An Efficient Synthesis of 6-Nitro- and 6-Amino-3*H*-imidazo[4,5-*b*]pyridines by Cyclocondensation of 1-Substituted 1*H*-Imidazol-5-amines with 3-Nitro-4*H*-chromen-4-one

Dmytro Ostrovskyi,[a] Viktor O. Iaroshenko,*[a,b] Andranik Petrosyan,[a] Sergii Dudkin,[a] Iftikhar Ali,[a] Alexander Villinger,[a] Andrei Tolmachev,[b,c] Peter Langer*[a,d]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
Fax +49(381)4986412; E-mail: viktor.iaroshenko@uni-rostock.de; E-mail: iva108@googlemail.com; E-mail: peter.langer@uni-rostock.de

[b] National Taras Shevchenko University, 62 Volodymyrska st., 01033 Kyiv-33, Ukraine

[c] 'Enamine Ltd.', 23 A. Matrosova st., 01103 Kyiv, Ukraine

[d] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany

Received 11 May 2010

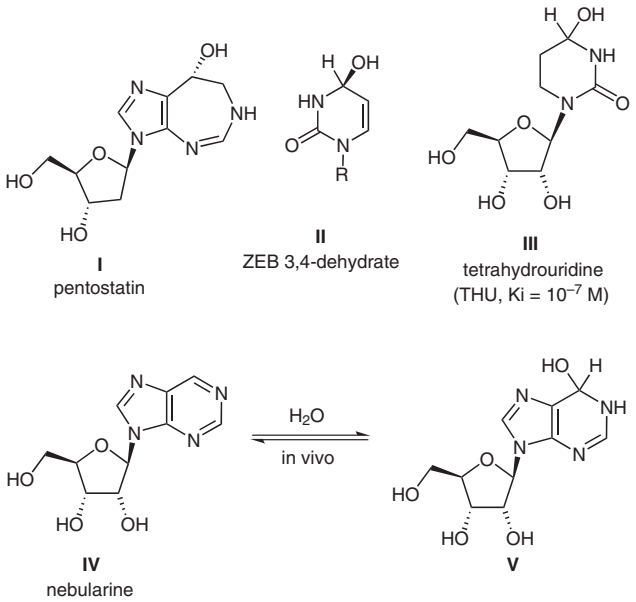
Abstract: The reaction of 3-nitro-4*H*-chromen-4-one with in situ generated 1-substituted 5-amino-1*H*-imidazoles affords a set of 1-substituted 6-nitro-3*H*-imidazo[4,5-*b*]pyridines which represent potential adenosine deaminase (ADA) inhibitors. Reduction of the nitro group results in the formation of the corresponding 6-amino-3*H*-imidazo[4,5-*b*]pyridines.

Key words: cyclization, chromones, N-heterocycles, imidazoles, purine isosteres

Imidazo[4,5-*b*]pyridines (1-desazapurines) constitute an important class of heterocyclic compounds which exhibit a wide range of pharmacological properties.[1] Some of the 1-desazapurines are potential phosphodiesterase inhibitors,[2] GPR4 receptor antagonists,[3a] or inhibitors of aurora kinase.[3b,c]

In the recent two decades, 1-desazapurines became one of the most important scaffolds for the design and synthesis of adenosine deaminase (ADA) inhibitors. Adenosine deaminase (adenosine aminohydrolase, ADA) and adenylate deaminase (5′-adenylic acid deaminase, AMP deaminase, AMPDA) are metalloenzymes which are involved in the purine salvage metabolic pathway and catalyze the deamination of adenosine and 5′-phosphate adenosine (adenylic acid, AMP) to the corresponding inosines.[4] ADA enzymes play a key role in the purine de novo biosynthesis.[5–8] ADA enzymes became important targets for drug design, since it was found that disorders of the ADA function impairs the action of the human immune system. This results in severe combined immunodeficiency (SCID), characterized by severe T-lymphocyte dysfunction and agammaglobulinemia.[9] Furthermore, ADA enzyme abnormalities have been reported also in acquired immunodeficiency syndrome (AIDS),[10] in tuberculosis,[11] in Parkinson's disease,[12a] in viral hepatitis,[12b] in some leukemia diseases,[13] and in many other diseases including cancer.[13]

One popular strategy in drug design to achieve the best inhibition of a current enzyme is to mimic the transition state of the enzyme activity.[14] Pentostatin (**I**), coformycin and their analogues represent ADA transition-state analogous inhibitors which show a strong, nearly irreversible interaction with the receptor[15] (Scheme 1). Pyrimidine nucleosides **II**, **III**, containing a tetrahedral carbon or phosphorus atom instead of carbon atom C(4), are potent inhibitors of cytidine deaminase (CDA,[16] Scheme 1). Zebularine (pyrimidin-2-one ribonucleoside) binds in a hydrated form (zebularine 3,4-dihydrate **II**) to the active site of the enzyme.[16a]



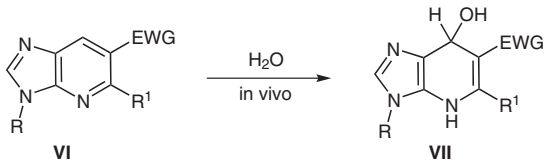
Scheme 1 Potent ADA and CDA inhibitors

Recently, it has been demonstrated that purine-type nucleosides and nucleotides, which are able to undergo covalent hydration in the aglycone ring system, are potent inhibitors of the enzymes adenosine deaminase (ADA) and AMP deaminase, respectively. Commercially available drug nebularine (**IV**) exhibits a strong anticancer activity and represents another potent ADA inhibitor.[17a] The correspondent 5′-monophosphate is a selective AMPDA inhibitor.[17b] The mechanism of action is mainly based on enzyme-catalyzed stereospecific addition of a water molecule or hydroxide ion, in the presence of a Zn^{2+} ion, to the

SYNLETT 2010, No. 15, pp 2299–2303
Advanced online publication: 30.07.2010
DOI: 10.1055/s-0030-1258538; Art ID: G12910ST
© Georg Thieme Verlag Stuttgart · New York

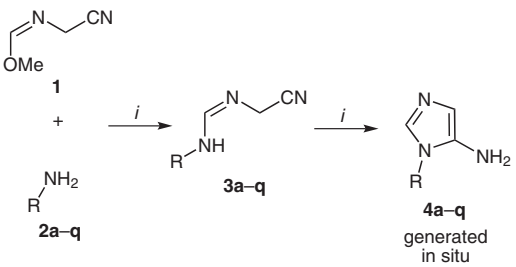
Downloaded by: Universität Rostock. Copyrighted material.

C(6) position of **IV** to give 6-hydroxy-1,6-dihydropurine ribonucleoside (HDPR) **V**.[18] This mechanism was established by X-ray structures of the complex HDPR with the native and mutant ADA.[18]



Scheme 2 6-Acceptor-substituted 3*H*-imidazo[4,5-*b*]pyridines as new potential ADA and CDA inhibitors

Continuing our research program dedicated to the design and synthesis of novel inhibitors of ADA, we searched for new purine-type scaffolds **VI** which, with respect to the position of the electron-withdrawing substituents, would facilitate the above-mentioned addition of a water molecule. We believe that the introduction of a strong electron-withdrawing group (EWG) located at position 1 of the purine or pseudo purine system will increase the electron deficiency of position 6. This would result in a facile addition of water in vivo leading to the formation of the hydrate **VII** (Scheme 2). We have focussed our attention to the nitro group, because of its strong electron-withdrawing properties. In addition, it is known that 3-nitropyridines as well as their heteroannulated analogues are able to react with O-, N-, and C-nucleophiles to give stable Meisenheimer-type compounds.[19] It is known that the above-mentioned nitro derivatives undergo, depending on the pH, a reaction with water to give stable hydrates.[19,20] Therefore, they are expected to be promising scaffolds for the development of ADA transition-state mimetics.

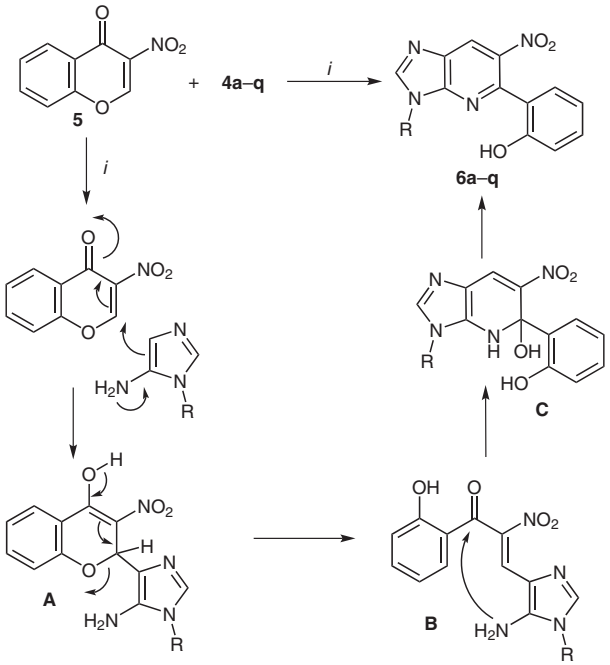


Scheme 3 *Reagents and conditions*: (i) CH_2Cl_2, argon, reflux, 2 h.

Based on our experience in the chemistry of electron-rich aminoheterocycles,[21] we have developed a new synthetic approach to 6-nitro-3*H*-imidazo[4,5-*b*]pyridines and the results of our efforts are reported herein.

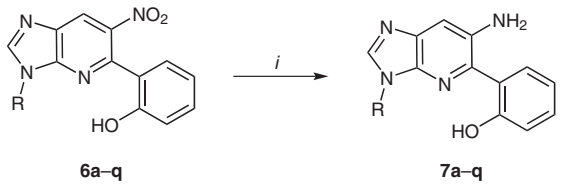
3-Nitro-4*H*-chromen-4-one[22] (**5**) and its derivatives are readily available in three steps from commercially available 4-hydroxy-2*H*-chromen-2-one. The chemistry of **5** has not been extensively studied so far.[23] Reactions of **5** with ureas, thioureas, amidines, and 1,3,5-tricarbonyl compounds have been reported. It occurred to us that the reaction of **5** with 5-aminoimidazoles may provide a convenient synthetic approach to 6-nitro-3*H*-imidazo[4,5-*b*]pyridines **VI** (Scheme 2, EWG = NO_2).

5-Aminoimidazoles **4a–q** were generated in situ, following our previously reported procedure,[24] by reaction of methyl *N*-(cyanomethyl)formimidate (**1**) with amines **2a–q** to give **3a–q** and subsequent cyclization (Scheme 3).



Scheme 4 *Reagents and conditions*: (i) CH_2Cl_2, reflux, 5 h.

Treatment of the in situ generated imidazoles **4a–q** with an equivalent amount of 3-nitro-4*H*-chromen-4-one (**5**) afforded the 1-substituted 6-nitro-3*H*-imidazo[4,5-*b*]-pyridines **6a–q** in good to excellent yields (Scheme 4).[25,26] The reaction was carried out in dichloromethane under argon atmosphere under reflux for 5 hours. In most cases, the reaction was complete after 1–2 hours, and the product could be isolated by simple filtration of the precipitate formed.



Scheme 5 *Reagents and conditions*: (i) MeOH, H_2, Pd/C (10 mol%), 20 °C, 2 d.

The formation of products **6a–q** can be explained by conjugate addition of the enamine carbon atom of **4a–q** to the double bond of **5** to give intermediate **A**. Subsequent pyrone ring opening delivers intermediate type **B**. The intramolecular attack of the amino group to the carbonyl group affords intermediate **C** which undergoes elimination of water to give pyridines **6**.

Downloaded by: Universität Rostock. Copyrighted material.

Table 1 Yields of Imidazo[4,5-*b*]pyridines **6a–q** and **7a–q**

6, **7**	R	Yield of **6** (%)[a]	Yield of **7** (%)[a]
a	*t*-Bu	96[c]	92[c]
b	All	41[c]	82[c,e]
c	*n*-heptyl	86[b]	84[c]
d	cyclopropyl	69[b]	86[d]
e	cyclopentyl	77[c]	92[c]
f	cyclohexyl	82[c]	85[c]
g	4-methoxybenzyl	85[b]	83[c]
h	3-methoxybenzyl	99[b]	82[d]
i	2,3-(dimethoxy)benzyl	87[c]	78[c]
j	2-(chloro)benzyl	76[b]	76[c]
k	4-(chloro)benzyl	79[b]	71[c]
l	2-[(4-methoxy)phenyl]ethyl	72[b]	78[c]
m	2-[(3,4-dimethoxy)phenyl]ethyl	91[c]	75[c]
n	2-[(2-methoxy)phenyl]ethyl	73[b]	79[c]
o	2-(phenyl)ethyl	82[c]	80[c]
p	(pyridin-4-yl)methyl	76[b]	79[c]
q	2-(pimethylamino)ethyl	88[c]	81[c]

[a] Yields of isolated products.
[b] Isolated by filtration.
[c] Isolated by column chromatography (EtOAc–*i*-PrOH).
[d] Isolated by filtration through Celite.
[e] Allyl substituent was reduced to propyl.

The structure of **6g** was confirmed by an X-ray crystal structure analysis.[27] The imidazo[4,5-*b*]pyridine unit has, as expected in the solid state, a flat structure.

6-Amino-imidazo[4,5-*b*]pyridines were previously recognized as VR1-type capsaicin receptor ligands,[28a] and as inhibitors of src-family tyrosine kinases.[28b] Some of these molecules are used to control or prevent cancer.[28c,d]

Due to the importance of 6-aminoimidazo[4,5-*b*]-pyridines, we studied their synthesis by hydrogenation of **6** in the presence of Pd/C (10 mol%, Scheme 5).[29]

The hydrogenation of **6a–q** afforded the 6-aminoimidazo[4,5-*b*]pyridines **7a–q**[30] with excellent yields. It is noteworthy that, in the case of **7g–k**, no cleavage of the benzyl group was observed, and in a case of **6b** allyl group was reduced to propyl to give the corresponding 2-(6-amino-3-propyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenol (**7b**).

In conclusion, we have reported a new facile method for the synthesis of functionalized 6-nitro-3*H*-imidazo[4,5-*b*]pyridines by cyclocondensation of 3-nitro-4*H*-chromen-4-one with 5-aminoimidazoles. The reduction of the nitro group afforded the corresponding 6-amino-3*H*-imidazo[4,5-*b*]pyridines. We have shown that the developed procedure can be applied to the synthesis of diverse sets of functional druglike scaffolds. The biological evaluation of the synthesized compounds is currently studied in our laboratories.

Acknowledgment

Financial support by the State of Mecklenburg-Vorpommern (scholarships for V.O.I., D.O., A.P., and S.D.) and by the State of Pakistan (HEC scholarship for I.A.) is gratefully acknowledged.

References and Notes

(1) (a) Dubey, P. K.; Kumar, R. V.; Naidu, A.; Kulkarni, S. M. A. *Asian J. Chem.* **2002**, *14*, 1129. (b) Lee, S. Ch.; Choi, J. S.; Oh, J. H.; Park, B.; Kim, Y. E.; Lee, J. H.; Shin, D.; Kim, Ch. M.; Hyun, Y.-L.; Lee, Ch. S.; Cho, J.-M.; Ro, S. WO 2007083978, **2007**, *Chem. Abstr.* **2007**, *147*, 817587. (c) Kelly, M. G.; Kincaid, J.; Duncton, M.; Sahasrabudhe, K.; Janagani, S.; Upasani, R. B.; Wu, G.; Fang, Y.; Wei, Zh.-L. US 2006194801, **2006**; *Chem. Abstr.* **2006**, *145*, 889269. (d) Randolph, J. T.; Chen, H.; Degoey, D. A.; Flentge, Ch. A.; Flosi, W. J.; Grampovnik, D. J.; Huang, P. P.; Hutchinson, D. K.; Kempf, D. J.; Klein, L. L.; Yeung, M. C. US 2005159469, **2005**; *Chem. Abstr.* **2005**, *143*, 641882. (e) Kivlighn, S. D.; Zingaro, G. J.; Gabel, R. A.; Broten, T. P.; Schorn, T. W.; Schaffer, L. W.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Siegl, P. K. S. *Am. J. Hypertens.* **1995**, *8*, 58.

(2) (a) Pagani, E. D.; Dundore, R. L.; Bode, D. C.; Bacon, E. R.; Singh, B.; Lesher, G. Y.; Buchholz, R. A.; Silver, P. J. *J. Cardiovasc. Pharmacol.* **1994**, *24*, 403. (b) Joseph, E. C.; Rees, J. A.; Dayan, A. *Toxicol. Pathol.* **1996**, *24*, 436. (c) Garvey, D. S.; Saenz de Tejada, I.; Earl, R. A.; Khanapure, S. P. US 6331543, **2001**; *Chem. Abstr.* **2001**, *136*, 916407.

(3) (a) Ida, K.; Otsubo, N.; Kuboyama, T.; Arai, H.; Watanabe, A.; Saki, M.; Hiura, N.; Manabe, H.; Takada, H.; Saito, J. WO 2005082905, **2005**; *Chem. Abstr.* **2005**, *143*, 979654. (b) Magnuson, S.; Dixon, J.; Phillips, B.; Khire, U.; Wang, L.; Zhang, Zh.; Patel, M.; Kumarasinghe, E. S.; Wickens, P.; Olague, A. WO 2007064932, **2007**; *Chem. Abstr.* **2007**, *147*, 618350. (c) Bavetsias, V.; Sun, C.; Bouloc, N.; Reynisson, J.; Workman, P.; Linardopoulos, S.; McDonald, E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6567.

(4) Zielke, C. I.; Suelter, C. H. *Purine, Purine Nucleoside, and Purine Nucleotide Aminohydrolases,* In *The Enzymes*, Vol. 4; Boyer, P. D., Ed.; Academic Press: New York, **1971**, 47.

(5) (a) Cristalli, G.; Costanzi, S.; Lambertucci, C.; Lupidi, G.; Vittori, S.; Volpini, R.; Camaioni, E. *Med. Res. Rev.* **2001**, *21*, 105. (b) Maydanovych, O.; Beal, P. A. *Chem. Rev.* **2006**, *106*, 3397. (c) Nair, V. *IMPDH Inhibitors: Discovery of Antiviral Agents Against Emerging Diseases,* In *Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats*; Torrence, P. F., Ed.; John Wiley and Sons: Hoboken, **2005**, Chap. 8, 179–202. (d) Shu, Q.; Nair, V. *Med. Res. Rev.* **2008**, 219.

(6) (a) Agarwal, R. P. *Pharmac. Ther.* **1982**, *17*, 399. (b) Weber, G. *Cancer Res.* **1983**, *43*, 3466.

(7) Pankiewicz, K. W.; Goldstein, B. M. *Inosine Mono Phosphate Dehydrogenase, ACS Symposium Series 839*; American Chemical Society: Washington DC, **2003**.

Downloaded by: Universität Rostock. Copyrighted material.

(8) (a) Burns, C. M.; Chu, H.; Rueter, S. M.; Hutchinson, L. K.; Canton, H.; Sanders-Bush, E.; Emeson, R. B. *Nature (London)* **1997**, *387*, 303. (b) Higuchi, M.; Single, F. N.; Kohler, M.; Sommer, B.; Sprengel, R.; Seeburg, P. H. *Cell* **1993**, *75*, 1361.

(9) (a) Giblett, E. R.; Anderson, J. E.; Cohen, F.; Pollara, B.; Meuwissen, H. J. *Lancet* **1972**, *2*, 1067. (b) Hirshhorn, R. *Clin. Immunol. Immunopathol.* **1995**, *76*, 219.

(10) (a) Niedzwicki, J. G.; Kouttab, N. M.; Mayer, K. H.; Carpenter, C. C.; Parks, R. E. Jr.; Abushanab, E.; Abernethy, D. R. *J. Acquir. Immune Defic. Syndr.* **1991**, *4*, 178. (b) Salvatore, D.; Claudio, M. M.; Anna, P. M. *Clin. Chem.* **1987**, *33*, 1675. (c) Valenzuela, A.; Blanco, J.; Callebaut, C.; Jacotot, E.; Lluis, C.; Hovanessian, A. G.; Franco, R. *J. Immunol.* **1997**, *158*, 3721.

(11) (a) Ungerer, J. P. J.; Oosthuizen, H. M.; Retief, J. H.; Bissbort, S. H. *Chest* **1994**, *106*, 33. (b) Banales, J. L.; Rivera Martinez, E.; Perez Gonzalez, L.; Selman, M.; Raymond, Y.; Nava, A. *Arch. Med. Res.* **1999**, *30*, 358.

(12) (a) Chiba, S.; Matsumoto, H.; Saitoh, M.; Kasahara, M.; Matsuya, M.; Kashiwagi, M. A. *J. Neurol. Sci.* **1995**, *132*, 170. (b) Gakis, C. *Eur. Respir. J.* **1996**, *9*, 632.

(13) (a) Demeocq, F.; Viallard, J. L.; Boumsell, L.; Richard, Y.; Chassgne, J.; Plagne, R.; Lemerle, J.; Bernard, A. *Leuk. Res.* **1982**, *6*, 211. (b) Carlucci, F.; Rosi, F.; Di Pietro, C.; Marinello, E. *Biochim. Biophys. Acta* **1997**, *1360*, 203.

(14) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*, 2nd ed.; Elsevier Academic Press: New York, **2004**, 617; ISBN 0-12-643732-7.

(15) Agarwal, R. P.; Spector, T.; Parks, R. E. *Biochem. Pharmacol.* **1977**, *26*, 359.

(16) (a) Frick, L.; Yang, C.; Marquez, V. E.; Wolfenden, R. *Biochemistry* **1989**, *28*, 9423. (b) Ashley, G. W.; Bartlett, P. A. *J. Biol. Chem.* **1984**, *259*, 13621.

(17) (a) Shewach, D. S.; Krawczyk, S. H.; Acevedo, O. L.; Townsend, L. B. *Biochem. Pharmacol.* **1992**, *44*, 1697. (b) Frieden, C.; Kurz, L. C.; Gilbert, H. R. *Biochemistry* **1980**, *19*, 5303.

(18) (a) Wang, Z.; Quiocho, F. A. *Biochemistry* **1998**, *37*, 8314. (b) Wilson, D. K.; Rudolph, F. N.; Quiocho, F. A. *Science* **1991**, *252*, 1278. (c) Kinoshita, T.; Nishio, N.; Nakanishi, I.; Sato, A.; Fujii, T. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2003**, *59*, 299.

(19) (a) Illuminati, G.; Stegel, F. *Tetrahedron Lett.* **1968**, *39*, 4169. (b) Terrier, F.; Chatrousse, A.-P.; Schaal, R. *J. Org. Chem.* **1972**, *37*, 3010. (c) Biffin, M. E. C.; Miller, J.; Moritz, A. G.; Paul, D. *Aust. J. Chem.* **1970**, *23*, 957. (d) Terrier, F.; Sebban, M.; Goumont, R.; Halle, J. C.; Moutiers, G.; Cangelosi, I.; Buncel, E. *J. Org. Chem.* **2000**, *65*, 7391.

(20) Seeliger, F.; Blazej, S.; Bernhardt, S.; Makosza, M.; Mayr, H. *Chem. Eur. J.* **2008**, *14*, 6108.

(21) (a) Iaroshenko, V. O.; Sevenard, D. V.; Kotljarov, A. V.; Volochnyuk, D. M.; Tolmachev, A. O.; Sosnovskikh, V. Ya. *Synthesis* **2009**, 731. (b) Iaroshenko, V. O.; Wang, Y.; Sevenard, D. V.; Volochnyuk, D. M. *Synthesis* **2009**, 1851. (c) Iaroshenko, V. O.; Sevenard, D. V.; Volochnyuk, D. M.; Wang, Y.; Martiloga, A.; Tolmachev, A. O. *Synthesis* **2009**, 1865. (d) Iaroshenko, V. O.; Wang, Y.; Zhang, B.; Volochnyuk, D. M.; Sosnovskikh, V. Ya. *Synthesis* **2009**, 2393. (e) Kotljarov, A.; Irgashev, R. A.; Iaroshenko, V. O.; Sevenard, D. V.; Sosnovskikh, V. Ya. *Synthesis* **2009**, 3233. (f) Kotljarov, A.; Iaroshenko, V. O.; Volochnyuk, D. M.; Irgashev, R. A.; Sosnovskikh, V. Ya. *Synthesis* **2009**, 3869. (g) Iaroshenko, V. O. *Synthesis* **2009**, 3967.

(22) (a) Perrella, F. W.; Chen, S.-F.; Behrens, D. L.; Kaltenbach, R. F. III.; Seitz, S. P. *J. Med. Chem.* **1994**, *37*, 2232. (b) Becket, G. J. P.; Ellis, G. P. *Tetrahedron Lett.* **1976**, *9*, 719.

(23) (a) Takagi, K.; Tanaka, M.; Murakami, Y.; Ogura, K.; Ishii, K.; Morita, H.; Aotsuka, T. *J. Heterocycl. Chem.* **1987**, *24*, 1003. (b) Connor, D. T.; Young, P. A.; von Strandtmann, M. *J. Heterocycl. Chem.* **1981**, *18*, 697. (c) Haas, G.; Stanton, J. L.; Winkler, T. *J. Heterocycl. Chem.* **1981**, *18*, 619.

(24) Wesch, T.; Iaroshenko, V. O.; Groth, U. *Synlett* **2008**, 1459.

(25) **General Procedure for the Synthesis of Compounds 6a–q**
To a Schlenk flask, set with reflux, CH_2Cl_2 (2.5 mL), primary amine (0.00131 mol), and methyl *N*-(cyanomethyl)-formimidate (**1**, 0.128 g, 0.00131 mol) were added under an argon atmosphere at r.t. The reaction mixture was refluxed during 2 h and after that, the mixture was cooled down to r.t., and then to 0 °C on an ice bath. Afterwards 3-nitro-4*H*-chromen-4-one (0.25 g, 0.00131 mol) was added, and the mixture continued to stir at the same temperature for 15–20 min (the color of reaction mixture became intensively red) and then refluxed for 5 h. The formed precipitate was filtered, and the obtained solid was washed with CH_2Cl_2 and dried. In the case of homogenous solution, the solvent was evaporated to dryness, and the residue was purified by column chromatography (EtOAc–*i*-PrOH = 5:1), to give **6a–q** as light yellow crystals.

(26) **2-(3-*tert*-Butyl-6-nitro-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenol (6a)**
^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.82 (s, 9 H, *t*-Bu), 6.87 (d, 1 H, H-6′, ^3J = 9 Hz), 7.01 (t, 1 H, H-4′, ^3J = 9 Hz), 7.30 (t, 1 H, H-5′, ^3J = 9 Hz), 7.57 (d, 1 H, H-3′, ^3J = 9 Hz), 8.71 (s, 1 H, H-5), 8.74 (s, 1 H, H-2), 9.95 (s, 1 H, OH). ^{13}C NMR (250 MHz, DMSO-d_6): δ = 28.5 (CH_3), 57.7 [$(CH_3)_3C$], 115.1 (C-4′), 119.5 (C-6′), 123.6 (C-5′), 125.7 (C-3′), 130.2 (C-2′), 130.5 (C-1′), 133.9 (C-7), 142.8 (C-4), 144.7 (C-5), 147.1 (C-9), 148.2 (C-6), 154.5 (C-2). MS (EI): *m/z* (%) = 313 $[M + 1]^+$(11), 312 $[M]^+$(98), 210 $[M - C_{12}H_9N_3O]^+$(77).

(27) CCDC-782287 contain the crystallographic data (excluding structure factors) for the structures of **6g** reported in this paper. This data have been deposited with the Cambridge Crystallographic Data Centre as supplementary material and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif.

(28) (a) Dubois, L.; Evanno, Y.; Gille, C.; Malanda, A. WO 2009112677, **2009**. (b) Boyd, E.; Brookfield, F.; Gridley, J.; Honold, K.; Lau, R.; Scheiblich, S. WO 2007014707, **2007**. (c) Engh, R.; Hertenberger, H.; Honold, K.; Masjost, B.; Rueger, P.; Schaefer, W.; Scheiblich, S.; Schwaiger, M. WO 2007017143, **2007**. (d) Honold, K.; Kaluza, K.; Masjost, B.; Schaefer, W.; Scheiblich, S. WO 2006066914, **2006**.

(29) **General Procedure for the Synthesis of Compounds 7a–q**
To a 100 mL Schlenk flask, filled with 200 mg of corresponding imidazo[4,5-*b*]pyridine **6a–q** in MeOH (30 mL), Pd/C (20 mg, 10 mol%) was added. The flask was fitted with a septum, and then held under vacuum for 3 min, after that it was filled with hydrogen. Holding under vacuum was repeated one more time, and after sequent filling with hydrogen, the reaction mixture has been stirred for 2 d under H_2 atmosphere. After the reaction was stopped, the mixture was filtered through Celite pad and filtrate was evaporated to dryness or (if necessary) was purified by column chromatography (EtOAc–*i*-PrOH = 5:1) to give **7a–q** as light brown crystals.

Downloaded by: Universität Rostock. Copyrighted material.

(30) **2-(3-*tert*-Butyl-6-amino-3*H*-imidazo[4,5-*b*]pyridin-5-yl)phenol (7a)**

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.75 (s, 9 H, *t*-Bu), 4.86 (s, 2 H, NH_2), 6.97 (t, 1 H, H-4′, ^3J = 9 Hz), 6.98 (d, 1 H, H-6′, ^3J = 9 Hz), 7.28 (t, 1 H, H-5′, ^3J = 9 Hz), 7.47 (d, 1 H, H-3′, ^3J = 9 Hz), 7.48 (s, 1 H, H-5), 8,25 (s, 1 H, H-2), 10.27 (s, 1 H, OH). ^{13}C NMR (250 MHz, DMSO-d_6): δ = 28.6 (CH_3), 56.1 [$(CH_3)_3C$], 113.5 (C-4′), 116.7 (C-6′), 119.4 (C-5′), 127.2 (C-3′), 129.1 (C-2′), 131.7 (C-1′), 136.2 (C-9), 137.5 (C-5), 140.2 (C-6), 141.0 (C-7), 142.6 (C-4), 154.6 (C-2). MS (EI): *m/z* (%) = 282 $[M]^+$(71), 225 [M – $C_{12}H_9N_4O]^+$(100).

Downloaded by: Universität Rostock. Copyrighted material.