

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, triazolopyrimidopyridoiso-quinoline, triazinolopyrimidopyridoiso-quinoline

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 α_2 -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 A_{2a} 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 (Elnagdi 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 (^{13}C NMR) using CDCl_3 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 LabmateTM microwave apparatus (300 W with ChemDriverTM Software). Elemental analyses were carried out at the Micro analytical Center of Cairo University. 6,7-dimethoxy-3,4-dihydroisoquinoline-1-acetonitrile **1** (Osbond, 1951) and the hydrazonoyl halides **13a** (Eweiss & Osman, 1980), **13b** (Shawali & Abdelhamid, 1976) and **15** (Shawali et al. 1975) were prepared as previously described.

2.1 Synthesis of Compounds 4a-c

To a solution of arylidenemalononitrile (5 mmol) and 6,7-dimethoxy-3,4-dihydroisoquinolin-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) ν_{max} 2152 ($\text{C}\equiv\text{N}$), 2186 ($\text{C}\equiv\text{N}$), 3354, 3471 (NH_2) cm^{-1} . ^1H NMR (CDCl_3) δ 2.8 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.9 (s, 6H, two OCH_3), 4.0 (m, 1H, isoquinoline-3H), 4.3 (s, 2H, NH_2), 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 ($\text{M}^+ + 2$), 419, 418 (M^+), 351, 321, 307, 263, 176, 140, 75. Anal. Calcd. For $\text{C}_{23}\text{H}_{19}\text{ClN}_4\text{O}_2$ (418.87) C, 65.94; H, 4.57; N, 13.37. Found C, 65.62; H, 4.48; N, 13.10%

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) ν_{max} 2179 ($\text{C}\equiv\text{N}$), 2185 ($\text{C}\equiv\text{N}$), 3232, 3364 (NH_2) cm^{-1} . ^1H NMR (CDCl_3) δ 2.9 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 4.0 (m, 1H, isoquinoline-3H), 4.2 (s, 2H, NH_2), 4.3 (s, 1H, pyridine-4H), 6.0 (s, 2H, OCH_2O), 6.7 (s, 1H, isoquinoline-8H), 6.8-7.3 (m, 3H), 7.7 (s, 1H, isoquinoline-5H) ppm. MS: m/z 429 ($\text{M}^+ + 1$), 428 (M^+), 427, 426, 381, 361, 307, 291, 268, 63. Anal. Calcd. For $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_4$ (428.14) C, 67.28; H, 4.71; N, 13.08. Found C, 67.09; H, 4.61; N, 13.00%.

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) ν_{max} 2187 ($\text{C}\equiv\text{N}$), 2197 ($\text{C}\equiv\text{N}$), 3354, 3471 (NH_2) cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$) δ 2.8 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 4.0 (m, 1H, isoquinoline-3H), 4.3 (s, 2H, NH_2), 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. ^{13}C NMR ($\text{DMSO}-d_6$) δ 29.84, 44.13, 56.88, 57.55, 60.17, 86.17, 112.58, 115.99, 116.09, 120.55, 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 414 (M^+), 348, 317, 289, 275, 238, 169, 139, 75. Anal. Calcd. For $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_3$ (414.45) 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**.

2-(4-Chlorophenyl)-9,10-dimethoxy-4-ethoxymethyleneamino-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile **5a**. mp 205 °C (benzene), yield 84%, IR (KBr) ν_{max} 2185 ($\text{C}\equiv\text{N}$), 2199 ($\text{C}\equiv\text{N}$) cm^{-1} . ^1H NMR (CDCl_3) δ 1.4 (t, $J = 7\text{Hz}$, 3H), 2.8 (m, 2H), 3.5 (m, 1H), 3.8 (m, 1H), 3.9 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 4.4 (q, $J = 7\text{Hz}$, 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, $\text{N}=\text{CH}$) ppm. MS: m/z 476 ($\text{M}^+ + 2$), 475, 474 (M^+), 417, 402, 335, 307, 291, 233, 167, 75. Anal. Calcd. For $\text{C}_{26}\text{H}_{23}\text{ClN}_4\text{O}_3$ (474.93) C, 65.74; H, 4.88; N, 11.80. Found, C, 65.55; 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) ν_{max} 2185 ($\text{C}\equiv\text{N}$), 2197 ($\text{C}\equiv\text{N}$) cm^{-1} . ^1H NMR (CDCl_3) δ 1.4 (t, $J = 7\text{Hz}$, 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. MS: m/z 486 (M⁺+2), 484 (M⁺), 445, 412, 335, 307, 290, 247, 178, 126. Anal. Calcd. For C₂₇H₂₄N₄O₅ (484.50) C, 65.74; H, 4.88; N, 11.80. Found, C, 65.55; H, 4.74; N, 11.67%.

2-(4-Methoxyphenyl)-4-ethoxymethyleneamino-9,10-dimethoxy-6,7-dihydro-2(H)-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile **5c**. mp 175 °C (ethanol), yield 83%, IR (KBr) $\nu_{\max}$ 2191 (C≡N), 2200 (C≡N) cm⁻¹. ¹H NMR (DMSO-d₆) δ 1.4 (t, J = 7Hz, 3H), 2.8 (m, 2H, isoquinoline-4H), 3.5 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH₃), 3.8 (m, 1H, isoquinoline-3H), 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), 6.9-7.3 (m, 4H), 7.8 (s, 1H, isoquinoline-5H), 8.0 (s, 1H, N=CH) ppm. ¹³C NMR (DMSO-d₆) δ 15.73, 30.04, 44.04, 56.90, 57.46, 57.55, 65.63, 73.79, 83.61, 112.81, 115.72, 116.07, 120.64, 121.58, 122.97, 130.07, 130.49, 133.51, 137.86, 146.45, 148.45, 152.73, 155.01, 160.67, 162.51 ppm. MS: m/z 470 (M⁺), 412, 398, 367, 335, 305, 291, 233, 167, 75. Anal. Calcd. For C₂₇H₂₆N₄O₄ (470.52) C, 68.92; H, 5.57; N, 11.91. Found C, 68.82; H, 5.45; N, 11.76%

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 **6a**. mp 180 °C (acetic acid), yield 92%, IR (KBr) $\nu_{\max}$ 2200 (C≡N), 3160 (NH), 3301, 3321 (NH₂) cm⁻¹. ¹H NMR (CDCl₃) δ 2.8 (m, 2H, isoquinoline-4H), 3.7 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH₃), 3.9 (s, 3H, OCH₃), 4.5 (m, 1H, isoquinoline-3H), 4.6 (s, 1H, pyridine-4H), 4.8 (s, 2H, NH₂), 5.90 (s, 1H, NH), 6.7 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 4H, ArH's), 7.7 (s, 1H, isoquinoline-5H), 8.66 (s, 1H, pyrimidine-2H) ppm. ¹³C NMR (CDCl₃) δ 28.48, 45.21, 55.35, 55.60, 78.89, 97.19, 110.93, 111.32, 119.93, 120.01, 122.00, 128.30, 130.19, 131.61, 133.01, 145.01, 145.38, 145.93, 146.50, 149.63, 150.02, 153.92. MS: m/z 462, 460, 445, 428, 339, 324, 308, 270, 182, 166, 140, 120, 91, 65. Anal. Calcd. For C₂₄H₂₁ClN₆O₂ (460.91) C, 62.53; H, 4.59; N, 18.23. Found C, 62.45; H, 4.46; N, 18.20%.

4-Amino-2-(1,3-benzodioxol-5-yl)-11,12-dimethoxy-3-imino-3,4,8,9-tetrahydro-2(H)-pyrimido[5',4':5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile **6b**. mp 221 °C (acetic acid), yield 94%, IR (KBr) $\nu_{\max}$ 2181 (C≡N), 3135 (NH), 3313, 3438 (NH₂) cm⁻¹. ¹H NMR (CDCl₃) δ 2.8 (m, 2H, isoquinoline-4H), 3.7 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH₃), 3.9 (s, 3H, OCH₃), 4.4 (m, 1H, isoquinoline-3H), 4.5 (s, 1H, pyridine-4H), 4.77 (s, 2H, NH₂), 5.87 (s, 1H, NH), 5.9 (s, 2H, OCH₂O), 6.7 (s, 1H, isoquinoline-8H), 6.8-7.0 (m, 3H, ArH's), 7.7 (s, 1H, isoquinoline-5H), 8.64 (s, 1H, pyrimidine-2H) ppm. ¹³C NMR (DMSO-d₆) δ 28.53, 44.78, 55.34, 56.08, 78.81, 97.20, 101.69, 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⁺), 455, 438, 349, 334, 318, 260, 204, 165, 121, 91, 65. Anal. Calcd. For C₂₅H₂₂N₆O₄ (470.48) C, 63.82; H, 4.71; N, 17.86. Found C, 63.55; H, 4.59; N, 17.75%.

4-Amino-11,12-dimethoxy-3-imino-2-(methoxyphenyl)-3,4,8,9-tetrahydro-2(H)-pyrimido[5',4':5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile **6c**. mp 175 °C (acetic acid), yield 95%, IR (KBr) $\nu_{\max}$ 2179 (C≡N), 3280 (NH), 3318, 3435 (NH₂) cm⁻¹. ¹H NMR (CDCl₃) δ 2.8 (m, 2H, isoquinoline-4H), 3.7 (m, 1H, isoquinoline-3H), 3.8 (s, 3H, OCH₃), 3.9 (s, 3H, OCH₃), 4.0 (s, 3H, OCH₃), 4.4 (m, 1H, isoquinoline-3H), 4.5 (s, 1H, pyridine-4H), 4.75 (s, 2H, NH₂), 5.86 (s, 1H, NH), 6.7 (s, 1H, isoquinoline-8H), 6.8-7.0 (m, 4H), 7.7 (s, 1H, isoquinoline-5H), 8.64 (s, 1H, pyrimidine-2H). ¹³C NMR (DMSO-d₆) δ 28.47, 45.03, 55.98, 56.01, 60.09, 78.81, 97.82, 110.97, 111.16, 116.13, 120.01, 120.12, 122.91, 129.38, 131.02, 131.71, 145.64, 146.00, 146.69, 149.73, 150.11, 153.60, 154.64. MS: m/z 458, 456, 441, 425, 333, 319, 303, 271, 233, 204, 165, 121, 91, 65. Anal. Calcd. For C₂₅H₂₄N₆O₃ (456.49) C, 65.77; H, 5.30; N, 18.41. Found C, 65.49; H, 5.19; N, 18.34%.

2.4 Synthesis of 2-aryl-13,14-dimethoxy-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 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**. mp 229 °C, yield 78%, IR (KBr) $\nu_{\max}$ 2179 (C≡N) cm⁻¹. ¹H NMR (CDCl₃) δ 3.0 (m, 2H, isoquinoline-4H), 3.9 (s, 3H, OCH₃), 4.0 (s, 3H, OCH₃), 4.1 (m, 1H, isoquinoline-3H), 4.5 (m, 1H, isoquinoline-3H), 5.5 (s, 1H, pyridine-4H), 6.8 (s, 1H, isoquinoline-8H), 7.2-7.5 (m, 4H), 7.9 (s, 1H, isoquinoline-5H), 8.32 (s, 1H, pyrimidine-2H), 9.13 (s, 1H, triazole-3H) ppm. ¹³C NMR (CDCl₃) δ 28.39, 45.63,

55.36, 55.51, 78.91, 98.34, 110.82, 11.21, 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 $C_{25}H_{19}ClN_6O_2$ (470.91) C, 63.75; H, 4.07; N, 17.85. Found C, 63.65; H, 3.91; N, 17.60%.

2.5 Synthesis of compounds 8a-c

A solution of each of **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-methyl-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 ($C\equiv N$) cm^{-1} . 1H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 2.9 (m, 2H, isoquinoline-4H), 3.9 (m, 1H, isoquinoline-3H), 4.0 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 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. ^{13}C NMR ($DMSO-d_6$) δ 14.30, 28.41, 45.40, 55.62, 55.71, 79.76, 97.30, 111.21, 119.70, 121.30, 122.00, 122.80, 132.00, 132.90, 139.00, 139.90, 144.11, 144.24, 145.62, 146.61, 147.15, 151.21, 152.30, 165.20. MS: m/z 486 ($M^+ + 2$), 485, 484 (M^+), 410, 373, 329, 245, 111, 75. Anal. Calcd. For $C_{26}H_{21}ClN_6O_2$ (484.93) C, 64.39; H, 4.36; N, 17.33. Found C, 64.22; H, 4.21; N, 17.20%.

2-(1,3-Benzodioxol-5-yl)-13,14-dimethoxy-4-methyl-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 **8b**. mp 221 °C, yield 73%, IR (KBr) ν_{max} 2184 ($C\equiv N$) cm^{-1} . 1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 2.88 (m, 2H, isoquinoline-4H), 3.9 (m, 1H, isoquinoline-3H), 4.0 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 4.34 (m, 1H, isoquinoline-3H), 5.44 (s, 1H, pyridine-4H), 5.91 (s, 2H, OCH_2O), 6.7 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 3H), 7.75 (s, 1H, isoquinoline-5H), 8.96 (s, 1H, pyrimidine-2H) ppm. ^{13}C NMR ($DMSO-d_6$) δ 14.31, 28.26, 46.21, 55.56, 55.74, 78.99, 98.61, 101.73, 107.92, 110.63, 110.92, 118.82, 120.92, 121.30, 122.31, 131.90, 138.90, 142.01, 145.21, 145.36, 146.34, 146.82, 151.62, 152.36, 154.30, 157.38, 164.90. MS: m/z 496 ($M^+ + 2$), 495, 494 (M^+), 468, 373, 357, 299, 219, 121, 65. Anal. Calcd. For $C_{27}H_{22}N_6O_4$ (494.50) C, 65.58; H, 4.48; N, 17.00. Found C, 65.33; H, 4.41; N, 17.01%.

13,14-Dimethoxy-2-(4-methoxyphenyl)-4-methyl-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 **8c**. mp 227 °C, yield 71%, IR (KBr) ν_{max} 2189 cm^{-1} . 1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 2.88 (m, 2H, isoquinoline-4H), 3.82 (m, 1H, isoquinoline-3H), 3.93 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 4.34 (m, 1H, isoquinoline-3H), 5.44 (s, 1H, pyridine-4H), 6.7 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 4H), 7.75 (s, 1H, isoquinoline-5H), 8.98 (s, 1H, pyrimidine-2H) ppm. ^{13}C NMR ($DMSO-d_6$) 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 $C_{27}H_{24}N_6O_3$ (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) benzoyl chloride (0.7 mL, 5 mmol) was added. The reaction mixture was refluxed for 4h, 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 ($C\equiv N$) cm^{-1} . 1H NMR ($CDCl_3$) δ 2.94 (m, 2H, isoquinoline-4H), 3.93 (m, 1H, isoquinoline-3H), 4.05 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 4.41 (m, 1H, isoquinoline-3H), 5.43 (s, 1H, pyridine-4H), 6.76 (s, 1H, isoquinoline-8H), 7.21-7.94 (m, 9H, Ar'H), 7.80 (s, 1H, isoquinoline-5H), 8.99 (s, 1H, pyrimidine-2H) ppm. ^{13}C NMR ($DMSO-d_6$) 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 $C_{31}H_{23}ClN_6O_2$ (547.00) C, 68.06; H, 4.24; N, 15.36. Found C, 67.90; H, 4.13; N, 15.23%.

2-(1,3-Benzodioxol-5-yl)-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 **9b**. mp 176 °C, yield 79%, IR (KBr) ν_{max} 2179 ($C\equiv N$) cm^{-1} . 1H NMR ($CDCl_3$) δ 2.90 (m, 2H, isoquinoline-4H), 3.93 (m, 1H, isoquinoline-3H), 4.02 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 4.33 (m, 1H, isoquinoline-3H), 5.44 (s, 1H, pyridine-4H), 5.93 (s, 2H, OCH_2O), 6.77 (s, 1H, isoquinoline-8H), 7.2-7.4 (m, 8H, Ar'H), 7.77 (s, 1H, isoquinoline-5H), 8.92 (s, 1H, pyrimidine-2H) ppm. ^{13}C

NMR (DMSO- d_6) 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, 127.26, 128.63, 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 $C_{32}H_{24}N_6O_4$ (556.57) C, 69.05; H, 4.31; N, 15.10. Found C, 68.90; H, 4.32; N, 15.01%.

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 **9c**. mp 310 °C, yield 79%, IR (KBr) $\nu_{\max}$ 2190 (C $\equiv$ N) cm^{-1} . ^1H NMR (CDCl_3) δ 2.91 (m, 2H, isoquinoline-4H), 3.83 (m, 1H, isoquinoline-3H), 3.90 (s, 3H, OCH $_3$), 4.03 (s, 3H, OCH $_3$), 4.12 (s, 3H, OCH $_3$), 4.32 (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-5H), 8.91 (s, 1H, pyrimidine-2H) ppm. ^{13}C NMR (DMSO- d_6) 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, 152.64, 156.37, 165.93. MS: m/z 543, 542, 456, 435, 419, 349, 333, 271, 206, 121, 77. Anal. Calcd. For $C_{32}H_{26}N_6O_3$ (542.58) C, 70.82; H, 4.83; N, 15.50. Found C, 70.78; H, 4.71; N, 15.33%.

2.7 Synthesis of ethyl 2-(chlorophenyl)-1-cyano-10,11-dihydro-13,14-dimethoxy-2(H)-1,2,4-triazolo[3",2":6',1']pyrimido[5',4':5,6]pyrido[2,1-a]isoquinoline-4-carboxylate **10**

To a solution of **6a** (2.30 g, 5 mmol) in ethanol (30 mL), diethylxalate (0.73 g, 5 mmol) was added. The reaction mixture was refluxed for 3h, 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) $\nu_{\max}$ 1647 (CO), 2182 (C $\equiv$ N) cm^{-1} . ^1H NMR (CDCl_3) δ 1.4 (t, J = 7 Hz, 3H), 3.0 (m, 2H, isoquinoline-4H), 3.9 (s, 6H, two OCH $_3$), 4.1 (m, 1H, isoquinoline-3H), 4.4 (m, 1H, isoquinoline-3H), 4.5 (q, J = 7 Hz, 2H), 5.6 (s, 1H, pyridine-4H), 6.8 (s, 1H, isoquinoline-8H), 7.2-7.5 (m, 4H), 7.9 (s, 1H, isoquinoline-5H), 9.18 (s, 1H, pyrimidine-2H) ppm. MS: m/z 544 (M^+ +2), 543, 542 (M^+), 513, 431, 403, 307, 263, 235, 113, 111, 75. Anal. Calcd. For $C_{28}H_{23}ClN_6O_4$ (542.97) C, 61.93; H, 4.27; N, 15.48. Found C, 61.05; H, 3.81; N, 14.88%.

2.8 Hydrolysis of Compound **10**

A suspension of **10** (2.7 g, 5 mmol) in an aqueous solution of potassium hydroxide (10 mL, 10%) was refluxed for 2 h. The reaction mixture was cooled, poured onto hydrochloric acid (100, 1N). The crude product was collected and crystallized from dimethylformamide to give compound **12**. mp 310 °C, yield 75%, IR (KBr) $\nu_{\max}$ 1730 (CO), 2182 (CN), 3430 (OH) cm^{-1} . ^1H NMR (CDCl_3) δ 3.0 (m, 2H), 3.91 (s, 6H, two OCH $_3$), 4.1 (m, 1H), 4.4 (m, 1H), 5.6 (s, 1H), 6.8 (s, 1H), 7.2-7.5 (m, 4H), 7.9 (s, 1H), 9.2 (s, 1H), 12.5 (s, 1H) ppm. Anal. Calcd. For $C_{28}H_{19}ClN_6O_4$ (514.11) C, 60.64; H, 3.72; N, 16.32. Found C, 60.35; H, 3.51; N, 16.08%.

2.9 Decarboxylation of **12**

Copper powder (0.2 g) was added to suspension solution of **12** (2.57 g, 5 mmol) in quinoline (15 mL). The solution mixture was stirred while being refluxed for 4 h and cooled. The reaction mixture was poured onto hydrochloric acid (50 mL, 1N). The solution was extracted with dichloromethane. The organic layer was washed and dried over anhydrous sodium sulfate, then filtered. The solvent was evaporated and the solid that separated was crystallized from dimethylformamide to give a product identical in all respects (mp, mmp, and spectral data) with **7a**.

2.10 Reaction of Compound **6a** with Hydrazonoyl Halides **13a,b**

To a hot solution of **6a** (2.30 g, 5 mmol) and the appropriate hydrazonoyl halides **13a** or **13b** (5 mmol) in chloroform (30 mL) was added triethylamine (0.7 mL, 5 mmol). The mixture was refluxed for 18 h. and the solvent was evaporated under reduced pressure. The crude product was collected and crystallized from dimethylformamide to give the products **14Ba** and **14Bb**, respectively.

2-(4-Chlorophenyl)-14,15-dimethoxy-2(H)-5-methyl-4-phenylazo-11,12-dihydro-6(H)-1,2,4-triazino[3",2":6',1']pyrimido[5',4':5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile **14Ba**. Mp 280 °C, yield 74%, IR (KBr) $\nu_{\max}$ 2191 (C $\equiv$ N), 3268 (NH) cm^{-1} . ^1H NMR (DMSO- d_6) δ 2.23 (s, 3H, CH $_3$), 2.98 (m, 2H, isoquinoline-4H), 3.78 (s, 3H, OCH $_3$), 3.85 (s, 3H, OCH $_3$), 3.98 (m, 1H, isoquinoline-3H), 4.21 (m, 1H, isoquinoline-3H), 5.24 (s, 1H, pyridine-4H), 6.77 (s, 1H, isoquinoline-8H), 7.14-7.70 (m, 9H, Ar'H), 7.80 (s, 1H, isoquinoline-5H), 8.54 (s, 1H, pyrimidine-2H), 9.03 (s, 1H, NH) ppm. ^{13}C NMR (DMSO- d_6) δ 21.31, 28.53, 44.90, 55.84, 55.93, 78.91, 98.61, 112.69, 118.71, 119.69, 122.91, 122.83, 127.63, 127.83, 128.34, 129.61, 132.41, 133.19, 137.63, 138.92, 141.22, 142.63, 144.37, 145.26, 145.82, 147.20, 152.01, 152.76, 153.17. MS: m/z 604, 603, 602, 400, 359, 298, 264, 235, 111, 77. Anal. Calcd. For $C_{33}H_{27}ClN_8O_2$ (603.07) C, 65.72; H, 4.51; N, 18.58. Found C, 65.35; H, 4.41; N, 18.20%.

2-(4-Chlorophenyl)-14,15-dimethoxy-2(H)-5-phenyl-4-phenylazo-11,12-dihydro-6(H)-1,2,4-triazino[3'',2'':6',1']pyrimido[5',4':5,6]pyrido[2,1-a]isoquinoline-1-carbonitrile **14Bb**. Mp 290 °C, yield 97%, IR (KBr) $\nu_{\max}$ 2191 (C≡N), 3267 (NH) cm^{-1} . ^1H NMR (DMSO- d_6) δ 3.01 (m, 2H, isoquinoline-4H), 3.86 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 4.00 (m, 1H, isoquinoline-3H), 4.26 (m, 1H, isoquinoline-3H), 5.30 (s, 1H, pyridine-4H), 6.79 (s, 1H, isoquinoline-8H), 7.16-7.72 (m, 14H, Ar'H), 7.80 (s, 1H, isoquinoline-5H), 8.54 (s, 1H, pyrimidine-2H), 9.03 (s, 1H, NH) ppm. ^{13}C NMR (DMSO- d_6) δ 28.61, 45.64, 55.73, 55.92, 78.82, 98.12, 112.72, 118.62, 120.73, 121.10, 123.40, 127.52, 127.68, 128.40, 128.63, 128.82, 129.21, 129.64, 132.32, 133.24, 135.23, 137.68, 139.22, 143.63, 144.62, 145.12, 145.25, 145.90, 146.83, 152.21, 153.60, 158.71. MS: m/z 666, 665, 664, 462, 416, 315, 264, 235, 111, 77. Anal. Calcd. For C₃₈H₂₉ClN₈O₂ (665.14) C, 68.61; H, 4.40; N, 16.85. Found C, 68.30; H, 4.20; N, 16.70%.

2.11 Synthesis of 2-(4-chlorophenyl)-14,15-dimethoxy-2(H)-4-phenylhydrazono-5(4H)-oxo-11,12-dihydro-6(H)-1,2,4-triazino[3'',2'':6',1']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 **13a,b**. the compound prepared was crystallized from dimethylformamide, mp 190 °C, yield 84%, IR: (KBr) $\nu_{\max}$ 1639 (C=O), 2190 (C≡N), 3210 (NH), 3310 (NH) cm^{-1} . ^1H NMR (CDCl₃) δ 2.78 (m, 2H), 3.86 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 4.02 (m, 1H), 4.40 (m, 1H), 5.23 (s, 1H, pyridine-4H), 6.61-8.30 (m, 14H, ArH's, two NH) ppm. Ms: m/z (%) 606, 605, 400, 315, 236, 235, 111, 77. Anal. Calcd. For C₃₂H₂₅ClN₈O₃ (605.04) C, 63.52; H, 4.16; N, 18.52. Found C, 63.32; H, 3.92; N, 17.94%.

3. Results and Discussion

The precursors of the title compounds, namely 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 6,7-dimethoxy-3,4-dihydroisoquinoline-1-acetonitrile **1** (Scheme 1). Thus, treatment of arylidenemalononitrile **2a-c** with **1** in boiling acetonitrile in the presence of piperidine afforded a single product in each case, as evidenced by TLC analysis. The ^1H NMR spectra of all compounds revealed signals near δ 4.3 (s, 2H, NH₂), 4.4 (s, 1H, -CHAr), 6.8-7.4 (m, Ar-H) in addition to the signals of the dihydroisoquinoline moiety. The IR spectra showed two nitrile absorption bands near ν 2152 and 2186 cm^{-1} in addition to the bands of amino group at ν 3354 and 3471 cm^{-1} . The mass spectrum of each compound **4a-c** gave molecular ion peak with high intensity.

Also, in one step the products **4a-c** 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 ^1H NMR spectra of all products revealed characteristic signals for ethoxy group at δ 1.4 (t, J = 7.1 Hz, 3H) and at δ 4.42 (q, J = 7.1 Hz, 2H) as well as a singlet signal at δ 8.0 assignable to a proton of CHOEt group. The mass spectrum of each compound exhibited a molecular ion peak with high intensity.

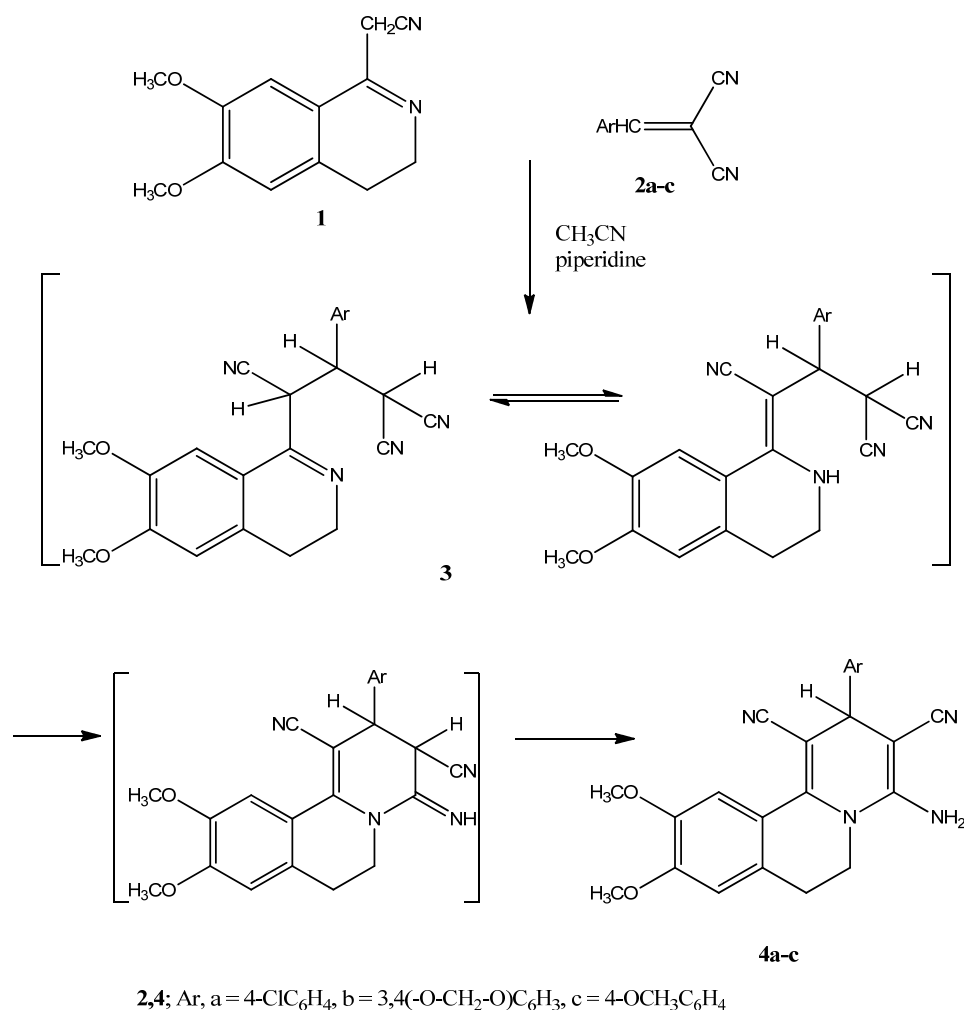
Treatment of **5a-c** with hydrazine hydrate in ethanol at ambient temperature gave the corresponding 4-amino-3-imino-2-aryl-3, 4, 8, 9 -tetrahydro-2(H)-pyrimido [5',4':5,6] pyrido [2,1-a] isoquinoline-1-carbonitrile derivatives **6a-c**. The structures proposed for these products were established from their correct elemental analyses and spectroscopic data. Their IR revealed the absence of nitrile absorption frequencies. The ^1H NMR spectra for **6a-c** showed signals near δ 8.64-8.66 ppm corresponding to the pyrimidine protons, near δ 5.86-5.90 ppm assignable to NH protons and near δ 4.75-4.80 ppm assignable to NH₂ 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']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 NH₂ groups, which were observed in compound **6a**. The ^1H NMR spectrum showed two characteristic signals at δ 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. ^1H 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**.

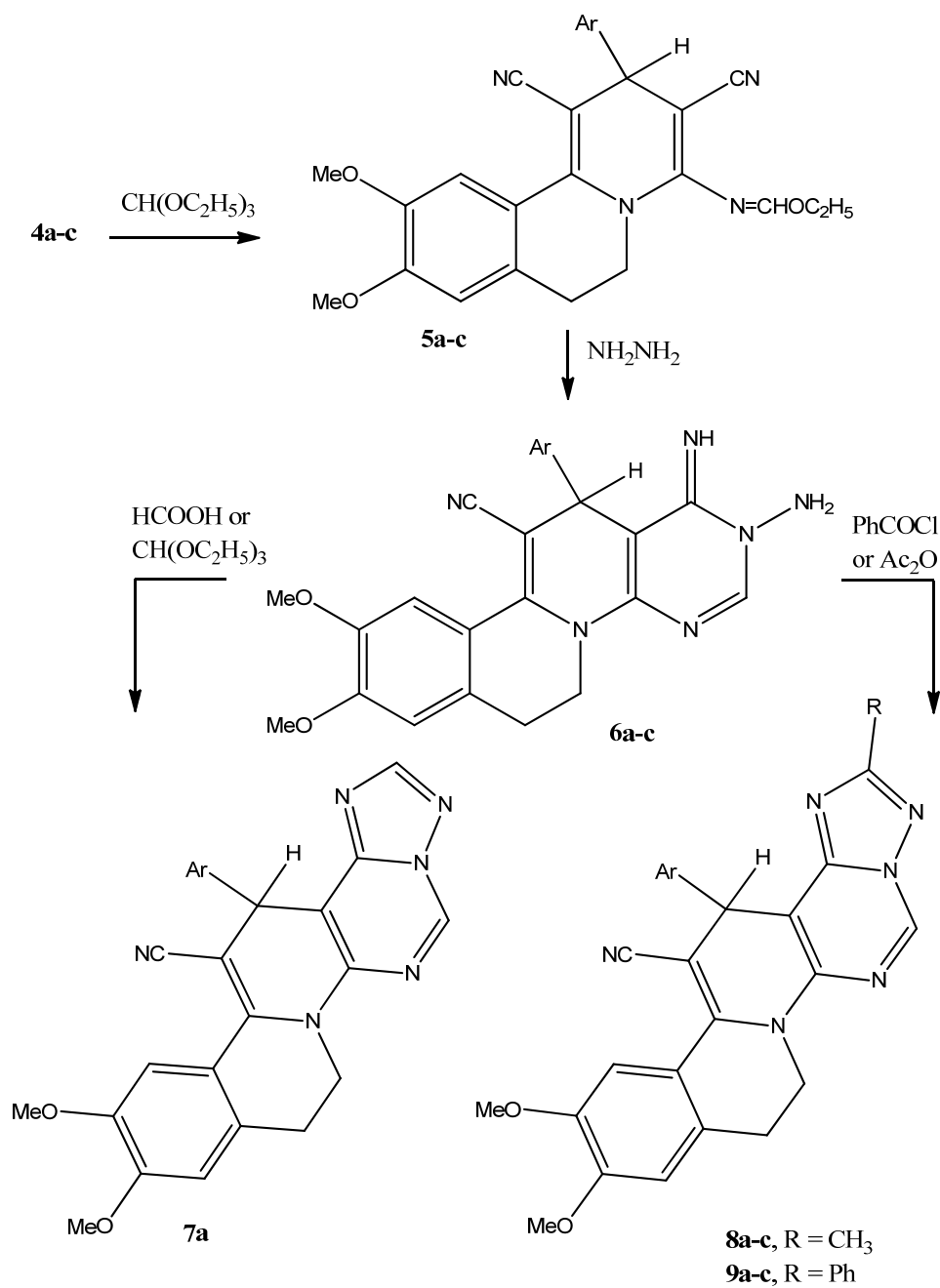
Compound **6a** was refluxed in diethyloxalate and gave a single product **10**. Both mass spectrum and elemental analyses were consistent with the formula $C_{28}H_{23}ClN_6O_4$. Two possible structures namely **10** and **11** can be written for the isolated product formula. The former was assigned 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 $\lambda_{\max}$ 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.

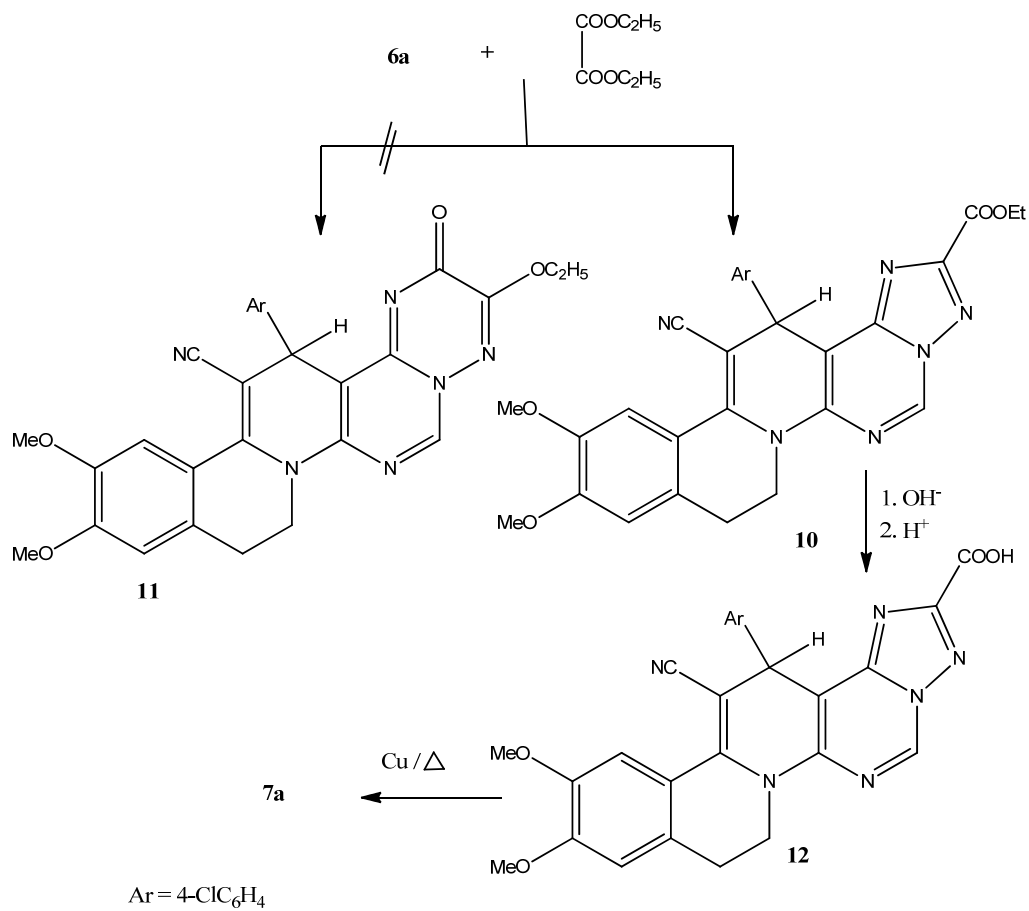


Scheme 1. Synthesis of pyrido[2,1-a]isoquinoline derivatives 4a-c

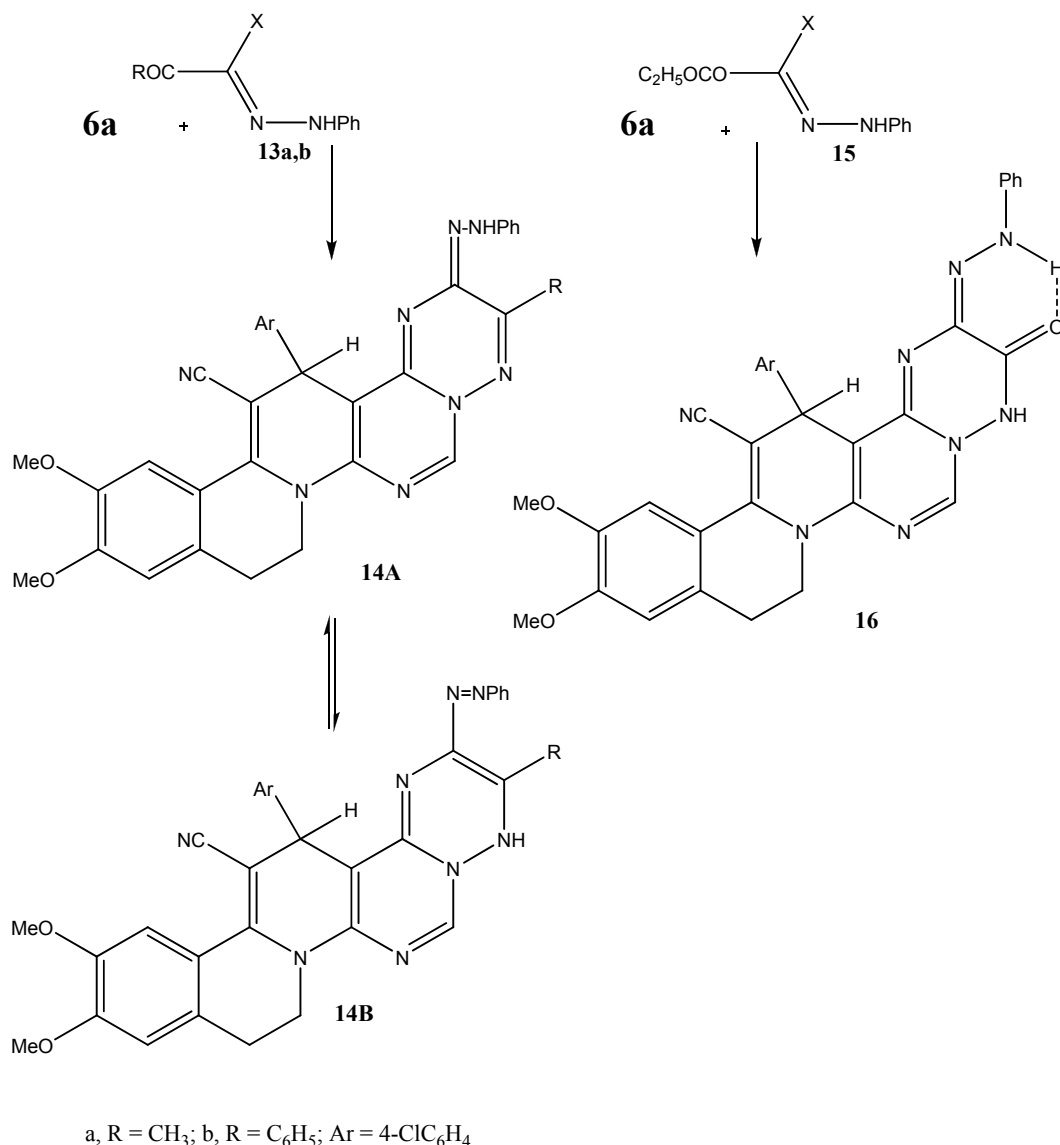


5,7,8,9; Ar, a = 4-ClC₆H₄, b = 3,4(-O-CH₂-O)C₆H₃, c = 4-OCH₃C₆H₄

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-triazinolopyrimidopyridoisoquinoline-1-carbonitrile 14 and 4-phenylhydrazono-triazinolopyrimidopyridoisoquinoline-1-carbonitrile 16

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