

Synthesis and Antianxiety Activity of Some New Pentaazacyclopenta[a]-naphthalenepyrido[2,3-d]pyrimidine Derivatives

Said Aly Said

Chemistry Department, Faculty of Science, Zagazig University, Egypt

Abstract: A series of pyrido[2,3-d]pyrimidine, pentaazacyclopenta[a]naphthalene and their derivatives were synthesized using 2-amino-6-methyl-4-phenylnicotinonitrile (1) as a starting material. Compound 1 was treated with triethylorthoformate, phenylisothiocyanate, carbondisulfide, or ammonium thiocyanate to give the corresponding substituted pyrido-pyrimidine derivatives 2-5, respectively. When, compound 5 was coupled with ethylcyanoacetate or diethylmalonate gave 2-thioxo-pyrimidin-4-one pyridopyrimidines 6 and 7, respectively. Compound 2 was reacted with several reagents to produce some new pyrido-pyrimidine and pentaazacyclopenta[a]naphthalene derivatives 8-15. The pharmacological screening showed that many of these obtained compounds have good antianxiety activity comparable to diazepam® as positive control. The structure assignments of the new compounds based on chemical and spectroscopic evidence. The detailed synthesis, spectroscopic data and pharmacological properties are reported.

Key words: 2-Amino-6-methyl-4-phenylnicotinonitrile • Pyrido[2,3-d]pyrimidine • Pentaazacyclopenta[a]naphthalene • Antianxiety activity

INTRODUCTION

In previous work we have found that certain substituted pyridine and pyrimidine derivatives show antimicrobial [1-4] and antitumor activities [5-7]. In addition, the biological and antianalgesic activities of many heterocyclic compounds containing a sulfur atom have been reviewed [8-10]. On the other hand, thienopyrimidine and thioxopyrimidine derivatives have promising biological [11] and anticancer activity [12,13]. Recently, some new thienopyrimidinone derivatives have been synthesized [14]. Recently, some new substituted pyrimidine derivatives have been synthesized, which exhibit analgetic, anti-inflammatory, antiparkinsonian and androgenic-anabolic activities [15-19]. In view of these observations and as continuation of our previous work on pyrimidine chemistry, we synthesized some new pyridopyrimidines, pentaazacyclopenta[a]-naphthalenes and tested their antianxiety activity comparable to diazepam® as positive control.

MATERIALS AND METHODS

Melting points were determined on open glass capillaries using a Electrothermal IA 9000 digital melting

point apparatus. Elemental analyses were performed on Elementar, Vario EL, Microanalytical Unit, National Research Center, Cairo Egypt and were found within $\pm 0.4\%$ of the theoretical values. Infrared spectra were recorded on Carlzeise Spectrophotometer model "UR 10" spectrophotometer using the KBr disc technique. $^1\text{H-NMR}$ spectra were recorded on Varian Gemini 270 MHz spectrometer (DMSO-d_6) and the chemical shifts are given in δ (ppm) downfield from tetramethylsilane (TMS) as an internal standard. The mass spectra were measured using a Finnigan SSQ 7000 mass spectrometer. Follow up of the reactions and checking the purity of the compounds was made by TLC on silica gel-aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany).

Synthesis of N-(3-cyano-6-methyl-4-phenyl-pyridin-2-yl)-formimidic acid ethyl ester (2):

A mixture of 1 (1.05 g, 5 mmol) and triethyl orthoformate (2 ml) in acetic anhydride (10 ml) was refluxed for 1h. After cooling, the precipitate was filtered off, washed with water, dried and crystallized from ethanol to give 2. Yield 70%; M.p. 108-110 °C. IR (KBr) $\nu = 2224$ ($\text{C}\equiv\text{N}$), 1660 ($\text{C}=\text{N}$) cm^{-1} ; $^1\text{H-NMR}$ (DMSO-d_6) $\delta = 1.23$ (t, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.87 (q, 2H, CH_2), 7.22 - 7.48 (m, 6H, Ar-H + $\text{N}=\text{CH}$), 7.52 (s, 1H, pyrid-CH); $^{13}\text{C-NMR}$ (DMSO-d_6) $\delta = 13.45$, 23.10 (2CH_3), 65.15 (CH_2),

125.15, 127.65, 135.85 (Ph-C), 114.90 (C=N), 98.45, 106.25, 152.30, 161.75, 171.65 (Pyrid-C), 161.75 (CH=N); MS m/z: (M); 266 ($M^+ + 1$, 8), corresponding to the molecular formula and at 64 (100, base peak); Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.38; H, 5.64; N, 15.80.

Synthesis of 4-imino-7-methyl-3,5-diphenyl-3,4-dihydro-1H-pyrido[2,3-d]pyrimidine-2-thione (3): A mixture of 1 (1.05g, 5 mmol) and phenyl isothiocyanate (0.66 ml, 5 mmol) in dry dioxane (30 ml) in the presence of triethylamine (3 drops) was heated under reflux for 6 h. The obtained solid was collected by filtration, dried and crystallized from DMF to give 3. Yield 60%, M.p. 120-122 °C. IR (KBr) $\nu = 3380-3290$ (NH), 1655 (C=N), 1248 (C=S) cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.55$ (s, 3H, CH_3), 6.61-7.47 (m, 10H, Ar-H), 7.52 (s, 1H, pyrid-CH), 8.83 and 9.81 (2s, 2H, 2 NH exchangeable with D_2O); MS m/z: (M); 343 ($M^+ - 1$, 4), corresponding to the molecular formula and at 81 (100, base peak); Anal. Calcd for $C_{20}H_{16}N_4S$: C, 69.74; H, 4.65; N, 16.27; S, 9.31. Found: C, 69.68; H, 4.64; N, 16.24; S, 9.22.

Synthesis of 7-methyl-5-phenyl-1H-pyrido[2,3-d]pyrimidine-2,4-dithione (4): A solution of 1 (1.05 g, 5 mmol) and carbon disulphide (20 ml) in dimethyl formamide (25 ml) in the presence of sodium methoxide [prepared from 0.5 g of sodium and 15 ml of absolute methanol] was refluxed for 4 h. The reaction mixture was added to 4 M sodium hydroxide, the precipitate was removed by filtration. The filtrate was acidified with dilute hydrochloric acid, the obtained solid was filtered off, washed with water, dried and crystallized from DMF to give 4. Yield 60%, M.p. 240-242 °C. IR (KBr) $\nu = 3420-3354$ (NH), 1658 (C=N), 1250 (C=S) cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.54$ (s, 3H, CH_3), 6.88-7.42 (m, 6H, Ar-H + pyrid-CH), 8.40 and 10.54 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C -NMR (DMSO- d_6) $\delta = 23.35$ (CH_3), 125.05, 127.55, 135.80 (Ph-C), 99.05, 106.48, 145.50, 146.35, 156.95 (Pyrid-C), 168.80, 178.15 (2C=S); MS m/z: (M); 285 (M^+ , 4), corresponding to the molecular formula and at 64 (100, base peak); Anal. Calcd for $C_{14}H_{11}N_3S_2$: C, 58.94; H, 3.85; N, 14.72; S, 22.47. Found: C, 58.86; H, 3.82; N, 14.68; S, 22.40.

Synthesis of (7-methyl-5-phenyl-2-thioxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-thiourea (5): To a solution of 1 (1.05g, 5 mmol) in acetic acid (15 ml), ammonium thiocyanate (1.14 g, 15 mmol) was added. The reaction mixture was refluxed for 10 h., after cooling, the

reaction mixture was diluted with water, the separated solid was filtered off, washed with hot ethanol, dried and crystallized from methanol to give 5. Yield 70%, M.p. 182-184 °C. IR (KBr) $\nu = 3450-3328$ (NH, NH_2), 1660 (C=N), 1250-1245 (C=S) cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.65$ (s, 3H, CH_3), 3.88 (s, 2H, NH_2 exchangeable with D_2O), 6.61-7.47 (m, 5H, Ar-H), 7.53 (s, 1H, pyrid-CH), 8.80 and 10.58 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C -NMR (DMSO- d_6) $\delta = 23.46$ (CH_3), 125.18, 127.60, 135.78 (Ph-C), 98.25, 107.05, 145.15, 146.75, 157.90 (Pyrid-C), 181.35, 182.20 (2C=S), 158.70 (CH); MS m/z: (M); 327 (M^+ , 4), corresponding to the molecular formula $C_{15}H_{13}N_5S_2$ and at 57 (100, base peak). Anal. Calcd for $C_{15}H_{13}N_5S_2$: C, 55.02; H, 3.98; N, 21.39; S, 19.59. Found: C, 54.95; H, 3.94; N, 21.34; S, 19.55.

Synthesis of Compounds 6 and 7: A mixture of 5 (1.64 of 5 mmol) and ethyl cyanoacetate or diethylmalonate (5 mmol) in butanol (30 ml) was heated under reflux for 8h. The solid that separated on cooling was collected by filtration, dried and crystallized from the proper solvent to give the compounds 6 and 7, respectively.

6-Amino-1-(7-methyl-5-phenyl-2-thioxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (6): Yield 60%, M.p. 218-220 °C (BuOH). IR (KBr) $\nu = 3390-3325$ (NH, NH_2), 1685 (C=O), 1658 (C=N), 1248 (C=S) cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.51$ (s, 3H, CH_3), 4.01 (s, 2H, NH_2 exchangeable with D_2O), 4.21 (s, 1H, CH), 7.10-7.42 (m, 5H, Ar-H), 7.48 (s, 1H, pyrid-CH), 8.67 and 9.80 (2s, 2H, 2 NH exchangeable with D_2O); MS m/z: (M); 394 (M^+ , 100), corresponding to the molecular formula; Anal. Calcd for $C_{18}H_{14}N_6O_2S_2$: C, 54.81; H, 3.58; N, 21.30; S, 16.26. Found: C, 54.76; H, 3.52; N, 21.26; S, 16.21.

1-(7-Methyl-5-phenyl-2-thioxo-1,2-dihydropyrido[2,3-d]pyrimidin-4-yl)-2-thioxodihydro-pyrimidine-4,6-dione (7): Yield 65%, M.p. 205-207 °C (BuOH). IR (KBr) $\nu = 3410-3360$ (NH), 1688, 1692 (2C=O), 1662 (C=N), 1248, 1250 (2C=S) cm^{-1} ; 1H -NMR (DMSO- d_6) $\delta = 2.51$ (s, 3H, CH_3), 3.36 (s, 2H, CH_2), 6.85-7.42 (m, 5H, Ar-H), 7.52 (s, 1H, pyrid-CH), 9.22 and 9.70 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C -NMR (DMSO- d_6) $\delta = 23.35$ (CH_3), 46.80 (CH_2), 126.15, 127.48, 136.05 (Ph-C), 98.18, 107.10, 145.35, 147.08, 157.75 (Pyrid-C), 162.10 (CH), 164.35, 170.85 (2C=O), 181.15, 181.25 (2C=S); MS m/z: (M); 395 (M^+ , 10), corresponding to the molecular formula and at 91 (100, base peak); Anal. Calcd for $C_{18}H_{13}N_5O_2S_2$: C, 54.67; H, 3.31; N, 17.71; S, 16.22. Found: C, 54.63; H, 3.26; N, 17.66; S, 16.18.

Synthesis of Compounds 8 and 9: To a solution of 2 (1.32g, 5 mmol) in absolute ethanol (50 ml), phenylhydrazine (0.54 ml, 5 mmol) or hydrazine hydrate (0.13 ml, 25 mmol) was added. The reaction mixture was refluxed for 2h, concentrated under reduced pressure, cooled and the separated solid was filtered off, dried and crystallized from the proper solvent to give the compounds 8 and 9, respectively.

(4-Imino-7-methyl-5-phenyl-4H-pyrido[2,3-d]pyrimidin-3-yl)-phenyl-amine (8): Yield 60%, M.p. 150-152 °C (EtOH). IR (KBr) $\nu = 3385$ (NH), 1660 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.49$ (s, 3H, CH_3), 6.75-7.48 (m, 10H, Ar-H), 7.52 (s, 1H, pyrid-CH), 7.73 (s, 1H, pyrimid-CH), 10.50 and 11.29 (2s, 2H, 2 NH exchangeable with D_2O); $^{13}\text{C-NMR}$ (DMSO- d_6) $\delta = 24.05$ (CH_3), 111.65, 117.20, 125.88, 127.30, 127.38, 136.25, 149.05 (2 Ph-C), 105.50, 114.40, 145.12, 146.14, 159.28 (Pyrid-C), 161.85 (CH), 162.15 (C=NH); MS m/z: (M); 329 (M+2, 14), corresponding to the molecular formula $\text{C}_{20}\text{H}_{17}\text{N}_5$, and at 91 (100, base peak). Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_5$: C, 73.37; H, 5.23; N, 21.39. Found: C, 73.32; H, 5.18; N, 21.32.

4-Imino-7-methyl-5-phenyl-4H-pyrido-[2,3-d]pyrimidin-3-ylamine (9): Yield 75%, M.p. 140-142 °C (EtOH). IR (KBr) $\nu = 3426$ -3335 (NH, NH_2), 1662 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.52$ (s, 3H, CH_3), 4.50 (s, 2H, NH_2 exchangeable with D_2O), 6.80-7.55 (m, 5H, Ar-H), 7.50 (s, 1H, pyrid-CH), 7.68 (s, 1H, pyrimid-CH), 10.58 (s, 1H, NH exchangeable with D_2O); MS m/z: (M); 251 (M^+ , 36), corresponding to the molecular formula $\text{C}_{14}\text{H}_{13}\text{N}_5$ and at 236 (100, base peak); Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_5$: C, 66.92; H, 5.21; N, 27.87. Found: C, 66.88; H, 5.17; N, 27.84.

Synthesis of Compounds 10 and 11: A mixture of 9 (2.5 g, 10 mmol), triethyl orthoformate or chloroacetyl chloride (10 mmol) in dry dioxane (30 ml) was refluxed for 5 h. The obtained solid was filtered off, dried and crystallized from the proper solvent to give the compounds 10 and 11, respectively.

7-Methyl-9-phenyl-1,3,3a,5,6-pentaaza-cyclopenta [a]naphthalene (10): Yield 70%, M.p. 180-182 °C (benzene). IR (KBr) $\nu = 1660$ (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.53$ (s, 3H, CH_3), 6.75-7.40 (m, 6H, Ar-H), 7.53 (s, 1H, pyrid-CH), 7.70 (s, 1H, pyrimid-CH); $^{13}\text{C-NMR}$ (DMSO- d_6) $\delta = 23.95$ (CH_3), 125.82, 127.28, 135.98 (Ph-C), 106.40, 119.40, 147.10, 152.90, 156.42 (Pyrid-C), 139.30, 145.88 (pyrimid-C), 149.22 (CH-triazol); MS m/z: (M); 262

(M^+ +1, 100), corresponding to the molecular formula $\text{C}_{15}\text{H}_{11}\text{N}_5$ and as base peak; Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_5$: C, 68.95; H, 4.24; N, 26.80. Found: C, 68.90; H, 4.20; N, 26.75.

2-Chloromethyl-7-methyl-9-phenyl-1,3,3a,5,6-pentaazacyclopenta[a]naphthalene (11): Yield 65%, M.p. 140-142 °C (benzene). IR (KBr) $\nu = 1658$ (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.56$ (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 6.80-7.47 (m, 5H, Ar-H), 7.52 (s, 1H, pyrid-CH), 7.81 (s, 1H, pyrimid-CH); $^{13}\text{C-NMR}$ (DMSO- d_6) $\delta = 24.0$ (CH_3), 39.45 (CH_2), 125.78, 127.48, 136.15 (Ph-C), 106.44, 119.64, 147.18, 153.28, 156.42 (Pyrid-C), 139.82, 145.64 (pyrimid-C), 158.10 (triazol-C); MS m/z: (M); 309 (M^+ , 56), corresponding to the molecular formula $\text{C}_{16}\text{H}_{12}\text{ClN}_5$, and at 64 (100, base peak); Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{ClN}_5$: C, 62.13; H, 3.90; Cl, 11.45; N, 22.61. Found: C, 61.98; H, 3.86; Cl, 11.40; N, 22.58.

7-Methyl-9-phenyl-1,3,3a,5,6-pentaazacyclopenta [a]naphthalene-2-thione (12): A mixture of 9 (1.25g, 5 mmol), carbon disulphide (0.38 g, 5 mmole) and potassium hydroxide (5 mmol) in ethanol (15 ml) was refluxed for 10 h on a water bath. The reaction mixture was evaporated under reduced pressure, the residue was dissolved in water, the precipitate was removed by filtration. The clear filtrate was acidified with acetic acid and the formed solid was filtered off, dried and crystallized from DMF/EtOH to give 12. Yield 80%, M.p. 188-190 °C. IR (KBr) $\nu = 1665$ (C=N), 1248 (C=S) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.56$ (s, 3H, CH_3), 6.72-7.40 (m, 5H, Ar-H), 7.55 (s, 1H, pyrid-CH), 7.76 (s, 1H, pyrimid-CH), 10.82 (s, 1H, NH exchangeable with D_2O); MS m/z: (M); 292 (M^+ -1, 4), corresponding to the molecular formula $\text{C}_{15}\text{H}_{11}\text{N}_5\text{S}$ and at 77 (100, base peak); Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_5\text{S}$: C, 61.42; H, 3.78; N, 23.87; S, 10.93. Found: C, 61.36; H, 3.72; N, 23.82; S, 10.88.

Synthesis of Compounds 13 and 14: A mixture of 9 (1.25 g, 5 mmol) and ethyl cyanoacetate or diethyl oxalate (10 mmol) in absolute ethanol (20 ml) was refluxed for 6h. After cooling, the product was collected by filtration, dried and crystallized from the proper solvent to give the compounds 13 and 14, respectively.

(7-Methyl-9-phenyl-1,3,3a,5,6-pentaazacyclopenta [a]naphthalen-2-yl)-aceto-nitrile (13): Yield 70%, M.p. 194-196 °C (EtOH). IR (KBr) $\nu = 2218$ (C=N), 1662 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) $\delta = 2.51$ (s, 3H, CH_3), 3.80 (s, 2H, CH_2CN), 6.75-7.42 (m, 5H, Ar-H), 7.48 (s, 1H, pyrid-

CH), 7.54 (s, 1H, pyrimid-CH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ = 23.98 (CH_3), 18.30 (CH_2), 125.70, 127.42, 135.95 (Ph-C), 106.38, 119.58, 147.28, 153.18, 156.32 (Pyrid-C), 139.68, 145.98 (pyrimid-C), 158.64 (triazol-C), 117.28 ($\text{C}=\text{N}$); MS m/z: (M); 299 (M^+ -1, 10), corresponding to the molecular formula $\text{C}_{17}\text{H}_{12}\text{N}_6$ and at 91 (100, base peak); Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_6$: C, 67.99; H, 4.03; N, 27.98. Found: C, 67.93; H, 4.00; N, 27.92.

7-Methyl-9-phenyl-1,3,3a,5,6-pentaazacyclopenta [a]naphthalene-2-carboxylic acid ethyl ester (14): Yield 65%, M.p. 170-172 °C (EtOH). IR (KBr) ν = 1735 ($\text{C}=\text{O}$, ester), 1660 ($\text{C}=\text{N}$) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 1.21 (t, 3H, CH_3 , ester), 2.49 (s, 3H, CH_3), 4.15 (q, 2H, CH_2 -ester), 6.75-7.48 (m, 5H, Ar-H), 7.52 (s, 1H, pyrid-CH), 7.59 (s, 1H, pyrimid-CH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ = 14.00, 24.05 (2CH_3), 58.45 (CH_2), 125.48, 127.36, 135.88 (Ph-C), 106.42, 119.50, 147.20, 153.05, 156.12 (Pyrid-C), 139.28, 148.28 (pyrimid-C), 152.60 (triazol-C), 159.35 ($\text{C}=\text{O}$); MS m/z: (M); 333 (M^+ , 4), corresponding to the molecular formula $\text{C}_{18}\text{H}_{12}\text{N}_5\text{O}_2$ and at 56 (100, base peak); Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_5\text{O}_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.82; H, 4.50; N, 20.96.

2,7-Dimethyl-9-phenyl-1,3,3a,5,6-pentaazacyclopenta [a]naphthalene (15): A solution of 9 (1.25 g, 5 mmol) in acetic acid anhydride (10 ml) was heated under reflux for 5 hr. The solvent was evaporated under reduced pressure and the separated solid was crystallized from ethanol to give 15. Yield 65%, M.p. 103-105°C. IR (KBr) ν = 1665 ($\text{C}=\text{N}$) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ = 2.35 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.61-7.46 (m, 5H, Ar-H), 7.53 (s, 1H, pyrid-CH), 7.75 (s, 1H, pyrimid-CH); MS m/z: (M); 275 (M^+ , 18), corresponding to the molecular formula $\text{C}_{16}\text{H}_{13}\text{N}_5$ and at 145 (100, base peak); Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.75; H, 4.70; N, 25.38.

Pharmacological Screening

Antianxiety Activity

Procedure: The testing apparatus consists of a light and a dark chamber divided by a photocell-equipped zone. A polypropylene animal cage 44 x 21 x 21 cm is darkened with black spray over one third of its surface. A partition containing a 13 cm long x 5 cm high opening separates the dark one third from the bright two third of the cage. The cage rests on an Animex® activity monitor, which counts total 10 locomotors activity. As electronic system using four sets of photocells across the partition automatically

counts movements through the partition and clocks the time spent in the light and dark compartments. Naïve male albino mice with a body weight between 18 and 25 g are placed into the cage the animals are treated 30 min. before the experiment with the test drugs or the vehicle intraperitoneally and are then observed for 10 min [20, 21].

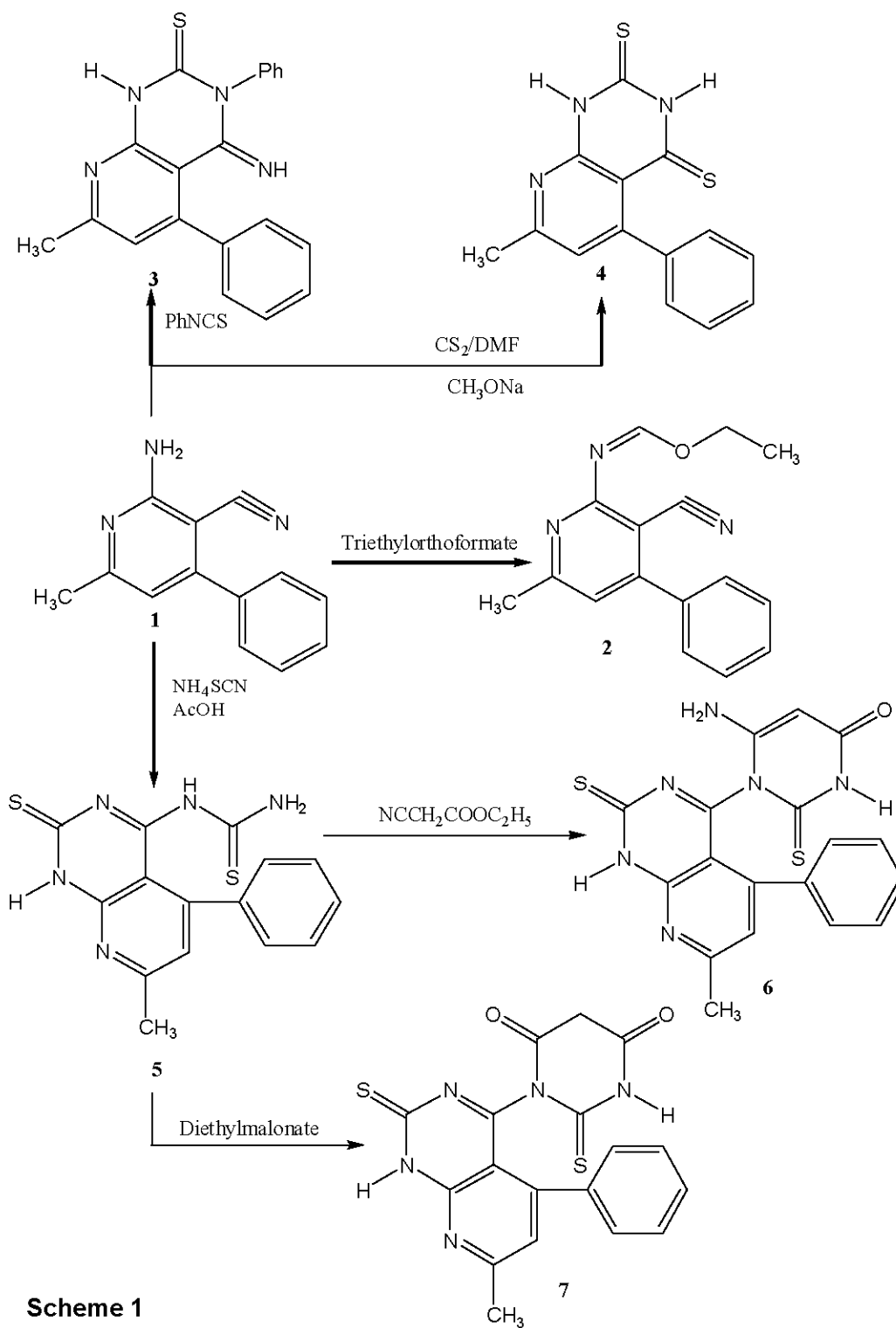
RESULTS AND DISCUSSION

In our previous work we reported the synthesis and a preliminary biological activity screening of several pyridine derivatives based on 2-amino-6-methyl-4-phenylnicotinonitrile (1) [22], which was prepared as starting material according to literature method [23]. Treatment of 1 with triethyl orthoformate in refluxing acetic anhydride gave the cyanoaminopyrane 2. On the other hand, reaction of compound 1 with phenyl isothiocyanate in refluxing dioxane containing triethyl amine as a catalyst or with carbon disulfide in the presence of sodium methoxide afforded the corresponding pyrido[2,3-d]pyrimidinethione derivatives 3 and 4, respectively. Reaction of 1 with ammonium thiocyanate in refluxing acetic acid gave pyrido[2,3-d]pyrimidine thiourea derivative 5, which was condensed with ethyl cyanoacetate or diethyl malonate in refluxing butanol to give the corresponding pyrido[2,3-d]pyrimidine-2-thioxopyrimidinone derivatives 6 and 7 (Scheme 1).

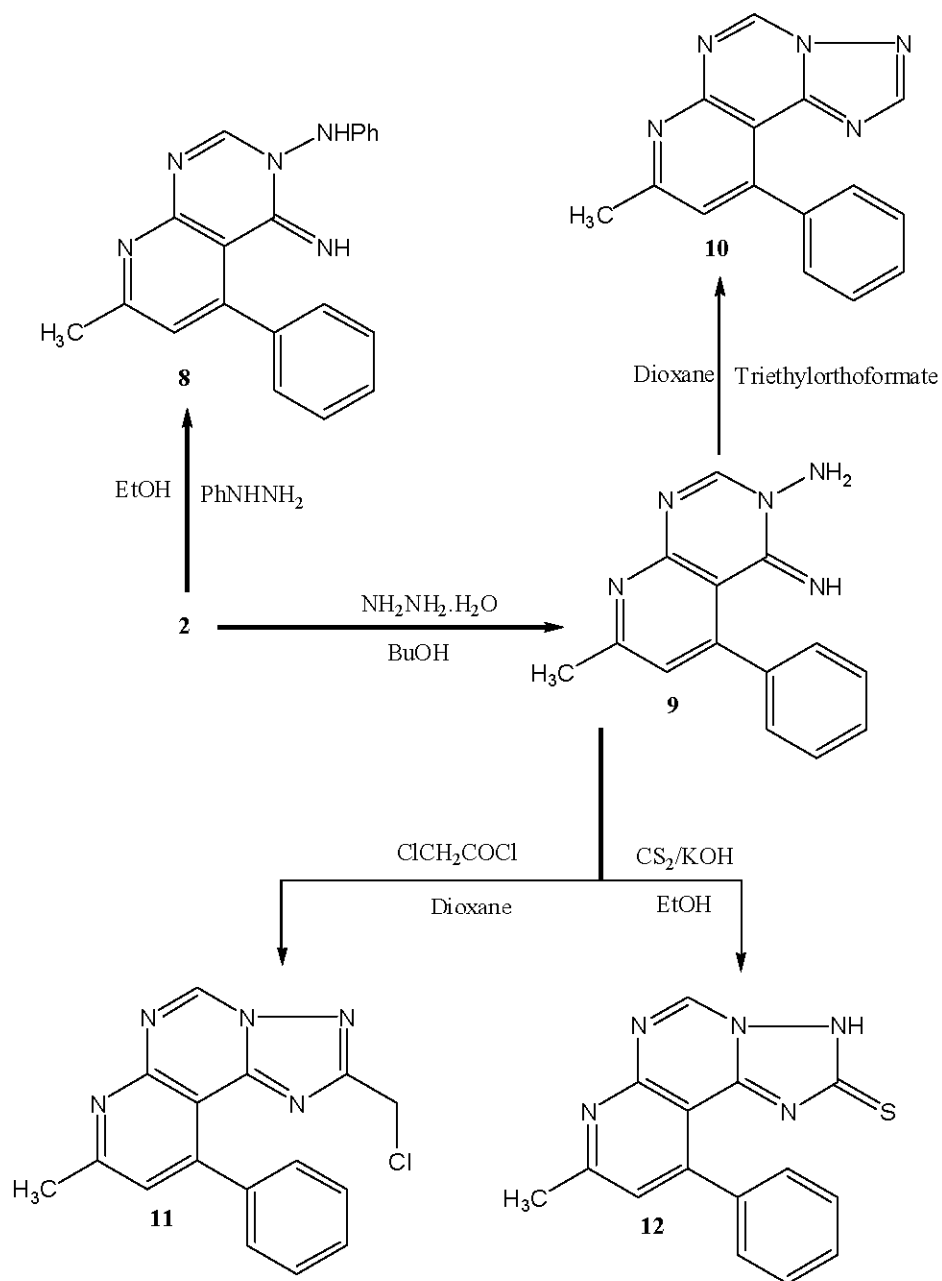
Compound 2 was treated with phenyl hydrazine or hydrazine hydrate in refluxing ethanol to afford the corresponding iminopyrido[2,3-d]pyrimidine derivatives 8 and 9, respectively. Treatment of 9 with triethylorthoformate or chloroacetylchloride in refluxing dry dioxane gave the corresponding pentaazacyclopenta [a]naphthalene derivatives 10 and 11, respectively. Also, 9 was condensed with carbon disulfide in the presence of potassium hydroxide to give pentaazacyclopenta[a]naphthalene-2-thione derivative 12 (Scheme 2).

Compound 9 was treated with ethyl cyanoacetate or diethyl oxalate in refluxing ethanol to give pentaazacyclopenta[a]naphthalen-2-acetonitrile 13 and penta-azacyclopenta[a]-naphthalene-2-carboxylic acid ethyl ester 14, derivatives respectively. In addition, treatment of compound 9 with acetic anhydride to give the corresponding compound 15 (Scheme 3).

Pharmacological Screening: All animals were obtained from the Animal House Colony, Research Institute of Ophthalmology, Giza, Egypt.



Scheme 1



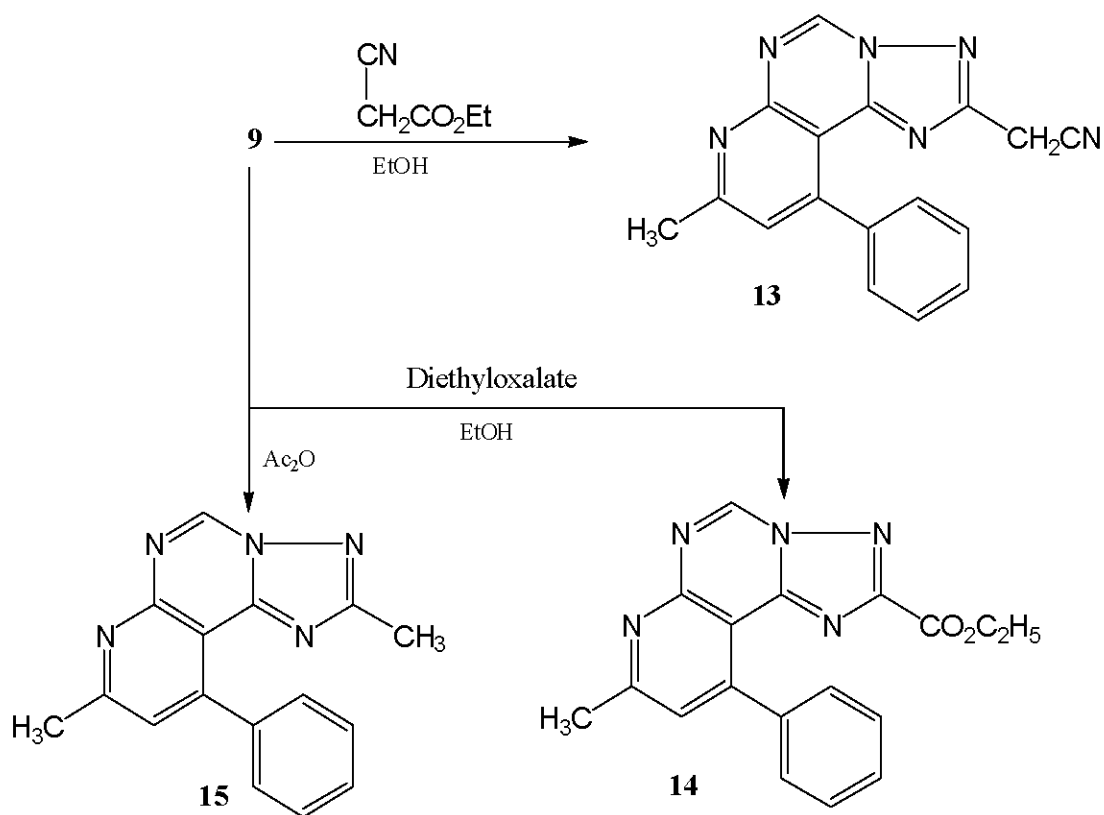
Scheme 2

Antianxiety Activity

Purpose and Rational: Crawley *et al.* [24] described a simple behavior model in mice to detect compounds with anxiolytic effects. Mice tend to explore a novel environment but to retreat from the aversive properties of a brightly-lit open field in a two-chambered system, where mice can freely move between a brightly-lit open field and a dark corner,

animals show more crossing between the two chambers and more locomotor activity after treatment with anxiolytics.

Evaluation: Dose-response curves are obtained and the number of crossings through the partition between the light and the dark chamber are compared with total activity counts during the 10 min.



Scheme 3

Table 1: Anti-anxiety activity of new synthesized compounds

Compound No.	Relative potency to diazepam
2	10.18
3	2.25
4	5.15
5	3.48
6	2.26
7	4.10
8	9.12
9	8.35
10	4.85
11	7.75
12	3.20
13	6.45
14	2.85
15	3.18
Diazepam	1.000

All the tested compounds showed potent anti-anxiety activities at least 2 times more active than diazepam. Compound 2 is the most potent showing 10 times diazepam activities, the next potent compounds 8, 9, 11, 13 and 4 where their relative potency to diazepam are 9, 8, 7, 6 and 5, respectively. The relative activities of

other compounds to that of diazepam lies between 2 (compound 3) and 4 (compound 10). The order of potency in descending order is 10, 7, 5, (12, 15), 14, (6, 3).

Structure Activity Relationship (SAR):

- Cyanopyridine is more potent than pyrido[2,3-d]pyrimidine and pentaazacyclo-penta-[a]naphthalene
- Pyrido[2,3-d]pyrimidine nucleus is essential for activity
- Pentaazacyclo-penta-[a]naphthalene moiety also not essential for activity
- Pyrido[2,3-d]pyrimidine derivatives increases the anti-anxiety activity.

CONCLUSION

The compounds combined both potent activities alongside the high safety margin deduced from their excellent therapeutic window. The order of potency in descending order is 2, 8, 9, 11, 13, 4, 10, 7, 5, (12, 15), 14, (3, 6).

ACKNOWLEDGEMENT

The kind help of Dr. Mohamed M. Abdulla, Research Units, Hi-Care Pharmaceutical Co., Cairo, Egypt, for carrying out the pharmacological screening is highly appreciated

REFERENCES

1. Amr, A.E., 2000. Indian J Heterocycl. Chem., 10: 49-58.
2. Attia, A., O.I. Abdel-Salam and A.E. Amr, 1997. Egypt J. Chem., 40(4): 317-325.
3. Attia, A., O.I. Abdel-Salam, A.E. Amr, I. Stibor and M. Budesinsky, 2000. Egypt. J. Chem., 43(2): 187-201.
4. Attia, A., O.I. Abdel-Salam, M.H. Abou-Ghali and A.E. Amr, 1995. Egypt. J. Chem., 38(5): 543-553.
5. Amr, A.E., O.I. Abdel-Salam, A. Attia and I. Stibor, 1999. Collect. Czech Chem. Commun., 64: 288-298.
6. Attia, A., O.I. Abdel-Salam and A.E. Amr, 2000. Egypt. J. Chem., 43(4): 297-307.
7. Braña, M.F., J.M. Castellano, M. Morán, M.J. Pérez de Vega, X.D. Qian, C.A. Romerdahl and G. Keilhauer, 1995. Europ. J. Med. Chem., 30: 235-239.
8. Jiban, K.C., F. John, J.A.G. Norman, H. Linda, A.P. Ian, W.S. Colin, J.S. David, E.T. David and C.W. Francesca, 1980. J. Med. Chem., 23(8): 884-889.
9. Mylonas, S. and A. Mamalis, 2005. J. Heterocycl. Chem., 42(7): 1273-1281.
10. Fahmy, H.H. and G.A. Soliman, 2001. Arch. Pharm. Res., 24(3): 180-189.
11. De Clercq, E., 1986. J. Med. Chem., 29: 1561-1569.
12. Hammam, A.G., M. Sharaf and N.A. Abdel-Hafez, 2001. Ind. J. Chem., 40B: 213-221.
13. Hammam, A.G., A.F.M. Fahmy, A.E. Amr and A.M. Mohamed, 2003. Ind. J. Chem. Sec. B., 42B: 1985-1993.
14. Yousif, N.M., F.A. Gad, A.F. Fahmy, M.S. Amine and H.H. Sayed, 1996. Phosphorus Sulfur and Silicon, 117: 11-19.
15. Amr, A.E., M.I. Hegab, A.A. Ibrahim and M.M. Abdalah, 2003. Monatsh. Chem., 134: 1395-1409.
16. Amr, A.E. and M.M. Abdulla, Ind. J. Heterocycl. Chem., 12: 129-134.
17. Amr, A.E., M.S. Nermien and M.M. Abdulla, 2007. Monatsh. Chem., 138: 699-707.
18. Amr, A.E., M.M. Ashraf, F.M. Salwa, A.A. Naglaa and A.G. Hammam, 2006. Bioorg. Med. Chem., 14: 5481-5488.
19. Amr, A.E., H.H. Sayed and M.M. Abdulla, 2005. Arch. Pharm. Chem. Life Sci., 338: 433-440.
20. Costall, B., C.A. Hendrie, M.C. Kelly and R.J. Naylor, 1987. Neuropharmacol., 26: 195-200.
21. Kilfoil, T., A. Michel, D. Montgomery and R.L. Whithing, 1989. Neuropharmacol., 28: 901-905.
22. Said, A.S., 2009. Monatsh. Chem., 140: 573-579.
23. Nehad, A.A., A.E. Amr and A.I. Alhusien, 2007. Monatsh. Chem., 138: 559-567.
24. Crawley, J. and F.K. Pharmacol. Biochem. Behav., 13: 167-170.