Studies with 6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl-acetonitrile: Novel Syntheses of 1-Azolyl- and Pyridoisoquinolines

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The reaction of 3,4-dihydroisoquinolin-1-yl-acetonitrile with DMFDMA afforded the enaminonitrile **5**. Compound **5** was reacted with 2-aminobenzimidazole to yield 4-amino-3-(dihydroisoquinolin-1-yl)-benzo[4,5]imidazo[1,2-*a*]pyrimidine (**11**) and with acetonitrile derivatives to afford pyrido[2,1-*a*]isoquinolines (**15a** – **g**).

Key words: (6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)-acetonitrile, Enaminonitrile, Malononitrile, 2-Aminobenzimidazole, DMFDMA

Introduction

The chemistry of isoquinolines has always been of considerable interest [1 – 5]. A large number of isoquinolines have important pharmacological applications as anesthetics (**1**), antihypertension agents like quinapril, quinaprilate and debrisoquine, antifungal agents such as 2,2′-hexadecamethylenedisoquinolinium dichloride (**2**), disinfectants like *N*-laurylisoquinolinium bromide (**3**) and vasodilators, with the well-known example of papaverine (**4**) (Fig. 1) [6 – 9].

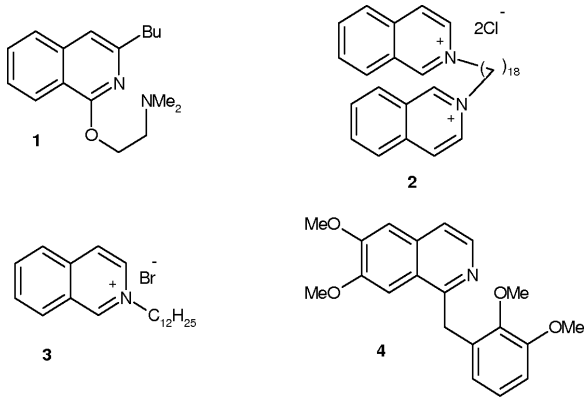
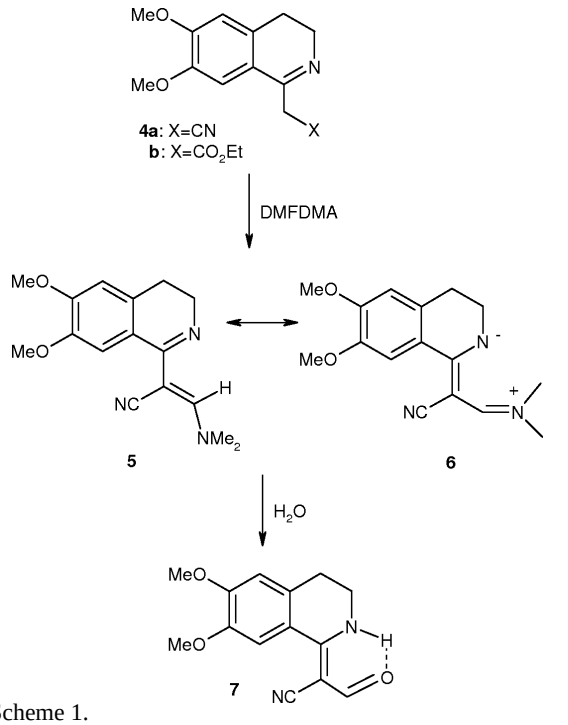


Fig. 1. Isochinoline moities.

Results and Discussion

In the last decade our group has been interested in developing syntheses for 1-substituted tetrahydroisoquinolines utilizing the readily obtainable 3,4-dihydroisoquinolines **4a**, **b** as starting materials [10 – 15]. In conjunction with this work we report here the synthesis and reactivity of enaminonitrile **5**. Thus, reacting **4a** with dimethylformamide dimethylacetal (DMFDMA) afforded the enamine **5** in excellent yield. Attempts to crystallize **5** from protic solvents resulted in ready hydrolysis into the formyl derivative **7**. The ready hydrolysis of **5** may be a result of electron withdrawal by the ring nitrogen atom that leads to a significant contribution of resonance form **6** (Scheme 1).

Compound **5** reacted with 2-aminobenzimidazole **8** to yield a product that may be formulated as 2-(3,4-dihydroisoquinolin-1-yl)-3-(1*H*-benzimidazol-2-ylamino)-acrylonitrile (**10**) or isomeric 4-amino-3-(3,4-dihydroisoquinolin-1-yl)-benzo[4,5]imidazo[1,2-*a*]pyrimidine (**11**). The structure of **11** was established based on an IR spectrum that revealed the absence of the nitrile absorption at $\sim 2200-2230$ cm^{-1} as required for the conjugated nitrile function in **10**. It is believed that 2-aminobenzimidazole **8** initially undergoes a Michael-type addition to **5** yielding intermediate Michael adduct **9** which readily loses dimethylamine to yield **10** which then cyclizes under the reaction conditions into **11**. Conclusive evidence for structure **11** was also obtained by independent synthesis from benzimidazol-2-yl-*N*,*N*-dimethylformamidine [16] **13** with **4a** (Scheme 2). However, the



Scheme 1.

possibility that Michael adduct **9** cyclized into **12** before eliminating dimethylamine to yield **10** cannot be excluded (Scheme 2).

Next, compound **5** also reacted readily with ethyl cyanoacetate to yield a product of condensation *via* dimethylamine elimination. This was formulated as **15a** rather than **14a** based on its ^{1}H NMR spectrum which revealed the absence of two doublets at $\delta \approx 5.6$ and 6.9 ppm for C-sp^3 protons. Similarly, malononitrile, sulfonylacetonitrile, *p*-toluylsulfonylacetonitrile, benzoylacetonitrile, cyanoacetamide and cyanoacetanilide also reacted with **5** to yield **15b** – **g**, respectively (Scheme 3).

The enaminonitrile **5** reacted with benzothiazol-2-yl-acetonitrile **16a** to yield a product of condensation *via* dimethylamine elimination, and several isomeric structures can be assumed for this adduct. X-Ray crystal structure determination confirmed the structure of pyrido[2,1-*a*]isoquinoline **17a** for this reaction product [17] (Fig. 2). It is thus believed that the active methylene nitrile moiety in benzothiazol-2-yl-acetonitrile has initially added to the activated double bond in **5** and this was followed by direct ring closure to give **17a**. Similarly, benzoimidazol-2-yl-acetonitrile **16b** reacted with **5** yielding **17b** (Scheme 3).

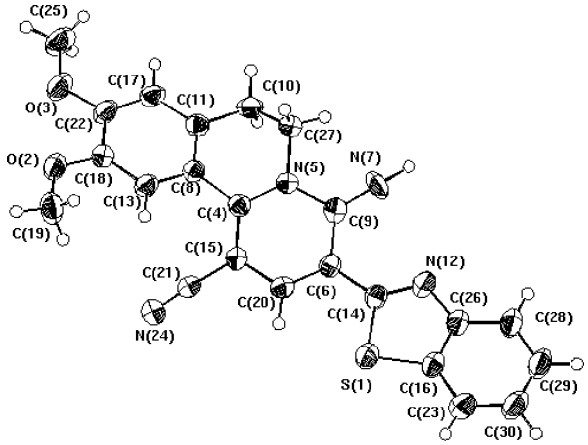
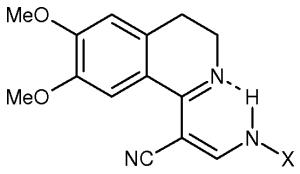


Fig. 2. Molecular structure of **17a**.



18a, X=NH$_2$
b, X=OH

Fig. 3. Acyclic enamine.

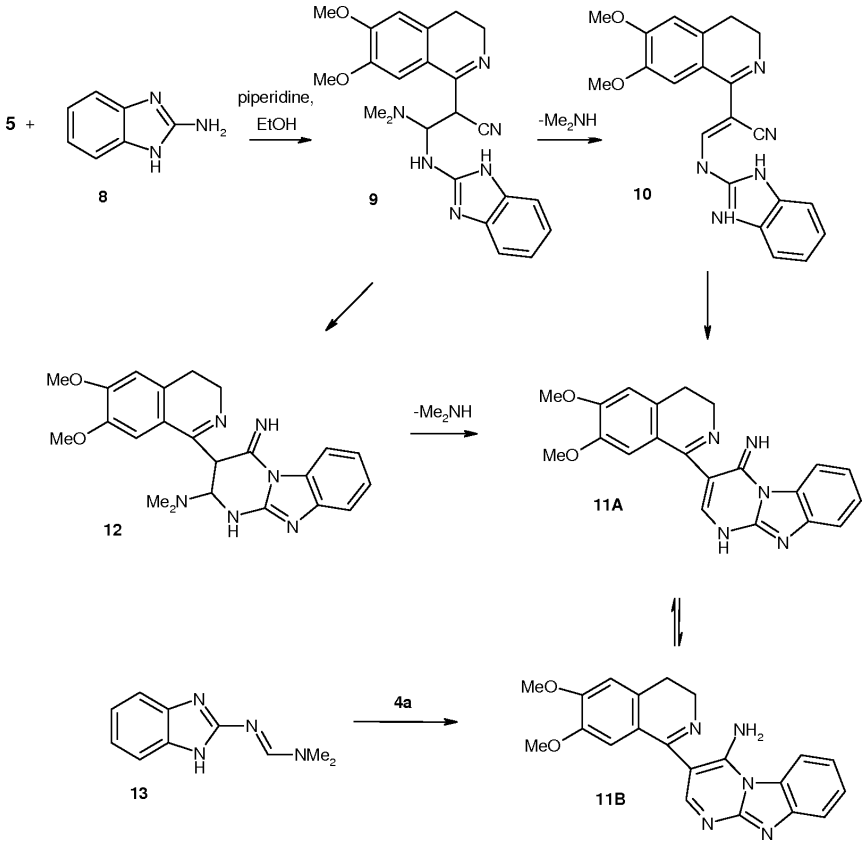
Attempts to prepare pyrazolyl- or isoxazolyl-isoquinolines *via* reaction of **5** with hydrazine hydrate and hydroxylamine hydrochloride, respectively, resulted only in the formation of acyclic enamines **18a**, **b**. These compounds could not be cyclized under a variety of conditions indicating most likely that these products adopted the hydrogen bonded *E* configuration (Fig. 3).

Conclusion

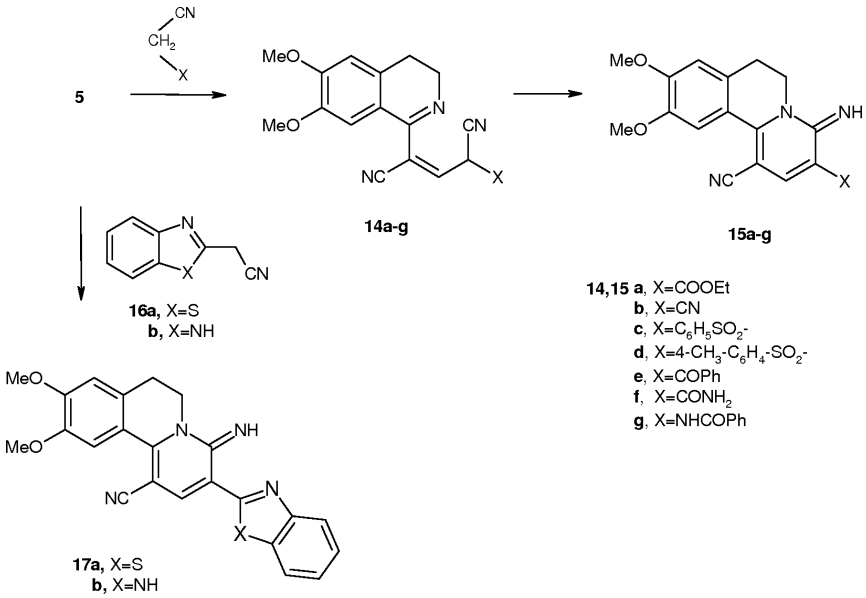
We could demonstrate that 3-dimethyamino-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-acrylonitrile (**5**) is a readily obtainable and versatile reagent which can easily be used for synthesizing both 1-azolyl- and pyrido[2,1-*a*]isoquinolines.

Experimental Section

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded from KBr pellets on a Pye Unicam SP 3-300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide [D$_6$]DMSO solu-



Scheme 2.



Scheme 3.

tion at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as internal reference. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

*3-Dimethylamino-2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-acrylonitrile (**5**)*

A mixture of **4a** (2.3 g, 0.01 mol) and DMFDMA (0.016 mol) was refluxed for 1 h. The solid product was filtered off and crystallized from dry benzene. – M. p. 155 °C. Yield: 85 %. – IR: $\nu = 2175$ (CN) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): $\delta = 2.56-2.62$ (m, 2H, CH_2), 3.25 (s, 6H, $2CH_3$), 3.48 – 3.55 (m, 2H, CH_2), 3.89 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 6.68 (s, 1H), 7.31 (s, 1H), 7.39 (s, 1H). – ^{13}C NMR (75 MHz, [D_6]DMSO): $\delta = 28.19$, 48.97, 57.96, 58.21, 77.51, 112.33, 113.08, 122.39, 123.54, 134.70, 149.06, 152.88, 152.92, 156.53, 164.29. – $C_{16}H_{19}N_3O_2$ (285.35): calcd. C 67.35, H 6.71, N 14.73; found C 67.25, H 6.65, N 14.61.

*2-(6,7-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-3-oxo-propionitrile (**7**)*

A solution of **5** was refluxed for 1 h in ethanol. The solid product was collected and crystallized from ethanol. – M. p. 193 °C. Yield: 80 %. – IR: $\nu = 1628$ (CO), 2187 (CN), 3155 (NH) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): $\delta = 2.84-2.91$ (m, 2H, CH_2), 3.46 – 3.55 (m, 2H, CH_2), 3.95 (s, 6H, $2CH_3O$), 6.74 (s, 1H), 7.99 (s, 1H), 9.35 (s, 1H), 12.06 (br., 1H, NH). – ^{13}C NMR (75 MHz, [D_6]DMSO): $\delta =$ 29.60, 40.96, 58.14, 58.32, 81.66, 112.69, 113.29, 119.86, 124.51, 134.02, 149.93, 155.15, 164.71, 190.17 (CO). – $C_{14}H_{14}N_2O_3$ (258.28): calcd C 65.11, H 5.46, N 10.85; found C 65.02, H 5.33, N 10.74.

*4-Amino-3-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-benzo[4,5]imidazo[1,2-a]-pyrimidine (**11**)*

Method A: A mixture of **5** (2.85 g, 0.01mol) and 2-aminobenzimidazole **8** (0.01 mol) was refluxed in ethanol in presence of piperidine for 3 h. The solid product was filtered off and crystallized from dimethylformamide to give **11**.

Method B: A mixture of **4a** (2.3 g, 0.01mol) and **13** (0.01 mol) was refluxed in ethanol in presence of piperidine for 3 h. The solid product was filtered off and crystallized from dimethylformamide to give **11**. – M. p. 222 °C. Yield: 75 %. – IR: $\nu = 3300$, 3283 (NH_2) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.64 – 2.69 (m, 2H, CH_2), 3.55 – 3.59 (m, 2H, CH_2), 3.71 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 6.97 (s, 1H), 7.01 (s, 1H), 7.09 – 7.78 (m, 4H, Ar-H), 8.44 (s, 1H), 9.37 (br., 2H, NH_2). – ^{13}C NMR (75 MHz, [D_6]DMSO): $\delta = 25.49$, 46.0, 55.77, 55.94, 111.14, 111.53, 112.03, 114.53, 118.39, 120.28, 121.24, 125.61, 130.25, 132.98, 146.89, 151.01, 152.18, 152.25, 152.25, 153.24, 163.74. – $C_{21}H_{19}N_5O_2$ (373.42): calcd C 67.55, H 5.13, N 18.75; found C 67.46, H 5.05, N 18.68.

*General procedure for preparation of compounds **15a – g** and **17a, b***

A mixture of **5** (2.85 g, 0.1 mol) and ethyl cyanoacetate, malononitrile, sulfonyl-acetonitrile, *p*-toluylsulfonylacetonitrile, benzoylacetonitrile, cyanoacetamide or cyanoacetanilide and benzothiazol-2-acetonitrile (**16a**) or benzoimidazol-2-acetonitrile (**16b**) (0.1 mol) was refluxed in ethanol for 1 h. A solid was formed which was collected by filtration and crystallized from dimethylformamide to give compounds **15a – g**, and **17a, b** respectively.

*Ethyl 1-cyano-4-imino-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]-isoquinolin-3-carboxylate (**15a**)*

M. p. 208 °C. Yield: 80 %. – IR: $\nu = 1705$ (CO), 2206 (CN), 3309 (NH) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): $\delta = 1.37$ (t, 3H, CH_3), 2.87 – 2.94 (m, 2H, CH_2), 3.97 (s, 6H, $2CH_3O$), 4.26 – 4.38 (m, 4H, $2CH_2$), 7.10 (s, 1H), 7.82 (s, 1H), 7.92 (s, 1H), 9.08 (br., 1H, NH). – ^{13}C NMR (75 MHz, [D_6]DMSO): $\delta = 14.03$, 26.76, 55.92, 56.09, 60.91, 81.18, 111.02, 111.55, 111.92, 118.22, 119.50, 133.62, 141.79, 147.10, 152.95, 153.01, 153.96, 154.67, 164.43. – $C_{19}H_{19}N_3O_4$ (353.38): calcd. C 64.58, H 5.42, N 11.89; found C 64.55, H 5.38, N 11.86.

*4-Imino-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1,3-dicarbonitrile (**15b**)*

M. p. 220 °C. Yield: 84 %. – IR: $\nu = 2207$, 2222 (2CN), 3320 (NH) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): $\delta =$ 2.87 – 2.92 (m, 2H, CH_2), 3.94 (s, 6H, $2CH_3O$), 4.25 – 4.36 (m, 2H, CH_2), 6.79 (s, 1H), 7.27 (br., 1H, NH), 7.48 (s, 1H), 7.84 (s, 1H). – ^{13}C NMR (75 MHz, [D_6]DMSO): $\delta = 29.50$, 43.69, 58.26, 58.39, 85.41, 102.39, 112.18, 113.54, 117.06, 120.16, 120.37, 134.64, 145.63, 150.05, 155.59, 156.08, 156.87. – $C_{17}H_{14}N_4O_2$ (306.33): calcd. C 66.66, H 4.61, N 18.29; found C 66.60, H 4.55, N 18.22.

*4-Imino-9,10-dimethoxy-3-phenylsulfonyl-6,7-dihydro-4H-pyrido[2,1-a]-isoquinoline-1-carbonitrile (**15c**)*

M. p. 242 °C. Yield: 83 %. – IR: $\nu = 2207$ (CN), 3344 (NH) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): $\delta = 2.87-2.90$ (m, 2H, CH_2), 3.97 (s, 6H, $2CH_3O$), 4.19 – 4.24 (m, 2H, CH_2), 6.77 (s, 1H), 7.59 – 7.65 (m, 3H, Ar-H), 7.89 (s, 1H), 7.96 – 7.98 (d, 2H, Ar-H), 8.11 (s, 1H), 8.22 (br., 1H, NH). – $C_{22}H_{19}N_3O_4S$ (421.48): calcd. C 62.69, H 4.54, N 9.97, S 7.61; found C 62.60, H 4.52, N 9.84, S 7.50.

*4-Imino-9,10-dimethoxy-3-(4-toluenesulfonyl)-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**15d**)*

M. p. 256 °C. Yield: 81 %. – IR: $\nu = 2199$ (CN), 3320 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.46$ (s, 3H, CH_3), 2.82 – 2.88 (m, 2H, CH_2), 3.96 (s, 6H, $2CH_3O$), 4.17 – 4.20 (m, 2H, CH_2), 6.77 (s, 1H), 7.26 (s, 1H), 7.36 – 7.40 (d, 2H), 7.79 – 7.83 (d, 2H). 8.07 (s, 1H), 8.16 (br., 1H, NH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 23.60$, 29.54, 43.05, 58.22, 58.36, 84.43, 112.07, 113.53, 120.44, 121.02, 125.94, 129.58, 132.11, 134.72, 138.66, 143.17, 147.07, 149.94, 154.54, 155.36, 156.82. – $C_{23}H_{21}N_3O_4S$ (435.51): calcd. C 63.43, H 4.86, N 9.65, S 7.36; found C 63.36, H 4.81, N 9.57, S 7.28.

*3-Benzoyl-4-imino-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**15e**)*

M. p. 210 °C. Yield: 80 %. – IR: $\nu = 1651$ (CO), 2206 (CN), 3294 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.93 - 300$ (m, 2H, CH_2), 3.97 (s, 3H, CH_3O), 3.99 (s, 3H, CH_3O), 4.19 – 4.24 (m, 2H, CH_2), 6.83 (s, 1H), 7.50 – 7.66 (m, 6H, Ar-H), 7.91 (s, 1H), 9.61 (br., 1H, NH). – $C_{23}H_{19}N_3O_3$ (385.43): calcd. C 71.68, H 4.97, N 10.90; found C 71.55, H 4.91, N 10.80.

*3-Aminocarbonyl-1-cyano-4-imino-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]-isoquinoline (**15f**)*

M. p. 266 °C. Yield: 74 %. – IR: $\nu = 1677$ (CO), 2207 (CN), 3062, 3190 (NH_2), 3347 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.88 - 2.90$ (m, 2H, CH_2), 3.81 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.09 – 4.14 (m, 2H, CH_2), 7.09 (s, 1H), 7.74 (s, 1H), 7.80 (s, 1H), 7.39 (br., 2H, NH_2), 9.33 (br., 1H, NH). – $C_{17}H_{16}N_4O_3$ (324.34): calcd. C 62.95, H 4.97, N 17.27; found C 62.88, H 4.92, N 17.15.

*1-Cyano-4-imino-9,10-dimethoxy-3-phenylaminocarbonyl-6,7-dihydro-4H-pyrido-[2,1-a]isoquinoline (**15g**)*

M. p. 262 °C. Yield: 80 %. – IR: $\nu = 1658$ (CO), 2205 (CN), 3001, 3343 (2NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.97 - 2.99$ (m, 2H, CH_2), 3.82 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.08 – 4.14 (m, 2H, CH_2), 7.09 – 7.12 (m, 2H), 7.32 – 7.37 (m, 2H), 7.64 – 7.67 (m, 3H), 7.81 (s, 1H), 8.95 (br., 1H, NH), 10.21 (br., 1H, NH). – $C_{23}H_{20}N_4O_3$ (400.44): calcd. C 68.99, H 5.03, N 13.99; found C 68.91, H 4.96, N 13.85.

*3-(Benzothiazol-2-yl)-4-imino-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**17a**)*

M. p. 266 °C. Yield: 81 %. – IR: $\nu = 2203$ (CN), 3249 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.94 - 2.99$ (m, 2H, CH_2), 3.83 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 4.24 – 4.28 (m, 2H, CH_2), 7.08 (s, 1H), 7.42 – 7.49 (m, 2H, Ar-H), 7.77 – 7.80 (m, 2H, Ar-H), 7.99 – 8.07 (m, 2H, Ar-H), 10.15 (br., 1H, NH). – $C_{23}H_{18}N_4O_2S$ (414.49): calcd. C 66.65, H 4.38, N 13.52, S 7.74; found C 66.59, H 4.32, N 13.48, S 7.65.

*3-(1H-Benzoimidazol-2-yl)-4-imino-9,10-dimethoxy-6,7-dihydro-4H-pyrido[2,1-a]-isoquinoline-1-carbonitrile (**17b**)*

M. p. 264 °C. Yield: 83 %. – IR: $\nu = 2201$ (CN), 3141, 3354 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.72 - 2.97$ (m, 2H, CH_2), 3.77 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 4.23 – 4.27 (m, 2H, CH_2), 7.11 (s, 1H), 7.22 – 7.55 (m, 4H, Ar-H), 7.62 (br., 1H, NH), 7.86 (s, 1H), 8.05 (s, 1H), 10.54 (br., 1H, NH). – $C_{23}H_{19}N_5O_2$ (397.44): calcd. C 69.51, H 4.82, N 17.62; found C 69.42, H 4.73, N 17.45.

*General procedure for preparation of compounds **18a**, **b***

A mixture of **5** (2.85 g, 0.1 mol) and hydrazine hydrate or hydroxylamine hydrochloride (0.1 mol) was refluxed in ethanol in the presence of piperidine (0.1 mol) for 1 h. A solid was formed and collected by filtration and crystallized from dimethylformamide to give compounds **18a**, **b**, respectively.

*2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)-3-hydrazino-acrylonitrile (**18a**)*

M. p. 253 °C. Yield: 77 %. – IR: $\nu = 2203$ (CN), 3205 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.66 - 2.69$ (m, 2H, CH_2), 3.76 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 4.22 – 4.27 (m, 2H, CH_2), 6.99 (s, 1H), 7.01 (s, 1H), 8.18 (s, 1H), 14.21 (br., 3H, NH_2, NH). – $C_{14}H_{16}N_4O_2$ (272.31): calcd. C 61.75, H 5.92, N 20.57; found C 61.55, H 5.72, N 20.47.

*2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)-3-hydroxylamino-acrylonitrile (**18b**)*

M. p. 188 °C. Yield: 77 %. – IR: $\nu = 2187$ (2CN), 3162 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.84 - 2.87$ (m, 2H, CH_2), 3.47 – 3.52 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 7.00 (s, 1H), 7.76 (s, 1H), 7.80 (br., 1H, NH), 9.26 (s, 1H). – $C_{14}H_{15}N_3O_3$ (273.29): calcd. C 61.53, H 5.53, N 15.38; found C 61.33, H 5.22, N 15.31.

*Crystallographic analysis of **17a***

Crystals were mounted on a glass fiber. X-ray data collection was performed on an Enraf Nonius FR 590 diffractometer at 20 ± 1 °C using ω scans. The structure was solved by Direct Methods using SIR 92 and refined by full-matrix least-squares. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically. – *Crystal data*: $C_{23}H_{18}N_4O_2S$, $M_r = 414.487$, triclinic, space group $P\bar{1}$, $a = 8.4542(4)$, $b = 8.8390(4)$, $c = 13.4641(7)$ Å, $\alpha = 104.123(2)$, $\beta =$

95.198(3), $\gamma = 90.543(2)^\circ$, $Z = 2$, $D_x = 1.417\ \mathrm{Mg\,m^{-3}}$, 5521 reflections measured, $\theta_{max} = 27.8^\circ$, $wR = 0.113$. Fig. 2 shows the molecular structure. Further crystal structure data have been deposited.

CCDC 611653 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

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[17] Crystal data of **17a** (CCDC 611653) can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.