Synthesis of Functionalized *H*-[1]Benzopyrano[2,3-*b*]pyridines by the *Friedländer* Approach: Antimycobacterial and Antimicrobial Profile

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A series of functionalized *H*-[1]benzopyrano[2,3-*b*]pyridine derivatives were synthesized by the *Friedländer* reaction of 2-amino-4-oxo-4*H*-chromene-3-carbonitriles **1** with malononitrile, ethyl cyanoacetate, or acetophenone (*Scheme*). The synthesized compounds **2**–**4** were screened for their *in vitro* activity against antitubercular, antibacterial, and antifungal species (*Fig.*, *Table*). Among the synthesized compounds, **3c** and **4f** were the most active with 99% inhibition against *Mycobacterium tuberculosis* $H_{37}Rv$, while compounds **2f**, **3f**, and **4d** exhibited 69%, 63%, and 61% inhibition, respectively. The 4-amino-7,9-dibromo-1,5-dihydro-2,5-dioxo-2*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**3b**) showed the most potent antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa*. Several chromeno[2,3-*b*]pyridine derivatives showed equal or more potency against *Staphylococcus aureus* and *Candida albicans.*

Introduction. – Microbial disease is the most aggressive and fastest growing disease in many countries throughout the world. The widespread uses of antibiotics have led to the appearance of multidrug-resistant microbial pathogens. Currently, the widespread selective pressure and the efficient dissemination channels for multidrug-resistant organisms are major factors that may have contributed to the rapid emergence of the resistant organisms [1].

Naturally occurring chromenones (= *H*-1-benzopyranones) play an important role in life science [2]. Many of the derivatives of chromenone such as xanthenones have been reported to be active against bacteria including methicillin/multidrug-resistant ones, vancomycin-resistant *Enterococci*, and *Mycobacterium tuberculosis* [3–7]. Some chromenones even surpass the antimicrobial activity of traditional antibiotics. Many condensed heterocyclic systems bearing a fused pyridine ring system also play an important role as potential medicinal agents and stimulated considerable interest in their synthesis. The fused pyridine analogues have been described to have several biological and medicinal activities [8].

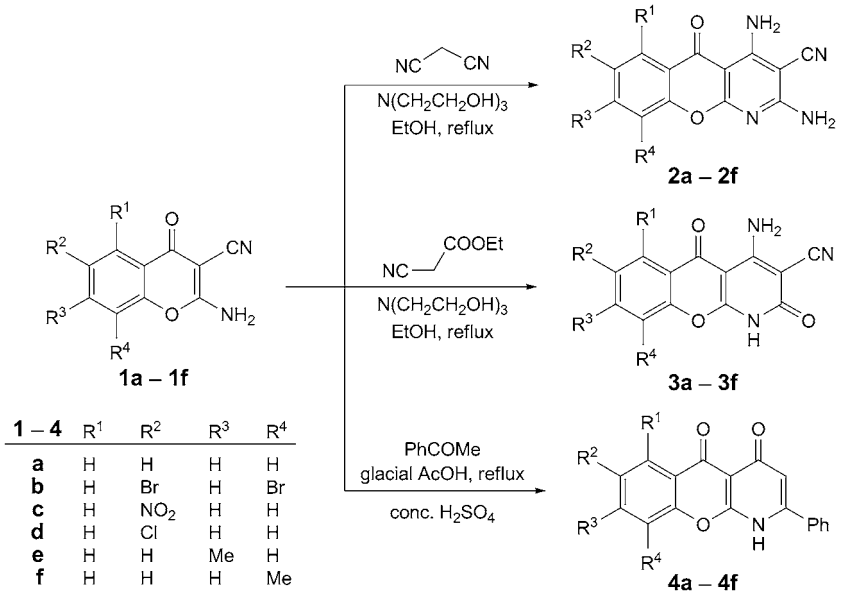
In drug-discovery processes, it is important to identify unique low-molecular-mass scaffolds from the literature which show structural variation with promising bioactivity. The combination of entirely different pharmacophoric moieties fused with natural products may lead to the development of new classes of therapeutically active molecules. In continuation of our ongoing research program aimed at the development of some new bioactive pyran-based heterocyclic compounds, we decided to synthesize

functionalized chromeno[2,3-*b*]pyridine (= *H*-[1]benzopyrano[2,3-*b*]pyridine) derivatives [9–12].

Numerous previously reported methods describe the synthesis of azaheterocycles and related polyfunctional substituted pyridines, such as the *Friedländer*, *Skraup*, *Döbner von Miller*, and *Combes* reaction [13]. Among these interesting cyclization reactions, the *Friedländer* reaction involving 2-aminobenzonitriles have been found to be quite extensively studied [14–19]. The 2-aminobenzonitriles can easily be converted into functionalized pyridine and pyrimidine derivatives with reagents such as malononitriles, cyanoacetate, isocyanates, and carbon disulfide, which may exhibit promising biological activity. In this article, we report the synthesis of novel chromeno[2,3-*b*]pyridines by the cyclization of functionalized chromenone derivatives with malononitrile, ethyl cyanoacetate, or acetophenone, and their antimicrobial and antitubercular activities.

2. Results and Discussion. – 2.1. *Chemistry.* To the best of our knowledge, chromeno[2,3-*b*]pyridines have not yet been thoroughly investigated, and there is a limited number of methods involving the few-step synthesis of chromeno[2,3-*b*]pyridines by simple cyclization of functionalized chromenone derivatives. The modified synthesis of chromenone derivatives **1a**–**1f** was carried out by the conversion of substituted 2-(acetyloxy)benzoic acids to their corresponding acid chlorides with $SOCl_2$ and subsequent treatment with malononitrile [20][21]. The functionalized chromenones **1** were then used as precursors for the synthesis of the chromeno[2,3-*b*]pyridines **2**–**4** by simple reaction with malononitrile, ethyl cyanoacetate, or acetophenone under optimum reaction conditions (*Scheme*). The structures of the

Scheme. *Synthetic Route to Chromeno[2,3-*b*]pyridines* **2**–**4**



1 – 4	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	Br	H	Br
c	H	NO_2	H	H
d	H	Cl	H	H
e	H	H	Me	H
f	H	H	H	Me

synthesized compounds were established on the basis of physical and spectroscopic data (IR and ^{1}H-NMR), including some representative ^{13}C-NMR spectra.

Compounds **1** were transformed to the corresponding 2,4-diamino-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **2** upon treatment with malononitrile in boiling EtOH in the presence of a catalytic amount of 2,2′,2″-nitrilotris[ethanol]. The IR spectrum of **2a** [22] revealed absorption bands corresponding to the amine (3308 and 3138 cm^{-1}), cyano (2228 cm^{-1}), and ketone function (1662 cm^{-1}). Its ^{1}H-NMR spectrum showed a broad *s* of an aromatic NH_2 group (δ(H) 8.44) and the δ(H) values expected for the aromatic H-atoms, revealing unambiguous signals for H–C(6) and H–C(8) (δ(H) 7.67 (*d*) and 7.17 (*t*), each with an *ortho* coupling $J = 8.08$ Hz). The signals at δ(C) 63.9 (*C*–C≡N) and 171.1 (C–NH_2) in the ^{13}C-NMR spectrum confirmed that malononitrile had reacted with NH_2 and C≡N of 2-amino-4-oxo-4*H*-chromene-3-carbonitrile (**1a**).

The analogous reaction of **1** with ethyl cyanoacetate afforded the corresponding 4-amino-1,5-dihydro-2,5-dioxo-2*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **3**. The ^{1}H-NMR spectrum of **3a** showed a *s* at δ(H) 8.41 for an NH moiety and a broad *s* at δ(H) 8.93 for an NH_2 group present at the pyridine ring. Signals at δ(C) 119.7 (C≡N), 165.1 (C–NH_2), and 153.0 (C=O on the pyridine ring) in the ^{13}C-NMR spectrum confirmed that ethyl cyanoacetate had reacted with NH_2 and C≡N of **1a**.

Finally, cyclocondensation of **1** with acetophenone in AcOH and in the presence of a catalytic amount of concentrated H_2SO_4 solution furnished 2-phenyl-4*H*-chromeno[2,3-*b*]pyridine-4,5(1*H*)-diones **4**. The IR spectrum of **4a** established the absence of C≡N and NH_2 groups, and bands at 1727 cm^{-1} (C=O) and 3192 cm^{-1} (NH) confirmed the formation of a pyridinone moiety. In the ^{1}H-NMR spectrum of **4a**, the NH group of the pyridinone was observed at δ(H) 8.95. Signals at δ(C) 96.4 (CH), 154.4 (Ph–*C*), and 179.0 (C(4)=O) in the ^{13}C-NMR spectrum confirmed that acetophenone had reacted with NH_2 and C≡N of the 2-amino-4-oxo-4*H*-chromene-3-carbonitrile (**1a**).

2.2. *Antitubercular Activity.* The determination of antitubercular activity was carried out against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTCC-200) at the concentration of 62.5 μg/ml, and the values are shown in the *Figure*. Rifampicin was used as standard drug. All the compounds were tested for their antitubercular activity by the *Löwenstein–Jensen* medium (conventional method) [23]. Compounds **3c** and **4f** showed 99% inhibition of *Mycobacterium tuberculosis* $H_{37}Rv$ (MTCC-200) at a concentration of 65.5 μg/ml. The activity of compounds **2**–**4** changed on substitution at the benzo moiety with two Br (**b**), an NO_2 (**c**), a Cl (**d**) and a Me group (**e** and **f**), and also with the functional groups at the pyridine ring. However, two NH_2 groups at the pyridine ring (see **2**) resulted in a poor activity, even though substituents are present at the benzo moiety (except for **2f**). The 9-Me group rendered improved antitubercular activity as compared to the 8-Me group on the benzo moiety. In general, the keto and amine functions at the pyridine moiety of **3a**–**3f** play a favorable role for activity, as shown by the reduced activity of **2a**–**2f**, where the keto group at C(2) was replaced by an amino group. Among the Ph-substituted pyridine scaffolds **4a**–**4f**, only the 9-methyl derivative was found to be the most active against *Mycobacterium tuberculosis* $H_{37}Rv$.

2.3. *Antibacterial and Antifungal Activities.* All of the synthesized compounds were tested for their antibacterial and antifungal activity (*MIC*) *in vitro* by the broth dilution

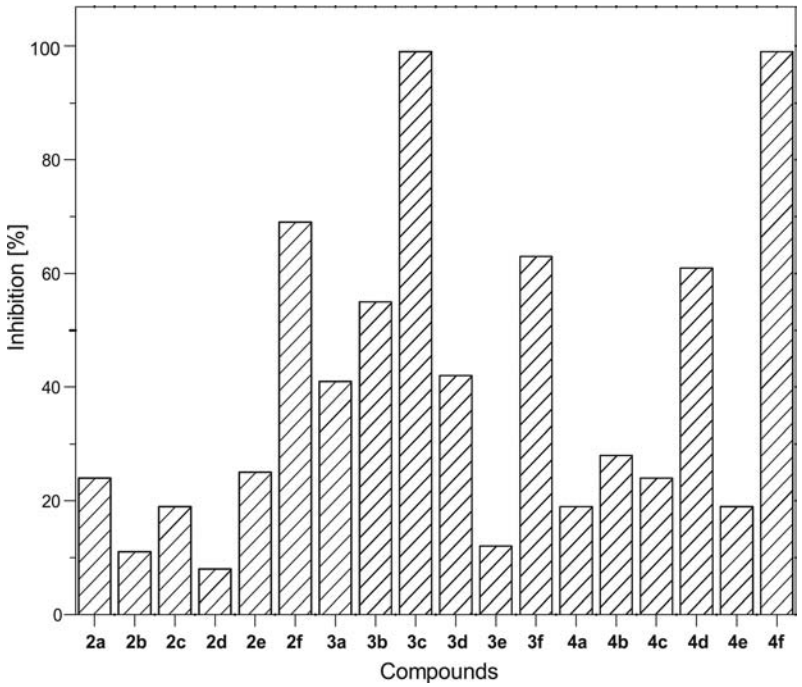


Figure. *Antitubercular activity of chromeno[2,3-*b*]pyridines* **2**–**4**

method [24]. *Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442) as *Gram*-positive and *Escherichia coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688) as *Gram*-negative bacterial strains, as well as the *Candida albicans* (MTCC-227) and *Aspergillus niger* (MTCC-282) fungal strains were used for the *in vitro* studies with **1**–**4** (*Table*), which were compared with ampicillin and griseofulvin as standard drugs for bacterial and fungal strains, respectively. Compounds **2a** and **3c** and ampicillin showed similar antibacterial activity (100 μg/ml) against *E. Coli*. Compound **3b** was the most active against *E. Coli*, whereas compound **2d** showed an activity closer to that of ampicillin. Against *P. aeruginosa*, only the activity of compound **3b** was similar to that of ampicillin. Among the synthesized compounds, **1b**, **1e**, **1f**, **2b**, **2d**, **2e**, **3a**, **3b**, and **3c** showed the best activities (100–200 μg/ml) against *S. aureus*, while all the compounds showed poor activity against *S. pyogenus* bacteria.

The antifungal data revealed that compounds **2b**, **3b**, **4c**, and **4d** showed better activity (250 μg/ml each) than griseofulvin (500 μg/ml) against *C. albicans*, while compound **4f** showed the highest activity (200 μg/ml). However, all the compounds were not active against *A. niger*.

Thus, several of the synthesized novel chromeno[2,3-*b*]pyridines possessed antimicrobial activities against tested bacteria and fungi, which indicated that this basic moiety can be further investigated as a scaffold for antimicrobial drugs. However, it is also evident that the substituents at the benzo moiety and pyridino ring altered the activity of the chromeno[2,3-*b*]pyridines significantly.

Table. *Antimicrobial Assay of the Synthesized Compounds* **1**–**4**[a])

Compound	Minimal bactericidal concentrations [μg/ml]				Minimal fungicidal concentrations [μg/ml]	
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*
1a	250	200	250	200	1000	1000
1b	250	200	200	250	500	>1000
1c	500	250	250	250	>1000	1000
1d	250	500	250	500	500	1000
1e	250	200	150	250	500	>1000
1f	500	500	200	250	500	>1000
2a	100	150	250	250	1000	1000
2b	500	250	150	200	250	>1000
2c	200	200	500	500	500	1000
2d	150	200	100	250	1000	>1000
2e	250	200	100	250	500	1000
2f	250	250	500	500	500	>1000
3a	200	250	200	500	1000	>1000
3b	62.5	100	200	250	250	>1000
3c	100	150	150	200	1000	>1000
3d	250	500	500	500	500	500
3e	500	500	250	250	1000	>1000
3f	250	500	250	500	1000	>1000
4a	250	250	500	500	500	>1000
4b	150	250	250	250	1000	>1000
4c	500	500	250	250	250	>1000
4d	250	200	500	500	250	1000
4e	250	250	500	500	500	1000
4f	200	250	500	500	200	500
A	100	100	250	100	–	–
B	–	–	–	–	500	100

[a]) Ampicillin (**A**) and griseofulvin (**B**) were used as standard drugs for bacterial strains and fungal strains, respectively.

3. Conclusion. – A family of novel functionalized chromeno[2,3-*b*]pyridine derivatives were synthesized by the *Friedländer* approach. These fused tricyclic ring systems showed good antitubercular and antimicrobial activities. The antitubercular evaluation of these chromeno[2,3-*b*]pyridines revealed some potent molecules depending on their substitution pattern. The presence of a keto and amine function at the pyridine ring produced significant antitubercular activity. Among the synthesized compounds, **3c** and **4f** showed 99% inhibition against *Mycobacterium tuberculosis* H37Rv. Introduction of different substituents at the benzo moiety of the chromeno[2,3-*b*]pyridine scaffold led to derivatives exhibiting comparable or higher antibacterial activities against *S. aureus* as compared with ampicillin. Against *E. coli*, compound **3b** was the most active.

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Experimental Part

1. *General*. All org. solvents used for the syntheses were of anal. grade; they were dried and freshly distilled under a moisture-free atmosphere. TLC (reaction monitoring): silica gel plates (*Merck*), toluene/AcOEt 7.5 : 2.5; visualization by I_2 vapor or UV light. M.p.: open glass capillaries; uncorrected. IR Spectra: *Hitachi-270-50* double-beam and *Nicolet-iS10* FT-IR spectrometer (*Thermo Fisher*); KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-Avance-II-400* spectrophotometer (400 MHz); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. Elemental analysis: *Perkin-Elmer-2400-C,H,N* analyzer; accuracy $\pm 0.4\%$ of theoretical values.

2. *2-Amino-4-oxo-4*H*-1-benzopyran-3-carbonitriles* **1a**–**1f**: *General Procedure.* The synthetic procedure is reported in [12].

*2-Amino-4-oxo-4*H*-1-benzopyran-3-carbonitrile* (**1a**): See [21].

*2-Amino-6,8-dibromo-4-oxo-4*H*-1-benzopyran-3-carbonitrile* (**1b**)*:* Colorless solid. Yield 78%. M.p. $>300°$. IR (KBr): 3277, 3096 (NH_2), 2228 (C≡N), 1666 (C=O), 1626 (C=N), 726 (C–Br). ^{1}H-NMR: ($CDCl_3$/(D_6)DMSO): 7.90 (*d*, *J* = 2.0, H–C(7)); 8.20 (*d*, *J* = 2.0, H–C(5)); 9.01 (br. *s*, NH_2).

*2-Amino-6-nitro-4-oxo-4*H*-1-benzopyran-3-carbonitrile* (**1c**): Brown solid. Yield 71%. M.p. $>300°$. IR (KBr): 3295, 3079 (NH_2), 2225 (C≡N), 1661 (C=O), 1616 (C=N), 1520 (C–NO_2). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 7.49 (*d*, *J* = 9.08, H–C(8)); 8.22 (*dd*, *J* = 2.84, 2.88, H–C(7)); 8.75 (*dd*, *J* = 2.80, H–C(5)); 8.97 (br. *s*, NH_2, D_2O exchangeable).

*2-Amino-6-chloro-4-oxo-4*H*-1-benzopyran-3-carbonitrile* (**1d**): See [21].

*2-Amino-7-methyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile* (**1e**): Beige solid. Yield 77%. M.p. $>300°$. IR (KBr): 3257, 3121 (NH_2), 2224 (C≡N), 1669 (C=O), 1611 (C=N), 1360 (Me–Ar). ^{1}H-NMR ((D_6)DMSO): 2.45 (*s*, Me–C(7)); 7.06 (*s*, H–C(8)); 7.18 (*d*, *J* = 7.8, H–C(6)); 7.93 (*d*, *J* = 7.88, H–C(5)); 9.00 (br. *s*, NH_2, D_2O exchangeable).

*2-Amino-8-methyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile* (**1f**): See [21].

3. *2,4-Diamino-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carbonitriles* **2a**–**2f**: *General Procedure* A mixture of **1** (0.005 mol) and malononitrile (0.33 g, 0.005 mol) in abs. EtOH (20 ml) containing 2,2′,2″-nitrilotris[ethanol] (0.51 g, 0.005 mol) was heated under reflux for 8 h. The mixture was left to cool to r.t., then poured into ice cold H_2O (50 ml) and neutralized with dil. HCl soln. The separated precipitates were filtered off and recrystallized from MeOH: **2a**–**2f**.

*2,4-Diamino-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**2a**) [22]. Beige crystals. Yield 67%. M.p. 242–244°. IR (KBr): 3308, 3138 (2 NH_2), 2228 (C≡N), 1662 (C=O), 1615 (C=N). ^{1}H-NMR ((D_6)DMSO): 6.66–6.73 (*m*, H–C(7), H–C(9)); 7.17 (*ddd*, *J* = 8.08, 2.16, 1.82, H–C(8)); 7.67 (*dd*, *J* = 8.08, 1.82, H–C(6)); 8.33 (br. *s*, NH_2, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$): 78.66; 115.8; 117.5; 117.4; 123.2; 133.4; 151.6; 169.7 (arom. C); 63.9 (*C*–C≡N); 171.1 (NH_2–C(2)); 158.2 (NH_2–C(4)); 112.6 (C≡N); 189.5 (C=O).

*2,4-Diamino-7,9-dibromo-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**2b**): Beige crystals. Yield 72%. M.p. 216–218°. IR (KBr): 3283, 3074 (2 NH_2), 2228 (C≡N), 1678 (C=O), 1633 (C=N), 721 (C–Br). ^{1}H-NMR ((D_6)DMSO): 7.84 (*d*, *J* = 2.04, H–C(8)); 8.13 (*d*, *J* = 2.04, H–C(6)); 8.45 (br. *s*, NH_2, D_2O exchangeable).

*2,4-Diamino-7-nitro-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**2c**): Brown crystals. Yield 63%. M.p. 252–254°. IR (KBr): 3292, 3082 (2 NH_2), 2229 (C≡N), 1665 (C=O), 1626 (C=N), 1526 (C–NO_2). ^{1}H-NMR ((D_6)DMSO): 7.19 (*d*, *J* = 9.2, H–C(9)); 8.42 (*dd*, *J* = 2.84, 9.2, H–C(8)); 8.78 (*dd*, *J* = 2.84, H–C(6)); 8.37 (br. *s*, NH_2, D_2O exchangeable).

*2,4-Diamino-7-chloro-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**2d**): Beige crystals. Yield 69%. M.p. 280–282°. IR (KBr): 3299, 3126 (2 NH_2), 2225 (C≡N), 1665 (C=O), 1626 (C=N), 814 (C–Cl). ^{1}H-NMR ((D_6)DMSO): 7.23 (*d*, *J* = 8.8, H–C(9)); 7.54 (*dd*, *J* = 2.68, 8.8, H–C(8)); 7.92 (*d*, *J* = 2.68, H–C(6)); 8.39 (br. *s*, NH_2, D_2O exchangeable).

*2,4-Diamino-8-methyl-5-oxo-5*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**2e**): Light brown crystals. Yield 61%. M.p. 243–245°. IR (KBr): 3313, 3137 (2 NH_2), 2224 (C≡N), 1666 (C=O), 1628 (C=N), 1358 (Me–Ar). ^{1}H-NMR ((D_6)DMSO): 2.46 (*s*, Me–C(8)); 7.10 (*d*, *J* = 1.28, H–C(9)); 7.21 (*dd*, *J* = 7.88, 1.28, H–C(7)); 7.92 (*d*, *J* = 7.88, H–C(6)); 8.29 (br. *s*, NH_2, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$): 87.6; 111.7; 115.4; 120.8; 123.2; 145.7; 147.0; 169.6 (arom. C); 20.1 (Me); 62.8 (*C*–C≡N); 172.6 (NH_2–C(2)); 158.3 (NH_2–C(4)); 110.1 (C≡N); 188.3 (C=O).

*2,4-Diamino-9-methyl-5-oxo-5*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**2f**): Light brown crystals. Yield 65%. M.p. 225–227°. IR (KBr): 3309, 3126 (2 NH_2), 2223 (C≡N), 1665 (C=O), 1625 (C=N), 1363 (Me–Ar). ^{1}H-NMR ((D_6)DMSO): 2.38 (*s*, Me–C(9)); 6.64 (*t*, *J* = 7.56, H–C(7)); 7.27 (*dd*, *J* = 7.24, 2.82, H–C(8)); 7.68 (*dd*, *J* = 7.84, 1.24, H–C(6)); 8.35 (br. *s*, NH_2, D_2O exchangeable).

4. *4-Amino-1,5-dihydro-2,5-dioxo-2*H-*[1]benzoprano[2,3-*b*]pyridine-3-carbonitriles* **3a**–**3f**: *General Procedure.* A mixture of **1** (0.005 mol) and ethyl cyanoacetate (0.56 g, 0.005 mol) in abs. EtOH (20 ml) containing 2,2′,2″-nitrilotris[ethanol] (0.51 g, 0.005 mol) was heated under reflux for 8 h. The mixture was left to cool to r.t., then poured into ice cold H_2O (50 ml), and neutralized with dil. HCl soln. The separated precipitates were filtered off and recrystallized from MeOH: **3a**–**3f**.

*4-Amino-1,5-dihydro-2,5-dioxo-2*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**3a**): Beige crystals. Yield 65%. M.p. 211–213°. IR (KBr): 3306, 3141 (NH_2), 2225 (C≡N), 1662, 1697 (C=O), 1616 (C=N). ^{1}H-NMR ((D_6)DMSO): 7.44–7.61 (*m*, H–C(7), H–C(9)); 7.94 (*ddd*, *J* = 8.04, 2.16, 1.8, H–C(8)); 8.12 (*dd*, *J* = 8.04, 1.8, H–C(6)); 8.41 (*s*, NH); 8.93 (br *s*, NH_2). ^{13}C-NMR ($CDCl_3$): 74.0; 115.2; 117.8; 120.6; 125.0; 126.2; 133.6; 152.7 (arom. C); 80.4 (*C*–C≡N); 119.7 (C≡N); 153.0 (C(2)=O); 165.1 (NH_2–C(4)); 173.6 (C(5)=O).

*4-Amino-7,9-dibromo-1,5-dihydro-2,5-dioxo-2*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**3b**): Beige crystals. Yield 68%. M.p. 207–209°. IR (KBr): 3321, 3136 (NH_2), 2221 (C≡N), 1669, 1717 (C=O), 1628 (C=N), 726 (C–Br). ^{1}H-NMR ((D_6)DMSO): 7.87 (*d*, *J* = 2.0, H–C(8)); 8.17 (*d*, *J* = 2.0, H–C(6)); 8.58 (*s*, NH); 9.11 (br. *s*, NH_2).

*4-Amino-1,5-dihydro-7-nitro-2,5-dioxo-2*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**3c**): Beige crystals. Yield: 61%. M.p. >300°. IR (KBr): 3318, 3093 (NH_2), 2228 (C≡N), 1663, 1689 (C=O), 1612 (C=N), 1522 (C–NO_2). ^{1}H-NMR ((D_6)DMSO): 7.59 (*d*, *J* = 9.01, H–C(9),); 8.42 (*dd*, *J* = 9.01, 2.88, H–C(8)); 8.57 (*dd*, *J* = 2.88, H–C(6)); 8.73 (*s*, NH); 9.08 (br. *s*, NH_2).

*4-Amino-7-chloro-1,5-dihydro-2,5-dioxo-2*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**3d**): Yellow crystals. Yield 54%. M.p. 165–167°. IR (KBr): 3265, 3098 (NH_2), 2236 (C≡N), 1668, 1694 (C=O), 1618 (C=N), 822 (C–Cl). ^{1}H-NMR ((D_6)DMSO): 7.26 (*d*, *J* = 8.78, H–C(9)); 7.66 (*dd*, *J* = 8.78, 2.6, H–C(8)); 7.95 (*d*, *J* = 2.6, H–C(6)); 8.43 (*s*, NH); 9.10 (br. *s*, NH_2). ^{13}C-NMR ($CDCl_3$): 80.7; 120.7; 123.8; 124.7; 128.7; 133.5; 150.1; 171.4 (arom. C); 79.4 (*C*–C≡N); 118.7 (C≡N); 152.9 (C(2)=O); 165.5 (NH_2–C(4)); 171.1 (C(5)=O).

*4-Amino-1,5-dihydro-8-methyl-2,5-dioxo-2*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**3e**): Yellow crystals. Yield 77%. M.p. 217–219°. IR (KBr): 3300, 3127 (NH_2), 2223 (C≡N), 1736, 1665 (C=O); 1615 (C=N), 1358 (Me–Ar). ^{1}H-NMR: ($CDCl_3$/(D_6)DMSO): 2.45 (*s*, Me–C(8)); 7.09 (*d*, *J* = 1.22, H–C(9)); 7.16 (*dd*, *J* = 7.88, 1.22, H–C(7)); 7.94 (*d*, *J* = 7.88, H–C(6)); 8.0 (*s*, NH); 9.09 (br. *s*, NH_2).

*4-Amino-1,5-dihydro-9-methyl-2,5-dioxo-2*H-*[1]benzopyrano[2,3-*b*]pyridine-3-carbonitrile* (**3f**): Yellow crystals. Yield 68%. M.p. 241–243°. IR (KBr): 3327, 3095 (NH_2), 2227 (C≡N), 1711, 1668 (C=O), 1625 (C=N), 1373 (Me–Ar). ^{1}H-NMR: $CDCl_3$/(D_6)DMSO): 2.34 (*s*, Me–C(9)); 6.78 (*t*, *J* = 7.48, H–C(7)); 7.29 (*dd*, *J* = 7.26, 2.88, H–C(8)); 8.08 (*dd*, *J* = 7.28, 1.22, H–C(6)); 8.19 (*s*, NH); 9.02 (br. *s*, NH_2).

5. *2-Phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-diones* **4a**–**4f**: *General Procedure.* A mixture of **1** (0.005 mol) and acetophenone (0.6 g, 0.005 mol) in AcOH (20 ml) containing 2 drops of conc. H_2SO_4 soln. was heated under reflux for *ca.* 8 h. The mixture was left to cool to r.t. and then poured into ice-cold H_2O (50 ml). The separated precipitates were filtered off and recrystallized from MeOH: **4a**–**4f**.

*2-Phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-dione* (**4a**): Beige crystals. Yield 67%. M.p. 204–206°. IR (KBr): 3192 (NH), 1727, 1661 (C=O); 1635 (C=N). ^{1}H-NMR ((D_6)DMSO): 6.52 (*s*, CH); 7.68–8.39 (*m*, 9 CH); 8.95 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 96.4, 117.3; 123.1; 124.6; 125.4; 127.9; 129.5; 133.1; 133.3; 154.4; 154.9; 161.8 (arom. C); 98.2 (C–H); 174.8 (C(5)=O); 179.0 (C(4)=O).

*7,9-Dibromo-2-phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-dione* (**4b**): Beige crystals. Yield 62%. M.p. 213–215°. IR (KBr): 3196 (NH), 1731, 1668 (C=O), 1629 (C=N), 718 (C–Br). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 6.54 (*s*, CH); 7.61–7.88 (*m*, 5 arom. H); 7.75 (*d*, *J* = 2.01, H–C(8)); 8.17 (*d*, *J* = 2.01, H–C(6)); 9.05 (*s*, NH).

*7-Nitro-2-phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-dione* (**4c**): Brown crystals. Yield 58%. M.p. >300°. IR (KBr): 3293 (NH), 1672, 1660 (C=O), 1616 (C=N), 1531 (C–NO_2). ^{1}H-NMR ((D_6)DMSO): 6.49 (*s*, CH); 7.64–7.91 (*m*, 5 arom. H); 7.98 (*d*, *J* = 10.88, H–C(9)); 8.65 (*dd*, *J* = 10.88, 2.56, H–C(8)); 8.83 (*d*, *J* = 2.56, H–C(6)); 8.97 (*s*, NH).

*7-Chloro-2-phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-dione* (**4d**): Yellow crystals. Yield 62%. M.p. 204–206°. IR (KBr): 3207 (NH), 1712, 1664 (C=O), 1627 (C=N), 811 (C–Cl). ^{1}H-NMR ((D_6)DMSO): 6.80 (*s*, CH); 7.22–7.49 (*m*, 5 arom. H); 7.81 (*d*, *J* = 8.8, H–C(9)); 7.92 (*dd*, *J* = 8.8, 2.65, H–C(8)); 8.43 (*d*, *J* = 2.65, H–C(6)); 8.98 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 120.4; 121.3; 124.9; 125.7; 126.1; 127.4; 128.5; 132.5; 132.8; 153.4; 153.8; 161.8 (arom. C); 98.2 (C–H); 173.0 (C(5)=O); 179.0 (C(4)=O).

*8-Methyl-2-phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-dione* (**4e**): Beige crystals. Yield 67%. M. p. 210–212°. IR (KBr): 3189 (NH), 1720, 1668 (C=O), 1614 (C=N), 1357 (Me–Ar). ^{1}H-NMR ((D_6)DMSO): 2.39 (*s*, Me–C(8)); 6.78 (*s*, CH); 6.96–8.02 (*m*, 8 arom. H); 8.92 (*s*, NH).

*9-Methyl-2-phenyl-4*H-*[1]benzopyrano[2,3-*b*]pyridine-4,5(1*H*)-dione* (**4f**): Brown crystals. Yield 65%. M.p. 227–229°. IR (KBr): 3189 (NH); 1720, 1668 (C=O), 1614 (C=N), 1361 (Me–Ar). ^{1}H-NMR ((D_6)DMSO): 2.31 (*s*, Me–C(9)); 6.82 (*s*, CH); 6.89–7.78 (*m*, 8 arom. H); 8.86 (*s*, NH).

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