Synthesis of New Derivatives of Heterocyclic Compounds Containing Pyridine, Pyrimidine and Triazole Ortho-Fused to Isoquinoline Moiety

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Abstract

4-Amino-9,10-dimethoxy-2-phenyl-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile derivatives 4a-c were obtained from the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline-1-acetonitrile 1 with arylidenemalononitrile 2a-c in boiling acetonitrile in the presence of piperidine. The reaction of 4a-c with triethyl orthoformate in acetic anhydride at reflux give the ethoxymethyleneamino derivatives 5a-c. Compounds 5a-c were reacted with hydrazine hydrate and give the corresponding 4-amino-3-imino-2-aryl-3,4,8,9-tetrahydro-2(H)-pyrimido[5′,4′:5,6] pyrido[2,1-a]isoquinoline-1-carbonitrile derivatives 6a-c. Refluxing compound 6a in an excess of triethyl orthoformate give 7a. When compounds 6a-c were refluxed with acetic anhydride or benzoyl chloride in pyridine, they afford the corresponding 4-methyl and 4-phenyl derivatives 8a-c and 9a-c, respectively. Compound 6a was refluxed in diethyloxalate and give product 10. Also, the reaction of 6a with C-acylhydrazonoyl halides 13a,b in refluxing chloroform in the presence of triethylamine afford 14a,b. Correct elemental analyses and spectral data (IR, 1H NMR, 13C NMR and MS) confirm the structure of the synthesized compounds.

Keywords: pyrido[2,1-a]isoquinoline, triazolopyrimidopyridoisoquinoline, triazinopyrimidopyridoisoquinoline

1. Introduction

Isoquinoline derivatives have been shown to possess a wide range of biological activities including anticancer (Mukherjee et al., 2010; Knolker & Agarwal, 2005), anti-inflammatory (Barbosa-Filho et al., 2006) antidepressant (Maryanoff et al. 1984; Rajagopalan 1984), antimalarial (Buchana et al., 2009) and anti-HIV (Kashiwada et al., 2005). They also act as potential cetylcholinesterase inhibitors (Markmee et al., 2006), as a2-adrenoreceptor antagonist (Chung et al., 2000) and exhibit antidepressant (Maryanoff et al., 1987) and antispasmodic effects (Chandra et al., 2001). Also, pyrimidines and pyridopyrimidines are reported to show a broad spectrum of pharmacological properties such as antimicrobial (Kanth et al., 2006; Chan et al., 2005; Vry et al., 2004), central nervous system (CNS) depressant, analgesic, anti-inflammatory (Sondhi et al., 1999; Boyle et al., 2001; Lee et al., 2001; Hafez et al., 2008), and anti-HIV (Rawal et al., 2007). In addition, [1,2,4]triazolo[4,3-a]pyrimidines are pharmacological scaffold that represent a wide range of biological activities such as antitumor (Hafez & El-Gazzar, 2009), anti-inflammatory (Hafez et al., 2008), adenosine A2 receptor antagonist (Vu et al., 2004), acetohydroxy acid synthase inhibitor (Chen et al., 2010) and antimalaria parasite (Phillips et al., 2008). Thus, it was of interest to synthesize ring systems combining the isoquinoline, pyridine, pyrimidine and triazole moieties in order of their possible biological properties. Although several examples of the triazoloazines have been reported in literature (Elmagdi et al., 1990; Quiroga et al., 1999; Elwan et al., 1996; Hassaneen et al., 2001) there is only our previous report contains 1,2,4-triazole ring fused with pyrimidopyridoisoquinoline ring system (Abdallah et al., 2009). In continuation of our previous work on isoquinoline, the present study was designed to synthesis some new derivatives of tri-, tetra- and penta-ortho-fused heterocyclic compounds especially pyridoisoquinoline, pyrimidopyridoisoquinoline and triazolo/triazinopyrimidopyridoisoquinoline.
2. Experimental

**General.** Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (1H NMR) and at 75 MHz (13C NMR) using CDCl3 as solvent and TMS as internal standard. Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMS QP 1000 EX spectrometer. Microwave irradiation was carried out using a CEM Discover LabmateM microwave apparatus (300 W with ChemDriver™ Software). Elemental analyses were carried out at the Micro analytical Center of Cairo University.

2.1 Synthesis of Compounds 4a-c

To a solution of arylidenemalononitrile (5 mmol) and 6,7-dimethoxy-3,4-dihydroisouinolin-1-acetonitrile (1.15 g, 5 mmol) in acetonitrile (40 mL) was added 4 drops of piperidine at room temperature. The reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 mL) where it solidified. The crude product was collected and crystallized from dimethylformamide to give 4a-c. The compounds 4a-c were also prepared by refluxing equimolar amounts of 1, the appropriate aldehyde and malononitrile under similar conditions described above.

4-Amino-2-(4-chlorophenyl)-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile 4a. Yield 86%, mp 236 °C, IR (KBr) νmax 2152 (C≡N), 2186 (C≡N), 3354, 3471 (NH2) cm⁻¹. 1H NMR (CDCl3) δ 2.8 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.9 (s, 6H, two OCH3), 4.0 (m, 1H, isoquinoline-3H), 4.3 (s, 2H, NH2), 4.4 (s, 1H, pyridine-4H), 6.7 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 4H), 7.7 (s, 1H, isoquinoline-5H) ppm. MS: m/z 420 (M++2), 419, 418 (M+), 351, 321, 307, 263, 176, 140, 75. Anal. Calcd. For C24H20N4O4 (428.14) C, 67.28; H, 4.71; N, 13.08. Found C, 67.09; H, 4.61; N, 13.00%.

4-Amino-2-(1,3-benzodioxol-5-yl)-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile 4b. Yield 80%, mp 137 °C, IR (KBr) νmax 2179 (C≡N), 2185 (C≡N), 3232, 3364 (NH2) cm⁻¹. 1H NMR (CDCl3) δ 2.9 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH3), 3.9 (s, 3H, OCH3), 4.0 (m, 1H, isoquinoline-3H), 4.2 (s, 2H, NH2), 4.3 (s, 1H, pyridine-4H), 6.0 (s, 2H, OCH2O), 6.7 (s, 1H, isoquinoline-8H), 6.8-7.3 (m, 3H), 7.7 (s, 1H, isoquinoline-5H) ppm. MS: m/z 429 (M++1), 428 (M+), 427, 426, 381, 361, 307, 291, 268, 63. Anal. Calcd. For C23H19ClN4O3 (418.87) C, 65.94; H, 4.57; N, 13.37. Found C, 65.62; H, 4.48; N, 13.10%.

4-Amino-2-(4-methoxyphenyl)-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile 4c. Yield 77%, mp 192 °C, IR (KBr) νmax 2187 (C≡N), 2197 (C≡N), 3354, 3471 (NH2) cm⁻¹. 1H NMR (DMSO-d6) δ 2.8 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH3), 3.9 (s, 3H, OCH3), 4.0 (s, 3H, OCH3), 4.0 (m, 1H, isoquinoline-3H), 4.3 (s, 2H, NH2), 4.4 (s, 1H, pyridine-4H), 6.7 (s, 1H, isoquinoline-8H), 6.9-7.3 (m, 4H), 7.7 (s, 1H, isoquinoline-5H) ppm. 13C NMR (DMSO-d6) δ 29.84. 44.13, 57.55, 56.88, 55.87, 60.17, 86.17, 112.58, 115.99, 116.09, 121.77, 122.84, 123.21, 129.68, 130.02, 132.27, 138.22, 147.12, 148.52, 152.44, 154.45, 177.36 ppm. MS: m/z 429 (M++1), 428 (M+), 427, 426, 381, 361, 307, 291, 268, 63. Anal. Calcd. For C23H20N4O3 (464.45) C, 69.55; H, 5.35; N, 13.52. Found C, 69.29; H, 5.22; N, 13.30%.

2.2 Synthesis of Compounds 5a-c

A mixture of 4-amino-2-aryl-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile derivatives 4a-c (5 mmol), triethyl orthoformate (3 mL) and acetic anhydride (20 mL) was heated under reflux for 5 h. The excess of acetic anhydride was distilled off under reduced pressure and the solid that precipitated on cooling was filtered. The crude product was crystallized from the proper solvent to give 5a-c. The compounds 5a-c were also prepared by refluxing equimolar amounts of 4a-c, the appropriate aldehyde and malononitrile under similar conditions described above.

2-(4-Chlorophenyl)-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile 5a. Mp 205 °C (benzene), yield 84%, IR (KBr) νmax 2185 (C≡N), 2199 (C≡N) cm⁻¹. 1H NMR (CDCl3) δ 1.4 (t, J = 7Hz, 3H), 2.8 (m, 2H), 3.5 (m, 1H), 3.8 (m, 1H), 3.9 (s, 3H, OCH3), 4.0 (s, 3H, OCH3), 4.4 (q, J = 7Hz, 2H), 4.5 (s, 1H, pyridine-4H), 6.7 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 4H), 7.8 (s, 1H, isoquinoline-5H), 8.00 (s, 1H, N=CH) ppm. MS: m/z 476 (M++2), 475, 474 (M+), 417, 402, 335, 307, 291, 233, 167, 75. Anal. Calcd. For C25H21ClN3O3 (476.47) C, 69.59; H, 4.88; N, 11.80. Found C, 69.55; H, 4.74; N, 11.67%.

2-(1,3-Benzodioxol-5-yl)-4-ethoxymethyleneamino-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile 5b. Mp 182 °C (ethanol), yield 83%, IR (KBr) νmax 2185 (C≡N), 2197 (C≡N) cm⁻¹. 1H NMR (CDCl3) δ 1.4 (t, J = 7Hz, 3H), 2.8 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.8 (m, 1H,
isoquinoline-3H), 3.9 (s, 3H, OCH3), 4.0 (s, 3H, OCH3), 4.2 (s, 1H, pyridine-4H), 4.4 (q, J = 7Hz, 2H), 6.0 (s, 2H, OCH2O), 6.7 (s, 1H, isoquinoline-8H), 6.9-7.4 (m, 3H), 7.8 (s, 1H, isoquinoline-5H), 8.02 (s, 1H, N=CH) ppm. 13C NMR (CDCl3)

δ (ppm) 14.8 (t, J = 7Hz, 3H), 2.8 (m, 2H, isoquinoline-4H), 3.7 (s, 1H, NH), 3.9 (s, 3H, OCH3), 4.4 (s, 1H, pyridine-4H), 4.77 (s, 2H, NH2), 5.87 (s, 1H, isoquinoline-8H), 6.8-7.0 (m, 3H), 7.7 (s, 1H, isoquinoline-5H), 8.6 (s, 1H, pyrimidine-2H) ppm.

2.3 Synthesis of Compounds 6a-c

Hydrazine hydrate (10 mL) was added to a suspension of 5a-c (10 mmol) in ethanol (40 mL). The reaction mixture was stirred at room temperature for 4 h. The precipitate which formed was filtered off, washed with water, dried in air and crystallized from the indicated solvent to give product 6a-c.

4-Amino-2-(chlorophenyl)-11,12-dimethoxy-3-imino-3,4,8,9-tetrahydro-2(H)-pyrimido[5′,4′:5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile derivatives 7a

δ (ppm) 15.9 (s, 3H, OCH3), 3.9 (s, 3H, OCH3), 4.0 (s, 3H, OCH3), 4.4 (q, J = 7Hz, 2H), 4.5 (s, 1H, pyridine-4H), 4.8 (s, 2H, NH2), 5.90 (s, 1H, isoquinoline-8H), 6.7-7.4 (m, 4H), 7.8 (s, 1H, isoquinoline-5H), 8.64 (s, 1H, pyrimidine-2H) ppm.

13C NMR (DMSO-d6) δ 28.47, 45.03, 55.98, 56.01, 78.81, 97.82, 101.97, 108.38, 110.41, 110.94, 111.31, 120.03, 120.18, 121.03, 121.21, 131.66, 140.96, 145.42, 145.87, 146.43, 149.92, 150.08, 152.40, 154.74, 158.68. MS: m/z 472 (M+2), 471, 470 (M+), 454, 438, 349, 334, 318, 260, 204, 165, 121, 91, 65. Anal. Caled. For C27H24N4O5 (486.50) C, 62.89; H, 4.98; N, 17.54%.

2.4 Synthesis of 2-aryl-13,14-dimethoxy-11,12-dihydro-2(H)-1,2,4-triazolo[3′,2′:6′,1′]pyrimido[5′,4′:5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile derivatives 7a

A mixture of 4-amino-2-(4-chlorophenyl)-11,12-dimethoxy-3-imino-3,4,8,9-tetrahydro-2(H)-pyrimido[5′,4′:5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile 6a (5 mmol) with triethyl orthoformate (15 mL) or formic acid (15 mL) was refluxed for 4 h. After cooling, the precipitated product was collected by filtration and crystallized from dimethylformamide to give product 7a.

δ (ppm) 13.8 (t, J = 7Hz, 3H), 2.8 (m, 2H, isoquinoline-4H), 3.7 (s, 1H, NH), 3.9 (s, 3H, OCH3), 4.4 (s, 1H, pyridine-4H), 4.75 (s, 2H, NH2), 5.68 (s, 1H, NH), 6.7 (s, 1H, isoquinoline-8H), 6.6-7.0 (m, 4H), 7.7 (s, 1H, isoquinoline-5H), 8.64 (s, 1H, pyrimidine-2H) ppm.

13C NMR (CDCl3) δ 28.47, 45.03, 55.98, 56.01, 78.81, 97.82, 101.97, 108.38, 110.41, 110.94, 111.31, 120.03, 120.18, 121.03, 121.21, 131.66, 140.96, 145.42, 145.87, 146.43, 149.92, 150.08, 152.40, 154.74, 158.68. MS: m/z 472 (M+2), 471, 470 (M+), 454, 438, 349, 334, 318, 260, 204, 165, 121, 91, 65. Anal. Caled. For C27H24N4O5 (486.50) C, 62.89; H, 4.98; N, 17.54%.
55.36, 55.51, 78.91, 98.34, 110.82, 112.01, 120.02, 120.61, 122.60, 128.29, 130.21, 131.62, 134.10, 145.62, 146.10, 146.71, 146.32, 149.52, 150.82, 151.72, 160.10. MS: m/z 472 (M+2), 471, 470 (M+), 359, 285, 235, 179, 111, 75. Anal. Calcd. For C_{26}H_{22}CIN_{10}O_{2} (470.91) C, 63.75; H, 4.20; N, 17.85. Found C, 63.65; H, 3.91; N, 17.60%.

2.5 Synthesis of compounds 6a-c

A solution of each 6a-c (5 mmol) in acetic anhydride (20 mL) was refluxed for 3 h. The reaction mixture was cooled and the solid that separated was collected and crystallized from dimethylformamide to give 8a-c.

2-(4-Chlorophenyl)-13,14-dimethoxy-4-phenyl-10,11-dihydro-2(H)-1,2,4-triazolo[3",2":6,1"]pyrimido[5",4":5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile 8a. mp 250 °C, yield 74%, IR (KBr) ν_{max} 2182 (C≡N) cm^{-1}.^1H NMR (CDCl₃) δ 2.45 (s, 3H, CH₃), 2.9 (m, 2H, isoquinoline-4H), 3.9 (m, 1H, isoquinoline-3H), 4.0 (s, 3H, OCH₃), 4.1 (s, 3H, OCH₃), 4.4 (m, 1H, isoquinoline-3H), 5.4 (s, 1H, pyridine-4H), 6.7 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 4H), 7.8 (s, 1H, isoquinoline-5H), 8.99 (s, 1H, pyrimidine-2H) ppm. ^13C NMR (DMSO-d₆) δ 14.26, 28.41, 43.25, 55.49, 55.81, 57.63, 78.63, 79.31, 111.03, 116.12, 119.17, 120.18, 123.10, 130.36, 131.71, 133.49, 137.90, 144.93, 145.46, 146.32, 146.40, 152.00, 152.54, 156.21, 166.10. MS: m/z 482 (M+2), 481, 480 (M+), 440, 373, 357, 299, 240, 224, 121, 77. Anal. Calcd. For C_{26}H_{21}ClN_{10}O_{2} (480.51) C, 67.49; H, 5.03; N, 17.49. Found C, 67.23; H, 4.90; N, 16.99%.

2.6 Synthesis of Compounds 9a-c

To a solution of each 6a-c (5 mmol) in pyridine (10 mL) benzyl chloride (0.7 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 h, then cooled and poured into cold hydrochloric acid (10 mL, 10%) with stirring. The solid that precipitated was collected, washed with cold water and finally crystallized from dimethylformamide to give 9a-c.

2-(4-Chlorophenyl)-13,14-dimethoxy-4-phenyl-10,11-dihydro-2(H)-1,2,4-triazolo[3",2":6,1"]pyrimido[5",4":5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile 9a. mp 320 °C, yield 68%, IR (KBr) ν_{max} 2180 (C≡N) cm^{-1}.^1H NMR (CDCl₃) δ 2.94 (m, 2H, isoquinoline-4H), 3.93 (m, 1H, isoquinoline-3H), 4.05 (s, 3H, OCH₃), 4.16 (s, 3H, OCH₃), 4.41 (m, 1H, isoquinoline-3H), 5.43 (s, 1H, pyridine-4H), 6.76 (s, 1H, isoquinoline-8H), 7.2-7.94 (m, 9H, ArH), 8.09 (s, 1H, pyrimidine-2H) ppm. ^13C NMR (DMSO-d₆) δ 28.32, 44.92, 55.58, 55.81, 78.69, 97.41, 111.34, 118.93, 120.83, 123.10, 127.33, 127.79, 128.69, 129.21, 131.79, 132.21, 132.63, 138.71, 139.28, 143.92, 145.13, 145.72, 145.90, 147.00, 151.45, 153.41, 164.92. MS: m/z 548 (M+2), 547, 546 (M+), 472, 469, 407, 361, 244, 111, 75. Anal. Calcd. For C_{26}H_{22}ClN_{10}O_{2} (547.00) C, 68.06; H, 4.24; N, 15.36. Found C, 67.90; H, 4.13; N, 15.23%.
To a hot solution of 6a (2.30 g, 5 mmol) in ethanol (30 mL), diethyloxalate (0.73 g, 5 mmol) was added. The reaction mixture was refluxed for 3 h, then cooled and the product that separated was collected and crystallized from acetic acid to give product 10. mp 250 °C, yield 74%, IR (KBr) νmax 1647 (CO), 2182 (C≡N) cm⁻¹. ¹H NMR (CDCl₃) δ 1.4 (t, J = 7 Hz, 3H), 2.23 (s, 3H, CH₃), 2.98 (m, 2H, isoquinoline-4H), 3.78 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.98 (m, 2H, isoquinoline-4H), 4.31 (m, 1H, pyridine-4H), 6.42 (s, 1H, isoquinoline-5H), 9.49 (s, 1H, pyridine-2H) ppm. ¹³C NMR (CDCl₃) δ 28.24, 45.87, 55.71, 55.84, 78.89, 97.93, 101.52, 108.93, 109.90, 111.23, 119.62, 120.89, 122.32, 123.00, 126.83, 129.09, 131.67, 132.01, 139.74, 143.00, 145.32, 146.00, 147.14, 147.22, 150.96, 153.43, 153.92, 157.61, 168.21. MS: m/z 558, 557, 556, 530, 469, 435, 419, 361, 278, 204, 121, 65. Anal. Calcd. For C₁₂H₁₀N₂O₄ (558.57) C, 61.93; H, 4.27; N, 15.48. Found C, 61.05; H, 3.81; N, 14.88%. 

13,14-Dimethoxy-2-(4-methoxyphenyl)-4-phenyl-10,11-dihydro-2(H)-1,2,4-triazolo[3,2‴:6″,1″]pyrimido[5′:4′:5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile 9e. mp 310 °C, yield 79%, IR (KBr) νmax 2190 (C≡N) cm⁻¹. ¹H NMR (CDCl₃) δ 2.91 (m, 2H, isoquinoline-4H), 3.78 (s, 3H, OCH₃), 4.12 (s, 3H, OCH₃), 4.30 (m, 1H, isoquinoline-3H), 5.44 (s, 1H, pyridine-4H), 6.75 (s, 1H, isoquinoline-8H), 7.18-7.90 (m, 9H), 7.75 (s, 1H, isoquinoline-3H), 8.54 (s, 1H, pyrimidine-2H) ppm. ¹³C NMR (CDCl₃) δ 28.42, 44.60, 55.36, 55.74, 57.58, 78.53, 79.26, 110.67, 115.98, 118.78, 121.02, 122.98, 127.31, 128.71, 129.10, 130.46, 131.80, 132.21, 133.48, 137.60, 145.24, 145.32, 146.21, 146.43, 152.26, 156.64, 156.37, 165.93. MS: m/z 543, 542, 456, 435, 419, 349, 333, 271, 206, 121, 77. Anal. Calcd. For C₃₂H₂₆N₆O₃ (542.58) C, 70.82; H, 4.83; N, 15.50. Found C, 70.78; H, 4.71; N, 15.33%. 


To a solution of 6a (2.30 g, 5 mmol) in an aqueous solution of potassium hydroxide (10 mL, 10%) was refluxed 2 h. The reaction mixture was cooled, poured onto hydrochloric acid (100, 1N). The crude product was collected and crystallized from dimethylformamide to give a product identical in all respects (mp, mmp, and spectral data) with 7a.
2-(4-Chlorophenyl)-14,15-dimethoxy-2(H)-5-phenyl-4-phenylazo-11,12-dihydro-6(H)-1,2,4-triazolo[3′,2′:6,1′][3,2′:5,6]pyrimido[5′,4′:5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile \(16\). This compound was prepared using the same method described for the synthesis of \(14\) using hydrazonoyl chloride \(15\) in place of \(13\). The compound prepared was crystallized from dimethylformamide, mp 190 °C, yield 84%, IR: (KBr) \(v_{\text{max}}\) 1639 (C=O), 1700 (C=O), 3210 (NH), 3310 (NH) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.3 (s, 2H, NH\(_2\)), 4.4 (s, 1H, -CH\(_3\)), 6.8-7.4 (m, Ar-H) in addition to the signals of the triazine moiety. The IR spectra showed two nitrile absorption bands at 2220 and 2242 cm\(^{-1}\) in addition to the bands of amino group at \(\nu\) 3210 (NH), 3310 (NH) cm\(^{-1}\). The mass spectrum of each compound showed a molecular ion peak with high intensity.

3. Results and Discussion

The precursors of the title compounds, namely 4-amino-9,10-dimethoxy-2-phenyl-6,7-dihydroisoquinoline-1-acetonitrile \(1\) were prepared by refluxing equimolar amounts of isoquinoline-1-acetonitrile, aryl aldehyde and malononitrile in ethanol in the presence of piperidine. The pathway for formation of 4a-c was shown in scheme 1. The reaction started with Michael addition to give 3 which upon cyclization led to the formation of 4.

Reaction of 4a-c each with triethyl orthoformate in acetic anhydride at reflux afforded the ethoxymethyleneamino derivatives 5a-c in almost quantitative yields (Scheme 2). The structures of the resulting products were confirmed by their elemental analyses, spectral data and their chemical reactions described below. Thus, the IR spectra revealed the absence of the bands of the amino group and the \(^1\)H NMR spectra of all products revealed characteristic signals for ethoxy group at \(\delta\ 1.4\ (t, J = 7.1\ Hz, 3H)\) and at \(\delta\ 4.42\ (q, J = 7.1\ Hz, 2H)\) as well as a singlet signal at \(\delta\ 8.0\) assignable to a proton of CHOEt group. The mass spectrum of each compound exhibited a molecular ion peak with high intensity.

Treatment of 5a-c with hydrazine hydrate in ethanol at ambient temperature gave the corresponding 4-amino-3-imino-2-aryl-3, 4, 8, 9 -tetrahydro-2(H)-pyrimido [5′,4′:5,6] pyrido [2,1-a] isoquinoline-1-carbonitrile derivatives 6a-c. The structures proposed for these products were established from their correct elemental analyses and spectroscopic data. Their IR revealed the absence of nitrile absorption frequencies. The \(^1\)H NMR spectra for 6a-c showed signals near \(\delta\ 8.64-8.66\) ppm corresponding to the pyrimidine protons, near \(\delta\ 5.86-5.90\) ppm assignable to NH protons and near \(\delta\ 4.75-4.80\) ppm assignable to NH\(_2\) protons. The \(^13\)C NMR spectra of 6 were also compatible with the proposed structure. Further confirmation of the structures of 6a-c was achieved from their reactions with triethylorthoformate, acetic anhydride and benzoyl chloride. Thus, refluxing compound 6a in an excess of triethylorthoformate gave product 7a, which was identified on the basis of correct elemental analyses and spectroscopic data as 2-(4-chlorophenyl)-13,14-dimethoxy-10,11-dihydro-2(H)-1,2,4-triazolo [3′,2′:6,1′][3,2′:5,6]pyrimido[5′,4′:5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile (Scheme 2). The IR spectrum of 7a doesn't display absorption bands for the NH and NH\(_2\) groups, which were observed in compound 6a. The \(^1\)H NMR spectrum showed two characteristic signals at \(\delta\ 8.32\) and 9.13 ppm assignable to the pyrimidine and the triazole protons respectively. In addition, when 6a-c were refluxed with acetic anhydride or benzoyl chloride in pyridine, it afforded the corresponding 4-methyl and 4-phenyl derivatives 8a-c and 9a-c, respectively (Scheme 2). The structures of 8 and 9 were established on both elemental analyses and spectroscopic data. \(^1\)H NMR
spectra of 8 and 9 showed the absence of the signal of the triazole ring proton at δ 9.13 ppm, instead, it displayed a singlet signal near δ 2.45-2.48 ppm assignable to methyl group in compound 8. Compound 6a was refluxed in diethyloxalate and gave a single product 10. Both mass spectrum and elemental analyses were consistent with the formula C_{28}H_{23}ClN_{6}O_{4}. Two possible structures namely 10 and 11 can be written for the isolated product formula. The former was assigned to be the isolated product since it gave compound 7a via hydrolysis and decarboxylation of the resulting acid 12 (Scheme 3). The structures of the product 10 and the corresponding acid 12 were confirmed by their correct elemental analyses and compatible spectroscopic data (Experimental).

The reaction of 6a with C-acylhydrazonoyl halides 13a,b in refluxing chloroform in the presence of triethylamine afforded, in each case, a single product as evidenced by TLC analysis (Scheme 4). The results of elemental analyses and the mass spectra of the products were consistent with 14A and its isomeric structure 14B. The product was assigned structure 14B since the hydrazone structure 14A was excluded depending on their electronic spectra as they revealed a characteristic absorption maxima at λmax 361 (log ε 4.43) and λ 400 (log ε 4.40) assignable to arylazo chromophore (Burawoy et al., 1952; Yao, 1964; Yao & Resnick, 1962). The correct structure 14B was further evidenced by spectroscopic data. The IR spectra of 14Ba and 14Bb exhibited an NH absorption band near ν 3268 cm⁻¹ and the ¹H NMR spectra showed that the corresponding singlet signal to NH proton at δ 9.03 ppm disappeared upon shaking the solution of 14Ba with deuterium oxide. Under similar reaction conditions N-phenyl-C-ethoxycarbonylmethanohydrazonoyl chloride 15 reacted with 6a and gave compound 16. The IR spectrum of 16 showed three absorption bands at ν 1639, 3210 and 3310 cm⁻¹ assignable to the amide carbonyl, hydrazone NH and NH of triazine groups, respectively.

Scheme 1. Synthesis of pyrido[2,1-a]isoquinoline derivatives 4a-c
Scheme 2. Synthesis of triazolopyrimidopyridoisoquinoline-1-carbonitrile 7, 8 and 9

5, 7, 8, 9: Ar, a = 4-ClC₆H₄, b = 3, 4(6-O-CH₃-O)C₆H₃, c = 4-OCH₃C₆H₄

Scheme 2. Synthesis of triazolopyrimidopyridoisoquinoline-1-carbonitrile 7, 8 and 9
Scheme 3. Synthesis of ethyl triazolopyrimidopyridoisoquinoline-4-carboxylate 10
Scheme 4. Synthesis of 4-phenylazo-triazinolopyridopyridoisoquinoline-1-carbonitrile 14 and 4-phenylhydrazono-triazinolopyridopyridoisoquinoline-1-carbonitrile 16

References


