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A NOVEL FUSED PYRIDOPYRIMIDINE DERIVATIVES: SYNTHESIS AND CHARACTERIZATION

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ABSTRACT

Because of its potent and significant pharmacological activities, The 2-amino-4,6-bis(4-chlorophenyl) nicotinonitrile **(1)** used as a starting material to synthesis of pyridopyrimidine derivatives **3–7**. On the other hand, we used the pyridopyrimidine **4** to synthesis of tricycle heterocyclic derivatives; pyridopyrimidotriazine **8–10**; pyridotriazolopyrimidine **11–13** and pyridotetrazolopyrimidine **14**.

Keywords: pyridopyrimidine, pyridopyrimidotriazine, pyridotriazolopyrimidine and pyridotetrazolopyrimidine.

INTRODUCTION

Pyridopyrimidine derivatives are a privileged bicyclic ring system. Due to its potent and significant biological activities it has great pharmaceutical importance; synthesis of these compounds is considerable interest. Fused pyridopyrimidine derivatives if present in compounds involved in research aimed at evaluating new products that possess interesting biological activities. The fused pyridopyrimidine derivatives play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells DNA and RNA are based on aromatic heterocycles.[1,2] They are known to exhibit pharmacological activates such as CNS depressant, neuroleptic, and turberculostatic, and anticancer agent,[3–5] antifolate,[6] antibacterial,[7] tyrosine kinas activity,[8] antimicrobial,[9] calcium channel antagonist,[10] antiinflammatory and analgesic activity,[11] antileishmania,[12] tuberculostatic,[13] anti-convulsant,[14] diuretic and potassium-sparing,[15] and anti-aggressive activities.[16] Antiviral activities.[17,18] Recently, pyridopyrimidine derivatives used as inhibitors of stable toxin a (STa) for their ability to inhibit cyclic nucleotide synthesis in the presence of stable toxin a of Escherichia coli.[19] This encouraged us to become involved in a program directed to the development of syntheses of various new pyridopyrimidines and fused pyridopyrimidines.

MATERIALS AND METHODS

All melting points are uncorrected and measured using Electro-Thermal IA 9100 apparatus (Shimadzu, Japan). Infrared spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer, National Research Center, Cairo, Egypt. ^{1}H-NMR spectrum was determined on a Jeol-Ex-500 NMR spectrometer and chemical shifts were expressed as part per million; (δ values, ppm) against TMS as internal reference, National Research Center, Cairo, Egypt. Mass spectra were recorded on EI + Q1 MSLMR UPLR, National Research Center, Cairo, Egypt. Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Center, Cairo, Egypt.

5,7-Bis(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2). A mixture of **1**(3.39 g, 1 mmol) and excess of formic acid (10 mL) was heated under reflux for 3 h. After completion of reaction, the reaction mixture was left to cool to room temperature, and then poured onto ice cold water (50 mL). The product was separated by filtration and washed with cold water. The crude product was purified by recrystallization from Dioxane to give compound **2**.Yield 71%, m.p.223–225˚C. IR spectrum (KBr, ν, cm^{-1}): 3110 (NH) and 1667 (C=O). ^{1}H NMR (DMSO-d$_6$, δ ppm): 7.24 (s, 1H, pyridine-

H); 7.61–8.62 (m, 8H, Ar-H); 8.73 (s, 1H, pyrimidine-H); 9.04 (s, 1H, NH; D_2O exchangeable). Ms, *m/z* (%): 367 (M^+, 32), 369 (M^+ +2, 19), 371 (M^+ +4, 3). Anal. Calc. For $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; Cl, 19.26; N, 11.41. Found: C, 61.69; H, 2.77; Cl, 18.98; N, 11.15.

4-Chloro-5,7-bis(4-chlorophenyl)pyrido[2,3-*d*] pyrimidine (3). Compound **2** (3.67 g, 1 mmol) was refluxed in phosphorus oxychloride (30 mL) for 3 h, cooled, poured onto ice-water to give a precipitate, which was filtered off, dried and recrystallized from Dioxane to afford compound **3**.Yield 56%; m.p. 166–168˚C. IR spectrum (KBr, ν, cm^{-1}): 3098 (C-H, aromatic); 2976 (C-H, aliphatic). ^{1}H NMR (DMSO-d_6, δ ppm): 7.26 (s, 1H, pyridine-H); 7.55–8.44 (m, 8H, Ar-H); 8.69 (s, 1H, pyrimidine-H). Ms, *m/z* (%): 385 (M^+, 17), 387 (M^+ +2, 16); 389 (M^+ +4, 5); 391(M^+ +6, 0.5). Anal. Calcd. For $C_{19}H_{10}Cl_3N_3$: C, 59.02; H, 2.61; Cl, 27.51; N, 10.87. Found: C, 58.79; H, 2.32; Cl, 27.22; N, 10.58.

5,7-Bis(4-chlorophenyl)-4-hydrazinopyrido[2,3-d]pyrimidine (4). A mixture of **3** (3.85 g, 1 mmol) and hydrazine hydrate (5 mL, 98%) was refluxed in absolute ethanol (20 mL) for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give compound **4**.Yield 93%; m.p. 189–191˚C. IR spectrum (KBr, ν, cm^{-1}): 3260 (NH_2); 3140 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 4.55 (s, 2H, NH_2; D_2O exchangeable); 7.29 (s, 1H, pyridine-H); 7.57–8.59 (m, 8H, Ar-H); 8.71 (s, 1H, pyrimidine-H); 9.11 (s, 1H, NH; D_2O exchangeable). Ms, *m/z* (%): 381 (M^+, 57), 383 (M^+ +2, 34); 385 (M^+ +4, 6). Anal. Calc. For $C_{19}H_{13}Cl_2N_5$: C, 59.70; H, 3.43; Cl, 18.55; N, 18.32. Found: C, 59.44; H, 3.16; Cl, 18.28; N, 18.07.

5-Amino-1-[5,7-bis(4-chlorophenyl)pyrido[2,3-d] pyrimidin-4-yl]-1,2-dihydro-3H- pyrazol-3-one (5). A mixture of compound **4** (7.62 g, 2 mmol) and ethyl cyoacetate (0.01 mol) was fused for 1 h then absolute ethanol (20 mL) was added dropwise and reflux continued for additional 2 h. The solid product, which formed, was filtered off and recrystallized from Dioxane to give compound **5**. Yield 57%; m.p. 231–233˚C. IR spectrum (KBr, ν, cm^{-1}): 3230 (NH_2); 3115 (NH); 1702 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 5.19 (s, 1H, pyrazole-H); 6.2 (s, 2H, NH_2; D_2O exchangeable); 7.29 (s, 1H, pyridine-H); 7.57–8.59 (m, 8H, Ar-H); 8.71 (s, 1H, pyrimidine-H); 9.46 (s, 1H, NH; D_2O exchangeable). Ms, m/z (%): 448 (M^+, 10), 450 (M^+ +2, 6); 452 (M^+ +4, 1). Anal. Calc. For $C_{22}H_{14}Cl_2N_6O$: C, 58.81; H, 3.14; Cl, 15.78; N, 18.71. Found: C, 58.55; H, 2.88; Cl, 15.52; N, 18.44.

2-[5,7-bis(4-chlorophenyl)pyrido[2,3-d]pyrimidin-4-yl]-5-methyl-2,4-dihydro -3H-pyrazol-3-one (6). To a solution of compound **4** (3.81 g, 1 mmol) in glacial acetic acid (20 mL), ethyl acetoacetate (0.01 mol) was added and the reaction mixture was refluxed for 5h. The solvent was removed under reduced pressure and the obtained product was recrystallized from acetic acid to give compound **6**. Yield 51%, m.p. 159–161˚C. IR spectrum (KBr, ν, cm^{-1}): 1678 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.20 (s, 3H, CH_3); 4.31 (s, 1H, pyrazole-H); 7.21 (s, 1H, pyridine-H); 7.53–8.41 (m, 8H, Ar-H); 8.63 (s, 1H, pyrimidine-H). Ms, m/z (%): 447 (M+, 17), 449 (M+2, 11); 451 (M+4, 2). Anal. Calc. For $C_{23}H_{15}Cl_2N_5O$: C, 61.62; H, 3.37; Cl, 15.82; N, 15.62. Found: C, 61.35; H, 3.09; Cl, 15.56; N, 15.33.

5,7-Bis(4-chlorophenyl)-4-(3,5-dimethyl-4,5-di hydro-1H-pyrazol-1-yl)pyrido[2,3-d]pyrimidine (7). A mixture of compound **4** (3.81 g, 1 mmol) and acetyl acetone (0.02 mol) in ethanol (20 mL) was refluxed for 8 h. The separated solid was filtered off, dried and recrystallized from ethanol to give **7**. Yield 67%; m.p. 223–225˚C. IR spectrum (KBr, ν, cm^{-1}): 3098 (C-H, aromatic); 2987 (C-H, aliphatic). ^{1}H NMR (DMSO-d_6, δ ppm): 2.18 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 6.08 (s, 1H, pyrazole-H); 7.36 (s, 1H, pyridine-H); 7.55–8.21 (m, 8H, Ar-H); 8.44 (s, 1H, pyrimidine -H). Ms, m/z (%): 445 (M^+, 25), 447 (M^+ +2, 16); 449 (M^+ +4, 3). Anal. Calcd. For $C_{24}H_{17}Cl_2N_5$: C, 64.58; H, 3.84; Cl, 15.89; N, 15.69. Found; C, 64.27; H, 3.58; Cl, 15.61; N, 15.41.

9,11-Bis(4-chlorophenyl)-2H-pyrido[2',3':4,5] pyrimido[6,1-c][1,2,4]triazin-3(4H)-one (8). To a solution of compound **4** (3.81 g, 1 mmol) in DMF (30 mL) and chloroacetyl chloride (0.01 mol) was added drop wise under stirring at room temperature. The reaction mixture was then heated for 9 h and after cooling, poured onto cold water with vigorous stirring. The precipitate was collected by filtration, washed with water, dried and recrystallized from DMF to give compound **8**.Yield 57%; m.p. 271–273˚C. IR spectrum (KBr, ν, cm^{-1}): 3120 (NH); 1665 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 4.59 (d, J = 9.15; 1H, CH_2); 4.63 (d, J = 9.13, 1H, CH_2); 7.31 (s, 1H, pyridine-H); 7.52–8.21 (m, 9H, 8 Ar-H + NH; D_2O exchangeable); 8.38 (s, 1H, pyrimidine-H). Ms, *m/z* (%): 421 (M^+, 41), 423 (M^+ +2, 26); 425 (M^+ +4, 4). Anal. Calc. For $C_{21}H_{13}Cl_2N_5O$: C, 59.73; H, 3.10; Cl, 16.79; N, 16.59. Found: C, 59.45; H, 2.83; Cl, 16.579; N, 16.31.

9,11-Bis(4-chlorophenyl)-2,3-dihydro-4H-pyrido[2',3':4,5]pyrimido[6, 1-c] [1,2,4] triazin-4-one (9). To a solution of compound **4** (3.81 g, 1

mmol) in DMF (30 mL) and bromoacetic acid (0.01 mol) was added drop-wise under stirring at room temperature. The reaction mixture was then heated for 3 h and after cooling, poured onto cold water with vigorous stirring. The precipitate was collected by filtration, washed with water, dried and recrystallized from DMF to give compound **9**.Yield 64%; m.p. 255–257˚C. IR spectrum (KBr, ν, cm^{-1}): 3170 (NH); 1690 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 4.11 (d, *J* = 8.96 Hz, 1H, CH_2); 4.17 (d; J = 9.01 Hz; 1H, CH_2); 7.28 (s, 1H, pyridine-H); 7.50–8.20 (m, 9H, 8 Ar-H + NH; D_2O exchangeable); 8.35 (s, 1H, pyrimidine-H). Ms, m/z (%): 421 (M+, 45), 423 (M^+ +2, 27); 425 (M^+ +4, 5). Anal. Calcd. For $C_{21}H_{13}Cl_2N_5O$: C, 59.73, H, 3.10; Cl, 16.79; N, 16.59. Found: C, 59.47, H, 2.84; Cl, 16.52; N, 16.33.

9,11-bis(4-chlorophenyl)-2H-pyrido[2',3':4,5] pyrimido[6,1-c][1,2,4]triazine-3,4-di one (10). A mixture of compound **4** (3.81 g, 1 mmol) and diethyloxalate (0.01 mol) in THF (50 mL) was refluxed for 16h and then cooled. The solid obtained was filtered off and recrystallized from Acetic acid to give compound **10**.Yield 48%, m.p. 181–183˚C. IR spectrum (KBr, ν, cm^{-1}): 3150 (NH); 1680 (C=O); 1710 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 7.33 (s, 1H, pyridine-H); 7.51-8.23 (m, 8H, Ar-H); 8.41 (s, 1H, pyrimidine-H); 9.21 (s, 1H, NH, D_2O exchangeable). Ms, m/z (%): 435 (M^+, 22), 437 (M^+ +2, 14); 439 (M^++4, 2). Anal. Calc. For $C_{21}H_{11}Cl_2N_5O_2$: C, 57.82; H, 2.54; Cl, 16.25; N, 16.05.Found: C, 57.56; H, 2.33; Cl, 15.975; N, 15.79%.

8,10-Bis(4-chlorophenyl)pyrido[3,2-e][1,2,4]tria-zolo[4,3-c]pyrimidine-3(2H)-thione (11). To an aqueous solution of **4** (3.81 g, 1 mmol) in ethanol (20 mL), carbon disulfide (10mL) was added, then the reaction mixture was refluxed on a water-bath for 3 h, cooled, poured onto ice-water, and neutralized with 2–3 drops of hydrochloric acid (35%). Theprecipitate was filtered off, left to dry and recrystallized from methanol to give **11**. Yield 46 %; m.p. 192–194˚C. IR spectrum (KBr, ν, cm_{-1}): 3115 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 7.31 (s, 1H, pyridine-H); 7.53-8.24 (m, 8H, Ar-H); 8.39 (s, 1H, pyrimidine-H); 8.90 (s, 1H, NH; D_2O exchangeable). Ms, *m/z* (%): 423 (M^+, 45), 425 (M^+ +2, 29); 427 (M^+ +4, 4). Anal. Calc. For $C_{20}H_{11}Cl_2N_5S$: C, 56.61; H, 2.61; Cl, 16.71; N, 16.51. Found: C, 56.35; H, 2.31; Cl, 16.44; N, 16.37.

8,10-Bis(4-chlorophenyl)pyrido[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (12). A mixture of compound **4** (3.81 g, 1 mmol) and triethyl orthoformate (20 mL) was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give **12**.Yield 53%; m.p. 175–177˚C. IR spectrum (KBr, ν, cm^{-1}): 3098 (C-H, aromatic); 2977 (C-H, aliphatic). ^{1}H NMR (DMSO-d_6, δ ppm): 7.41 (s, 1H, pyridine-H); 7.62–8.50 (m, 10H, 8 Ar-H+ pyrimidine -H+ Triazine -H). Ms, *m/z* (%): 391 (M^+, 21), 393 (M^+ +2, 13); 395 (M^+ +4, 2); 363 (M^+-N_2, 100). Anal. Calcd. For $C_{20}H_{11}Cl_2N_5$: C, 61.24; H, 2.83; Cl, 18.08; N, 17.85. Found C, 60.984; H, 2.57; Cl, 17.78; N, 17.57.

8,10-Bis(4-chlorophenyl)-3-methylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimi-dine (13). A mixture of compound **4** (3.81 g, 1 mmol), acetic anhydride (20 mL), and acetic acid (10 mL) was refluxed for 5 h, cooled, and poured onto ice-water. The precipitate was filtered off, left to dry and then recrystallized from methanol to give **13**. Yield 67%; m.p. 174–176˚C. IR spectrum (KBr, ν, cm^{-1}): 3092 (C-H, aromatic); 2981 (C-H, aliphatic). ^{1}H NMR (DMSO-d_6, δ ppm): 2.20 (s, 3H, CH_3); 7.41 (s, 1H, pyridine-H); 7.64–8.42 (m, 9H, 8 Ar-H+ pyrimidine -H). Ms, *m/z* (%): 405 (M^+, 33), 407 (M^+ +2, 21), 409 (M^+ +4, 3). Anal. Calc. For $C_{21}H_{13}Cl_2N_5$: C, 61.79; H, 2.96; Cl, 17.17; N, 16.99. Found C, 61.51; H, 2.38; Cl, 16.82; N, 16.74.

8,10-bis(4-chlorophenyl)pyrido[3,2-*e*]tetrazol-o[1,5-*c*]pyrimidine (14). To an ice-cold solution of compound **4** (3.81 g, 1 mmol) in glacial acetic acid (10 ml), a solution of sodium nitrite prepared by dissolving sodium nitrite (0.01 mol) in water (3 ml) was added drowsily in an ice-bath. The reaction mixture was allowed to stand overnight at room temperature and then was poured into water. The formed solid was filtered of, washed with water, dried and recrystallized from methanol to give **14**.Yield 79%; m.p. 187–189˚C. IR spectrum (KBr, ν, cm^{-1}): 3091 (C-H, aromatic); 2990 (C-aliphatic). ^{1}H NMR (DMSO-d_6, δ ppm): 7.38 (s, 1H, pyridine-H); 7.63–8.33 (m, 8H, Ar-H); 8.49 (s, 1H, pyrimidine-H). Ms, *m/z* (%): 392 (M^+, 35), 394 (M^++2, 22); 396 (M^+ +4, 4). Anal. Calc. for $C_{19}H_{10}Cl_2N_6$: C, 58.03; H. 2.56; Cl, 18.03; N, 21.37. Found: C, 57.79; H. 2.28; Cl, 17.81; N, 21.09.

RESULTS AND DISCUSSION

2-amino-4,6-bis(4-chlorophenyl)nicotinonitrile **(1)** was used as key compounds for this study and for syntheses of other fused heterocycles. Derivative **1** was prepared as reported previously,[20] The synthesis of pyrido[2,3-d]pyrimidin-4-one derivative **2** was achieved by refluxing compound **1** with formic acid. The IR spectrum of the latter compound showed the

absence of cyano group and the presence of C=O and NH groups. Its ^{1}H-NMR spectrum revealed a signal at (δ, ppm): 9.02 (s, 1H, NH, exchangeable with D_2O). The latter compound was converted to its corresponding 4-chloro derivative **3** by refluxing with phosphorus oxychloride; the IR of latter compound reveled the absence of signals characteristic for C=O and NH groups and its MS gave the characteristic isotopic pattern of three chlorine atoms (c.f. experimental). Hydrazinopyrido[2,3-d]pyrimidine derivative **4** was obtained from derivative **3** by heating with hydrazine hydrate (Scheme 1). The IR and ^{1}H-NMR spectra of compound **4** was revealed signals characteristic of NH_2 + NH (c.f. experimental). Condensation of hydrazino derivative **4** with different bifunctional compounds namely;ethyl cyanoacetate, ethyl acetoacetate and /or acetyl acetone yielded the hydrazones as intermediate that can't be separated and underwent ring closure under the same conditions (*in situ*) to give a variety of pyrazolo derivatives **5**–**7** (Scheme 3). The structures of the new products were established according to their elemental and spectroscopic data (c.f. experimental).

When hydrazino derivative **4** was subjected to react with chloro acetyl chloride and / or chloroacetic acid in warm DMF the pyrido[2',3':4,5]pyrimido[6,1-c][1,2,4]triazin-one **8** and **9** were formed respectively (Scheme 2) the structures of latter compounds were elucidated from their spectral measurements (c.f. experimental)

Heterocyclization of hydrazino derivative **4** *via* refluxing with diethyl oxalate in dry THF resulted in pyrido[2',3':4,5]pyrimido[6,1-c][1,2,4]triazine-3,4-dione **10** (Scheme 2). The IR spectrum of compound **10** showed bands for NH and two C=O groups (c.f. experimental).

In this investigation, and in continuation of our previous work in the synthesis of different fused triazolopyrimidines,[21] refluxing of compound **4** with carbon disulphide, triethyl orthoformate (TEOF) and/or acetic acid/acetic anhydride gave products assigned to the structures of pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines **11**–**13** were obtained respectively (Scheme 3, c.f. experimental).

Nitrozation of compound **4** gave the corresponding 8,10-bis(4-chloro phenyl) pyrido[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**14**). The IR and ^{1}H-NMR spectra of **14** revealed the absence of NH_2 and NH groups (Scheme 3, c.f. experimental).

CONCLUSION

In conclusion, we have successfully synthesis fused pyridopyrimidene, pyrazolo derivatives **5**-7, pyrido[3,2-e][1,2,4]triazolo[4.3-c]pyrimidines, pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine derivatives from low coast starting materials. It is demonstrated that as pyrimidine ring with fused and more nitrogen atoms the bioactivity of these compounds expected to increase. Finally, we expect a high bioactivity for these synthesized compounds.

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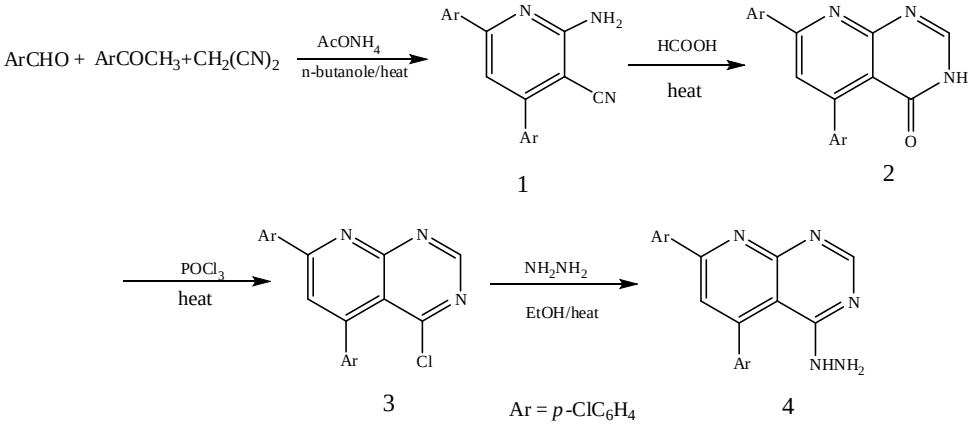
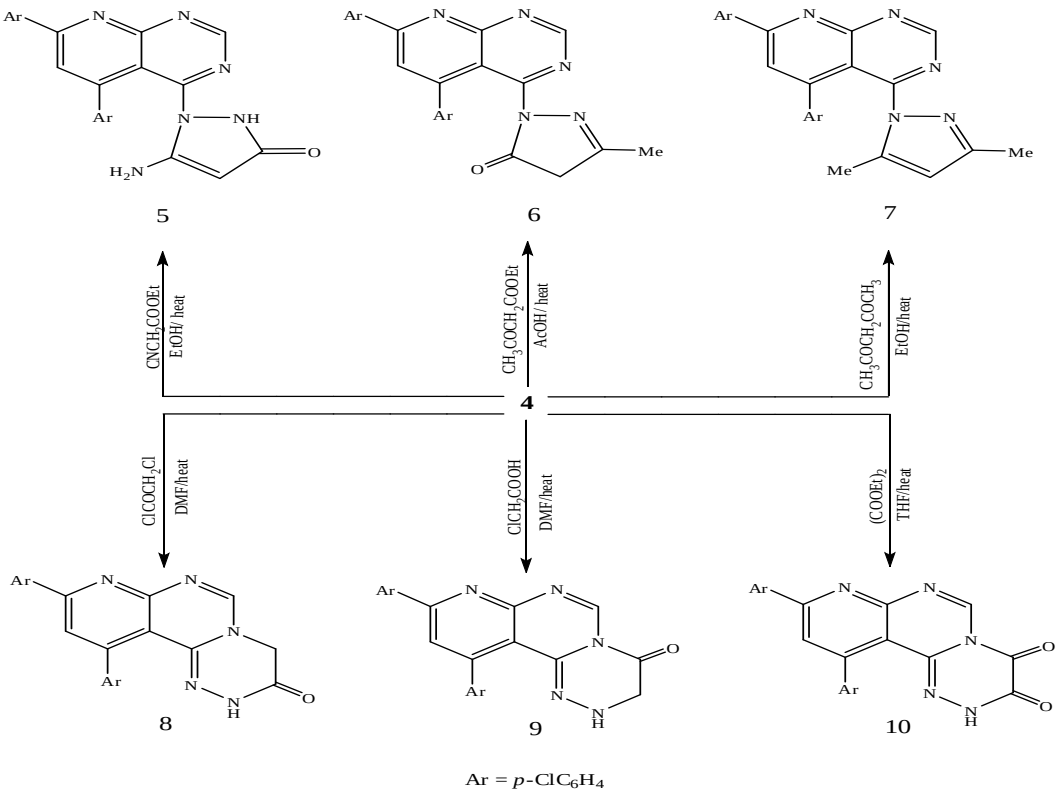
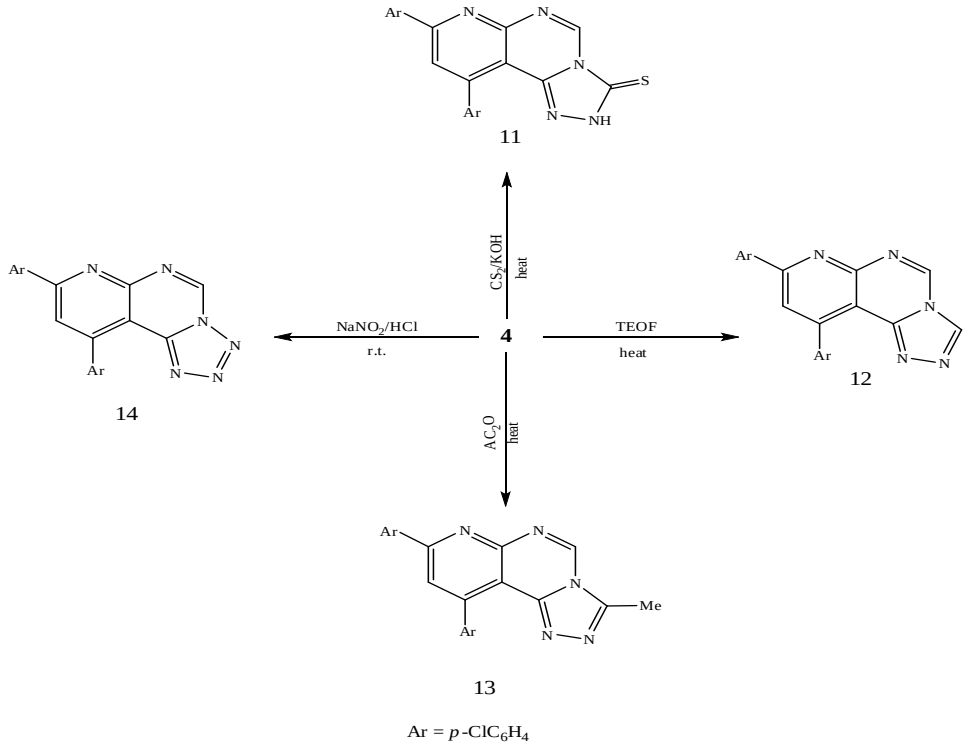


Scheme1: Synthesis of Starting compounds **2-4.**



Scheme 2: Synthesis of Compounds **5-10.**



Scheme 3: Synthesis of compounds **11-14.**

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