3]thiazin-5-imine (11). A mixture of **1** (3.2 g, 20 mmol) and 1*H*-benzo[*d*]imidazole-2-thiol (3 g, 20 mmol) in DMF (30 mL) containing few drops of triethylamine was refluxed for 6 h. After cooling, the reaction mixture was poured into ice–water, and the formed precipitate was filtered off, dried, and recrystallized from chloroform to give compound **11** (66%), mp 74–76°C; IR (KBr) υ (cm^{-1}), 2203 (CN); 3377 (NH); ^1H NMR ($CDCl_3$): δ/ppm, 2.4 (s, 3H, CH_3-C═N), 2.5 (s, 3H, CH_3-C═C), 5.0 (s, H, NH), 6.7 (s, H, pyridyl), 7.5 (m, 4H, phenyl). *Anal*. Calcd for $C_{15}H_{12}N_4S$ (280.35): C, 64.26; H, 4.31; N, 19.98; S, 11.44%. Found: C, 64.31; H, 4.37; N, 19.85; S, 11.41%.

5-Imino-2,4-dimethyl-9*H*-pyrido[3,2-*e*]thiazolo[3,4-*a*]pyrimidin-9-one (12). A mixture of **1** (3.2 g, 20 mmol) and 2-aminothiazol-4(5*H*)-one (2.3 g, 20 mmol) treated with sodium carbonate (0.01 mol) in DMF (40 mL) was refluxed for 4 h. After cooling, the reaction mixture was poured into ice–water, and the formed precipitate was filtered off, dried, and recrystallized from hexane to give compound **12** (72%), mp 123–125°C; IR (KBr) υ (cm^{-1}), 1663 (CO); 3434 (NH); ^1H NMR ($CDCl_3$): δ/ppm, 2.3 (s, 3H, CH_3-C═N), 2.4 (s, 3H, CH_3-C═C), 3.2 (s, H, S-CH), 4.9 (s, H, NH), 6.3 (s, H, pyridyl). *Anal*. Calcd for $C_{11}H_{10}N_4OS$ (246.29): C, 53.64; H, 4.09; N, 22.75; O, 6.50; S, 13.02%. Found: C, 53.48; H, 4.29; N, 22.93; O, 6.98; S, 13.28%.

2-(3-Cyano-4,6-dimethylpyridin-2-yloxy)benzoic acid (13). A mixture of **1** (3.2 g, 20 mmol) and salicylic acid (2.8 g, 20 mmol) treated with sodium carbonate (0.01 mol) in DMF (40 mL) was refluxed for 5 h. After cooling, the reaction mixture was poured into ice–water, and the precipitated solid product was filtered off, dried, and recrystallized from ethanol to give compound **13** (72%), mp 123–125°C; IR (KBr) υ (cm^{-1}), 3436 (OH), 2223 (CN), 1680 (CO); ^1H NMR ($CDCl_3$): δ/ppm, 2.39 (s, 3H, CH_3-C═N), 2.54 (s, 3H, CH_3-C═C), 6.3 (s, H, pyridyl), 7.1–7.5 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ/ppm, 169.24, 166.14, 161.86,

155.27, 154.18, 133.34, 132.53, 123.40, 121.21, 120.84, 117.91, 117.00, 91.71, 25.46, 17.65. *Anal*. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44; O, 17.89%. Found: C, 67.36; H, 4.63; N, 10.36; O, 17.73%.

2,2′-(Ethane-1,2-diylbis(azanediyl))bis(4,6-dimethylnicotinonitrile) (14). A mixture of **1** (1.64 g, 10 mmol) and ethane-1,2-diamine (1 mL) in acetonitrile (20 mL) containing Na_2CO_3 (1 g) was refluxed for 3 h. After cooling, the reaction mixture was poured into ice–water, and the precipitated solid product was filtered off, dried, and recrystallized from ethanol to give compound **14** (71%), mp 83–85°C; IR (KBr) υ (cm^{-1}), 2203 (CN); 3311 (NH); ^{1}H NMR ($CDCl_3$): δ/ppm, 2.33 (s, 6H, 2 × CH_3-C═N), 2.38 (s, 6H, 2 × CH_3-C═C), 3.5 (t, 4H, 2 × CH_2-NH, J = 11 Hz), 5.4 (s, 2H, 2 × NH-CH), 6.3 (s, 2H, 2 pyridyl). *Anal*. Calcd for $C_{18}H_{20}N_6$ (320.39): C, 67.48; H, 6.29; N, 26.23%. Found: C, 67.55; H, 6.22; N, 26.28%.

Antitumor activity. Different concentrations of the tested compounds were prepared (ED_{100}, ED_{50}, and ED_{25} 1 g/mL DMSO). The amount of DMSO was adjusted to give a final concentration of 0.1%. Ascites fluid obtained was aseptically aspirated from the peritoneal cavity of the donor animal (National Cancer Institute, Cairo, Egypt), which contains Ehrlich cell. The cells were grown partially floating and attach in AQ_4, a suspension culture (RPMI 1660 medium, Sigma Chemical, St. Louis), supplemented with 10% fetal bovine serum (GIBCO, UK). They were maintained at 37°C in humidified atmosphere with 5% CO_2 for 2 h. Viability of the cell obtained and used in control experiments (DMSO only without drug) exceeded 95% as determined by microscopic examination by using a hemocytometer and trypan blue stain (stain only the dead cells). Below this percentage, the cells were discarded, and the entire procedure was repeated for three times.

REFERENCES AND NOTES

[1] Hamdya, N. A.; Gamal-Eldeen, A. M. Eur J Med Chem 2009, 44, 4547.

[2] Bagley, M. C.; Chapaneri, K.; Dale, D. W.; Xiong, X.; Bower, J. J Org Chem 2005, 70, 1389.

[3] Gilchrist, T. L. J Chem Soc, Perkin Trans 1 2001, 2491.

[4] Son, J. K.; Zhao, L. X.; Basnet, A.; Thapa, P.; Karki, R. Y.; Jahng, Y.; Jeong, T. C.; Jeong, B. S.; Lee, C. S.; Lee, E. S. Eur J Med Chem 2008, 43, 675.

[5] Amr, A. G.; Abdulla, M. M. Bioorg Med Chem 2006, 14, 4341.

[6] Hammam, A. E. G.; Abd El-hafez, N. A.; Midura, W. H.; Mikolajczyk, M. Z Naturforsch 2000, 55b, 417.

[7] Abo-Ghalia, M.; Abdulla, M. M. Z.; Amr, A. E. Z Naturforsch 2003, 58b, 903.

[8] Ismail, M. M.; Ammar, Y. A.; El-Zahaby, H. S.; Eisa, S. I.; Barakat, E. S.; Arch Pharm 2007, 340, 476.

[9] Lu, Z.; Ott, G. R.; Anand, R.; Liu, R. Q.; Covington, M. B.; Vaddi, K.; Qian, M.; Newton, R. C.; Christ, D. D.; Trzaskos, J.; Duan, J. J. Bioorg Med Chem Lett 2008, 18, 1958.

[10] Waly, M. A.; EL-Hawary, I. I.; Hamama, W. S.; Zoorob, H. H. Accepted Article, J Heterocycl Chem JHET1020, 2011.

[11] Waly, M. A.; Ibrahim, I. T.; El-Sepelgy, O. Z. Monatsh Chem 2010, 141, 1253.

[12] Ellis, E. D.; Xu, J.; Valente, E. J.; Hamme, A. T. Tetrahedron Lett 2009, 50, 5516.

[13] Styles, V. L.; Morrison, R. W. J Org Chem 1985, 50, 346.

[14] Clarke, R. W.; Garside, S. C.; Lunts, L. H.; Hartley, D.; Hornby, R.; Oxford, A. W. J Chem Soc, Perkin Trans 1 1979, 1120.

[15] Sheeja, K. R.; Kuttan, G.; Kuttan, R. Amala Res Bull 1997, 17, 73.