# Preparation of 4-Substituted 3-Amino-2-chloropyridines, Synthesis of a Nevirapine Analogue

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A new method for preparing 3-amino-2-chloropyridines with a substituent (methyl, phenyl, carboxamide, methoxycarbonyl, acetyl, benzoyl and cyano) at the 4-position has been developed. An isoquinoline analogue of the reverse transcriptase inhibitor Nevirapine has been synthesized from the 4-amino-3-chloroisoquinoline.

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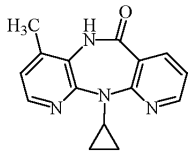
## Introduction.

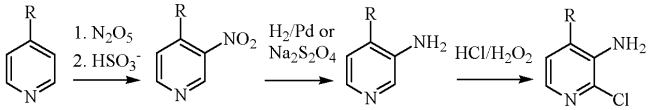
3-Amino- and 3-amino-2-chloropyridines with substituents at the 4-position are simple, but valuable substrates. These compounds are used as pharmaceuticals or their intermediates. For instance, 3,4-diaminopyridine [1,2] is a drug for the treatment of Lambert-Eaton myasthenic syndrome and Nevirapine (**I**) is the first non-nucleoside HIV-1 reverse transcriptase inhibitor [3] approved for clinical use. In addition, an amino group at the 3-position on a pyridine ring can react with a number of electrophiles or be replaced by a diazotization reaction. Halides at the 2-position can, on the other hand, undergo nucleophilic substitution reactions. These transformations potentially lead to a wide variety of 2,3,4-substituted pyridines, compounds that have not been readily available before due to low yielding, multi-step preparations.

We now wish to report a general synthetic route to 4-substituted 3-amino-2-chloropyridines, based on direct nitration of the pyridine substrates, followed by reduction and chlorination (Scheme 1).



Nevirapine (**I**)

Scheme 1




**1a-g** **2a-g** **3a-g** **4a-g**

## Results and discussion.

The synthesis of 4-substituted 3-amino-2-chloropyridines, especially 3-amino-2-chloro-4-methylpyridine has previously been extensively studied [3] as it is a pivotal intermediate in the commercial production of Nevirapine. Four different routes have been evaluated. Two of them involve initial condensation of ethylacetoacetate with cyanoacetamide to form the pyridine skeleton giving 44% and 59% overall yields of 3-amino-2-chloro-4-methylpyridine in 6 steps. Two other five-step routes *via* the 3-amino-4-methylpyridine involve initial nitration of the starting 2-amino-4-methylpyridine, but the required 3-nitro-isomer was obtained in 28-32% yields only, with the 5-nitro-isomer as the major reaction product together with extensive oxidative decomposition of the starting substrate [3]. The easiest way of producing 3-amino-4-methylpyridine would be nitration of the 4-methylpyridine and subsequent reduction. However, due to the electron-deficient nature of the pyridine ring, direct nitration of methylpyridines affords very poor yields [4]. Similar results have been obtained with other pyridine substrates; for example, pyridine itself has been nitrated under harsh conditions [5] in a 5% yield. Usually at least two electron-donating substituents are necessary for the nitration to take place successfully.

Some time ago we discovered a new nitration procedure for pyridine compounds at the 3-position [6]. Pyridine substrates were reacted with dinitrogen pentoxide and the resulting *N*-nitropyridinium nitrate reacted further with an aqueous solution of sulfur dioxide and hydrogen sulfite ion ($SO_2/HSO_3^-$). This gave moderate to good yields of 3-nitropyridines. The mechanism of the nitration reaction has also been thoroughly studied [7,8]. This method was used to prepare compounds **2a**-**h**; the yields of the nitrations are summarized in Table 1.

There are generally two methods of introducing chlorine at the 2-position on the pyridine ring; one involves a nucleophilic chlorination of the 3-nitropyridines, the other an electrophilic chlorination reaction on the 3-aminopyridines.

First we applied a 'nucleophilic approach'. Unfortunately, the nitropyridines were not sufficiently reactive and treatment with phosphorus oxychloride under reflux did not afford the desired product. To activate the pyridine ring for nucleophilic attack, nitropyridine compounds were transformed to 1-oxides and then reacted with phosphorus oxychloride. In this case, the chlorination reaction took place with simultaneous deoxygenation [9]. The product mixture contained 2- and 6-chloro-3-nitropyridines, deoxygenated 3-nitropyridine

Table 1

| Substrate | Procedure yields (%) | | | |
|---|---|---|---|---|
| | Nitration | Reduction | Chlorination at 2-position[a] | Dichlorination (2- and 6-positions)[b] |
| **1a** (R = methyl) | 70 (**2a**) | 97 (**3a**) | 89 (**4a**) | 5 |
| **1b** (R = phenyl) | 68 (**2b**) | 98 (**3b**) | 87 (**4b**) | 5 |
| **1c** (R = carboxamide) | 50 (**2c**) | 98 (**3c**) | 58 (**4c**) | 13 |
| **1d** (R = methoxycarbonyl) | 75 (**2d**) | 97 (**3d**) | 42 (**4d**) | 22 |
| **1e** (R = acetyl) | 75 (**2e**) | 69 (**3e**) | 46 (**4e**) | 14 |
| **1f** (R = benzoyl) | 74 (**2f**) | 83 (**3f**) | 47 (**4f**) | 17 |
| **1g** (R = cyano) | 45 (**2g**) | 88 (**3g**) | 12 (**4g**) | 12 |
| **1h** Isoquinoline | 42 (**2h**) | 97 (**3h**) | 86 (**4h**) | 6 |

[a] Isolated yields. [b] Yields determined by GC.

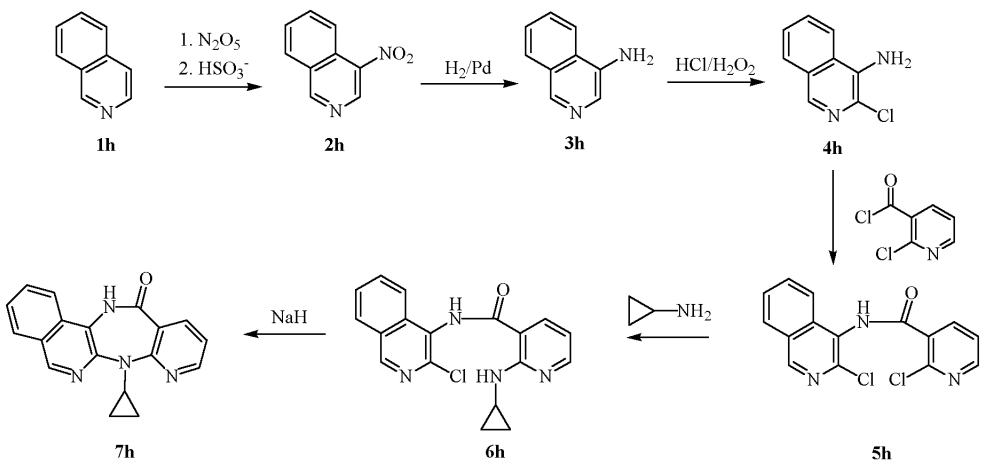
substrate and some starting compound. Although the 'nucleophilic approach' did not fail, the yields were only moderate. In addition, the chlorination was not selective and afforded barely separable 2- and 6-chloro-isomers.

The other approach involved an electrophilic chlorination reaction on the 3-aminopyridines. The 4-substituted 3-nitropyridines **2a**-**g** and 4-nitroisoquinoline **2h** were therefore reduced to the amino derivatives **3a**-**h**. Substrates **2a**, **2b**, **2c**, **2d**, **2g** and **2h** were reduced with hydrogen in the presence of a palladium catalyst. Compounds **2e** and **2f**, possessing a ketone group, were reduced with sodium hyposulfite [10] to prevent reduction of the ketone group to an alcohol group.

Electrophilic chlorination reactions on compounds **3a-h** gave 3-amino-2-chloropyridines **4a-g** and 4-amino-3-chloroisoquinoline **4h**. Four different chlorination methods [11] have been tried: 1. Gaseous chlorine from a cylinder, 2. sodium hypochlorite solution, 3. chlorine generated *in situ* by oxidation of concentrated hydrochloric acid with potassium chlorate and 4. chlorine generated *in situ* by oxidation of hydrochloric acid with hydrogen peroxide. Procedure 4 [12] run at 20 °C gave the best results both as to yield and composition of the product mixture. Yields were generally higher for substrates with an electron-donating 4-substituent [12], however chlorination was possible even with electron-withdrawing groups at the 4-position. A typical side-reaction was dichlorination at the 2- and 6-positions of the pyridine ring. Previously unreported chlorination of 4-aminoisoquinoline **3h** proceeded at the 3-position, analogously to the reaction on the pyridine ring.

As mentioned above, 3-amino-2-chloro-4-methylpyridine is an intermediate in the synthesis of the non-nucleoside reverse transcriptase inhibitor Nevirapine (**I**). However, due to the rapid reverse transcriptase mutation [13], there is a constant need to develop new drugs with improved profiles. The SAR study of dipyridodiazepinones [14] showed that the best activity was achieved with a methyl group at the 4-position, although 4-chloro and 4-ethyl compounds were also highly active. In contrast, electron-donating, electron-withdrawing, and/or hydrophilic groups reduced the activity. With 4-amino-3-chloroisoquinoline **4h** in our hands, we synthesized an isoquinoline analogue of Nevirapine **7h** (Scheme 2) with a fused benzene ring instead of a methyl group that would likely fulfil the above mentioned activity criteria. The 4-amino-3-chloropyridine **4h** was first condensed [14,15] with 2-chloronicotinoyl chloride to

Scheme 2



give 2-chloro-*N*-(3-chloro-4-isoquinolyl)-3-pyridinecarboxamide **5h** in 75% yield that was further reacted with cyclopropylamine in dimethyl sulfoxide to yield *N*-(3-chloro-4-isoquinolyl)-2-cyclopropylamino-3-pyridinecarboxamide **6h** in 86% yield. Treatment of **6h** with sodium hydride resulted in cyclization of the diazepin ring to afford the Nevirapine analogue **7h** in 15%. The antiviral activity of **7h** has not yet been evaluated.

## Conclusion.

We have shown that it is possible to synthesize a number of 4-substituted 3-amino-2-chloropyridines by a sequence of nitration, reduction and chlorination of the pyridine compounds (Scheme 1). An isoquinoline analogue **7h** of the reverse transcriptase inhibitor Nevirapine (**I**) has been synthesized (Scheme 2).

## EXPERIMENTAL

The NMR spectra were recorded on Bruker DPX 300 and 400 MHz spectrometers (tetramethylsilane as the internal standard). Mass spectra were recorded on a Fisons Instruments TRIO 1000 GC-MS System and Finnigan MAT 95 XL instrument. Melting points were determined on a Büchi oil bath apparatus and are uncorrected. Elemental analyses were determined by the Laboratory of Organic Elemental Analysis, Prague Institute of Chemical Technology, Czech Republic. Dinitrogen pentoxide was prepared from dinitrogen tetroxide and ozone [16], 2-chloronicotinoyl chloride from 2-chloronicotinic acid [15]. Synthesis and spectral data of the nitropyridines **2a**, **2b**, **2d**, **2e**, **2g** and 4-nitroisoquinoline **2h** have previously been reported [6].

### 3-Nitroisonicotinamide (**2c**).

Dinitrogen pentoxide (8.64 g, 80 mmoles) was dissolved in liquid sulfur dioxide (50 ml) at -38 °C and isonicotinamide (6.11 g, 50 mmoles) was added in portions. The mixture was stirred for 5 minutes at -38 °C, then poured onto ice (100 g) and stirred overnight (16 hours) at room temperature. The mixture was then neutralized with 5 *M* sodium hydroxide solution to *p*H 8 and extracted with ethyl acetate (3 x 200 ml). Combined organic phase was washed with 1 *M* hydrochloric acid (50 ml), dried over potassium carbonate and evaporated to give a colorless solid, yield 4.16 g (50%), mp 168-170 °C, $^1$H NMR (300 MHz, dimethyl-$d_6$ sulfoxide): δ 7.68 (1H, d, *J* = 4.9, H-5), 7.97 (1H, broad s, CONH), 8.31 (1H, broad s, CONH), 8.96 (1H, d, *J* = 4.9, H-6), 9.23 (1H, s, H-2), ir (FT): 629, 864, 1357, 1390, 1524, 1606, 1682, 3164, 3365 cm$^{-1}$, ms: 167 ($M^+$).

*Anal*. Calcd. for $C_6H_5N_3O_3$: C, 43.12; H, 3.02; N, 25.14. Found: C, 43.33; H, 3.33; N, 25.15.

### 4-Benzoyl-3-nitropyridine (**2f**).

Dinitrogen pentoxide (8.64 g, 80 mmoles) was dissolved in liquid sulfur dioxide (50 ml) at -38 °C and 4-benzoylpyridine (9.16 g, 50 mmoles) was added in portions. The mixture was stirred for 5 minutes at -38 °C, then poured onto ice (300 g) and stirred overnight (16 hours) at room temperature. The precipitate was filtered and dissolved in dichloromethane (200 ml). The solution was washed with saturated sodium bicarbonate solution (100 ml) and water (100 ml), dried over sodium sulfate and evaporated to give a light beige solid, yield 8.43 g (74%), mp 105-106 °C, $^1$H NMR (300 MHz, deuteriochloroform): δ 7.44 (1H, d, *J* = 4.9, H-5), 7.49 (2H, m, H-3',5'), 7.65 (1H, tt, *J* = 7.6, 1.2, H-4'), 7.74 (2H, m, H-2',6'), 9.01 (1H, d, *J* = 4.9, H-6), 9.49 (1H, s, H-2), ir (FT): 636, 700, 850, 1276, 1315, 1354, 1526, 1596, 1672 cm$^{-1}$, ms: 228 ($M^+$).

*Anal*. Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.24; H, 3.97; N, 12.24.

### General Hydrogenation Procedure to Prepare Compounds **3a**, **3b**, **3c**, **3d**, **3g** and **3h**.

A nitropyridine or isoquinoline (5 mmoles) was hydrogenated for 5 hours at room temperature in methanol (15 ml) in the presence of 5% Pd/C (100 mg) at a constant hydrogen pressure of 5 bars. The catalyst was removed by filtration and the filtrate evaporated to give a product.

### 3-Amino-4-methylpyridine (**3a**).

Compound **3a** was obtained in 97% yield (525 mg) of a colorless solid, mp 104-106 °C, $^1$H NMR (400 MHz, dimethyl-$d_6$ sulfoxide): δ 2.05 (3H, s, $CH_3$), 5.05 (2H, broad s, $NH_2$), 6.90 (1H, d, *J* = 4.7, H-5), 7.65 (1H, d, *J* = 4.7, H-6), 7.89 (1H, s, H-2), ir (FT): 814, 864, 1067, 1293, 1324, 1415, 1501, 1564, 1593, 1631, 3203, 3328, 3443 cm$^{-1}$, ms: 108 ($M^+$).

*Anal*. Calcd. for $C_6H_8N_2$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.25; H, 7.02; N, 25.53.

### 3-Amino-4-phenylpyridine (**3b**).

Compound **3b** was obtained in 98% yield (835 mg) of a light yellow solid, mp 79-80 °C, $^1$H NMR (400 MHz, deuteriochloroform): δ 3.81 (2H, broad s, $NH_2$), 7.03 (1H, d, *J* = 4.8, H-5), 7.36-7.51 (5H, m, H-2',3',4',5',6'), 8.07 (1H, d, *J* = 4.8, H-6), 8.16 (1H, s, H-2), ir (FT): 700, 742, 776, 827, 1229, 1330, 1416, 1547, 1634, 3157, 3432 cm$^{-1}$, ms: 170 ($M^+$).

*Anal*. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.69; H, 5.94; N, 16.52.

### 3-Aminoisonicotinamide (**3c**).

A water/methanol mixture (1:1) was used as the solvent for hydrogenation, yield 670 mg (98%) of a colorless solid, mp 150-152 °C, $^1$H NMR (300 MHz, dimethyl-$d_6$ sulfoxide): δ 6.59 (2H, broad s, $NH_2$), 7.39 (1H, d, *J* = 5.2, H-5), 7.42 (1H, broad s, CONH), 7.71 (1H, d, *J* = 5.2, H-6), 8.00 (1H, broad s, CONH), 8.11 (1H, s, H-2), ir (FT): 647, 788, 837, 1082, 1116, 1230, 1581, 1632, 3167, 3321 cm$^{-1}$, ms: 137 ($M^+$).

*Anal*. Calcd. for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.52; H, 5.34; N, 30.48.

### Methyl 3-Aminoisonicotinate (**3d**).

Compound **3d** was obtained in 97% yield (740 mg) of a light yellow solid, mp 81-83 °C, $^1$H NMR (400 MHz, deuteriochloroform): δ 3.91 (3H, s, $CH_3$), 5.70 (2H, broad s, $NH_2$), 7.58 (1H, d, *J* = 5.3, H-5), 7.93 (1H, d, *J* = 5.3, H-6), 8.20 (1H, s, H-2), ir (FT): 675, 786, 1128, 1198, 1235, 1318, 1425, 1619, 1701, 3132, 3435 cm$^{-1}$, ms: 152 ($M^+$).

*Anal*. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.18; H, 5.37; N, 18.41.

### 3-Amino-4-cyanopyridine (**3g**).

The crude product was crystallized from water, yield 524 mg (88%) of colourless crystals, mp 140-141 °C, $^1$H NMR (300

MHz, dimethyl-$d_6$ sulfoxide): δ 6.41 (2H, broad s, $NH_2$), 7.34 (1H, d, *J* = 5.0, H-5), 7.77 (1H, d, *J* = 5.0, H-6), 8.21 (1H, s, H-2), ir (FT): 808, 1247, 1425, 1563, 1651, 2225, 3179, 3397 $cm^{-1}$, ms: 119 ($M^+$).

*Anal.* Calcd. for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.33; H, 4.43; N, 35.40.

4-Aminoisoquinoline (**3h**).

Compound **3h** was obtained in 97% yield (980 mg) of a beige solid, mp 107-109 °C, $^1$H NMR (300 MHz, deuteriochloroform): δ 4.09 (2H, broad s, $NH_2$), 7.57 (1H, ddd, *J* = 8.2, 6.9, 1.2, H-7), 7.65 (1H, ddd, *J* = 8.3, 6.9, 1.4, H-6), 7.80 (1H, dd, *J* = 8.3, 1.2, H-5), 7.91 (1H, dd, *J* = 8.2, 1.4, H-8), 8.04 (1H, s, H-3), 8.73 (1H, s, H-1), ir (FT): 584, 747, 779, 847, 1333, 1403, 1461, 1509, 1574, 1646, 3171, 3413 $cm^{-1}$, ms: 144 ($M^+$).

*Anal.* Calcd. for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.17; H, 5.78; N, 19.42.

Compounds **2e** and **2f** were reduced with sodium hyposulfite according to procedure described in reference [10].

4-Acetyl-3-aminopyridine (**3e**).

4-Acetyl-3-nitropyridine (**2e**, 8.3 g, 50 mmoles) and sodium hyposulfite (52.2 g, 300 mmoles) in 95% ethanol (500 ml) were refluxed for 6 hours. The mixture was then cooled and the solvent evaporated. The residue was partitioned between ethyl acetate (200 ml) and water (200 ml). The organic phase was separated, and the aqueous phase was reextracted with ethyl acetate (200 ml). The combined organic phase was dried over sodium sulfate and evaporated to give a yellow solid, yield 4.7 g (69%), mp 89-91 °C, $^1$H NMR (400 MHz, dimethyl-$d_6$ sulfoxide): δ 2.53 (3H, s, $CH_3$), 7.13 (2H, broad s, $NH_2$), 7.54 (1H, d, *J* = 5.3, H-5), 7.77 (1H, d, *J* = 5.3, H-6), 8.24 (1H, s, H-2), ir (FT): 616, 1039, 1215, 1358, 1422, 1609, 1658, 3118, 3276, 3441 $cm^{-1}$, ms: 136 ($M^+$).

*Anal.* Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.26; H, 5.94; N, 20.53.

3-Amino-4-benzoylpyridine (**3f**).

4-Benzoyl-3-nitropyridine (**2f**, 2.23 g, 10 mmoles) and sodium hyposulfite (10.4 g, 60 mmoles) in 95% ethanol (100 ml) were refluxed for 6 hours. The mixture was then cooled and the solvent evaporated. The residue was partitioned between dichloromethane (50 ml) and water (50 ml). The organic phase was separated, and the aqueous phase was re-extracted with dichloromethane (50 ml). The combined organic phase was dried over sodium sulfate and evaporated to give a yellow solid, yield 1.64 g (83%), mp 131-133 °C, $^1$H NMR (400 MHz, dimethyl-$d_6$ sulfoxide): δ 6.87 (2H, broad s, $NH_2$), 7.09 (1H, d, *J* = 5.1, H-5), 7.54 (2H, m, H-3',5'), 7.65 (3H, m, H-2',4',6'), 7.75 (1H, d, *J* = 5.1, H-6), 8.32 (1H, s, H-2), ir (FT): 647, 709, 1222, 1296, 1323, 1424, 1632, 3314, 3444 $cm^{-1}$, ms: 198.1 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.47; H, 5.04; N, 14.18.

General Chlorination Procedure to Prepare Compounds **4a-h**.

An aminopyridine or isoquinoline substrate (5 mmoles) was dissolved in concentrated hydrochloric acid (10 ml) at 20 °C. Hydrogen peroxide (35%, 5.5 mmoles) was added dropwise during 30 minutes and the reaction mixture was stirred for another 30 minutes. The mixture was neutralized with sodium hydroxide solution to *p*H 8 and extracted with dichloromethane (2x20 ml). The organic phase was dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (eluent: 2-5% acetone in dichloromethane) to yield a product.

3-Amino-2-chloro-4-methylpyridine (**4a**).

Compound **4a** was obtained in 89% yield (635 mg) of a colorless solid, mp 66-67 °C, $^1$H NMR (400 MHz, deuteriochloroform): δ 2.21 (3H, s, $CH_3$), 4.03 (2H, broad s, $NH_2$), 6.93 (1H, d, *J* = 4.7, H-5), 7.71 (1H, d, *J* = 4.7, H-6), ir (FT): 820, 860, 1376, 1418, 1439, 1590, 1629, 3196, 3428 $cm^{-1}$, ms: 142 ($M^+$).

*Anal.* Calcd. for $C_6H_7N_2Cl$: C, 50.54; H, 4.95; N, 19.65. Found: C, 50.96; H, 5.02; N, 19.19.

3-Amino-2-chloro-4-phenylpyridine (**4b**).

Compound **4b** was obtained in 87% yield (890 mg) of a colourless solid, mp 100-102 °C, $^1$H NMR (400 MHz, deuteriochloroform): δ 4.21 (2H, broad s, $NH_2$), 6.99 (1H, d, *J* = 4.7, H-5), 7.41-7.45 (3H, m, H-2',4',6'), 7.48-7.52 (2H, m, H-3',5'), 7.83 (1H, d, *J* = 4.7, H-6), ir (FT): 709, 766, 1075, 1101, 1276, 1412, 1485, 1620, 3306, 2467 $cm^{-1}$, ms: 204 ($M^+$).

*Anal.* Calcd. for $C_{11}H_9N_2Cl$: C, 64.56; H, 4.43; N, 13.69. Found: C, 64.73; H, 4.60; N, 13.63.

3-Amino-2-chloroisonicotinamide (**4c**).

After chlorination and neutralization, the reaction mixture was extracted with ethylacetate, dried over sodium sulfate, evaporated and the residue purified by flash chromatography on silica gel (eluent:ethylacetate) to yield 500 mg (58%) of a colorless solid, mp 183-184 °C, $^1$H NMR (400 MHz, dimethyl-$d_6$ sulfoxide): δ 6.76 (2H, broad s, $NH_2$), 7.51 (1H, d, *J* = 5.0, H-5), 7.61 (1H, d, *J* = 5.0, H-6), 7.67 (1H, broad s, CONH), 8.18 (1H, broad s, CONH), ir (FT): 677, 780, 1117, 1252, 1395, 1575, 1600, 1698, 3160, 3368 $cm^{-1}$, ms: 171 ($M^+$).

*Anal.* Calcd. for $C_6H_9N_3ClO$: C, 42.00; H, 3.52; N, 24.49. Found: C, 42.03; H, 3.59; N, 24.07.

Methyl 3-Amino-2-chloroisonicotinate (**4d**).

Compound **4d** was obtained in 42% yield (390 mg) of a colourless solid, mp 95-96 °C, $^1$H NMR (400 MHz, deuteriochloroform): δ 3.94 (3H, s, $CH_3$), 6.23 (2H, broad s, $NH_2$), 7.61 (1H, d, *J* = 5.2, H-5), 7.72 (1H, d, *J* = 5.2, H-6), ir (FT): 726, 784, 1041, 1224, 1250, 1300, 1420, 1606, 1708, 3305, 3431 $cm^{-1}$, ms: 186 ($M^+$).

*Anal.* Calcd. for $C_7H_7N_2O_2Cl$: C, 45.06; H, 3.78; N, 15.01. Found: C, 44.86; H, 3.89; N, 15.06.

4-Acetyl-3-amino-2-chloropyridine (**4e**).

Compound **4e** was obtained in 46% yield (392 mg) of a yellow solid, mp 159-161 °C, $^1$H NMR (300 MHz, deuteriochloroform): δ 2.62 (3H, s, $CH_3$), 6.70 (2H, broad s, $NH_2$), 7.46 (1H, d, *J* = 5.2, H-5), 7.74 (1H, d, *J* = 5.2, H-6), ir (FT): 603, 638, 1092, 1205, 1250, 1287, 1360, 1423, 1578, 1604, 1657, 3307, 3425 $cm^{-1}$, ms: 170 ($M^+$).

*Anal.* Calcd. for $C_7H_7N_2ClO$: C, 49.28; H, 4.14; N, 16.42. Found: C, 49.36; H, 4.18; N, 16.29.

3-Amino-4-benzoyl-2-chloropyridine (**4f**).

Compound **4f** was obtained in 47% yield (550 mg) of a yellow solid, mp 100-101 °C, $^1$H NMR (400 MHz, deuteriochlo-

roform): δ 6.35 (2H, broad s, $NH_2$), 7.24 (1H, d, *J* = 5.1, H-5), 7.50 (2H, m, H-3',5'), 7.61 (1H, m, H-4'), 7.68 (2H, m, H-2',6'), 7.72 (1H, d, *J* = 5.1, H-6), ir (FT): 664, 708, 763, 798, 1110, 1216, 1244, 1290, 1422, 1573, 1598, 1641, 3298, 3433 $cm^{-1}$, ms: 232 ($M^+$).

*Anal*. Calcd. for $C_{12}H_9N_2ClO$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.84; H, 4.19; N, 11.79.

3-Amino-2-chloro-4-cyanopyridine (**4g**).

Compound **4g** was obtained in 12% yield (93 mg) of a colourless solid, mp 145-146 °C, $^1$H NMR (300 MHz, deuteriochloroform): δ 4.91 (2H, broad s, $NH_2$), 7.23 (1H, d, *J* = 5.0, H-5), 7.82 (1H, d, *J* = 5.0, H-6), ir (FT): 594, 834, 1080, 1111, 1182, 1426, 1463, 1538, 1634, 2231, 3354, 3477 $cm^{-1}$, ms: 153 ($M^+$).

*Anal*. Calcd. for $C_6H_4N_3Cl$: C, 46.93; H, 2.63; N, 27.36. Found: C, 47.14; H, 2.89; N, 26.97.

4-Amino-3-chloroisoquinoline (**4h**).

Compound **4h** was obtained in 86% yield (770 mg) of a beige solid, mp 115-116 °C, $^1$H NMR (300 MHz, deuteriochloroform): δ 4.55 (2H, broad s, $NH_2$), 7.58 (1H, ddd, *J* = 8.2, 6.8, 1.2, H-7), 7.68 (1H, ddd, *J* = 8.5, 6.8, 1.4, H-6), 7.78 (1H, dd, *J* = 8.5, 1.2, H-5), 7.91 (1H, dd, *J* = 8.2, 1.4, H-8), 8.52 (1H, s, H-1), $^{13}$C NMR (300 MHz, dimethyl-$d_6$ sulfoxide): δ 121.9, 125.6, 126.5, 127.2, 127.4, 128.1, 128.9, 135.2, 138.0 (C-1, dd, $^1J_{C\text{-}1,\ H\text{-}1}$ = 183.8, $^3J_{C\text{-}1,\ H\text{-}8}$ = 5.1), ir (FT): 580, 750, 848, 1077, 1144, 1407, 1443, 1635, 3194, 3314, 3426 $cm^{-1}$, ms: 178 ($M^+$).

*Anal*. Calcd. for C9H7N2Cl: C, 60.52; H, 3.95; N, 15.68. Found: C, 60.17; H, 4.16; N, 15.64.

2-Chloro-*N*-(3-chloro-4-isoquinolyl)-3-pyridinecarboxamide (**5h**).

4-Amino-3-chloroisoquinoline (**4h**, 893 mg, 5 mmoles) was dissolved in acetonitrile (10 ml) and pyridine (237 mg, 3 mmoles) was added. 2-Chloronicotinoyl chloride (880 mg, 5 mmoles) in acetonitrile (10 ml) was added and the mixture stirred at room temperature for 1 hour and then at 45 °C for 16 hours. Ethyl acetate (200 ml) and saturated sodium bicarbonate solution (100 ml) were added and the white precipitate dissolved at 50 °C. The organic phase was separated, dried at 50 °C over sodium sulfate and evaporated. The residue was crystallized from ethyl acetate to afford colourless crystals of **5h**, yield 1.20 g (75 %), mp 231-233 °C, $^1$H NMR (400 MHz, dimethyl-$d_6$ sulfoxide): δ 7.65 (1H, dd, *J* = 7.5, 4.8, H-5), 7.80 (1H, ddd, *J* = 8.1, 6.8, 0.8, H-7'), 7.96 (1H, ddd, *J* = 8.4, 6.8, 1.0, H-6'), 8.13 (1H, dd, *J* = 8.4, 0.8, H-5'), 8.25 (1H, dd, *J* = 7.5, 1.9, H-4), 8.29 (1H, dd, *J* = 8.1, 1.0, H-8'), 8.61 (1H, dd, *J* = 4.8, 1.9, H-2), 9.25 (1H, s, H-1'), 10.95 (1H, s, CONH), ir (FT): 756, 1080, 1409, 1523, 1581, 1670, 3184 $cm^{-1}$, ms: 317.0 ($M^+$), 282.0.

*Anal*. Calcd. for $C_{15}H_9N_3Cl_2O$: C, 56.63; H, 2.85; N, 13.21. Found: C, 56.38; H, 3.26; N, 13.20.

*N*-(3-Chloro-4-isoquinolyl)-2-cyclopropylamino-3-pyridinecarboxamide (**6h**).

2-Chloro-*N*-(3-chloro-4-isoquinolyl)-3-pyridinecarboxamide (**5h**, 636 mg, 2 mmoles) and cyclopropylamine (571 mg, 10 mmoles) in dimethyl sulfoxide (5 ml) were heated at 120 °C for 12 hours. Solvent was then evaporated and the residue dissolved in ethyl acetate (50 ml) and saturated sodium bicarbonate solution (50 ml). The organic phase was separated, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate) to afford a light yellow solid **6h**, yield 580 mg (86%), mp 199-202 °C, $^1$H NMR (400 MHz, acetone-$d_6$): δ 0.45 (2H, m, $(CH_2)_2$CH), 0.74 (2H, m, $(CH_2)_2$CH), 2.93 (1H, m, $(CH_2)_2$C*H*), 6.74 (1H, dd, *J* = 7.6, 4.9, H-5), 7.75 (1H, ddd, *J* = 8.0, 6.8, 1.3, H-7'), 7.86 (1H, ddd, *J* = 8.4, 6.8, 1.3, H-6'), 8.04 (1H, ddd, *J* = 8.4, 1.3, 1.0, H-5'), 8.24 (1H, ddd, *J* = 8.0, 1.3, 1.0, H-8'), 8.31 (1H, broad s, $(CH_2)_2$CHN*H*), 8.35 (1H, dd, *J* = 4.9, 1.6, H-6), 8.37 (1H, dd, *J* = 7.6, 1.6, H-4), 9.17 (1H, s, H-1'), 9.67 (1H, broad s, CONH), ir (FT): 765, 1261, 1394, 1497, 1580, 1631 $cm^{-1}$, ms: 338.1 ($M^+$).

*Anal*. Calcd. for $C_{18}H_{15}N_4ClO$: C, 63.81; H, 4.46; N, 16.54. Found: C, 63.71; H, 4.64; N, 15.79.

7-Cyclopropyl-7,13-dihydro-11*H*-isoquino[4,3-*b*]pyrido-[2,3-*e*][1,4]diazepin-11-one (**7h**).

*N*-(3-Chloro-4-isoquinolyl)-2-cyclopropylamino-3-pyridinecarboxamide (**6h**, 339 mg, 1 mmole) was dissolved in 2-methoxyethylether (5 ml) and sodium hydride (72 mg, 3 mmoles) was added. The mixture was refluxed for 3 hours, then cooled, poured into ice water (50 ml) and stirred for 1 hour. The mixture was extracted with ethyl acetate (50 ml), the organic phase separated, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate) to afford a light yellow solid **7h**, yield 45 mg (15%), mp 274-278 °C, $^1$H NMR (400 MHz, dimethyl-$d_6$ sulfoxide): δ 0.33-0.50 (2H, m, $(CH_2)_2$CH), 0.92 (2H, m, $(CH_2)_2$CH), 3.76 (1H, m, $(CH_2)_2$C*H*), 7.17 (1H, dd, *J* = 7.6, 4.8, H-5), 7.62 (1H, m, H-7'), 7.81 (1H, ddd, *J* = 8.4, 6.8, 1.2, H-6'), 8.02 (1H, dd, *J* = 7.6, 2.0, H-4), 8.10 (1H, d, *J* = 8.0, H-8'), 8.14 (1H, d, *J* = 8.4, H-5'), 8.50 (1H, dd, *J* = 4.8, 2.0, H-6), 9.06 (1H, s, H-1'), 10.61 (1H, broad s, CONH), ir (FT): 748, 1288, 1388, 1409, 1587, 1654 $cm^{-1}$, ms: 302.1 ($M^+$).

*Anal*. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 70.99; H, 4.96; N, 18.00.

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