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COMPETITIVE FORMATION OF CONDENSED AZINES AND DIHYDROPYRIDINES IN THE REACTION OF ETHYL 3,3-DIAMINO-ACRYLATE WITH *o*-HALO CARB-ALDEHYDES

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The reaction of ethyl 3,3-diaminoacrylate with quinoline-3-carbaldehydes and 3-nitrobenzaldehydes to give a dihydropyridine and condensed azine has been studied with respect to the number and reactivity of the halogen atoms in an ortho position to the formyl groups. For the series of quinoline-3-carbaldehydes it was found that the reaction course is determined by the number of chlorine atoms. 2- and 4-Chloroquinoline-3-carbaldehydes give dihydropyridines and a benzo[c][2,7-]naphthyridine is formed in the reaction with 2,4-dichloroquinoline-3-carbaldehyde. The main products in the case of nitrobenzaldehydes are dihydropyridines which points the deciding influence of the low electrophilicity of aromatic ring.

Keywords: benzonaphthyridine, dihydropyridine, ethyl 3,3-diaminoacrylate, Hantzsch reaction, cyclocondensation.

In our recent study of the reaction of α-acylacetamidines (which exist in solution in the tautomeric enediamine form) with 2-fluoro-5-nitrobenzaldehyde (**1**) and 4,6-dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde (**2**) the main reaction products are isoquinolines and pyrido[4,3-*d*]pyrimidines respectively [1, 2]. α-Acylacetamidines react as C,N-dinucleophiles. The reaction occurs with a uniform chemo-selectivity: the amidine α-carbon substitutes the halogen atom in the aromatic ring and the amino group binds to the formyl carbon atom. However, in the case of the reaction of ethyl 3,3-diaminoacrylate (**3**) with the aldehyde **1** the cyclocondensation is accompanied by a concurrent Hantzsch type reaction to form the dihydropyridine **6**. This reaction occurs using two molecules of the enediamine and one molecule of the aldehyde. Moreover, only the carbonyl group in the aldehyde reacts, the halogen atom at the aromatic ring being unaffected. In addition, a marked amount of the quinoline **5** is observed in the reaction which, as the dihydropyridine **6**, is formed as a result of an attack by the carbon nucleophilic center of the enediamine at the formyl group. At the same time, the reaction of enediamine **3** with compound **2** gives only the corresponding pyrido[4,3-*d*]pyrimidine in virtually quantitative yield.

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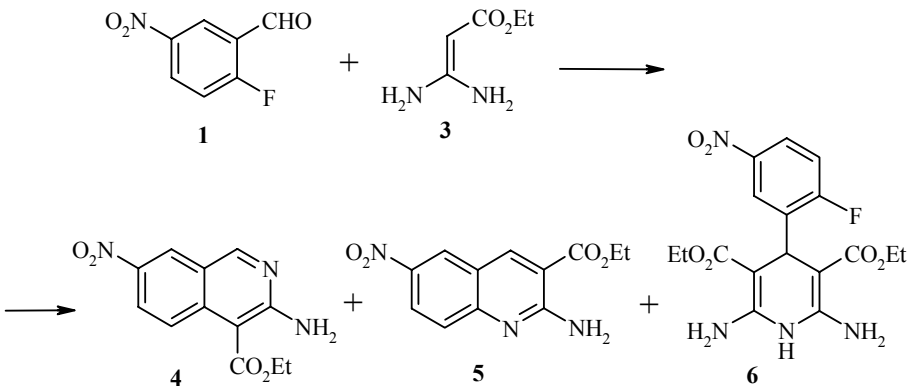
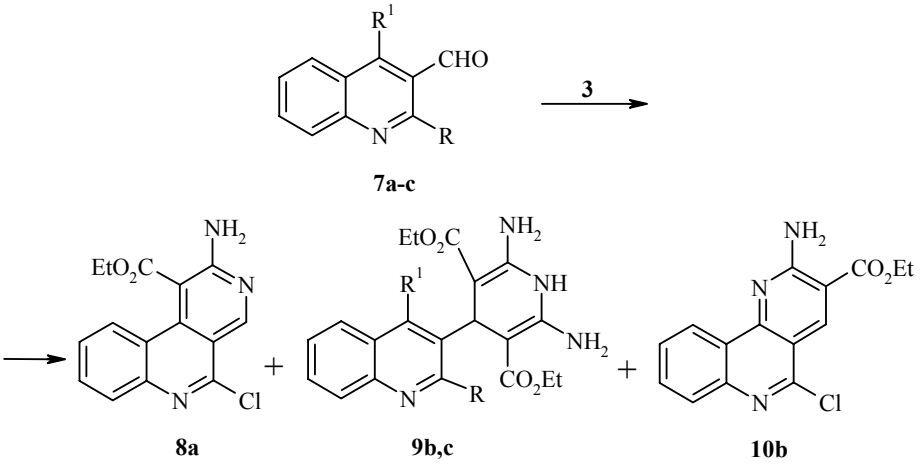


We propose that the different direction of the reaction of enediamine **3** with the aldehydes **1** and **2** occurs for two reasons. The first is a marked increase in the electrophilicity of the carbon atom bound with the halogen atom (increased halogen "activity") relative to the formyl group on changing from the benzaldehyde **1** to the pyrimidinecarbaldehyde **2**. The second is the presence of two *ortho* substituents in the carbaldehyde **2** which hinder the approach of the carbon nucleophilic center to the formyl group. In order to evaluate the effects of these factors on the reaction course we have studied the behavior of enediamine **3** in reactions with some π-deficient aldehydes differing in the number and reactivity of the halogen atoms in an *ortho* position to the formyl group.

The reactions were carried out in DMF at room temperature. The structure of the compounds prepared was confirmed from their ^{1}H and ^{13}C NMR spectra.

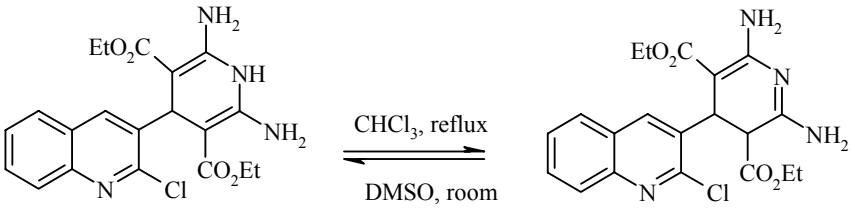


8a R = R^1 = Cl (77%); **9b** R = Cl, R^1 = H (42%), **c** R = H, R^1 = Cl (72%);
10b R = Cl, R^1 = H (25%)

The reaction of aldehyde **7a** with enediamine **3** gave the benzo[*c*][2,7]naphthyridine **8a** in 77% yield. Its NOESY correlation spectrum showed strong cross peaks between the signal for the methylene in the carbethoxy fragment and the H-10 proton doublet (7.97 ppm).

Treatment of the enediamine **3** with aldehyde **7b** gave the dihydropyridine **9b** as the main product. ^{1}H NMR of the reaction mixture of the dihydropyridine **9b** showed it to exist as the two tautomeric 1,4- and 3,4-dihydro forms in the ratio 10:7. However, on recrystallization from chloroform the 1,4-dihydropyridine **9b** is converted to the 3,4-dihydro form **9b'** which was separated and characterized. In the ^{1}H NMR spectrum of

the 3,4-dihydropyridine **9b'** the signals for the protons in positions 3 and 4 of the dihydropyridine ring appear as singlets. For proof of structure the COSY spectrum of the 3,4-dihydropyridine **9b'** was recorded and showed cross peaks due to weak spin-spin interaction between these protons. In addition weak cross peaks between the proton in position 4 of the dihydropyridine ring and the proton at position 4 of the quinoline ring were observed. Prolonged holding (~ 1 month) of the 3,4-dihydropyridine **9b'** in DMSO-d_6 solution caused complete conversion to the 1,4-dihydro form **9b**.



9b **9b'**

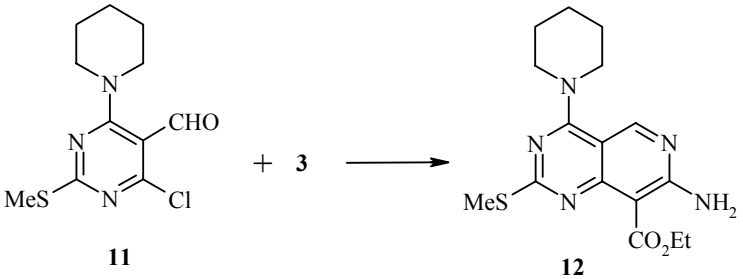
Besides the main product in this reaction the benzo*[h]*[1,6]naphthyridine **10b** was unexpectedly formed (25% yield). Its structure was identified by ^{1}H, ^{13}C, and NOESY spectra. Cross peaks were observed in the NOESY correlation spectrum due to NOE between the proton in position 4 and the ethoxycarbonyl group protons.

Related reactions have been described before [4]. The authors carried out a direct, noncatalyzed amination of a 5-azacinnoline using different amines. It was found that the oxidant in these reactions is atmospheric oxygen.

The reaction of the enediamine **3** with aldehyde **7b** was also carried out in alternative conditions, in fact at 50ºC and with stepwise addition of a solution of the enediamine **3** to a solution of the aldehyde in DMF. The yield of benzo[*h*][1,6]naphthyridine **10b** was 33%. When carrying out the reaction of aldehyde **7b** with the hydrochloride of the enediamine **3** in DMF in the presence of potassium carbonate at room temperature (conditions reported in [1]) only a 2:1 mixture of the 1,4-dihydropyridine **9b** and 3,4-dihydropyridine **9b'** was obtained and did not contain the benzonaphthyridine **10b**.

Reaction of aldehyde **7c** with the enediamine **3** also gives only the dihydropyridine **9c** as a mixture of tautomeric the 1,4- and 3,4-dihydroforms (ratio ~ 6:1) and containing a small amount of admixture. Pure 1,4-dihydropyridine **9c** was obtained in 86% yield by carrying out the reaction of aldehyde **7c** with the hydrochloride of the enediamine **3** in DMF at room temperature in the presence of potassium carbonate. The tautomeric 3,4-dihydropyridine is not observed when carrying out the reaction under these conditions. Despite the position 4 of the quinoline ring being more active towards nucleophilic attack than the position 2 we also did not observe the formation of benzonaphthyridines (products of substitution of the chlorine atom) in this case.

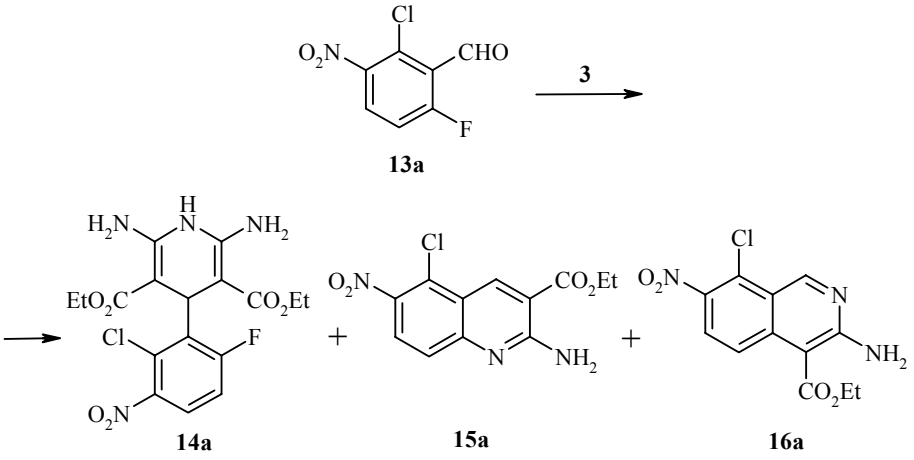
Aldehyde **11** reacts with the enediamine **3** by the same route as its analog – 4,6-dichloro-2-methylsulfanylpyrimidine-5-carbaldehyde (**2**) [2]. Only the single pyrido[4,3-*d*]pyrimidine product **12** was separated.



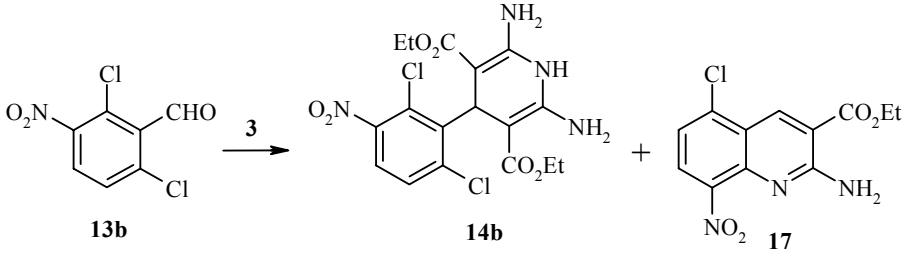
11 **12**

Its structure was confirmed from ^{1}H and ^{13}C NMR data. The value of the direct $^{1}J_{C5\text{-}H}$ spin-spin coupling of 179 Hz points to a positioning of the CH fragment directly next to the pyridine nitrogen atom thus allowing a choice between the two isomeric pyridopyrimidines. Cross peaks are seen in the NOESY correlation spectrum due to NOE between the methylsulfanyl group protons and those of the ethoxycarbonyl group which points to their relative close proximity and is only realized in the pyrido[4,3-*d*]pyrimidine structure **12**. As we expected the aldehyde **11** proved markedly less active than the aldehyde **2**, its reaction occurring at room temperature over 3.5 month while that with aldehyde **2** occurred over several minutes.

The reaction of enediamine **3** with aldehyde **13a** (as with aldehyde **1** [1]) gives a mixture of the dihydropyridine **14a** and, presumably, the quinoline **15a** and isoquinoline **16a** in the ratio 5:2:2. When the reaction was carried out using the enediamine hydrochloride in the presence of potassium carbonate the pure 1,4-dihydropyridine **14a** was obtained in 89% yield. Compounds **15a** and **16a** could not be separated and conclusions about their structure are only made on the basis of the ^{1}H NMR spectrum of the reaction mixture.



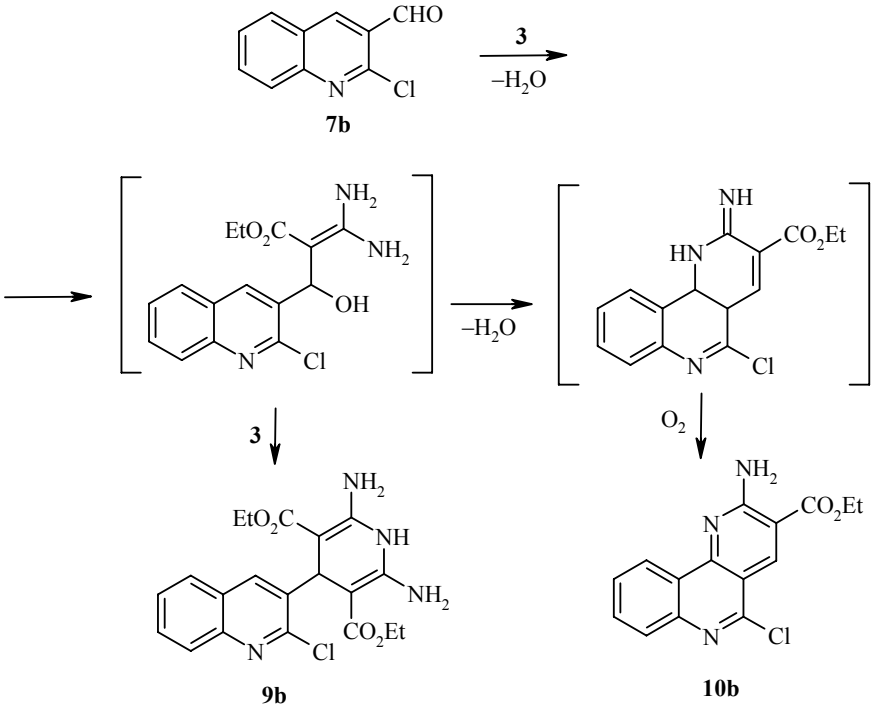
The aldehyde **13b** proved to be much less active than aldehyde **13a** and its reaction significantly slower. A 2:1 mixture of the dihydropyridine **14b** and quinoline **17** was obtained. The dihydropyridine **14b** exists as a 2:1 mixture of two rotamers as shown by the double set of signals in the ^{1}H NMR spectrum.



The quinoline structure is, in fact, indicated for compound **17** by the value of the direct $^{1}J_{C4\text{-}H}$ spin-spin coupling of 166.3 Hz (for C-1 in isoquinoline $^{1}J_{C1\text{-}H}$ = 178 Hz and for C-4 in quinoline $^{1}J_{C4\text{-}H}$ = 162 Hz [3], depending little on the nature of the ring substituent). The fact that the chlorine atom is actually situated in an *ortho* position to the nitro group can be deduced since the ^{1}H NMR spectrum of quinoline **17** does not coincide with the spectrum of quinoline **15a** formed by the reaction of enediamine **3** with aldehyde **13a**.

The results of the reactions in the quinolinecarbaldehyde series convincingly prove a decisive role for the presence of two chloro atoms in *ortho* positions to the formyl group for determining the reaction route. While in the reactions with aldehydes **7b** and **7c** the halogen atoms are not affected but the dihydropyridines **9b**

and **9c** are formed the aldehyde **7a** gives only the benzonaphthyridine **8a**. The reaction occurs at the more active 4 position. The formation of the benzonaphthyridine **10b** in the reaction of aldehyde **7b** with enediamine **3** is somewhat unexpected. However, it also agrees with our proposal that it is the product of oxidation of the secondary intermediate, most likely formed after addition of one molecule of the enediamine carbon nucleophilic center to the formyl group and cyclization by addition of the amino group to position 4.



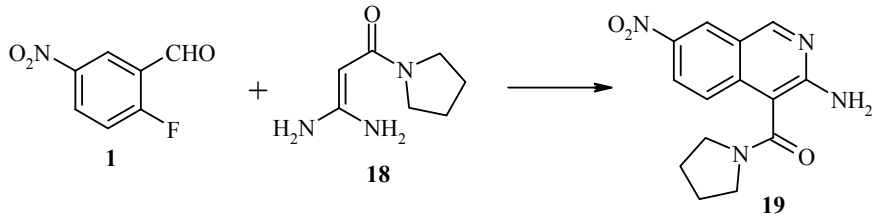
The aldehyde **11** reacts with the same chemoselectivity as the chloropyrimidinecarbaldehyde **2** [2] and, in fact, the carbon nucleophilic center takes part in the stage of aromatic nucleophilic substitution of the halogen and the nitrogen atom of the enediamine forms a bond with the formyl group. This result confirms the proposal that the effect of the two *ortho* substituents is to hinder the approach to the formyl group and this determines the reaction course despite the lowered activity of the ring.

The result of the reaction of enediamine **3** with aldehyde **13a** is overall similar to the result with aldehyde **1**. A marked effect was not observed for the additional chlorine atom in the *ortho* position. However some increase was seen in the fraction of cyclocondensation products involving the fluorine atom. In fact, the ratio of dihydropyridine **14a**, quinoline **15a**, and isoquinoline **16a** is 5:2:2 in the separated mixture while it is 10:3:3 for the analogous products in the reaction with aldehyde **2**.

The aldehyde **13b** proved to be markedly less reactive. The outcome of its reaction with enediamine **3** does not agree with the initial proposal for the effect on the reaction course of the two halogen atoms in the *ortho* position to the formyl group. Both main separated products, dihydropyridine **14b** and quinoline **17** are formed *via* attack of the carbon nucleophilic center of the enediamine at the formyl group. It may be linked to the very low reactivity of the ring (chlorine atom "activity") in aldehyde **13b**. Becides that the chlorine is strongly less active than the fluorine, the presence of the chlorine atom *ortho* to the nitro group possible decreases its electron acceptor influence on the ring. Hence it can be proposed that the aromatic nucleophilic substitution reaction takes place so slowly in this case that the addition at the formyl group predominates despite the steric hindrance. Moreover, for the intermediate formed after addition of one molecule of enediamine, there are two possible routes for continuing the reaction. The first is addition of a second molecule

to form the dihydropyridine and the second is cyclization with substitution of a chlorine atom to form the quinoline **17**. This is a very similar result to that achieved in the reaction of enediamine **3** with 2-chloroquinoline-3-carbaldehyde (**7b**) where, in addition to the dihydropyridine **9b** formed by the Hantzsch reaction, some amount of the product of initial attack of the α-carbon at the formyl group is formed and this is subsequently cyclized to an aromatic ring. In this case, even in the absence of a leaving group, cyclization occurs at the more active 4 position *via* oxidative substitution of a hydrogen atom. For the 2,6-dichloro-3-nitrobenzaldehyde (**13b**) the chlorine atom situated *ortho* to the nitro group is more active.

It was noted that only in the case of the single enediamine (diaminoacrylate **3** [1]) does the reaction of enediamines with aldehyde **1** form a dihydropyridine. Thus the reaction of aldehyde **1** with the enediamine **18** forms only the isoquinoline **19** in high yield.



Furthermore, even in reaction with 2-chloro-5-nitrobenzaldehyde in which the halogen atom is markedly less active, the enediamine **18** gives only the isoquinoline **19** although in low yield (30%). Characteristic signals for a dihydropyridine of type **6** were completely absent in the ^{1}H NMR spectrum of the reaction mixture.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (300 and 75 MHz) using DMSO-d_6 (compounds **8a, 9b',c, 10b, 12, 13a, 14a, 17, 19**) or $CDCl_3$ (compound **11**) solvent with the signals of the solvent at 2.50 and 7.26 ppm for the ^{1}H nucleus and 39.7 and 77.7 ppm for the ^{13}C nucleus respectively. The spin-spin couplings in the ^{1}H NMR spectra were measured to a first order approximation. Mass spectra were taken on a Finnigan MAT Incos 50 instrument. Elemental analysis was carried out on a Hewlett Packard HP-185B CHN analyzer. The purity of the materials and extent of the reaction course were monitored by TLC on Silufol UV-254 plates. Aldehydes **13a** and **13b** were prepared by nitration of commercially available 6-chloro-2-fluoro- and 2,6-dichlorobenzaldehydes under the conditions reported for 2-fluoro-5-nitrobenzaldehyde (**1**) [5].

Reaction of Diaminoacrylate 3 with 2,4-Dichloroquinoline-3-carbaldehyde (7a) [6]. Enediamine **3** (1.17 g, 9.0 mmol) was added to a solution of aldehyde **7a** (0.97 g, 4.3 mmol) in dry DMF (5 ml). The solution was left overnight at 4ºC. The precipitate was filtered, washed with water, and dried to give **ethyl 2-amino-5-chlorobenzo[*c*][2,7]naphthyridine-1-carboxylate (8a)** (1.0 g, 77%); mp 225-227ºC. A sample purified for analysis was prepared by crystallization from acetonitrile. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.3, CH_3); 4.48 (2H, q, *J* = 7.3, CH_2); 7.24 (2H, s, NH_2); 7.66 (1H, t, *J* = 7.8, H-9); 7.82 (1H, t, *J* = 7.8, H-8); 7.89 (1H, d, *J* = 7.8, H-10); 7.97 (1H, d, *J* = 7.8, H-7); 9.23 (1H, d, H-3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.4 (CH_3); 63.0 (CH_2); 102.3 (C-1); 112.5 (C-10a); 121.5 (C-4a); 126.5 (C-9); 127.8 (C-10); 129.9 (C-8); 132.4 (C-7); 139.1 (C-10b); 146.0 (C-6a); 150.8 (C-2); 153.5 (C-4; $^1J_{C\text{-}H}$ = 183); 158.9 (C-5); 169.4 (CO). Found, %: C 59.90; H 4.00; N 13.78. $C_{15}H_{12}ClN_3O_2$. Calculated, %: C 59.71; H 4.01; N 13.93.

Reaction of Diaminoacrylate 3 with 2-Chloroquinoline-3-carbaldehyde (7b). A. Enediamine **3** (1.02 g, 7.8 mmol) was added to a solution of compound **7b** [7] (0.72 g, 3.7 mmol) in dry DMF (10 ml) and left for 4 days at room temperature. Solvent was evaporated at 40ºC at reduced pressure. The residue was treated with water (40 ml) and left for 2 h at 4ºC. The precipitate was filtered off, washed with water, and dried to give a mixture (1.3 g) of dihydropyridine **9b**, dihydropyridine **9b'**, and the benzonaphthyridine **10b**. Signals for the 1,4-dihydropyridine **9b** were seen in the ^{1}H NMR spectrum of the mixture at 0.95 (6H, t, J = 8.0, CH_3); 3.84 (4H, q, J = 8.0, CH_2); 5.06 (1H, s, H-4); 7.17 (4H, s, NH_2), and 8.71 ppm (1H, s, NH). The crystals obtained were mixed with chloroform (35 ml) and heated to reflux and the precipitate formed in the solution was filtered off, washed with water, and dried to give **diethyl 2,6-diamino-4-(2-chloro-3-quinolyl)-3,4-dihydropyridine-3,5-dicarboxylate (9b')** (0.65 g, 42%); mp 253-255ºC. A sample purified for analysis was prepared by crystallization from acetonitrile. ^{1}H NMR spectrum, δ, ppm: 0.93 (3H, t, J = 7.4, CH_3); 1.18 (3H, t, J = 7.3, CH_3); 3.63 (1H, s, H-3); 3.78 (1H, m, CH_2); 3.91 (1H, m, CH_2); 4.16 (2H, m, CH_2); 4.90 (1H, s, H-4); 6.72 (1H, s, 2-NH_2); 7.30 (1H, s, 3-NH_2); 7.53 (1H, s, 3-NH_2); 7.60 (1H, t, J = 8.0, H_{quin}-7); 7.77 (1H, s, H_{quin}-4); 7.78 (1H, t, J = 8.0, H_{quin}-6); 7.95 (2H, d, H_{quin}-5,8); 8.09 (1H, s, 2-NH_2). ^{13}C NMR spectrum, δ, ppm: 14.4 (CH_3); 15.0 (CH_3); 37.1 (C-4); 48.5 (C-3); 57.9 (CH_2); 61.5 (CH_2); 72.6 (C-5); 127.4 (C_{quin}-3); 127.9 (C_{quin}-6); 128.18 (C_{quin}-8); 128.22 (C_{quin}-5); 130.9 (C_{quin}-7); 134.8 (C_{quin}-4a); 137.2 (C_{quin}-4); 146.6 (C-2); 150.7 (C_{quin}-8a); 162.3 (C_{quin}-2); 168.3 (CO); 168.7 (CO). Found, %: C 57.49; H 5.11; N 13.44. $C_{20}H_{21}ClN_4O_4$. Calculated, %: C 57.63; H 5.08. N 13.44.

Benzonaphthyridine 10b contained in the filtrate was purified chromatographically eluting with chloroform containing 2% methanol. Recrystallization from ethanol gave **ethyl 2-amino-5-chloro-benzo[*h*][1,6]naphthyridine-3-carboxylate (10b)** (0.27 g, 25%); mp 181-183ºC. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.39 (3H, t, J = 7.3, CH_3); 4.40 (2H, q, J = 7.3, CH_2); 7.71 (1H, t, J = 8, H-9); 7.85 (1H, t, J = 8, H-8); 7.90 (1H, d, J = 8, H-10); 7.99 (1H, s, NH_2); 8.23 (1H, s, NH_2); 8.74 (1H, d, J = 8, H-7); 8.86 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 14.9 (CH_3); 62.4 (CH_2); 109.9 (C-3); 112.9 (C-4a); 124.2 (C-10a); 125.1 (C-9); 127.9 (C-10); 128.9 (C-8); 132.7 (C-7); 140.6 (C-4); 146.8 (C-6a); 150.4 (C-10b); 153.4 (C-2); 160.4 (C-5); 166.1 (CO). Mass spectrum, (EI, 70 eV), m/z (I_{rel}, %): 418 (12), 416 (34), 343 (100), 297 (26), 235 (23), 136 (21). Found, %: C 59.65; H 4.37; N 13.55. $C_{15}H_{12}ClN_3O_2$. Calculated, %: C 59.71; H 4.01; N 13.93.

B. A solution of the enediamine **3** (0.534 g, 4.1 mmol) in dry DMF (3 ml) was added dropwise with stirring to a solution of aldehyde **7b** (0.358 g, 1.9 mmol) in dry DMF (4 ml) over 9 h and left at room temperature overnight. The precipitate was filtered off, washed with water, and dried to give the benzonaphthyridine **10b** (0.185 g, 33%); mp 183-185ºC. Water (40 ml) was added dropwise to the filtrate and left for 2 h at 4ºC. The precipitate was filtered off, washed with water, and dried to give a mixture (195 mg) of dihydropyridine **9b** and dihydropyridine **9b'** in the ratio 10:7.

C. Potassium carbonate (0.9 g, 6.6 mmol) was added to a solution of the aldehyde **7b** (0.6 g, 3.1 mmol) and the enediamine hydrochloride **3** (1.1 g, 6.6 mmol) in dry DMF (10 ml), stirred for 4 h at room temperature, and left overnight. The reaction mixture was then poured into water (40 ml) and the precipitate formed was filtered off, washed with water, and dried to give a mixture (1.16 g, 89%) of the dihydropyridine **9b** and dihydropyridine **9b'** in the ratio 2:1.

Reaction of Diaminoacrylate 3 with 4-Chloroquinoline-3-carbaldehyde (7c). A. The enediamine **3** (0.6 g, 4.6 mmol) was added to a solution of the aldehyde **7c** [8] (0.42 g, 2.2 mmol) in dry DMF (5 ml) and then left overnight at room temperature. Solvent was evaporated off at 40ºC under reduced pressure. Water (20 ml) was added to the residue and left for 2 h at 4ºC. The precipitate was filtered off, washed with water, and dried to give a mixture (0.77 g, 72%) of the 1,4-dihydropyridine **9c** and 3,4-dihydropyridine **9c'** in the ratio ~ 6:1.

B. K_2CO_3 (0.705 g, 5.1 mmol) was added to a solution of the aldehyde **7c** (0.465 g, 2.4 mmol) and enediamine hydrochloride **3** (0.85 g, 5.1 mmol) in dry DMF (10 ml) and stirred for 4 h at room temperature. The reaction mixture was left overnight and poured into water (40 ml). The precipitate formed was filtered off, washed with water, and dried to give **diethyl 2,6-diamino-4-(4-chloro-3-quinolyl)-1,4-dihydropyridine-**

3,5-dicarboxylate (9c); mp 220-225ºC (decomp.). A sample purified for analysis was prepared by recrystallization from methylene chloride. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.96 (6H, t, *J* = 7.4, CH_3); 3.83 (4H, m, CH_2); 5.20 (1H, s, H-4); 7.16 (4H, s, NH_2); 7.68 (1H, t, *J* = 8.0, H_{quin}-7); 7.73 (1H, t, *J* = 8.0, H_{quin}-6); 7.95 (1H, d, *J* = 8.0, H_{quin}-5); 8.22 (1H, d, *J* = 8.0, H_{quin}-8); 8.68 (1H, d, H_{quin}-2); 8.71 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 15.2 (CH_3); 35.0 (C-4); 58.8 (CH_2); 76.9 (C-3); 124.6 (C_{quin}-3); 126.6 (C_{quin}-6); 128.4 (C_{quin}-5); 129.78, 129.82 (C_{quin}-4a,7); 137.8 (C_{quin}-8); 140.7 (C_{quin}-4); 147.1 (C-2); 152.8 (C_{quin}-8a); 154.8 (C_{quin}-2); 169.1 (CO). Found, %: C 57.19; H 5.28; N 13.64. $C_{20}H_{21}ClN_4O_4$. Calculated, %: C 57.63; H 5.08; N 13.44.

6-Chloro-2-methylsulfanyl-4-(1-piperidyl)pyrimidine-5-carbaldehyde (11). A solution of piperidine (0.38 g, 4.5 mmol) and triethylamine (0.46 g, 4.5 mmol) in absolute acetonitrile (5 ml) was added dropwise with stirring to a solution of the 2-methylsulfanyl-4,6-dichloropyrimidine-5-carbaldehyde (**2**) [9] (1 g, 4.5 mmol) in absolute acetonitrile (20 ml). The reaction mixture was stirred at room temperature for 3 h, left overnight, poured into water, and the precipitated crystals were filtered off, dried and recrystallized from acetonitrile. Yield of aldehyde **11** 0.81 g (66%); mp 120-122ºC. ^{1}H NMR spectrum, δ, ppm: 1.61 (6H, m, $CH_2CH_2CH_2$); 2.46 (3H, s, SCH_3); 3.54 (4H, m, CH_2NCH_2); 10.01 (1H, s, CHO).

Reaction of Diaminoacrylate 3 with 6-Chloro-2-methylsulfanyl-4-(1-piperidyl)pyrimidine-5-carbonitrile (11). Enediamine **3** (0.3 g, 2.3 mmol) was added to a solution of the aldehyde **11** (0.3 g, 1.1 mmol) in dry DMF (3 ml). It was left at room temperature for 4 months. The reaction mixture was poured into water and left for 2 h at 4ºC. The precipitate was filtered off, carefully washed with water, and dried. Recrystallization from acetonitrile gave **ethyl 7-amino-2-methylsulfanyl-4-(1-piperidyl)pyrido[4,3-*d*]pyrimidine-8-carboxylate (12)** (230 mg, 60%); mp 149-151ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.3, CH_3); 1.65 (6H, s, $CH_2CH_2CH_2$); 2.46 (3H, s, SCH_3); 3.73 (4H, s, CH_2NCH_2); 4.29 (2H, q, *J* = 7.3, CH_2); 7.09 (2H, s, NH_2); 8.72 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 14.3 ($OCH_2\underline{C}H_3$); 15.0 (SCH_3); 24.8 ($NCH_2CH_2\underline{C}H_2$); 26.4 ($NCH_2\underline{C}H_2CH_2$); 50.8 ($N\underline{C}H_2CH_2CH_2$); 61.3 ($O\underline{C}H_2CH_3$); 99.0 (C-8); 102.8 (C-4a); 153.1 (C-7); 156.3 (C-5, $^1J_{C—H}$ = 179); 160.0 (C-4); 162.3 (C-8a); 168.3 (CO); 171.5 (C-2). Found, %: C 55.37; H 5.94; N 20.09. $C_{16}H_{21}N_5O_2S$. Calculated, %: C 55.31; H 6.09; N 20.16.

Reaction of Diaminoacrylate 3 with 2-Chlorobenzaldehyde-6-fluoro-3-nitro- (13a). A. The enediamine **3** (0.805 g, 6.2 mmol) was added to a solution of compound **13a** (0.6 g, 2.5 mmol) in dry DMF (5 ml) and left overnight at room temperature. Solvent was evaporated off at 40°C under reduced pressure and water (30 ml) was added to the residue. It was left for 2 h at 4°C and the precipitate formed was filtered off, washed with water, and dried to give a mixture (1.15 g) of the dihydropyridine **14a**, quinoline **15a**, and isoquinoline **16a** in the ratio 5:2:2. ^{1}H NMR signals were seen for the quinoline **15a** (*J*, Hz) at 1.37 (3H, t, *J* = 7.3, CH_3); 4.40 (2H, q, *J* = 7.3, CH_2); 7.53 (2H, s, NH_2); 8.02 (1H, d, *J* = 9.8, H-8), 8.36 (1H, d, *J* = 9.8, H-7), and 8.92 ppm (1H, s, H-4). Signals were seen in the mixture for the isoquinoline **16a** at 1.37 (3H, t, *J* = 7.3, CH_3); 4.40 (2H, q, *J* = 7.3, CH_2); 7.53 (2H, s, NH_2); 8.15 (1H, d, *J* = 9.7, H-5); 8.45 (1H, d, *J* = 9.7, H-6), and 9.48 ppm (1H, s, H-1).

B. K_2CO_3 (0.712 g, 5.16 mmol) was added with stirring to a solution of the aldehyde **13a** (0.5 g, 2.46 mmol) and the enediamine hydrochloride **3** (0.86 g, 5.16 mmol) in dry DMF (10 ml) and stirred for 3 h at room temperature. The reaction mixture was poured into water (40 ml) and the precipitate formed was filtered off, washed with water, and dried to give the **diethyl 2,6-diamino-4-(2-chlorophenyl-6-fluoro-3-nitro)-1,4-dihydropyridine-3,5-dicarboxylate (14a)** (0.94 g, 89%); mp 151-153ºC. A pure sample for analysis was prepared by recrystallization from methylene chloride. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97 (6H, t, *J* = 7.4, CH_3); 3.84 (4H, m, CH_2); 5.31 (1H, br. s, H-4); 7.0-7.3 (4H, s, NH_2); 7.27 (1H, t, *J* = 9.4, H_{ar}-5); 7.78 (1H, dd, *J* = 5, *J* = 8.7, H_{ar}-4); 8.67 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.51 (CH_3); 32.01 (C-4); 58.31 (CH_2); 73.86 (C-3); 115.41 (C_{ar}-5); 122.91 (C_{ar}-4); 126.08 (C_{ar}-1); 136.65 (C_{ar}-2); 146.44 (C_{ar}-3); 152.89 (C-2); 163.00 (d, *J* = 24.2, C_{ar}-6); 168.62 (CO). Found, %: C 47.38; H 4.11; N 13.09. $C_{17}H_{18}ClFN_4O_6$. Calculated, %: C 47.62; H 4.23; N 13.07.

Reaction of Diaminoacrylate 3 with 2,6-Dichloro-3-nitrobenzaldehyde (13b). Enediamine **3** (0.745 g, 5.73 mmol) was added to a solution of aldehyde **13b** (0.6 g, 2.73 mmol) in dry DMF (5 ml) and left at room temperature for 2 weeks. The reaction mixture was poured into water (40 ml) and the precipitate formed was filtered off, washed with water, and dried to give a mixture (0.93 g) of the **diethyl 2,6-diamino-4-(2,6-dichloro-3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (14b**) and **ethyl 2-amino-5-chloro-8-nitroquinoline-2-carboxylate (17)** in the ratio 2:1. Signals for the dihydropyridine **14b** were seen in the ^{1}H NMR spectrum of the mixture (δ, ppm (*J*, Hz)): two rotamers 0.92 (6H, t, *J* = 7.4, CH_3); 3.78, 3.86 (4H, m, CH_2); 5.51, 5.56 (1H, s, H-4); 7.0-7.3 (4H, s, NH_2); 7.46 (1H, d, *J* = 8.7, H_{ar}-5); 7.68 (1H, d, *J* = 8.7, H_{ar}-4); 8.68, 8.72 (1H, s, NH). The mixture was separated on a chromatographic column using methylene chloride containing 5% methanol as eluent. Recrystallization from ethanol gave **17** (0.16 g, 20%); mp 209-211ºC (with decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 8.0, CH_3); 4.40 (2H, q, *J* = 8.0, CH_2); 7.47 (1H, d, *J* = 8.7, H-6); 7.6-8.1 (2H, s, NH_2); 8.13 (1H, d, *J* = 8.7, H-7); 8.86 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 14.3 (CH_3); 62.1 (CH_2); 112.5 (C-3); 120.3 (C-4a); 121.0 (C-6); 126.6 (C-7); 135.2 (C-5); 138.2 (C-4); 142.1 (C-8a); 144.2 (C-8); 157.7 (C-2); 165.3 (CO). Found, %: C 48.53; H 3.46; N 14.16. $C_{12}H_{10}ClN_3O_4$. Calculated, %: C 48.75; H 3.41; N 14.21.

3-Amino-7-nitro-4-pyrrolidinocarbonylisoquinoline (19). A solution of the aldehyde **1** (0.3 g, 1.8 mmol) and the enediamine **18** [2] (0.58 g, 3.7 mmol) in dry DMF (3 ml) was held at room temperature for 10 min. The mixture was poured into water (20 ml), potassium carbonate (0.1 g) was added, and the crystals formed were filtered off and dried to give the isoquinoline **19** (0.39 g, 77%); mp 181-184ºC. A pure sample for analysis was prepared by recrystallization from methanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70-2.00 (4H, d, $N(CH_2C\underline{H}_2)_2$); 2.90-3.70 (4H, m, $N(C\underline{H}_2CH_2)_2$); 6.61 (2H, s, NH_2); 7.47 (1H, d, *J* = 9.4, H-5); 8.20 (1H, dd, *J* = 3, *J* = 9.4, H-6); 8.93 (1H, d, *J* = 2, H-8); 9.19 (1H, s, H-1). ^{13}C NMR spectrum, δ, ppm: 24.9, 26.2 ($N(CH_2\underline{C}H_2)_2$); 46.1, 47.2 ($N(\underline{C}H_2CH_2)_2$); 106.4 (C-4); 120.4 (C-8a); 123.9 (C-5); 125.1 (C-6); 127.2 (C-8); 137.7 (C-4a); 142.0 (C-7); 155.2 (C-3); 156.6 (C-1); 165.3 (CO). Found, %: C 58.38; H 4.81; N 19.50. $C_{14}H_{14}N_4O_3$. Calculated, %: C 58.74; H 4.93; N 19.57.

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