HETEROCYCLES, Vol. 85, No. 12, 2012, pp. 2933 - 2947. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 25th August, 2012, Accepted, 1st October, 2012, Published online, 10th October, 2012
DOI: 10.3987/COM-12-12572

SYNTHESIS AND REACTIVITY OF 2-CHLORO-3-FORMYLPYRIDO-[2,1-*a*]ISOQUINOLINE DERIVATIVE. A NOVEL ROUTES TO PYRAZOLO[3',4':4,5]PYRIDO[2,1-*a*]ISOQUINOLINE AND ISOQUINO-LINO[2,1-*g*][1,6]NAPHTHYRIDINES

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Abstract – Treatment of 2-hydroxy-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile **2** with $POCl_3$/DMF gave 2-chloro-3-formylpyrido[2,1-*a*]isoquinoline derivative **3**. Compound **3** reacted with hydrazines **5a-d** to give the condensation products **6a-d**. Cyclization of **6a** gave pyrazolo[3',4':4,5]pyrido[2,1-*a*]isoquinoline derivative **7**. Treatment of **3** with ethoxycarbonylmethylenetriphenylphosphorane **10** afforded (*E*)-ethyl 3-(2-chloro-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl)acrylate **11**. Azidation of **11** yielded the corresponding azido compound **12**. Reduction of **12** gave the corresponding amino compound **13** which upon cyclization gave the novel tetracyclic product **14**. Compound **12** reacted with triphenylphosphine to give phosphorane compound **15**, which reacted with phenyl isothiocyanate to give a novel isoquinolino[2,1-*g*][1,6]naphthyridine derivative **18**. Refluxing of **11** with amines **19a-c** and thiophenols **22a-d** in ethanol produced the corresponding substitution products **20a-c** and **23a-d**, respectively. Cyclization of **20a** afforded isoquinolino[2,1-*g*][1,6]naphthyridine derivative **21**.

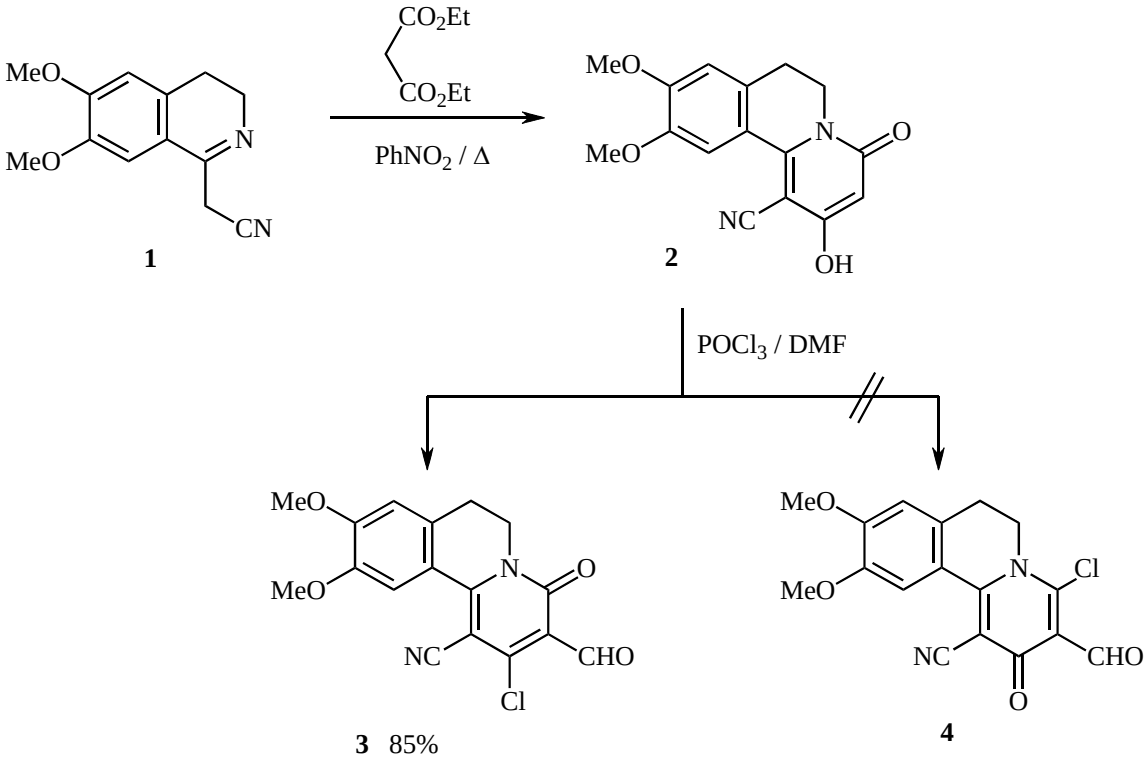
INTRODUCTION

Fused isoquinoline derivatives represent a very interesting class of compounds due to their significant biological and pharmaceutical activities.[1-4] Therefore, the synthesis of fused ring system incorporating isoquinoline moiety is an attractive goal for many authors.[5-17] Recently, we have been involved in the synthesis and chemistry of several fused isoqinoline derivatives.[18-29] In the present paper, we introduce a new and general route to pyrido[2,1-*a*]isoquinoline containing many reactive sites. The aim of this study,

on one hand is to prepare a novel tetracyclic compounds starting from readily obtainable materials in good yields and on the other hand, to prepare compounds that might have pharmacological activity.

RESULTS AND DISCUSSION

In the last decade our group has been interested in the synthesis of fused heterocyclic compounds incorporating isoquinoline moiety starting with 1-cyanomethylisoquinoline **1**.[24-29] In conjunction with this work we report here the synthesis of the starting 2-chloro-3-formyl-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile (**3**) (Scheme 1). Treatment of 1-cyanomethylisoquinoline **1** with diethyl malonate in nitrobenzene and refluxed for 30 min gave 2-hydroxy-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile (**2**) in 92% yield.[30] Treatment of **2** with the Vilsmeier-Haak reagent ($POCl_3$/DMF) at 60-70 °C for 5 h with stirring gave a single compound which analyzed correctly for $C_{17}H_{13}ClN_2O_4$. This was confirmed by ^{1}H NMR analysis of the crude reaction product in which only one singlet signal for formyl group was observed. Although the reaction of **2** with Vilsmeier-Haak reagent can lead to **3** and/or its isomer 4-chloro-3-formyl-9,10-dimethoxy-2-oxo-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile (**4**). The latter compound **4** was discarded on the basis of spectral analysis. The IR spectrum exhibited an absorption band at *v* 1657 cm^{-1} due to the amide group. In addition, single crystal X-ray analysis provided a good evidence for the formation of structure **3** (Figure 1) and ruled out the other possible structure **4** as outlined in Scheme 1.



Scheme 1

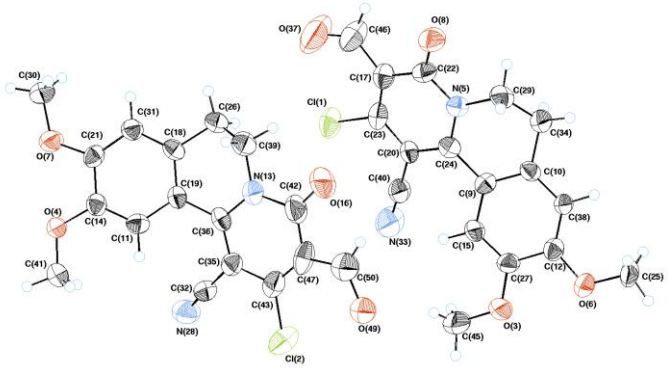
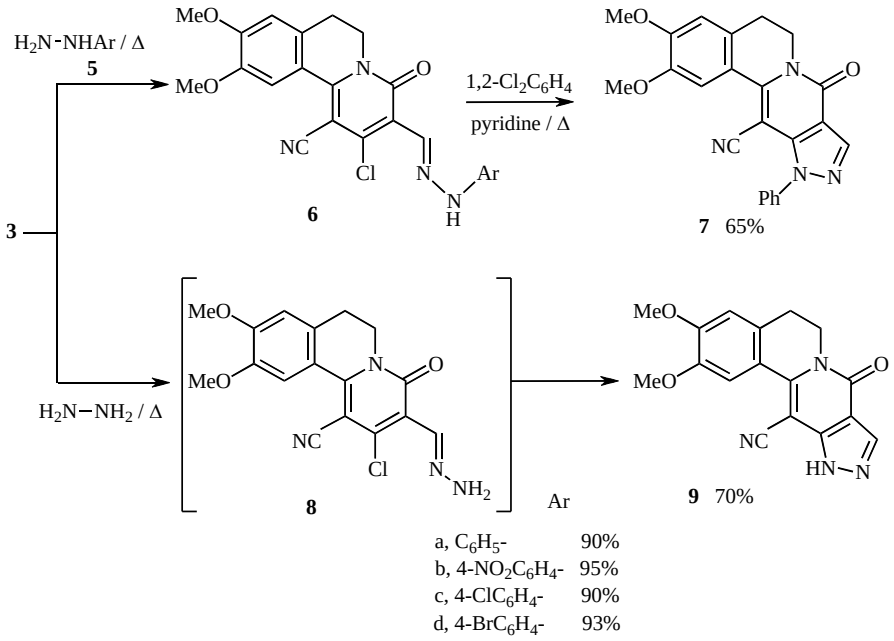


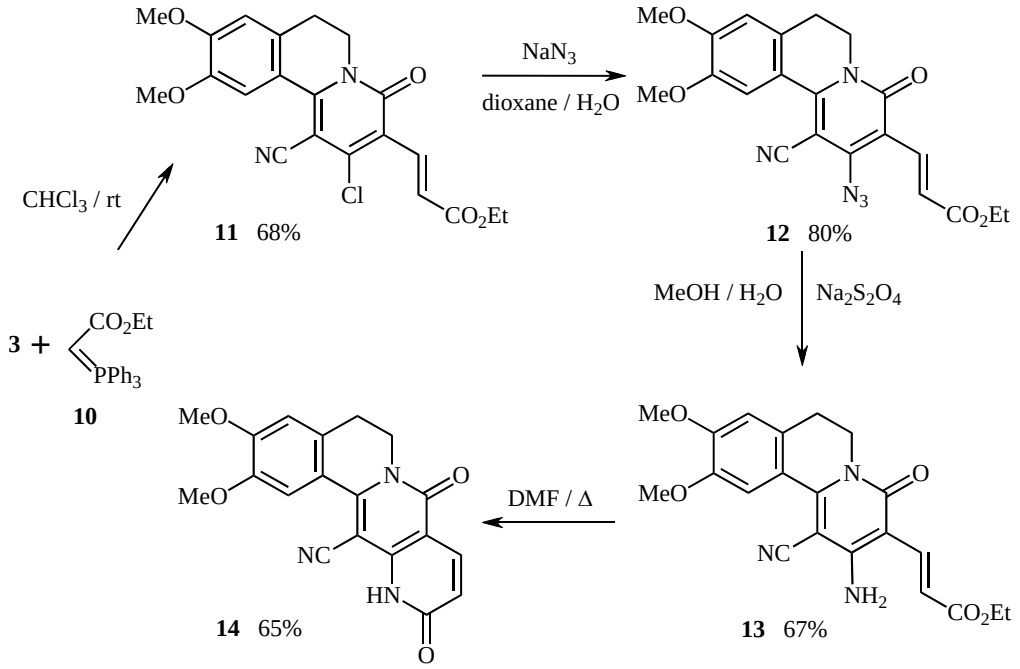
Figure 1. X-Ray single crystal of compound **3**

Refluxing of **3** with arylhydrazines **5a-d** in ethanol afforded the condensation products **6a-d** in excellent yields (90-95%) (Scheme 2). The structures of compounds **6a-d** were confirmed by elemental and spectral analyses. The IR spectra of compounds **6a-d** revealed the absence of C=O absorption of formyl group and showed an NH stretch at about ν 3228 cm^{-1}. Their mass spectra showed the molecular ion peaks. ^{1}H NMR spectra revealed the absence of the formyl group at δ 10.14 ppm. Refluxing **6a** in a mixture of 1,2-dichlorobenzene/pyridine for 20 h led directly to pyrazolo[3',4':4,5]pyrido[2,1-*a*]-isoquinoline **7** in 65% yield, *via* elimination of hydrogen chloride (Scheme 2). The structure of compound **7** was confirmed by elemental and spectral analyses. Mass spectrum showed a molecular ion peak at *m/z* 398 and its IR spectrum revealed the absence of NH band. The reaction of **3** with hydrazine hydrate under the same conditions afforded directly the fused pyrazole 2,3-dimethoxy-8-oxo-5,6,8,11-tetrahydro-pyrazolo[3',4':4,5]pyrido[2,1-*a*]isoquinoline-12-carbonitrile (**9**) which undoubtedly resulted *via* elimination of hydrogen chloride from the resulting condensation intermediate **8**. The structure of **9** was confirmed by both elemental and spectral analyses.



Scheme 2

Next, stirring of **3** with ethoxycarbonylmethylene triphenylphosphorane **10** in chloroform at room temperature gave (*E*)-ethyl 3-(2-chloro-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl)acrylate (**11**) (Scheme 3). The structure of **11** was based on its elemental and spectral analyses. The ^{1}H NMR spectrum showed two doublets at δ 7.88 and 7.38 ppm with coupling constant J = 16 Hz that indicated a *trans* configuration for the vinylic protons, also it showed two signals at δ 4.27 (q, 2H) and 1.31 (t, 3H) ppm for ethoxycarbonyl group in addition to signals of pyrido[2,1-*a*]isoquinoline moiety. Its mass spectrum showed the molecular ion peak at *m/z* 414 and its IR spectrum revealed two carbonyl bands at ν 1693 and 1651 cm^{-1} assignable to α,β-unsaturated ester and amide C=O groups, respectively. A further evidence for the assigned structure **11** is provided by its ^{13}C NMR spectrum which revealed two signals at δ 167 and 158 ppm assignable to C atoms of α,β-unsaturated ester and amide carbonyl groups.

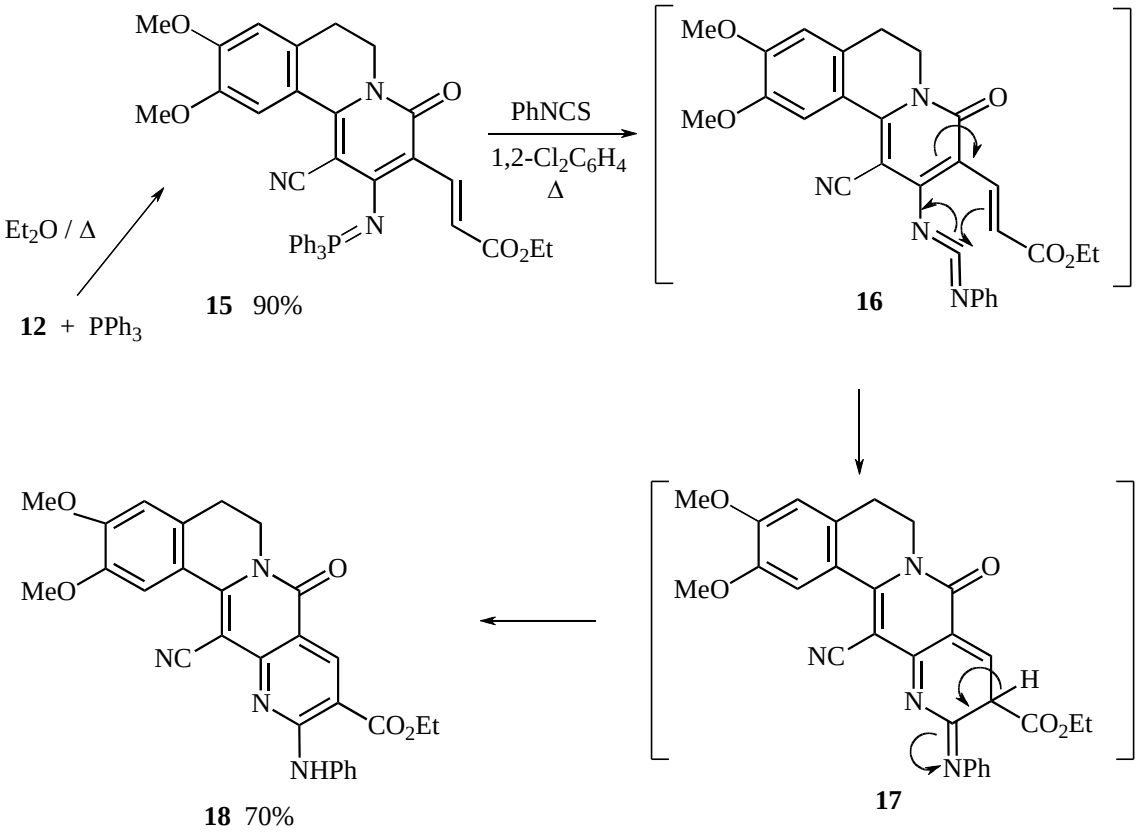


Scheme 3

Stirring of **11** with sodium azide in dioxane/water mixture for 3 h at room temperature gave the corresponding azido derivative **12** (Scheme 3). The structure of **12** was confirmed by elemental and spectral analyses. Thus, the IR spectrum gave a band at ν 2129 cm^{-1} assignable to azide group. Compound **12** was used to construct a novel tetracyclic system. Stirring of **12** with sodium dithionite in methanol/water mixture at room temperature for 24 h afforded the corresponding amino compound **13** (Scheme 3). The structure of compound **13** was confirmed by elemental and spectral analyses. In the IR analysis, while the azide stretch was missing (~ 2129 cm^{-1}), two new bands for the amino groups were clearly visible (3336 and 3251 cm^{-1}). Refluxing **13** in dimethylformamide for 100 h afforded the corresponding compound **14** *via* an intramolecular cyclization and elimination of ethanol (Scheme 3). The

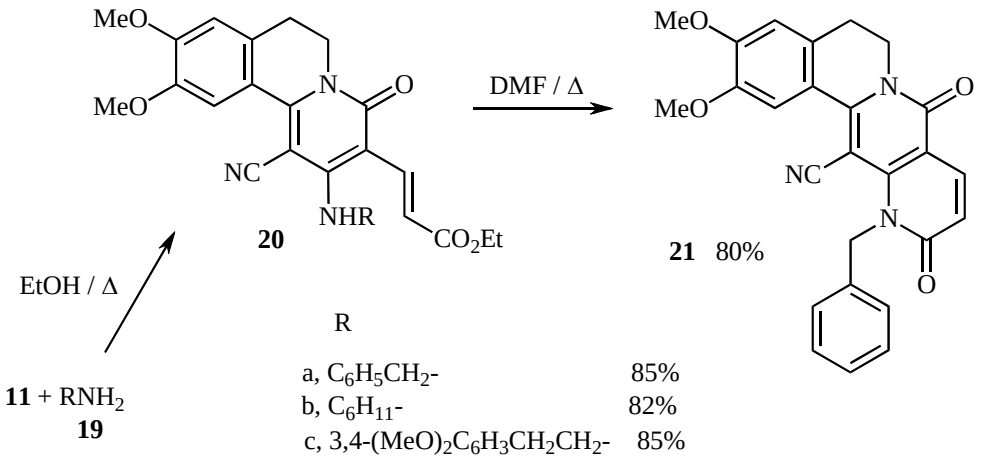
structure of compound **14** was established on the basis of elemental and spectral analyses. IR spectrum indicated the absence of bands of amino group and showed two bands at *v* 3201 and 1654 cm^{-1} assignable to NH and amide C=O groups. Its ^1H NMR spectrum showed the absence of triplet and quartet signals of ethyl group.

Tetracyclic system that incorporated naphthyridine moiety was prepared *via* iminophosphorane compound **15**. Refluxing **12** with triphenylphosphine in ether afforded the iminophosphorane **15** in an excellent yield. The IR spectrum revealed the absence of the azide group. The structure of **15** was further proved on the basis of elemental and spectral analyses. A novel ethyl 13-cyano- 2,3-dimethoxy-8-oxo-11-(phenylamino)-6,8-dihydro-5*H*-isoquinolino[2,1-*g*][1,6]naphthyridine-10-carboxylate (**18**) was obtained in 80% yield *via* refluxing iminophosphorane **15** with phenyl isothiocyanate in 1,2-dichlorobenzene for 6 h (Scheme 4). The pathway of formation of the novel tetracyclic system **18** can be explained by an initial Aza-Wittig type reaction between the iminophosphorane group and phenyl isothiocyanate to give the reactive intermediate carbodimide **16**, which yields a further intermediate **17** *via* intramolecular cyclization by nucleophilic attack of the β-carbon atom of the vinyl moiety. The latter undergoes a proton shift to give the final product **18** (Scheme 4).[31]

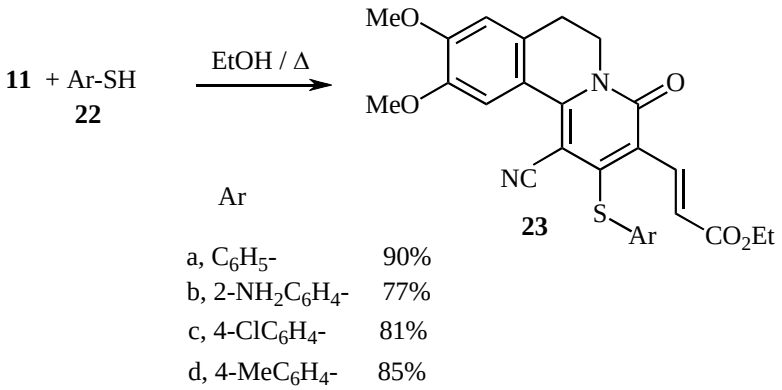


Scheme 4

Because of the high reactivity of chlorine atom in compound **11**, we directed our strategy to construct new derivatives of another novel tetracyclic system **21** containing naphthyridine moiety. Refluxing **11** with amine derivatives **19a-c** in ethanol for 6 h afforded the substitution products (*E*)-ethyl 3-(2-aralkylamino-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl)acrylate **20a-c** (Scheme 5). The structure of each product **20a-c** was confirmed by elemental and spectral analyses. Refluxing of compound **20a** in dimethylformamide for 90 h afforded the fused tetracyclic compound, namely 12-benzyl-2,3-dimethoxy-8,11-dioxo-6,8,11,12-tetrahydro-5*H*-isoquinolino[2,1-*g*][1,6]naphthyridine-13-carbonitrile (**21**) (Scheme 5). A conceivable reaction pathway for the formation of **21** from **20a** occurred by intramolecular cyclocondensation between the amino and ester groups. The structure of **21** was confirmed by elemental and spectral analysis. Its ^{1}H NMR spectrum indicated the absence of triplet and quartet signals assigned to ethoxycarbonyl group. The IR spectrum showed the absence of the bands at ν 3394 and 1697 cm^{-1} assigned to NH and ester carbonyl groups, respectively, and showed a band at ν 1658 cm^{-1} assigned to amide carbonyl group.



Scheme 5



Scheme 6

Also, refluxing of **11** with sulfur nucleophiles **22a-d** in ethanol in the presence of triethylamine afforded the substitution products **23a-d (**Scheme 6). The structures of the products **23a-d** were confirmed on the basis of their elemental and spectral analyses.

EXPERIMENTAL

Melting points were determined on a Stuart melting point apparatus and are uncorrected. IR spectra were measured as KBr pellets on a FTIR Bruker-Vector 22 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury VXR at 300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-Q-1000 EX mass spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Center, Cairo University. Isoquinoline-1-acetonitrile **1**,[32] 2-hydroxy-9,10-dimethoxy-4-oxo-6,7-dihydro-4*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile **2**[30] were prepared according to the procedures in the literature.

***Synthesis of 2-chloro-3-formyl-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido-[2,1-a]isoquinoline-1-carbonitrile* (3):** Phosphoryl chloride (70.0 g, 0.46 mol) was added dropwise over a period 30 min to DMF (12.0 g, 0.24 mol) at 0 °C. To the resulting mixture, compound **2** (40.0 g, 0.13 mol) was added and the reaction mixture was stirred at 60–70 °C for 5 h. After cooling, the reaction mixture was poured into cold H_2O (500 mL) and left for 3 h. The solid product was collected, washed with EtOH and crystallized from DMF to give compound **3** as orange crystals, mp 262-264 °C (DMF), 85% yield; IR (KBr) ν 2214 (CN), 1720 (C=O), 1657 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.98 (m, 2H), 3.84 (s, 3H), 3.91 (s, 3H), 4.11 (m, 2H), 7.15 (s, 1H), 7.89 (s, 1H), 10.14 (s, 1H) ppm; MS, *m/z* (%): 345 (M^++2, 9.9), 344 (M^+, 23.4), 316 (100.0), 301 (77.4). Anal. Calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; Cl, 10.28; N, 8.13. Found: C, 59.10; H, 3.60; Cl, 10.41; N, 7.91.

***Synthesis of (E)-3-((2-arylhydrazono)methyl)-2-chloro-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido-[2,1-a]isoquinoline-1-carbonitrile* (6a-d):** General procedure - A mixture of **3** (1.0 g, 3.0 mmol) and arylhydrazines **5** (3.0 mmol) in EtOH (30 mL) was refluxed for 5 h. The reaction mixture was cooled and the solid that separated was collected, dried and crystallized from DMF to give the condensation products **6a-d** in excellent yields (90-95%).

***(E)-2-Chloro-9,10-dimethoxy-4-oxo-3-((2-phenylhydrazono)methyl)-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile* (6a):** Orange crystals, mp 210-212 °C, 90% yield; IR (KBr) ν 3228 (NH), 2218 (CN), 1674 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.94 (m, 2H), 3.75 (s, 3H), 3.88 (s, 3H), 4.11 (m, 2H), 7.05-7.26 (m, 5H), 7.86 (s, 1H), 7.94 (s, 1H), 8.12 (s, 1H), 10.81 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 26.48, 40.23, 55.63, 55.86, 90.38, 110.76, 111.47, 112.16, 117.11, 117.64, 119.42, 119.81, 129.10, 130.13, 133.14,

137.61, 144.48, 146.74, 147.91, 152.16, 158.82 ppm; MS, *m/z* (%): 436 (M^++2, 4.1), 434 (M^+, 8.9), 398 (92.0), 383 (100.0). Anal. Calcd for $C_{23}H_{19}ClN_4O_3$: C, 63.52; H, 4.40; Cl, 8.15; N, 12.88. Found: C, 63.31; H, 4.30; Cl, 8.01; N, 12.61.

(E)-2-Chloro-9,10-dimethoxy-3-((2-(4-nitrophenyl)hydrazono)methyl)-4-oxo-6,7-dihydro-4H-pyrido-[2,1-a]isoquinoline-1-carbonitrile **(6b):** Red crystals, mp 302-304 °C, 95% yield; IR (KBr) *v* 3282 (NH), 2214 (CN), 1639 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.95 (m, 2H), 3.79 (s, 3H), 3.86 (s, 3H), 4.10 (m, 2H), 7.00 (s, 1H), 7.10 (d, 2H), 7.85 (s, 1H), 8.11 (d, 2H), 8.26 (s, 1H), 11.58 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 26.45, 40.44, 55.76, 55.99, 90.48, 110.89, 111.73, 112.07, 116.98, 117.58, 118.69, 126.16, 133.57, 135.74, 138.98, 140.20, 146.91, 149.30, 150.01, 152.61, 158.84 ppm; MS, *m/z* (%): 481 (M^++2, 15.1), 479 (M^+, 33.3), 443 (100.0), 428 (92.5). Anal. Calcd for $C_{23}H_{18}ClN_5O_5$: C, 57.57; H, 3.78; Cl, 7.39; N, 14.59. Found: C, 57.61; H, 3.61; Cl, 7.21; N, 14.41.

(E)-2-Chloro-3-((2-(4-chlorophenyl)hydrazono)methyl)-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido-[2,1-a]isoquinoline-1-carbonitrile **(6c):** Orange crystals, mp 250-252 °C, 90% yield; IR (KBr) *v* 3262 (NH), 2215 (CN), 1637 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.94 (m, 2H), 3.79 (s, 3H), 3.88 (s, 3H), 4.12 (m, 2H), 7.13 (s, 1H), 7.18 (d, 2H), 7.86 (d, 2H), 8.08 (s, 1H), 8.24 (s, 1H), 10.56 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 26.32, 40.21, 55.80, 55.98, 90.32, 110.89, 111.67, 112.04, 117.04, 117.87, 119.06, 125.12, 130.81, 136.67, 137.00, 139.17, 146.90, 148.58, 150.09, 152.94, 158.99 ppm; MS, *m/z* (%): 472 (M^++4, 10.2), 470 (M^++2, 6.8), 468 (M^+, 1.0), 84 (100.0). Anal. Calcd for $C_{23}H_{18}Cl_2N_4O_3$: C, 58.86; H, 3.87; Cl, 15.11; N, 11.94. Found: C, 58.73; H, 3.94; Cl, 15.33; N, 11.72.

(E)-3-((2-(4-Bromophenyl)hydrazono)methyl)-2-chloro-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido-[2,1-a]isoquinoline-1-carbonitrile **(6d):** Orange crystals, mp 240 °C, 93% yield; IR (KBr) *v* 3260 (NH), 2214 (CN), 1647 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.94 (m, 2H), 3.79 (s, 3H), 3.88 (s, 3H), 4.12 (m, 2H), 7.13 (s, 1H), 7.18 (d, 2H), 7.86 (s, 1H), 8.08 (d, 2H), 8.24 (s, 1H), 10.56 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 26.22, 40.20, 55.79, 55.99, 90.37, 110.09, 111.72, 112.03, 117.14, 117.87, 118.55, 124.06, 130.82, 134.53, 136.87, 139.25, 146.44, 148.59, 150.09, 152.73, 158.68 ppm; MS, *m/z* (%): 516 (M^++4, 8.5), 514 (M^++2, 36.2), 512 (M^+, 26.9), 460 (100.0). Anal. Calcd for $C_{23}H_{18}BrClN_4O_3$: C, 53.77; H, 3.53; Br, 15.55; Cl, 6.90; N, 10.90. Found: C, 53.79; H, 3.80; Br, 15.30; Cl, 7.03; N, 10.71.

Synthesis of 2,3-dimethoxy-8-oxo-11-phenyl-5,6,8,11-tetrahydropyrazolo[3',4':4,5]pyrido[2,1-a]-isoquinoline-12-carbonitrile **(7):** Refluxing of **6a** (0.8 g, 2.0 mmol) in a mixture of 1,2-dichlorobenzene and pyridine (30 mL, 1:1) for 20 h. The solvent was evaporated under vaccum and the residue was triturated with EtOH to give orange solid. The product was collected and crystallized from DMF to give **7** as orange crystals, mp 280-282 °C, 65% yield; IR (KBr) *v* 2210 (CN), 1678 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.03 (t,

2H), 3.74 (s, 3H), 3.85 (s, 3H), 4.14 (t, 2H), 7.10 (s, 1H), 7.55-7.64 (m, 5H), 7.72 (s, 1H), 8.44 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 27.27, 40.13, 55.74, 55.89, 75.32, 110.85, 111.50, 112.54, 115.78, 118.71, 127.40, 128.90, 129.72, 130.79, 133.60, 137.67, 140.07, 146.62, 150.07, 152.01, 156.41 ppm; MS, *m/z* (%): 398 (M^+, 94.8), 383 (100.0), 382 (65.5). Anal. Calcd for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.12; H, 4.31; N, 13.89.

***Synthesis of 2,3-dimethoxy-8-oxo-5,6,8,11-tetrahydropyrazolo[3',4':4,5]pyrido[2,1-a]isoquinoline-12-carbonitrile* (9):** A mixture of **3** (1.0 g, 3.0 mmol) and hydrazine hydrate (0.3 g, 6.0 mmol) was refluxed for 5 h then cooled. The solid that separated was collected, dried and crystallized from DMF to give **9** as pale yellow crystals, mp 308-310 °C, 70% yield; IR (KBr) *v* 3217 (NH), 2229 (CN), 1670 (C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.89 (m, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 4.09 (m, 2H), 7.06 (s, 1H), 7.58 (s, 1H), 7.82 (s, 1H), 14.15 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 27.44, 40.13, 55.69, 55.87, 82.01, 110.06, 110.91, 111.73, 117.25, 119.07, 131.51, 132.84, 134.25, 146.90, 148.07, 151.60, 161.94 ppm; MS, *m/z* (%): 322 (M^+, 90.6), 307 (100.0). Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.22; H, 4.12; N, 17.41.

***Synthesis of (E)-ethyl 3-(2-chloro-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]-isoquinolin-3-yl)acrylate* (11):** To a solution of [(ethoxycarbonyl)methylene]triphenylphosphorane (6.96 g, 20.0 mmol) in $CHCl_3$ (50 mL), compound **3** (6.88 g, 20.0 mmol) was added. The reaction mixture was stirred for 3 h at room temperature then evaporated to dryness under reduced pressure. EtOH (30 mL) was added to the residue and the solid formed was filtered, washed with EtOH and crystallized from MeCN to give compound **11** as yellow crystals, mp 230-232 °C, 68% yield; IR (KBr) *v* 2221 (CN), 1693 (C=O), 1651 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H), 2.93 (m, 2H), 3.96 (s, 3H), 4.02 (s, 3H), 4.21 (m, 2H), 4.27 (q, 2H), 6.80 (s, 1H), 7.38 (d, J = 16 Hz, 1H), 7.88 (d, J = 16 Hz, 1H), 7.91 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.20, 27.53, 40.40, 56.20, 56.34, 60.54, 90.57, 110.14, 111.62, 116.42, 117.84, 119.47, 124.99, 132.56, 134.28, 147.08, 147.96, 149.87, 153.18, 158.37, 167.37 ppm; MS, *m/z* (%): 416 (M^++2, 5.6), 414 (M^+, 16.3), 341 (100.0). Anal. Calcd for $C_{21}H_{19}ClN_2O_5$: C, 60.80; H, 4.62; Cl, 8.55; N, 6.75. Found: C, 60.71; H, 4.50; Cl, 8.41; N, 6.51.

***Synthesis of (E)-ethyl 3-(2-azido-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]iso-quinolin-3-yl)acrylate* (12):** A solution of **11** (2.07 g, 5.0 mmol) in dioxane-water mixture (4:1, v/v 60 mL) was treated with a solution of sodium azide (0.65 g, 10.0 mmol) in the same solvent. The reaction mixture was vigorously stirred for 3 h at room temperature then diluted with water (100 mL). The solid that precipitated was collected and crystallized from MeCN to afford compound **12** as yellow crystals, mp 260-262 °C, 80% yield; IR (KBr) *v* 2210 (CN), 2129 (N_3), 1697 (C=O), 1662 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H), 2.91 (m, 2H), 3.96 (s, 3H), 4.02 (s, 3H), 4.18 (m, 2H), 4.25 (q ,2H), 6.80 (s, 1H), 7.20 (d, J = 16 Hz, 1H), 7.78 (d, J = 16 Hz, 1H), 7.85 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.19, 27.53, 40.07,

56.18, 56.33, 60.41, 84.13, 110.20, 111.72, 112.52, 115.58, 117.81, 123.29, 132.66, 132.96, 147.68, 147.88, 150.96, 153.20, 159.20, 167.48 ppm; MS, *m/z* (%): 393 (M^+-N_2, 100.0), 347 (78.6), 332 (85.7). Anal. Calcd for $C_{21}H_{19}N_5O_5$: C, 59.85; H, 4.54; N, 16.62. Found: C, 59.71; H, 4.32; N, 16.41.

***Synthesis of (E)-ethyl 3-(2-amino-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate* (13):** To a stirred suspension of **12** (2.1 g, 5.0 mmol) in 4:1 MeOH-H_2O (40 mL), sodium dithionite (4.0 g, 20.0 mol) was added portionwise. The reaction mixture was stirred for 24 h then poured into H_2O (20 mL). The resulting solid product was filtered, washed with H_2O and crystallized from DMF to give compound **13** as yellow crystals, mp 218-220 °C, 67% yield; IR (KBr) *v* 3336-3251 (NH_2), 2206 (CN), 1708 (C=O), 1627 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.22 (t, 3H), 2.86 (m, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 4.00 (m, 2H), 4.13 (q, 2H), 7.08 (s, 1H), 7.09 (s, 2H), 7.19 (d, J = 16 Hz, 1H), 7.77 (d, J = 16 Hz, 1H), 7.80 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 14.36, 26.95, 40.13, 55.89, 56.02, 59.34, 79.35, 97.35, 110.93, 111.83, 115.80, 117.66, 118.17, 133.35, 135.95, 146.75, 150.45, 152.23, 154.55, 159.17, 167.97 ppm; MS, *m/z* (%): 395 (M^+, 11.5), 322 (100.0), 75 (90.4). Anal. Calcd for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.61; H, 5.50; N, 10.31.

***Synthesis of 2,3-dimethoxy-8,11-dioxo-6,8,11,12-tetrahydro-5H-isoquinolino[2,1-g][1,6]naphthyridine-13-carbonitrile* (14):** A suspension of **13** (1.18 g, 3.0 mmol) in DMF was refluxed for 100 h. The solvent was evaporated under reduced pressure and the residue was triturated with EtOH. The solid formed was collected, dried and crystallized from DMF to give **14** as yellow crystals, mp 260-262 °C, 65% yield; IR (KBr) *v* 3201 (NH), 2214 (CN), 1654 (C=O), 1630 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 2.92 (m, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 4.15 (m, 2H), 6.51 (d, J = 9 Hz, 1H), 6.81 (s, 1H), 7.53 (d, J = 9 Hz, 1H), 8.10 (s, 1H), 8.52 (s, 1H) ppm; MS, *m/z* (%): 349 (M^+, 84.3), 348 (48.0), 334 (100.0). Anal. Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.50; H, 4.12; N, 12.20.

***Synthesis of (E)-ethyl 3-(1-cyano-9,10-dimethoxy-4-oxo-2-((triphenylphosphoranylidene)amino)-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate* (15):** A solution of **12** (2.1 g, 5.0 mmol) and triphenylphosphine (1.3 g, 5.0 mmol) in dry Et_2O (25 mL) was refluxed for 1 h and cooled. The solid that precipitated was filtered, washed with EtOH and crystallized from MeCN to give compound **15** as yellow crystals, mp 240-242 °C, 90% yield; IR (KBr) *v* 2202 (CN), 1693 (C=O), 1643 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.08 (t, 3H), 2.91 (m, 2H), 3.70 (s, 3H), 3.84 (s, 3H), 3.95 (m, 2H), 4.01 (q, 2H), 6.87 (d, J = 16 Hz, 1H), 7.04 (s, 1H), 7.45-7.76 (m, 15H), 7.78 (d, J = 16 Hz, 1H), 7.83 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.02, 26.88, 40.33, 55.59, 55.70, 58.72, 84.60, 110.72, 112.06, 114.89, 118.33, 127.51, 128.56, 128.72, 129.95, 132.08, 132.21, 132.85, 138.68, 146.52, 149.21, 151.81, 153.01, 159.77, 167.34 ppm; MS, *m/z* (%): 655 (M^+, 5.9), 582 (26.1), 262 (100.0). Anal. Calcd for $C_{39}H_{34}N_3O_5P$: C, 71.44; H, 5.23; N, 6.41; P, 14.72. Found: C, 71.19; H, 5.40; N, 6.32; P, 14.53.

***Synthesis of ethyl 13-cyano-2,3-dimethoxy-8-oxo-11-(phenylamino)-6,8-dihydro-5H-isoquinolino-[2,1-g][1,6]naphthyridine-10-carboxylate* (18):** Phenyl isothiocyanate (0.12 g, 1.0 mmol) was added to a solution of **15** (0.65 g, 1.0 mmol) in 1,2-dichlorobenzene (10 mL). The reaction mixture was refluxed for 5 h and then the solvent was removed under reduced pressure. The solid was filtered and crystallized from DMF to give compound **18** as yellow crystals, mp 280-282 °C, 70% yield; IR (KBr) *v* 3255 (NH), 2206 (CN), 1693 (C=O), 1662 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H), 2.88 (m, 2H), 3.96 (s, 3H), 4.02 (s, 3H), 4.13 (m, 2H), 4.38 (q, 2H), 6.72 (s, 1H), 7.00-7.97 (m, 5H), 8.07 (s, 1H), 8.88 (s, 1H), 10.75 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.12, 27.93, 39.95, 56.09, 56.45, 61.79, 88.15, 108.22, 109.98, 110.18, 112.21, 117.89, 119.12, 120.40, 123.38, 128.71, 132.32, 138.65, 140.96, 147.71, 151.00, 152.33, 155.64, 156.20, 160.05, 166.53 ppm; MS, *m/z* (%): 496 (M^+, 100.0), 450 (12.46), 423 (20.8). Anal. Calcd for $C_{28}H_{24}N_4O_5$: C, 67.73; H, 4.87; N, 11.28. Found: C, 67.61; H, 4.91; N, 11.01.

***Synthesis of (E)-ethyl 3-(2-aralkylamino-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]-isoquinolin-3-yl)acrylate* (20a-c):** General procedure - A mixture of compound **11** (1.0 g, 3.0 mmol) and amines **19a-c** (3.0 mmol) in absolute EtOH (50 mL) was refluxed for 6 h. The solvent was evaporated then cooled. The resulting solid product was collected, washed with EtOH and crystallized from MeCN to give compounds **20a-c**.

***(E)-Ethyl 3-(2-(benzylamino)-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate* (20a):** Yellow crystals, mp 142-144 °C, 85% yield; IR (KBr) *v* 3394 (NH), 2194 (CN), 1697 (C=O), 1643 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.20 (t, 3H), 2.88 (t, 2H), 3.78 (s, 3H), 3.85 (s, 3H), 4.03 (t, 2H), 4.11 (q, 2H), 4.79 (d, 2H), 7.07 (s, 1H), 7.11 (d, J = 16 Hz, 1H), 7.24-7.40 (m, 6H), 7.56 (s, 1H), 7.74 (d, J = 16 Hz, 1H) ppm; ^{13}C NMR (DMSO) δ 14.33, 26.70, 40.14, 50.13, 55.76, 55.95, 59.46, 80.37, 101.45, 110.88, 112.57, 116.87, 117.92, 118.96, 127.82, 127.48, 128.45, 133.57, 136.28, 138.92, 146.68, 151.82, 152.57, 156.00, 159.24, 167.81 ppm; MS, *m/z* (%): 485 (M^+, 7.4), 412 (50.3), 91 (100.0). Anal. Calcd for $C_{28}H_{27}N_3O_5$: C, 69.26; H, 5.61; N, 8.65. Found: C, 68.98; H, 5.82; N, 8.51.

***(E)-Ethyl 3-(1-cyano-2-(cyclohexylamino)-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]iso-quinolin-3-yl)acrylate* (20b):** Yellow crystals, mp 138-140 °C, 82% yield; IR (KBr) *v* 3386 (NH), 2206 (CN), 1689 (C=O), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.22 (t, 3H), 1.24 (m, 10H), 2.90 (m, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 4.04 (m, 2H), 4.12 (q, 2H), 4.18 (m, 1H), 6.18 (d, 1H), 7.05 (d, J = 16 Hz, 1H), 7.09 (s, 1H), 7.63 (d, J = 16 Hz, 1H), 7.79 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 14.33, 24.81, 24.94, 26.78, 33.89, 40.40, 55.86, 55.97, 57.57, 59.52, 82.13, 102.42, 110.88, 112.75, 116.36, 118.12, 118.74, 133.57, 137.11, 146.70, 151.39, 152.49, 156.36, 159.39, 167.88 ppm; MS, *m/z* (%): 477 (M^+, 69.7), 476 (100.0), 340 (87.9). Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.70; H, 6.66; N, 8.70.

(E)-Ethyl 3-(1-cyano-2-((3,4-dimethoxyphenethyl)amino)-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate **(20c):** Yellow crystals, mp 137-139 °C, 85% yield; IR (KBr) *v* 3402 (NH), 2210 (CN), 1697 (C=O), 1647 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.22 (t, 3H), 2.90 (t, 2H), 2.95 (m, 2H), 3.63 (s, 3H), 3.65 (s, 3H), 3.72 (t, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 4.02 (m, 2H), 4.14 (q, 2H), 6.75-6.83 (m, 3H), 7.02 (d, J = 16 Hz, 1H), 7.08 (s, 1H), 7.33 (t, 1H), 7.67 (d, J = 16 Hz, 1H), 7.79 (s, 1H) ppm; ^{13}C NMR (DMSO) δ 14.37, 26.75, 40.44, 49.47, 55.13, 55.44, 55.79, 55.97, 59.54, 80.47, 100.64, 110.93, 111.85, 112.62, 116.03, 117.89, 118.91, 120.80, 123.20, 131.00, 133.60, 135.21, 136.70, 146.52, 147.37, 148.54, 151.59, 152.54, 156.44, 159.85, 167.96 ppm; MS, *m/z* (%): 559 (M^+, 12.5), 334 (61.7), 164 (100.0). Anal. Calcd for $C_{31}H_{33}N_3O_7$: C, 66.53; H, 5.94; N, 7.51. Found: C, 66.44; H, 5.71; N, 7.81.

Synthesis of 12-benzyl-2,3-dimethoxy-8,11-dioxo-6,8,11,12-tetrahydro-5H-isoquinolino[2,1-g][1,6]-naphthyridine-13-carbonitrile **(21):** A solution of **20a** (0.48 g, 1.0 mmol) in DMF (20 mL) was refluxed for 96 h. The solvent was evaporated under reduced pressure and EtOH (10 mL) was added to the residue. The solid precipitated was collected, dried and crystallized from DMF to give **21** as yellow crystals, mp 240-242 °C, 80% yield; IR (KBr) *v* 2206 (CN), 1658 (C=O), 1650 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 2.91 (m, 2H), 3.73 (s, 3H), 3.86 (s, 3H), 4.11 (m, 2H), 5.92 (s, 2H), 6.62 (d, J = 9 Hz, 1H), 7.08-7.35 (m, 7H), 8.17 (d, J = 9 Hz, 1H) ppm; ^{13}C NMR (DMSO) δ 26.70, 40.32, 47.25, 55.78, 55.92, 78.09, 106.93, 110.75, 113.32, 117.85, 118.42, 118.91, 126.14, 126.80, 128.26, 134.11, 136.65, 136.86, 146.35, 146.50, 152.94, 153.48, 158.30, 162.16 ppm; MS, *m/z* (%): 439 (M^+, 24.1), 408 (45.0), 91 (100.0). Anal. Calcd for $C_{26}H_{21}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 70.85; H, 4.71; N, 9.68.

Synthesis of (E)-ethyl 3-(2-arylthio)-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate **(23a-d):** General procedure - These compounds were prepared as previously described for the synthesis of **20** using arylthiols **22** in the presence of triethylamine instead of amines **19**. The resulting solid product was collected, washed with EtOH and crystallized from DMF to give compounds **23a-d**.

(E)-Ethyl 3-(1-cyano-9,10-dimethoxy-4-oxo-2-(phenylthio)-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate **(23a):** Yellow crystals, mp 180-182 °C, 90% yield; IR (KBr) *v* 2210 (CN), 1705 (C=O), 1654 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.26 (t, 3H), 3.00 (m, 2H), 3.79 (s, 3H), 3.91 (s, 3H), 4.10 (m, 2H), 4.11 (q, 2H), 7.00 (s, 1H), 7.03-7.20 (m, 5H), 7.14 (d, 1H), 7.79 (s, 1H), 8.06 (d, 1H) ppm; ^{13}C NMR (DMSO) δ 14.14, 26.45, 40.24, 55.69, 56.01, 60.00, 93.21, 110.62, 112.11, 116.91, 117.65, 121.72, 123.12, 130.16, 130.39, 134.25, 136.08, 137.90, 147.64, 147.89, 148.32, 150.99, 152.52, 158.36, 166.67 ppm; MS, *m/z* (%): 488 (M^+, 14.3), 415 (100.0). Anal. Calcd for $C_{27}H_{24}N_2O_5S$: C, 66.39; H, 4.95; N, 5.73; S, 6.55. Found: C, 66.11; H, 4.71; N, 5.61; S, 6.40.

(E)-Ethyl 3-(2-((2-aminophenyl)thio)-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate **(23b):** Yellow crystals, mp 200-202 °C, 77% yield; IR (KBr) *v* 3448-3348 (NH_2), 2214 (CN), 1697 (C=O), 1654 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.14 (t, 3H), 2.97 (m, 2H), 3.74 (s, 3H), 3.78 (s, 2H), 3.88 (s, 3H), 4.08 (m, 2H), 4.17 (q, 2H), 6.50-7.05 (m, 4H), 7.08 (d, 1H), 7.14 (s, 1H), 7.78 (s, 1H), 7.91 (d, 1H) ppm; ^{13}C NMR (DMSO) δ 14.12, 26.35, 40.23, 55.60, 55.90, 59.91, 92.21, 110.75, 112.00, 114.83, 115.48, 117.33, 117.64, 121.97, 122.19, 123.04, 129.29, 132.17, 133.61, 137.59, 146.62, 147.59, 149.84, 150.30, 152.90, 158.05, 166.49 ppm; MS, *m/z* (%): 503 (M^+, 9.13), 430 (74.7), 424 (100.0), 314 (88.6). Anal. Calcd for $C_{27}H_{25}N_3O_5S$: C, 64.41; H, 5.00; N, 8.35; S, 6.36. Found: C, 64.21; H, 4.87; N, 8.21; S, 6.22.

(E)-Ethyl 3-(2-((4-chlorophenyl)thio)-1-cyano-9,10-dimethoxy-4-oxo-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate **(23c):** Yellow crystals, mp 172-174 °C, 81% yield; IR (KBr) *v* 2215 (CN), 1682 (C=O), 1653 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.25(t, 3H), 2.99 (m, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 4.06 (m, 2H), 4.18 (q, 2H), 6.98 (s, 1H), 7.10-7.33 (m, 4H), 7.30 (d, 1H), 7.82 (s, 1H), 8.12 (d, 1H) ppm; ^{13}C NMR (DMSO) δ 14.11, 26.45, 40.13, 55.72, 56.00, 59.68, 93.04, 110.52, 112.09, 116.91, 117.77, 121.85, 123.02, 133.21, 135.88, 136.13, 136.99, 137.90, 148.35, 148.82, 148.91, 151.12, 152.48, 158.34, 166.57 ppm; MS, *m/z* (%): 524 (M^++2, 5.2), 522 (M^+, 11.9), 449 (100.0), 448 (88.3). Anal. Calcd for $C_{27}H_{23}ClN_2O_5S$: C, 62.01; H, 4.43; Cl, 6.78; N, 5.36; S, 6.12. Found: C, 62.20; H, 4.22; Cl, 6.51; N, 5.22; S, 6.01.

(E)-Ethyl 3-(1-cyano-9,10-dimethoxy-4-oxo-2-(p-tolylthio)-6,7-dihydro-4H-pyrido[2,1-a]isoquinolin-3-yl)acrylate **(23d):** Yellow crystals, mp 198-200 °C, 85% yield; IR (KBr) *v* 2218 (CN), 1705 (C=O), 1658 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 1.21 (t, 3H), 2.21 (s, 3H), 2.96 (m, 2H), 3.76 (s, 3H), 3.93 (s, 3H), 4.08 (m, 2H), 4.13 (q, 2H), 7.11 (s, 1H), 7.14-7.22 (m, 4H), 7.25 (d, 1H), 7.76 (s, 1H), 8.02 (d, 1H) ppm; ^{13}C NMR (DMSO) δ 14.16, 20.59, 26.42, 40.36, 55.72, 56.02, 60.13, 93.34, 110.85, 112.06, 117.56, 117.77, 122.71, 123.38, 129.21, 130.33, 133.78, 137.17, 137.90, 146.80, 147.55, 148.30, 150.80, 152.74, 158.41, 166.76 ppm; MS, *m/z* (%): 502 (M^+, 11.1), 430 (33.3), 429 (100.0). Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C, 66.92; H, 5.22; N, 5.75; S, 6.37. Found: C, 66.71; H, 5.41; N, 5.51; S, 6.60.

X-Ray structure determination of compound 3

The X-ray diffraction measurement was made on using maXus (Bruker Nonius, Delft & MacScience, Japan) at temperature 298 K and wavelength 0.71073 Å; radiation: Mo Kα. Crystal data for compound **3**: $C_{17}H_{13}ClN_2O_4$, M_r = 344.754, space group: Monoclinic, $P2_1/c$; unit cell dimensions: a = 23.5106 (6) Å, b = 17.7940 (4) Å, c = 7.2843 (2) Å, α = 90.00°, β = 90.1421 (9)°, γ = 90.00; volume: 3047.36 (13) $Å^3$; Z = 8; calculated density: D_x = 1.503 Mg m^{-3}; absorption coefficient: μ = 0.28 mm^{-1}; reflection 12763 measured, θ_{max} = 27.57°. Crystallographic data for the structural analysis of compound 3 has been deposited with the Cambridge Crystallographic Data Centre (CCDC) under the number 871967. Copies

of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel: +44 (0)1223 762911; www: http://www.ccdc.cam.ac.uk).

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