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SYNTHESIS OF TETRA- AND PENTA-HETEROCYCLIC COMPOUNDS INCORPORATED ISOQUINOLINE MOIETY

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Abstract — 7-Amino-2,3-dimethoxy-9-phenyl-5,6,9,6a-tetrahydropyridino[2,1-*a*]-isoquinoline-8,10-dicarbonitrile **5** was prepared via Michael addition reaction of benzylidenemalononitrile **2** with isoquinoline-1-carbonitrile **1**. Reaction of **5** with triethyl orthoformate and formamide led to the formation of the corresponding 4-ethoxymethylene and 4-aminopyrimidine derivatives of benzo[*a*]quinolizines **6** and **7**, respectively. Compound **6** reacted with hydrazine to give imino-amino compound **8**. The latter compound reacted with formic acid, triethy1 orthoformate, acetic anhydride or benzoy1 chloride to give the triazolopyrimidine derivatives **9**, **10** and **11**, respectively. Compound **8** reacted with hydrazonoy1 halides **12**, **13** and diethy1 oxalate to give triazinopyrimidine and triazolopyrimidine derivatives **16**, **17** and **20**, respectively.

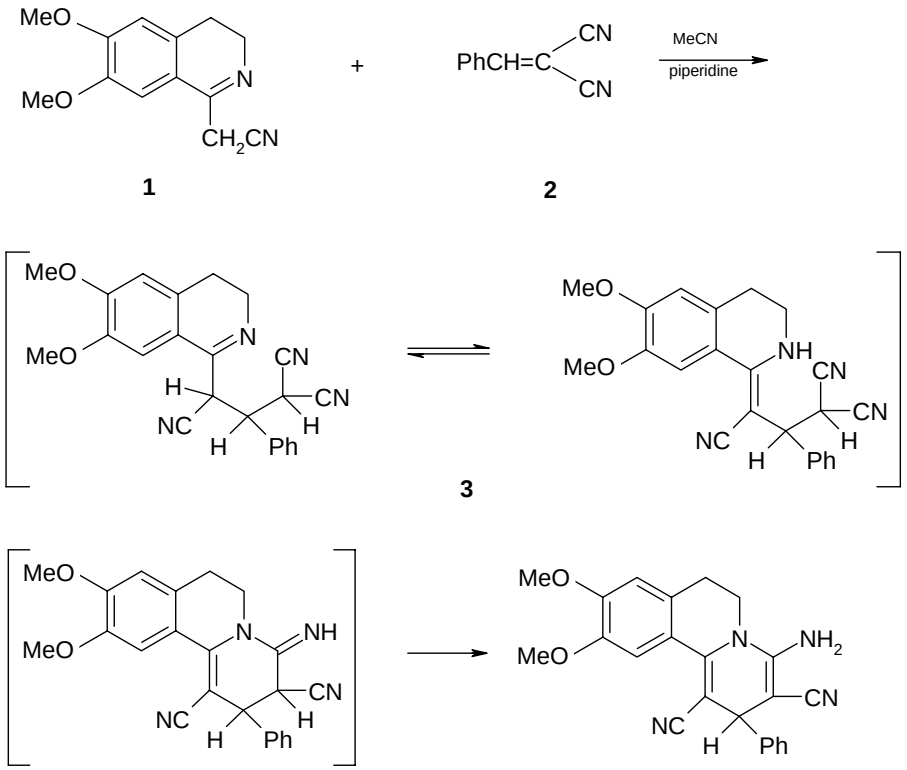
INTRODUCTION

The considerable biological and medicinal activities of azoloazines have stimulated considerable interest in the synthesis and chemistry of these compounds.[1-4] Although several examples of the azoloazines incorporated 1,2,4-triazole moiety have been reported in literature [1-4] there is no any example, to our knowledge, reported contains 1,2,4-triazole ring fused with pyrimidopyridoisoquinoline ring. In continuation of our previous work[3-5, 7-10] on the use of isoquinoline derivatives for the synthesis of heterocyclic compounds we wish to report the synthesis of some triazolo[1,5-*e*]pyrimidine and triazino[2',3'-6,1]pyrimidine.

RESULTS AND DISCUSSION

Treatment of benzylidene malononitrile **2** with 6, 7-dimethoxy-3, 4-dihydroisoquinoline-1-carbonitrile **1** in boiling acetonitrile in the presence of piperidine afforded a single product as evidenced by TLC

analysis. Structure **5** was assigned to the reaction product on the basis of elemental analyses and spectral data (MS, IR, ^{1}H and ^{13}C NMR), for example the ^{1}H NMR spectrum of the product revealed signals at δ 4.2 (s, 2H, NH_2) and 4.3 (s,1H) ppm assignable to proton of pyridine ring in addition to the signals of the dihydroisoquinoline moiety. Also the IR spectra showed two nitrile absorption bands at 2197 and 2185 in addition to bands at 3415 and 3336 cm^{-1} characteristic to the amino group. From the previous data, the product resulting from reaction of **2** with **1** was assigned 7-amino-2,3-dimethoxy-9-phenyl-5,6,9,6a-tetrahydropyridino[2,1-*a*]isoquinoline-8,10-dicarbonitrile **5**. The product **5** was also prepared in one step by refluxing equimolar amounts of **1**, benzaldehyde and malononitrile. The reaction started with Michael addition to give **3** which upon cyclization led to the formation of **5**.



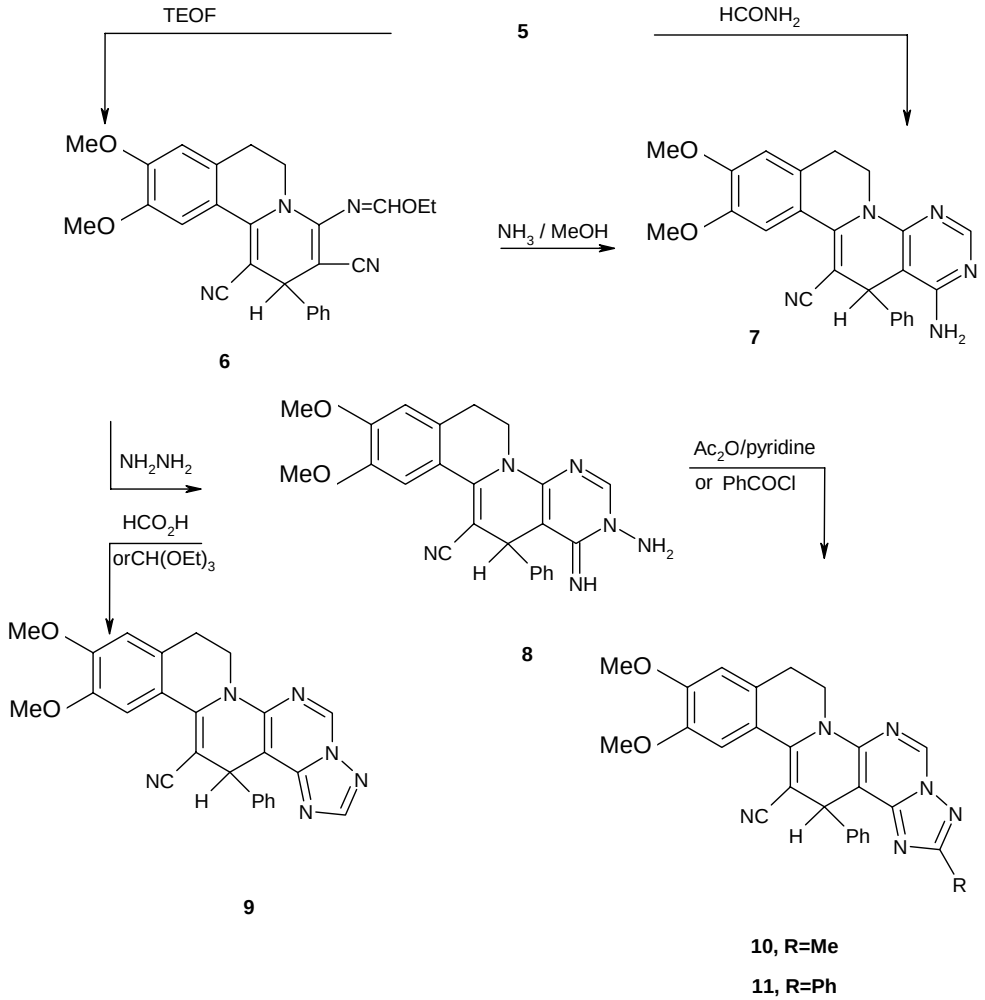
Scheme 1

Reaction of **5** with triethyl orthoformate in acetic anhydride at reflux afforded the ethoxymethyleneamino derivative **6** in almost quantitative yield (Scheme 2). The ^{1}H NMR spectrum of the product revealed characteristic signals for ethoxy group at δ 1.4 (t, J = 7 Hz, 3H) and 4.4 (q, J = 7Hz, 2H) as well as a signal at δ 7.9 ppm assignable to a proton of CHOEt. Also, the IR spectrum of **6** revealed the absence of the bands of the amino group. The above data together with the ^{13}C NMR confirmed that the product assigned structure **6**.

When compound **5** was refluxed with formamide it gave **7**. The structure of the latter product was established on the basis of its alternative synthesis from **6** and methanolic ammonia (Scheme 2). Both IR

and ^{1}H NMR spectroscopic data of the product were consistent with its assigned structure **7**.

Treatment of **6** with hydrazine hydrate in ethanol at room temperature gave **8**. The structure of **8** was confirmed by its analytical and spectroscopic data and their chemical reactions outlined in schemes 2 and 3. Reaction of **8** with formic acid or triethyl orthoformate at reflux afforded **9**. The formation of triazole ring involving both amino and imino groups was evidenced by the absence of their absorption bands in the IR spectrum of **9**.

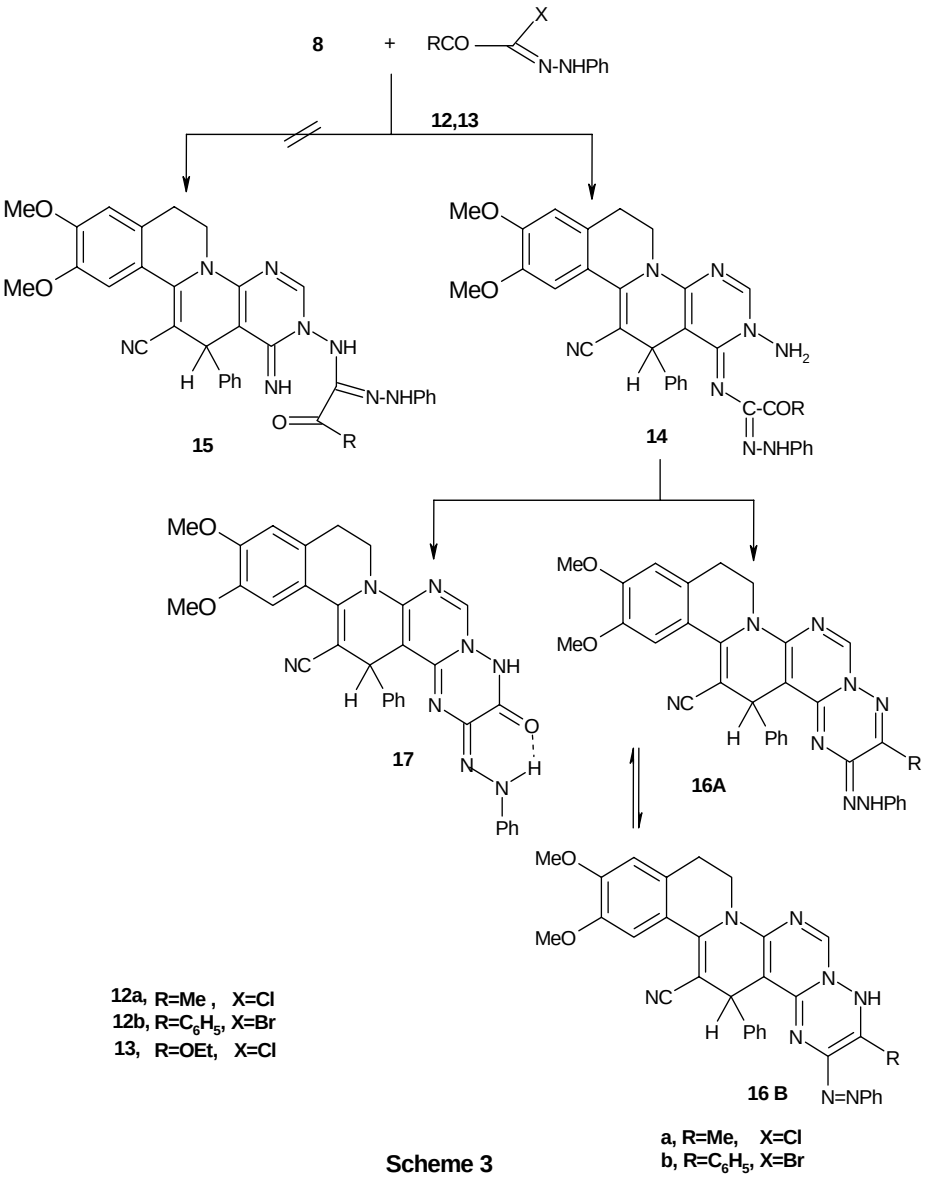


Scheme 2

Also the ^{1}H NMR spectrum of **9** revealed two characteristic signals at δ 8.3 (s,1H, triazolo-CH) and at δ 9.1 (s, 1H, pyrimidine-CH)ppm. Similarly, when compound **8** was refluxed in acetic anhydride or benzoyl chloride in pyridine, it afforded the corresponding 10-methyl and 10-phenyl derivatives **10** and **11** which were assigned on both elemental analyses and spectroscopic data. For example, the ^{1}H NMR spectra of **10** and **11** revealed the absence of the proton in triazole ring at δ 8.3 appeared in compound **9**; instead, it showed a singlet signal at δ 2.5 ppm assignable to a methyl group in **10**.

The reaction of **8** with C-acylhydrazonoyl halides **12a,b** in refluxing chloroform in the presence of triethylamine affordcd in cach case, a single product as evidenced by TLC analysis. The intermediates **15**

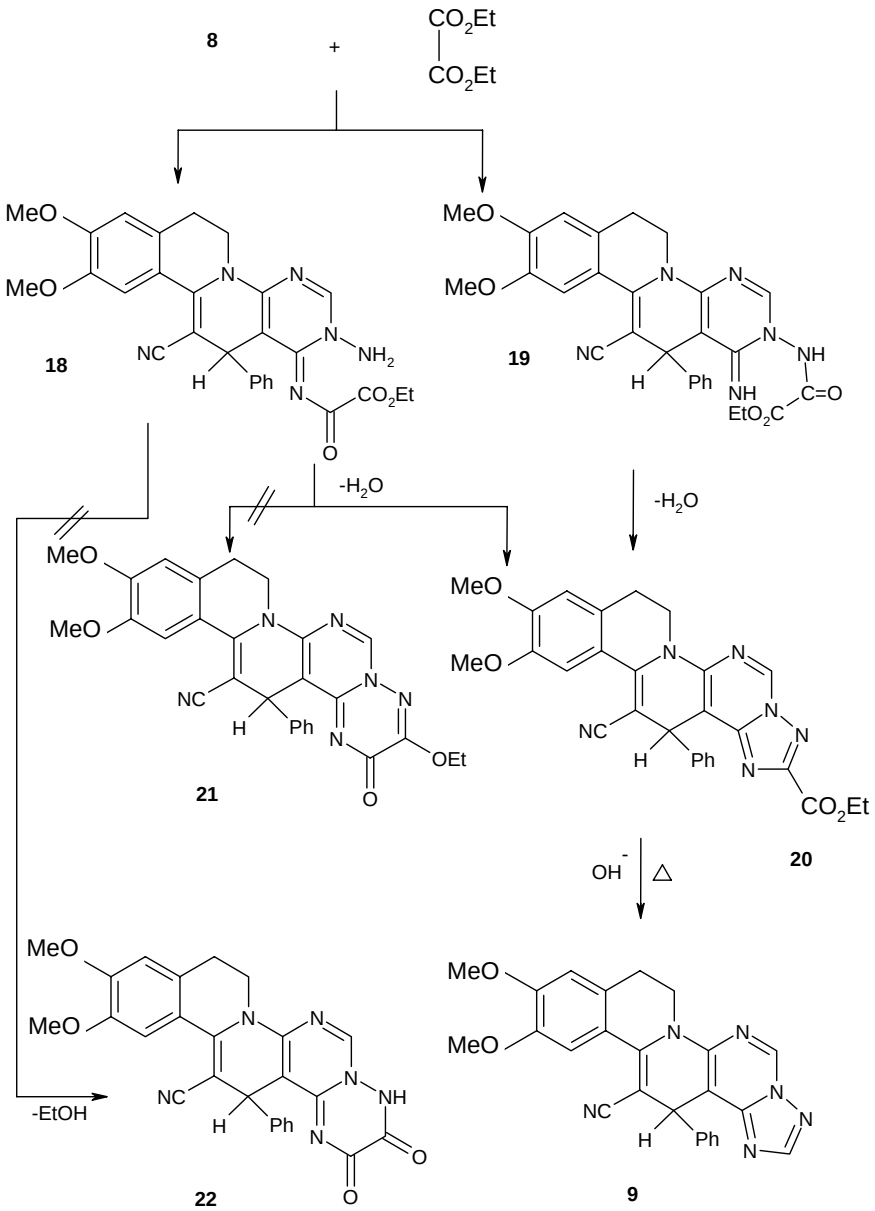
were discarded on the basis of imino-nitrogen are more basic, and in turn more nucleophilic, than that of the amino group. The results of elemental analyses of the products were found to be consistent with **16A** and its tautomeric structure **16B**, furthermore, the electronic absorption spectra of the isolated products excludes the hydrazone structure **16A** since they revealed a characteristic absorption maxima at λ 361 (log ε 4.43) and λ 400 (log ε 4.4) assignable to arylazo chromophore.[13] Accordingly, the product obtained from the reaction of **8** with **12a,b** was assigned structure **16Ba, 16Bb**.



Scheme 3

The latter structure was further evidenced by spectroscopic data, for example the ^{1}H NMR spectrum of **16B** showed that a signal of δ 9.1ppm corresponding to NH disappeared upon shaking the solution of **16Ba** with deuterium oxide. The IR spectrum of **16Bb** exhibited an NH absorption band at 3212 cm^{-1}. C-Ethoxycarbonylhydrazonoyl halide **13** reacted under similar rection condition with **8** to give compound **17** and the IR spectrum of **17** showed two bands at 3209 and 1636 cm^{-1} assignable to the hydrazone NH

and amido carbony1 groups, respectively. Its UV spectrum in ethanol revealed two bands in the regions λ_{max}250-300(log ε4.42) and λ_{max}300-360(log ε 4.22) nm assignable to hydrazone chromophoure[15] (Scheme 3). Refluxing of **8** with diethy1 oxalate afforded a single product whose elemental analysis and mass spectra were consistent with $C_{28}H_{24}N_6O_4$ formula (Scheme 4).



Scheme 4

Thus, formula **22** was discarded for the isolated product. Two possible structures were assigned for the resulting product **20** or **21**. The former was assigned to be the isolated product on the basis of its transformation to **9**. Thus saponification of **20** gave **9** via decarboxylation of the resulting acid (Scheme 4). The structure of the product **20** was confirmed by it analytical and spectroscopic data.

EXPERIMENTAL

All melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. IR spectra (KBr) were recorded on a Pye Unicam SP-300 IR spectrophotometer and Testscan Shimadzu FTIR 8000 series ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 and Varian EM 390 spectrometers for solution in deuterated chloroform using TMS as internal standard. Mass spectra were recorded on a GCMS- QP 1000 Ex Shimadzu, Japan. Elemental analyses were carried out at the Micro analytical Centre of Cairo University. The hydrazonoyl halides **12a**[14]**, 12b**[15] **and 13**[16] were prepared as previously described.

General procedure :

Synthesis of 7-amino-2,3-dimethoxy-9-phenyl-5,6,9,6a-tetrahydropyridino[2,1-a]isoquinoline-8,10-dicarbonitrile 5.

To a solution of benzylidene malononitrile **2** (0.77g, 5mmol) and 6,7-dimethoxy-3,4-dihydroisoquinoline-1-acetoniotrile **1** (1.15g, 5mmol) in acetonitrile (40 mL) was added 3-4 drops of piperidine at rt. The reaction mixture was refluxed for 3 h, the solvent was evaporated under reduced pressure and the residue was triturated with MeOH (10 mL) where it solidified the crude product was collected and crystallized from MeCN to give **5**: mp 210 ºC (MeCN); 78% yield; IR (KBr); υ 3415, 3336 (NH_2), 2197, 2185 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.8 (m,2H), 3.4 (m ,1H), 3.8 (m, 1H), 3.8 (s, 3H), 3.9 (s, 3H), 4.2 (s, 2H), 4.3 (s,1H), 6.7(s,1H), 7.2-7.4 (m, 5H), 7.7 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 41.1, 56.0 110.0, 110.6, 126.3, 127.7, 129.0 (CH_3 CH); 28.6, 41.9, 85.4, 120.4, 121.0, 129.2, 142.8, 145.4, 147.8, 151.1, 152.4, 167.2, 167.5 (CH_2, C,CN); m/z 384. Anal. Calcd for $C_{23}H_{20}N_4O_2$: C, 71.84; H, 5.24; N, 14.58. Found: C, 72.06; H, 5.02; N, 14.33 %.

Synthesis of 2,3-dimethoxy-7-(N-ethoxymethylene)-9-phenyl-5,6,9,6atetrahydropyridino[2,1-a] isoquinoline -8,10-dicarbonitrile 6.

7-Amino-2,3-dimethoxy-9-phenyl-5,6,9,6a-tetrahydropyridino[2,1-*a*]isoquinoline-8,10-dicarbonitrile **5** (1.9g, 5 mmol) was dissolved in acetic anhydride (30 mL), to the resulting solution, triethyl orthoformate (0.74g, 5 mmol) was added and the mixture was refluxed for 5 h. The excess acetic anhydride was distilled off under reduced pressure and the solid that precipitated on cooling was filtered and crystallized from EtOH to give **6:** mp 172 ^{o}C (EtOH); 86% yield; IR (KBr); υ 2198, 2183 (2CN), 1638 (N = CHOEt) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.4 (t, J = 7 Hz, 3H), 2.8 (m, 2H), 3.5 (m, 1H), 3.7 (m, 1H), 3.8 (s, 6H), 4.4 (q, J = 7 Hz, 2H), 4.5 (s, 1H), 6.6 (s, 1H) , 7.1- 7.3 (m, 5H), 7.8 (s, 1H), 7.9 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 42.5, 56.1, 56.2, 110.4, 111.3, 127.4, 128.1, 129.3, 153.7 (CH_3, CH); 27.0, 42.4, 64.4, 72.1, 81.9, 119.6, 120.1, 121.5, 131.0, 143.2, 145.6, 147.7, 151.4, 153.7, (CH_2, C, CN); m/z 440. Anal. Calcd for $C_{26}H_{24}N_4O_3$: C, 70.87; H, 5.49; N, 12.72. Found: C, 70.72; H, 5.36; N, 12.48 %.

Synthesis of 4-amino-8,9-dimethoxy-5-phenyl-5,11,12,12a-tetrahydroisoquinolino[2′,1′-6,1] pyridine [2,3-d] pyrimidine-6-carbonitrile 7.

Method A: A mixture of **5** (1.9g, 5 mmol) and formamide (10 mL) was refluxed for 3 h. The reaction mixture was cooled and added to cold water with stirring. The solid formed was collected and crystallized from DMF to give **7**: mp 225 ^{o}C (DMF); 83% yield; IR (KBr): υ 3500, 3300 (NH_2), 2198 (CN) cm^{-1}; Anal. Calcd for $C_{24}H_{21}N_5O_2$: C, 70.04; H, 5.14; N, 17.03. Found: C, 70.36; H, 4.81; N, 17.25 %.

Method B: *A* compound **6** (2.2 g, 5 mmol) was treated with methanolic ammonia (10 mL) at rt for 6 h. The solid that separated was collected and crystallized from DMF to give a compound which identical in all respects (mp, mixed mp, IR) with that compound prepared by method A .

Synthesis of 3-amino-8,9-dimethoxy-4-imino-5-phenyl-5,11,12,12a-tetrahydroisoquinolino[2′,1′-6,1]pyridine[2,3-d] pyrimidine-6-carbonitrile 8.

A mixture of **6** (2.2 g, 5 mmol) and hydrazine hydrate (5 mL) was stirred for 4 h in EtOH (20 mL) at rt. The solid that separated was filtered and crystallized from AcOH to give product **8**: mp 199 ^{o}C (AcOH); 63% yield; IR (KBr): υ 3311, 3142, 3060 (NH, NH_2), 2181 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.8 (m, 2H), 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (s, 3H), 4.5 (m, 1H), 4.6 (s,1H), 4.8 (s, 2H), 5.9 (s, 1H), 6.7 (s, 1H), 7.2-7.3 (m, 5H), 7.8 (s,1H), 8.0 (s, 1H); ^{13}C NMR (DMSO): 55.5, 55.6, 120.9, 122.0, 126.0, 127.1, 127.3, 128.4, 131.6, 149.5, 150.6, (CH_3, CH); 28.4, 79.9, 97.1, 110.8, 110.9, 119.3, 143.9, 145.6, 146.2, 146.5, 154.0(CH_2, C, CN); m/z 426. Anal. Calcd for $C_{24}H_{22}N_6O_2$: C, 67.57; H, 5.20; N, 19.71. Found: C, 67.81; H, 5.43; N, 19.94 %.

Synthesis of 4,5-dimethoxy-8-phenyl-1,2,8,11a,13b-pentahydroisoquinoline[2′,1′-6,11]pyridino[2,3-d]1,2,4-triazolo[1,5-e]pyrimidine-7-carbonitrile 9.

A solution of compound **8** (2.1g, 5 mmol) in formic acid or triethyl othoformate (5 mL) was refluxed for 5 h. The reaction mixture was cooled and the solid that precipitated was collected and crystallized from EtOH to give product **9:** mp 233 °C (EtOH); 66% yield; IR (KBr): υ 2183 (CN) cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.1 (m, 1H), 4.5 (m, 1H), 5.5 (s, 1H), 6.8 (s, 1H), 7.2-7.5 (m, 5H), 7.9 (s, 1H), 8.3 (s, 1H), 9.1 (s, 1H). Anal. Calcd for $C_{25}H_{20}N_6O_2$: C, 68.77; H, 4.62; N, 19.26. Found: C, 68.52; H, 4.43; N, 19.50%.

Synthesis of 4,5-dimethoxy-10-methyl-8-phenyl-1,2,8,11a,13b-pentahydroisoquinoline[2',1′-6,1] pyridino[2,3-d]1,2,4-triazolo[1,5-e]pyrimidine-7-carbonitrile 10.

A solution of **8** (2.1g, 5 mmol) in acetic anhydride (20 mL) was refluxed for 3 h. The mixture was cooled and the solid that separated was collected and crystallized from AcOH to give product **10:** mp 246 °C (AcOH); 67% yield; IR (KBr): υ 2185 (CN) cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 2.5 (s, 3H), 2.9 (m, 2H), 3.9 (m, 1H), 3.9 (s, 3H), 4.0 (s, 3H), 4.4 (m, 1H), 5.4 (s, 1H), 6.7 (s, 1H), 7.2-7.5 (m, 5H), 7.8 (s, 1H), 8.9 (s, 1H);

^{13}C NMR (DMSO): 14.2, 55.6, 55.7, 121.5, 121.8, 127.4, 128.8, 129.0, 131.6, 131.9, 146.6, 150.8, (CH_3, CH); 28.2, 79.8, 99.2, 110.9, 119.1, 138.9, 143.0, 144.9, 146.2, 151.1, 151.7, 166.1(CH_2, C, CN); m/z 450. Anal. Calcd for $C_{26}H_{22}N_6O_2$: C, 69.30; H, 4.92; N, 18.66. Found: C, 69.46; H, 4.75; N, 18.48 %.

Synthesis of 4,5-dimethoxy-8,10-phenyl-1,2,8,11a,13b-pentahydroisoquinoline[2',1'-6,l]pyridino[2,3-d]1,2,4-triazolo[1,5-e]pyrimidine-7-carbonitrile 11.

To a solution of **8** (2.1 g, 5 mmol) in pyridine (10 mL) benzoyl chloride (0.7 mL, 5 mmol) was added. The mixture was refluxed for 4 h, then cooled and poured into cooled hydrochloric acid (10%) with stirring. The solid that precipitated was collected, washed with cold water and finally crystallized from DMF to give product **11:** mp 276 °C (DMF); 65% yield; IR (KBr): υ 2186 (CN) cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.1 (m, 1H), 4.5 (m, 1H), 5.6 (s, 1H), 6.8 (s,1H), 7.3 (s, 1H), 7.2-8.8 (m, 10H), 9.1 (s, 1H); m/z 512. Anal. Calcd for $C_{31}H_{24}N_6O_2$: C, 72.62; H, 4.72; N, 16.40. Found: C, 72.40; H, 4.51; N, 16.17 %.

Synthesis of 11,12-dimethoxy-2-phenylazo-14-phenyl-8,14,4a-trihydro-4H-benzo[a] 1,2,4-triazino[2',3'-6,1]pyrimidine[4,5-f]quinolizine-13-carbonitrile 16 and 17 (general procedure).

To a hot solution of **8** (2.1g, 5 mmol) and the appropriate hydrazonoyl halide (5 mmol) in $CHCl_3$ (30 mL) was added triethylamine (0.7 mL, 5 mmol). The reaction mixture was refluxed for 18 h, and then the solvent was evaporated under reduced pressure. The crude product was collected and crystallized from DMF to give the products **16** and **17**.

11,12-dimethoxy-2-phenylazo-3-methyl-14-phenyl-8,14a,4a-trihydro-4H-benzo-[a]1,2,4-triazino[2',3'-6,1] pyrimidine[4,5-f]quinolizine-13-cabonitrile 16Ba.

mp 297°C (DMF); 61% yield; IR (KBr): υ 3212 (NH), 2187 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H), 3.0 (m,2H), 3.7 (s, 3H), 3.8 (s, 3H), 4.0 (m, 1H) , 4.3 (m, 1H), 5.2 (s,1H), 6.8 (s,1H), 7.1 (s,1H), 7.2-7.8 (m, 9H), 8.3 (s,1H), 8.5 (s, 1H), 9.1 (s, 1H, NH); m/z 568. Anal. Calcd for $C_{33}H_{28}N_8O_2$: C, 69.68; H, 4.96; N, 19.71. Found: C, 69.91; H, 4.83; N, 19.54 %.

11,12-dimethoxy-3,14-diphenyl-2-phenylazo-8,14a,4a-trihydro-4H-benzo[a]1,2,4-triazino[2,3-6,1]-pyrimidine[4,5-f]quinolizine-13-carbonitrile 16 Bb.

mp 250 °C (DMF); 65% yield; IR (KBr): υ 3213 (NH), 2189 (CN) cm^{-1}; m/z 630. Anal. Calcd for $C_{38}H_{30}N_8O_2$: C, 72.34; H, 4.79; N, 17.77. Found: C, 72.15; H, 4.63; N, 18.06 %.

11,12-dimethoxy-3-oxo-11,12-dimethoxy-2-phenylhydrazo-14-phenyl-8,14,4a-trihydro-2H,4H-benzo-[a]1,2,4-triazino[2',3'-6,1]pyrimidine[4,5-f]quinolizine-13- carbonitrile 17.

mp 190 °C (DMF); 64% yield; IR (KBr): υ 3309, 3209 (2NH), 2190 (CN); 1636 (CO) cm^{-1}; ^{1}H NMR

($CDC1_3$): δ 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (m, 2H), 4.4 (m, 1H), 5.1 (s, 1H), 6.6-8.2 (m, 15H); m/z 570. Anal. Calcd for $C_{32}H_{26}N_8O_3$: C, 67.33; H, 4.59; N, 19.64. Found: C, 67.54; H, 4.30; N, 19.44 %.

Synthesis of ethyl 7-cyano-4,5-dimethoxy-8-phenyl-1,2,8,11a,13b-pentahydroisoquinoline[2′,1′-6,1]-pyridino[2,3-d]1,2,4-triazolo[1,5-e]pyrimidine-10-carboxylate 20.

To a solution of **8** (2.1 g, 5 mmol) in EtOH (30 mL), diethyl oxalate (0.73 g, 5 mmol) was added. The reaction mixture was refluxed for 3 h, then cooled and the product that separated was coolected and crystallized from DMF to give product **20:** mp 235 °C (DMF); 60% yield; IR (KBr): υ 2195 (CN), 1715 (CO) cm^{-1}; ^1H NMR ($CDC1_3$): δ 1.4 (t, J = 7 Hz, 3H), 3.0 (m, 2H), 3.9 (s, 6H, $2CH_3$), 4.1 (m, 1H), 4.4 (m, 1H) 4.5 (q, J = 7 Hz, 2H), 5.6 (s, 1H), 6.8 (s,1H), 7.2-7.5 (m, 5H),7.9 (s, 1H), 9.2 (s, 1H); *m/z* 508. Anal. Calcd for $C_{28}H_{24}N_6O_4$: C, 66.11; H, 4.75; N, 16.53. Found: C, 66.35; H, 4.97; N, 16.32 %.

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