Article

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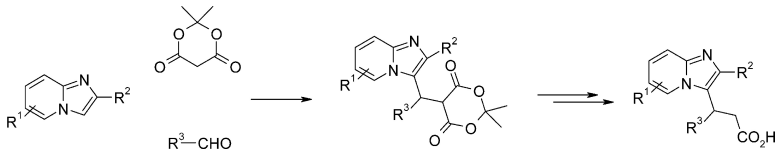
J. Comb. Chem., **2005**, 7 (4), 530-538• DOI: 10.1021/cc040101j • Publication Date (Web): 25 May 2005



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Articles

Procedure for the Parallel Preparation of 3-Imidazo[1,2-*a*]pyridin-3-yl-propionic Acid Derivatives Involving Meldrum's Acid

János Gerencsér,[†] Gábor Panka,[‡] Tamás Nagy,[†] Orsolya Egyed,[§] György Dormán,[†] László Ürge,*[,†] and Ferenc Darvas[†]

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Received June 11, 2004

We describe here an efficient and versatile method for the preparation of 3-imidazo[1,2-*a*]pyridin-3-yl-propionic acids involving, as a key step, a three-component Michael-type reaction. The extended and validated procedure allowed us to prepare various acids with three diversity points. The method was easily adaptable for parallel synthesis and an ∼2000-membered 3-imidazo[1,2-*a*]pyridin-3-yl-propionic acid amide library was prepared in a semiautomated manner.

Introduction

Pharmaceutical and agrochemical research requires an increasing number of novel compounds to cover previously unexplored areas in the chemical space. At the same time, there is also a need to increase the quality of the newly prepared molecules regarding their druglikeness and other predefined physicochemical parameters.

The indole-3-acetic acid derivatives play an important role in the alkaloid and biochemistry fields, providing useful cores and templates for the synthesis of potentially active natural products or naturelike analogues. For example, indole-3-acetic acid (**i**) (Figure 1) is a well-known plant growth hormone,[1] and some of its derivatives have recently been reported to be active against several human cancer cell lines.[2] Furthermore, in an in vitro Alzheimer disease model, indole-3-propionic acid (IPA) (**ii**) (Figure 1) has been found to protect primary neurons and neuroblastoma cells exposed to β-amyloid peptide against oxidative damage and death. Moreover, in kinetic competition experiments, the capacity of IPA to scavenge hydroxyl radicals exceeded that of melatonin.[3] Recently, indole-3-propionic acid derivatives were reported among the identified GPCR privileged structures.[17]

Oikawa et al. reported in the early 1980s[4] a new three-component coupling (3CC) reaction involving indole (**1**, with $R^1 = R^2 = H$), aldehydes (**2**), and Meldrum's acid (**3**) (Scheme 1). Recently, this multicomponent reaction, referred to as the Yonemitsu reaction, was also investigated by other groups.[5] As a result, the 3CC reaction was successfully applied and extended to various phenyl-ring-substituted indole derivatives, which proved to be a useful method in the synthesis of complex indole alkaloid precursors.[5] On the basis of this pioneering work, we have successfully completed the synthesis of a compound library around the general core of β-substituted indole-3-propionic acid (**6**) using a wide variety of phenyl-ring- and 1-substituted indoles, together with various aldehydes as diversity elements.[6]

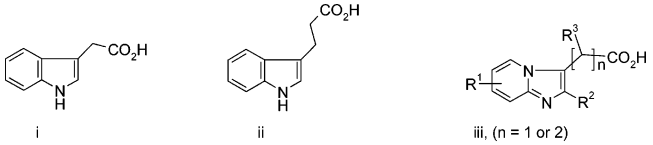

Figure 1. Biologically active indol-3-yl- and imidazo[1,2-*a*]-pyridin-3-yl-carboxylic acids.

The imidazo[1,2-*a*]pyridine ring can be considered a biosimilar "aza-indole" analogue. Despite the wide incidence of the imidazo[1,2-*a*]pyridine-core-based pharmacophores, its 3-acetic (**iii**, $n = 1$) or 3-propionic acid (**iii**, $n = 2$) analogues (Figure 1) are rarely presented in the literature due to synthetic limitations. Therefore, we studied a possible reaction route to obtain new 3-imidazo[1,2-*a*]pyridine-3-yl-propionic acids (**iii**, $n = 2$) as potentially biologically active compounds. In addition, we also investigated if Oikawa's original procedure on indoles[4] could be extended to the targeted "azalogues" as well.

Results and Discussion

After a thorough investigation of the literature, we found only two relevant citations about the synthesis of **iii** ($n = 2$). In the first paper,[7] only one parent analogue (**10**) was discussed, produced via the condensation of 2-amino-5-chloropyridine (**8**) with ethyl 4-benzoyl-4-bromobutyrate (**9**)

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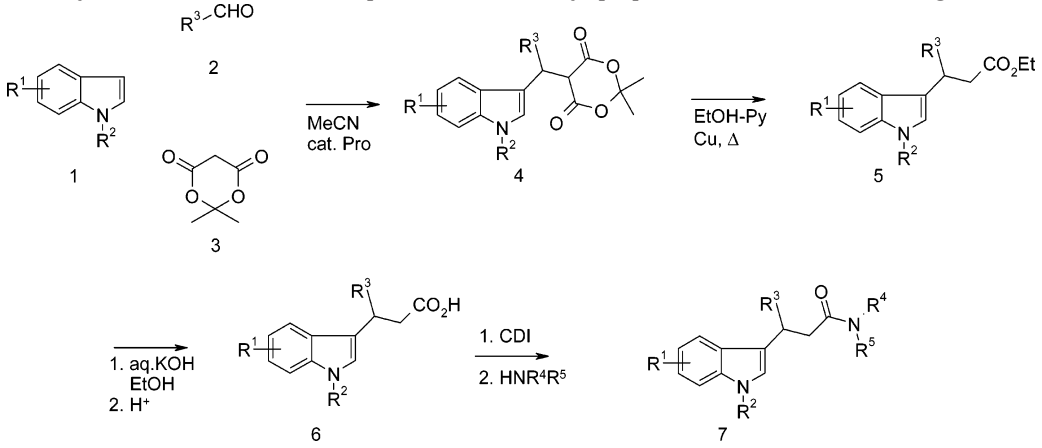
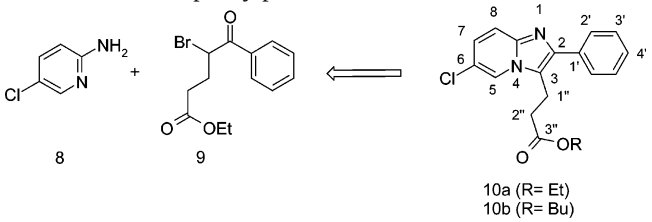
10.1021/cc040101j CCC: $30.25
Published on Web 05/25/2005

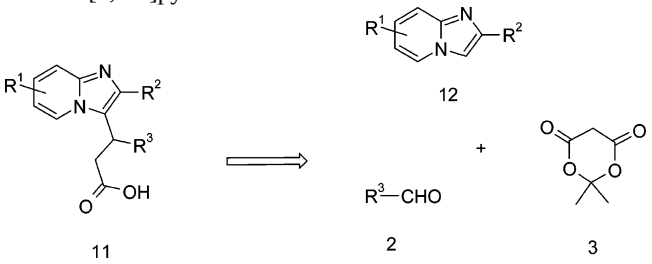
Scheme 1. General Synthetic Scheme for the Preparation of Indol-3-yl-propionic Acid Amides Involving Meldrum's Acid



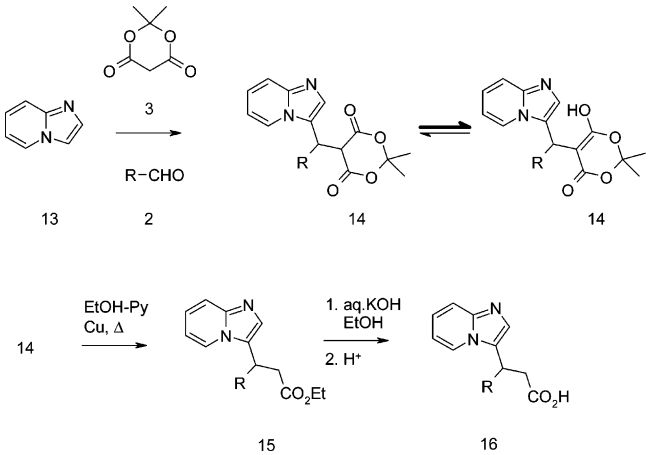
Scheme 2. Direct Synthesis of Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acid Derivatives via the Condensation of 2-Amino-5-chloropyridine and Ethyl 4-Bromo-5-oxo-5-phenylpentanoate



Scheme 3. Retrosynthetic Scheme for the Preparation of Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acid Derivatives; Extension of the Oikawa's Approach to Imidazo[1,2-*a*]pyridines

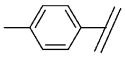
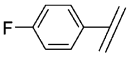
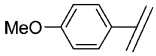
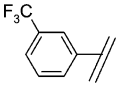
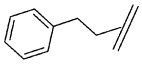


Scheme 4. Preparation of Monosubstituted Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acids



(Scheme 2). Using this method, the fused ring system formation was the key step of the synthesis, in which the bromobutyrate building block, anteriorly prepared by a multistep sequence, had already contained the desired propionyl side chain on the C-3 atom. Unfortunately, this reaction route gave only a low yield and was not applicable for parallel synthetic methodology.

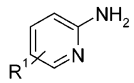
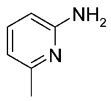
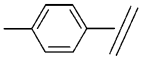
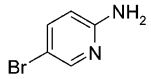
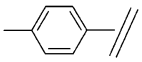
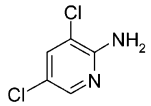
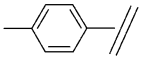
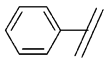
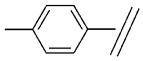
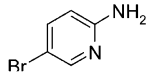
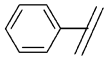
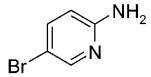
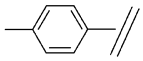
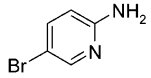
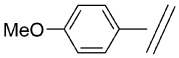
Table 1. Isolated Yields during the Synthesis of Monosubstituted Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acids

	R	14 (Yield %)	15 (Yield %)	16 (Yield %)
a	H	64	75	52
b		78	70	49
c		77	40	23
d		77	73	63
e		73	99	60
f		77	63	68
g		75	89	70
h		76	80	58
i		85	47	38
j		88	59	61
k		61	28	40
l		78	95	45

In a second reference,[8] the Yonemitsu reaction was applied in a patent, but only three specific examples were reported, having a general formula of **11** (where R^1= 6-Cl, 6-Me, and 6-Me; R^2 = 4-Cl−C_6H_4, 4-Me−C_6H_4, and 5-Me−thiophen-2-yl; R^3 = H, R = H, respectively). It is important to note that in these examples, only formaldehyde was applied as the aldehyde component. Furthermore, neither the 2-unsubstituted nor any variation in R^1-group was investigated.

Thus, we investigated the scope and limitations of the above 3CC reaction involving the "aza-indole analogue" imidazo[1,2-*a*]pyridines (**12**) instead of indoles (Scheme 3).

Table 2. Isolated Yields during the Synthesis of Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acids Substituted at Multiple Diversity Points[a]

		R^2	R^3	19 (Yield %)	20 (Yield %)	21 (Yield %)	22 (Yield %)
a		H		66	64	-*	-
b		H		96	80	96	50
c		H		84	42	82	67
d	H		H	57	75	37	19
e	H		H	70	63	71	91
f			H	82	90	58	85
g			H	87	87	78	72
h			H	51	84	35	32

[a] An asterisk (*) indicates a failed reaction.

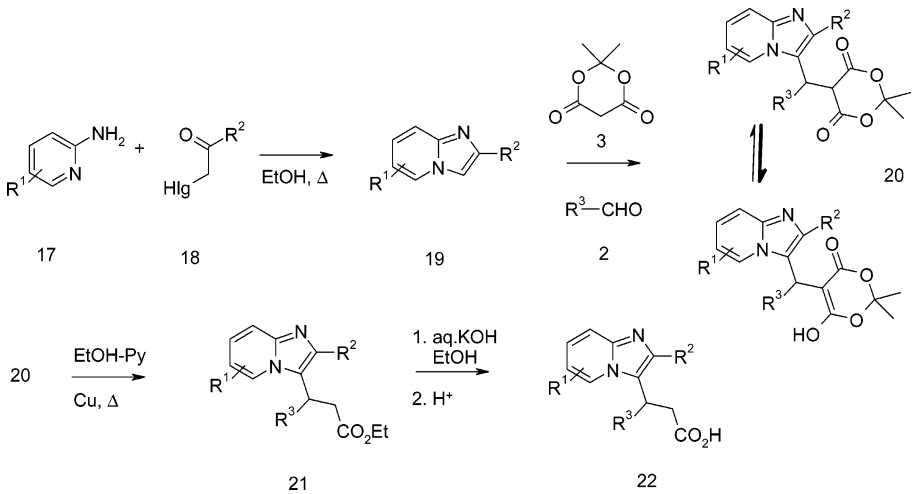
We started our study with the unsubstituted imidazo[1,2-*a*]pyridine (**13**) which reacted readily with Meldrum's acid (**3**) and not only with formaldehyde but also with a wide range of aldehydes in acetonitrile. The reactions were conducted in the presence of a catalytic amount of proline, affording the corresponding "Michael-type" Yonemitsu adduct (**14**) (Scheme 4). However, these intermediates were usually unstable in solution, and medium to massive decomposition was observed during a short-time storage under ambient conditions, even in solid state. We attempted to record the ^{1}H and ^{13}C NMR spectra and analyze a representative set of these Yonemitsu adducts, but the outcome was ambiguous. Depending on the rate of decomposition, the ^{1}H NMR assignation was possible only in a few cases, but for successful ^{13}C assignation, slower decomposition was even more essential due to the longer recording time. Thus, we could only obtain both ^{1}H and ^{13}C NMR data which was reliable in rare, exceptional cases. The relationship between the substituent pattern vs decomposition rate was not analyzed, and unambiguous correlation could not be found. For the **14** adducts, however, the incomplete data set suggested that they existed in the enolic form (Scheme 4). The structures of those species that could not be analyzed directly by standard spectroscopic methods due to their instability were indirectly proved by their successful transformation to the appropriate **15** esters and **16** acids. The applied aldehydes and the isolated yields are listed in Table 1.

We also tested the effect of the addition of different amino acids with different pK_a values (Pro, Arg, and Glu) in catalytic amounts. Proline was found to be the most superior in accordance with the method developed by Oikawa and co-workers.[4] Being aware of the lability of the Michael-type intermediates, they were immediately transformed, first, to the stable **15** esters by ethanolysis and a copper-catalyzed concomitant decarboxylation, followed by saponification, affording the targeted free carboxylic acids (**16**) (Scheme 4) in reasonable to good yields (Table 1). Further advantage of this three-step procedure lay upon the easy isolation and purification of the **16** carboxylic acids by simple extractive methods.

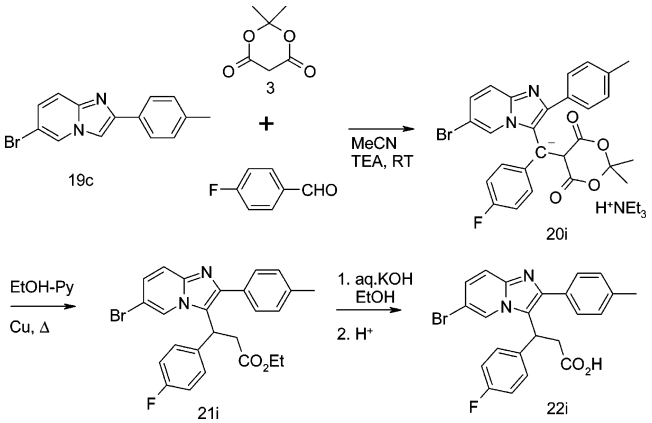
According to the procedure described in the literature,[9] we synthesized several imidazo[1,2-*a*]pyridines (**19a**−**c**) that bear different types of substituents in the pyridine ring, shown in Table 2. We found no significant substituent effects on the reactions and the chemical outcomes along the entire reaction sequence. For details, see Table 2.

In addition, we synthesized 2-aryl substituted analogues (**19d**−**h**, where R^2 = aryl, Table 2) of the parent core by the condensation of 2-aminopyridines (**17**) and 2-bromoacetophenones (**18**) using the general procedure and conditions cited.[10] The 2-aryl derivatives reacted smoothly in the three-component Yonemitsu reaction, but formaldehyde was the only applicable aldehyde component in these cases. Both the aromatic and the alkyl aldehydes failed to give the condensed products due to the inapplicable nature of the standard Yonemitsu conditions for the 2-substituted indoles (cat., DL-proline, heating in acetonitrile). A slightly modified procedure of the Yonemitsu reaction was recently reported, which opened new avenues for the successful use of

Scheme 5. Preparation of the Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acids Substituted at Multiple Diversity Points



Scheme 6. Modified Yonemitsu Reaction for 2-Aryl-imidazo[1,2-*a*]pyridines



2-substituted indole derivatives.[11] This involved simply adding 1 equiv of triethylamine to the reaction mixture instead of a catalytic amount of proline, which allowed the isolation of the Michael-type adduct as its triethylammonium salt. We tried to adapt the above procedure for our 2-aryl-imidazopyridines. Upon slight heating to 40−50 °C, not even a trace of the desired product could be detected in the reaction mixture. Finally, we found that the procedure was applicable, but only at room temperature. At this temperature, the Michael adduct spontaneously precipitated from the solution as a triethylammonium salt, shifting the equilibrium toward the complete formation of the desired target. The so-obtained Yonemitsu product (**20i**) was converted to the **21i** ester, followed by saponification, which led to the **22i** carboxylic acid using the same conditions as for **14** and **20** derivatives (Scheme 6).

The amidation of the carboxylic acids **16** and **22** with a series of amines was performed in 1,2-dichlorethane using 1,1′-carbodiimidazole as an activating agent under a robot-assisted parallel platform (Scheme 7). Although the cleavage and the concomitant decarboxylation of 5-substituted Meldrum's acid derivatives with amine nucleophiles leading to propionic acid amides, thus allowing a theoretically shorter reaction path, is known,[12] we found our three-step process more robust and general for solution-phase parallel synthesis. On the basis of our unsatisfactory parallel experiments in the direct amidation of the Yonemitsu indole adducts[5] together with the above-discussed poor stability of our **14** and **20** intermediates, we decided to exclude this direct amide formation sequence.

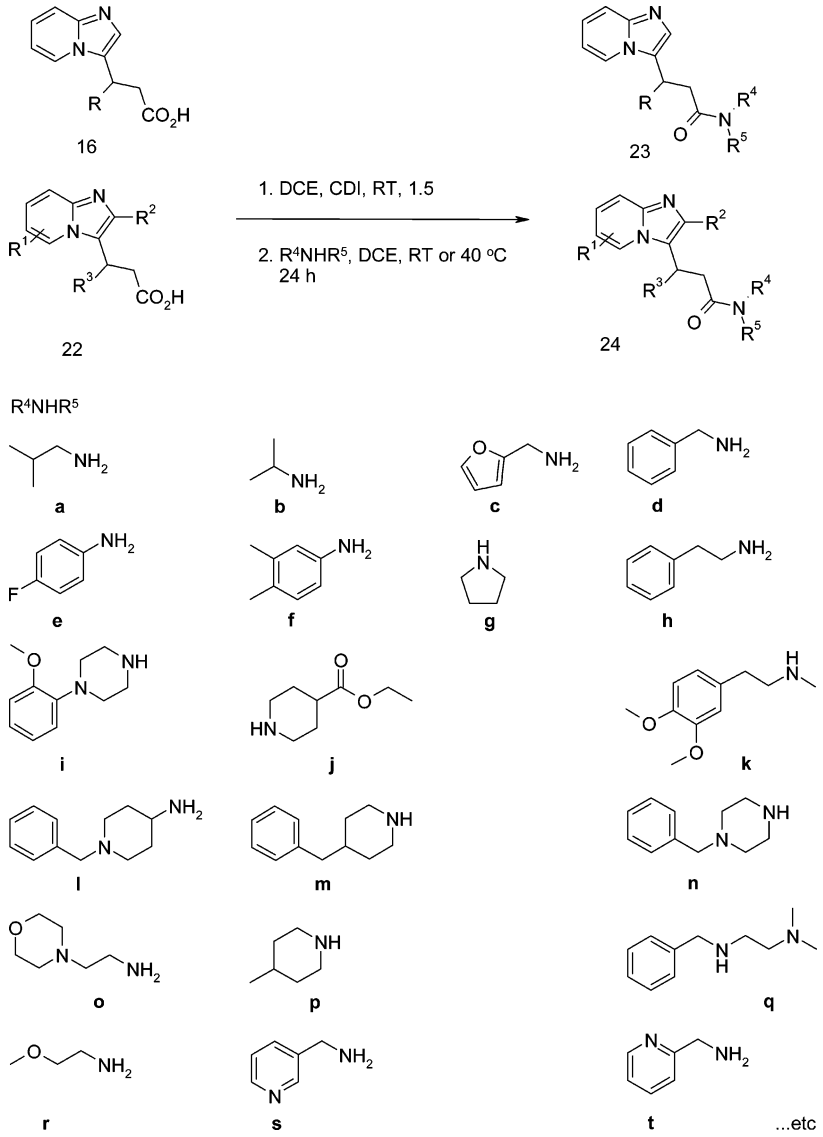
As another process-shortening option, we also considered the amidation of **15** and **21** esters, but due to their moderate purity and the contamination of the residual copper catalyst, this method was disadvantageous over the longer reaction sequence.

Conclusions

The presented three-step process proved to be a straightforward and convenient method for the preparation of various targeted acids. The process involved simple workup and purification procedures, omitting the chromatographic purification techniques along the whole reaction sequence. During the library synthesis, only those carboxylic acid derivatives were synthesized for which the standard Yonemitsu conditions (cat. DL-proline, heating in acetonitrile) were applicable.

On the basis of our experiments, we conclude that imidazo-[1,2-*a*]pyridines (**13** and **19a**-**h**) react smoothly with Meldrum's acid (**3**) and different aldehydes (**2**), giving the corresponding Michael-type adducts (**14** and **20a**-**h**), which can be further transformed to 3-imidazo[1,2-*a*]pyridine-3-yl-propionic acids (**16** and **22b**−**h**). The substituents on the pyridine ring do not affect the reaction, whereas aryl substituents in position 2 prevent the use of a wide range of aldehydes under the standard Yonemitsu conditions, limiting the reactants to only formaldehyde. Cochard's modification of the Yonemitsu procedure[11] allowed us to prepare one R^2,R^3-diaryl compound set (**20i**, **21i**, and **22i**); however, the generality of this extension has not been studied yet. The 3-component key step allowed us to prepare various acids with three diversity points, from which either R^1/R^2 or R^1/R^3 combinations can be varied with no practical limitation (R^1 = H, Cl, Me, Br; R^2 = H, aryl; R^3 = H, aryl, alkyl, aralkyl). However, the R^2/R^3 combination is limited, and at least one of them should be hydrogen under the standard Yonemitsu conditions. Finally, this method was applicable for parallel synthesis and a ∼2000-membered amide compound library was prepared in a semiautomated manner using CMT.[13] We will continue to study the applicability of the Yonemitsu reaction toward other heterocycles.

Scheme 7. Robot-Assisted Amidation of the Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acid Derivatives



Experimental Section

Materials and General Methods. The melting points were measured on a Boetius apparatus, and the data are uncorrected. The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian INOVA (400 MHz) spectrometer with TMS as an internal reference.

For HPLC runs, a LaChrom system (Merck-Hitachi) connected to an autosampler and a fraction collector based on a Cavro RSP 9000 (Cavro Scientific Instruments, Inc.) robotic workstation was used. The column type used was Purospher STAR RP-18 endcapped, 3 μm, 30 $\times$ 4 mm. The detection wavelengths were 220 or 254 nm.

MS data were collected on a ZQ singlequad (Micromass-Waters) mass spectrometer using an APCI interface. HRMS experiments were performed on a Micromass LCT spectrometer using an electrospray interface with a lock-mass sign of tetrabutylammonium ion.

IR spectra were measured on a Nicolet FTIR Magna 750 spectrophotometer.

For parallel synthesis, the RoboSynthon cascading reactor family (ComGenex International, South San Francisco) was employed.

Starting materials were purchased from commercial sources. Silica gel 60 F_{254} (Merck) plates were used for TLC. Solvents were dried and purified according to the well-established methods.[14] Evaporations were carried out under reduced pressure.

5-Methyl-imidazo[1,2-*a*]pyridine (**19a**) and 6-bromo-imidazo[1,2-*a*]pyridine (**19b**) were produced according to the literature.[9,15] These compounds were prepared according to the general procedures described below.

6,8-Dichloroimidazo[1,2-*a*]pyridine (19c). 2-Amino-3,5-dichloropyridine (3.26 g; 20 mmol) and chloroacetaldehyde (3.45 g; 4.2 mL; 44 mmol; 45 wt % aqueous solution) were converted to **19c** (3.14 g; 84%), according to the method in the literature.[9] mp: 146−148 °C (sintered at 110−112 °C). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 7.52 (1H, d, J = 1.7 Hz, H7), 7.65 (1H, d, J = 1.3 Hz, H3), 8.04 (1H, d, J = 1.3 Hz, H2), 8.92 (1H, d, J = 1.3 Hz, H5). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 115.6 (C3), 123.6 (C6), 128.2 (C5), 128.4 (C8), 133.1 (C7), 136.3 (C2), 144.8 (C9). IR (KBr) cm^{-1}: 1522, 1502, 1346, 1333, 1131, 1148, 847, 777, 732. HRMS: calcd, 186.9830; found, 189.9826.

General Procedure for Preparing 2-Aryl-imidazo[1,2-*a*]pyridines (19d−h). 2-Aminopyridine derivative (**17**, 50.0 mmol) and 2-bromoacetophenone derivative (**18**; 50.0 mmol) were stirred in EtOH (75 mL) under a nitrogen atmosphere at room temperature for 2 h and were then refluxed for an additional 10h. The reaction mixture was evaporated to dryness, the residue was triturated with diethyl ether, and the precipitated crystals were filtered off and washed with diethyl ether. If necessary, the products were recrystallized from an appropriate solvent to obtain **19d−h**.

6-Bromo-2-*p*-tolyl-imidazo[1,2-*a*]pyridine (19g). Title compound was obtained from 2-amino-5-bromopyridine (8.65 g; 50.0 mmol) and 2-bromo-1-*p*-tolylethanone (10.65 g; 50.0 mmol) as a white solid (12.5 g; 87%) after recrystallization from 2-propanol, using the general procedure. mp: sintered at 244−245 °C without melting. ^{1}H NMR ($CDCl_3$) δ (ppm) : 8.71 (1H, d, J = 0.5 Hz, H3), 7.92 (1H, d, J = 9.5 Hz, H8), 7.99 (1H, dd, J = 9.5, 1.8 Hz, H7), 9.28 (1H, dd, J = 1.8, 0.5 Hz, H5), 7.82 (2H, m, H2′ + H6′), 7.38 (2H, m, H3′ + H5′), 2.40 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2 (*C*H3), 110.9 (C6), 111.3 (C3), 114.1 (C8), 126.8 (C2′ + C6′), 128.4 (C7), 129.9 (C1′), 130.6 (C3′ + C5′), 135.8 (C5), 137.6 (C4′), 139.9 (C2), 141.0 (C9). IR (KBr) cm^{-1}: 3151, 2670, 1649, 1504, 810, 731. HRMS: calcd, 287.0184; found, 287.0183.

General Procedure for Preparing 5-Imidazo[1,2-*a*]-pyridin-3-ylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-diones (14a−l and 20a−h). Imidazo[1,2-*a*]pyridine derivative (**13** or **19a−c**; 10.0 mmol), Meldrum's acid (**3**, 1.444 g; 10.0 mmol), the appropriate alkyl- or arylaldehyde derivative or paraformaldehyde (**2**, 10.0 mmol), and DL-proline (58 mg; 0.5 mmol) were suspended in acetonitrile (20 mL). The reaction mixture was stirred at 50 °C for 10 h under a nitrogen atmosphere. The mixture was allowed to cool to room temperature, and the stirring was continued overnight. The precipitated product was collected by filtration and washed thoroughly with diethyl ether. The solid product was dried and stored at ambient temperature under nitrogen atmosphere, giving the desired product (**14a−l** and **20a−h**) as a white solid.

5-Imidazo[1,2-*a*]pyridin-3-ylmethyl-2,2-dimethyl-[1,3]-dioxane-4,6-dione (14a). The title compound was obtained as a white solid (1.757 g; 64%), starting from imidazo[1,2-*a*]pyridine (**13**, 1.188 g; 10.0 mmol) and paraformaldehyde (0.301 g; 10.0 mmol). mp: 148−149 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.40 (6H, s, 2*CH_3), 3.8 (1H, s, O*H*), 3.65 (2H, s, H1a″ + H1b″), 7.42 (1H, m, H6), 7.62−7.90 (3H, m, H2 + H7 + H8), 9.0 (1H, m, H5). ^{13}C NMR (DMSO-d_6): 19.9, 26.6 (2C), 57.9, 100.2, 113.0, 116.8, 120.0, 120.3, 128.2, 130.0, 132.2, 139.6, 165.8. IR (KBr) cm^{-1}: 3544, 1672, 1573, 1550, 1401, 1262, 1201, 1111, 1066, 881, 772. HRMS: calcd, 275.1032; found, 275.1030.

5-[(4-Fluorophenyl)-imidazo[1,2-*a*]pyridin-3-yl-methyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (14c). The title compound was obtained as a white solid (2.860 g; 77%), starting from imidazo[1,2-*a*]pyridine (**13**, 1.188 g; 10.0 mmol) and 4-fluoro-benzaldehyde (1.250 g; 10.0 mmol). mp: 167−169 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.44 (6H, s, 2*CH_3), 4.02 (1H, s, O*H*), 5.59 (1H, s, H1″), 7.12 (2H, m, H3‴ + H5‴), 7.32 (1H, s, H2), 7.46 (2H, m, H2‴ + H6‴), 7.47 (1H, dd, J = 8, 7 Hz, H7), 7.87 (1H, d, J = 8 Hz, H8), 8.47 (1H, d, J = 7 Hz, H5). ^{13}C NMR (DMSO-d_6) δ (ppm): 26.1 (2C), 36.2, 76.1, 99.7, 112.6, 114.7 (2C), 116.4, 121.3, 126.8, 130.5 (2C), 131.5, 138.1, 139.0, 139.2, 159.8, 162.2, 164.9. IR (KBr) cm^{-1}: 3431, 1680, 1570, 1388, 1256, 1091, 757. HRMS: calcd, 369.1250; found, 369.1243.

5-(6-Bromo-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-ylmethyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (20g). The title compound was obtained as a white solid (1.929 g; 87%), starting from 6-bromo-2-*p*-tolylimidazo[1,2-*a*]pyridine (**19g**, 1.436 g; 5.0 mmol). mp: 195−197 °C (decomp.). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ (ppm): 1.80 (6H, s, 2*CH_3), 2.44 (3H, s, CH_3), 3.88 (2H, s, CH_2), 7.40 (2H, m, H3′ + H5′), 7.62 (2H, m, H2′ + H6′), 8.0 (2H, m, H7 + H8), 9.3 (1H, m, H5). IR (KBr) cm^{-1}: 2694, 1782, 1749, 1509, 1313, 1203, 826. HRMS: calcd, 443.0606; found, 443.0608.

5-[(6-Bromo-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)-(4-fluorophenyl)-methyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (20i). 6-Bromo-2-*p*-tolylimidazo[1,2-*a*]pyridine (**19g**; 0.50 g; 1.74 mmol), Meldrum's acid (**3**; 0.251 g; 1.74 mmol), 4-fluorobenzaldehyde (0.216 g; 1.74 mmol), and triethylamine (176 mg; 1.74 mmol) were suspended in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 4 h under a nitrogen atmosphere. The precipitated product was collected by filtration and washed thoroughly with diethyl ether. The solid product was dried and stored at ambient temperature under nitrogen atmosphere, giving the title product **20i** (780 mg; 83%) as a white solid. mp: 169−171 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 1.22 (9H, t, $N^+(CH_2-CH_3)_3$), 1.60 (6H, s, 2*CH_3), 2.35 (3H, s, CH_3), 3.10 (6H, q, $N^+(CH_2-CH_3)_3$), 5.84 (1H, s, H1″), 6.84 (2H, m, H3‴ + H5‴), 7.09 (2H, m, H2‴ + H6‴), 7.16 (2H, m H3′ + H5′), 7.57 (2H, m, H2′ + H6′), 7.79 (1H, d, J = 8 Hz, H8), 7.86 (1H, dd, J = 8 + 2 Hz, H7), 8.70 (1H, d, J = 2 Hz, H5), 9.41 (1H, br s, *H*N^+Et_3). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 9.2 (3C), 21.6, 26.6 (2C), 37.1, 46.6 (3C), 71.7, 100.7, 109.6, 113.1, 115.1 (2C), 125.3, 126.2, 126.8, 129.3 (2C), 129.8 (2C), 130.2 (2C), 134.4, 135.4, 136.8, 137.8, 139.6, 156.3, 161.1, 166.3. IR (KBr) cm^{-1}: 2677, 2491, 1693, 1537, 1507, 1390, 1111, 771, 594. HRMS: calcd, 537.0825; found, 537.0820.

General Procedure for Preparing 3-Imidazo[1,2-*a*]-pyridin-3-yl-propionic Acid Ethyl Esters (15a−l and 21a−h). The 5-imidazo[1,2-*a*]pyridin-3-ylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-dione derivative (**14a−l** and **20a−h**) was dissolved in pyridine/ethanol (10:1 v/v; 1.5 mL/mmol), copper powder (3 mg/mmol) was added to it, and the mixture was refluxed for 2 h. The solvents were removed under reduced pressure. Some ethanol was added to the residue and evaporated to dryness. This procedure was repeated for several more cycles. The rest was taken up in dichloromethane and extracted first with 3 wt % aqueous HCl; next with 5 wt % aqueous NH_4Cl solution; then with 5 wt % aqueous Na_2CO_3 solution; and finally, with water. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness, yielding the title compounds.

3-Imidazo[1,2-*a*]pyridin-3-yl-propionic Acid Ethyl Ester (15a). The title compound was obtained (0.973 g; 75%)

starting from 5-imidazo[1,2-*a*]pyridin-3-ylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-dione (**14a**; 1.631 g; 5.94 mmol) using the general procedure. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.47 (1H, s, H2), 7.60 (1H, d, J = 8 Hz, H8), 7.15 (1H, t, J = 8 Hz, H7), 6.81 (1H, dd, J = 8, 5 Hz, H6), 7.98 (1H, d, J = 8 Hz, H5), 3.20 (2H, t, J = 7.5 Hz, H3a″ + H3b″), 2.78 (2H, t, J = 7.5 Hz, H2a″ + H2b″), 4.20 (2H, q, J = 8 Hz, O−CH_2−CH_3), 1.25 (3H, t, J = 8 Hz, O−CH_2−CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.1(O−CH_2−CH_3), 19.3 (C3″), 32.1 (C2″), 60.8 (O−CH_2−CH_3), 112.1 (C6), 118.0 (C8), 122.9 + 123.4 (C7 + C5), 123.0 (C3), 131.0 (C2), 146.0 (C9), 172.3 (C═O). IR (KBr) cm^{-1}: 2981, 1732, 1635, 1502, 1306, 1164, 1039, 753. HRMS: calcd, 219.1133; found, 219.1129.

3-(4-Fluorophenyl)-3-imidazo[1,2-*a*]pyridin-3-yl-propionic Acid Ethyl Ester (15c). The title compound was obtained (0.943 g; 40%) starting from 5-[(4-fluorophenyl)-imidazo[1,2-*a*]pyridin-3-yl-methyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (**14c**; 2.767 g; 7.51 mmol) using the general procedure. ^{1}H NMR (DMSO-d_6) δ (ppm): 7.60 (1H, s, H2), 7.48 (1H, d, J = 9.2 Hz, H8), 7.15 (1H, dd, J = 9.2, 6 Hz, H7), 6.78 (1H, t, J = 6 Hz, H6), 8.04 (1H, d, J = 6 Hz, H5), 7.03 (2H, m, H3‴ + H5‴), 7.32 (2H, m, H2‴ + H6‴), 4.80 (1H, t, J = 6.5 Hz, H3′), 3.02−3.20 (2H, dd, J = 15, 6.5 Hz, H2a″ + H2b″), 4.0 (2H, q, J = 7.5 Hz, O−CH_2−CH_3), 1.08 (3H, t, J = 7.5 Hz, O−CH_2−CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.3 (O−CH_2−CH_3), 38.2 (C3″), 40.9 (C2″), 61.1 (O−CH_2−CH_3), 112.5 (C6), 115.8 (C3‴ + C5‴), 117.8 (C8), 124.4 (C7), 124.6 (C5), 126.3 (C3), 130.1 (C2‴ + C6‴), 131.4 (C2), 137.4 (C1‴), 145.8(C9), 162.2 (C4‴), 171.1 (*C*═O). IR (KBr) cm^{-1}: 2981, 1732, 1604, 1508, 1370, 1222, 1158, 1036, 841, 750. HRMS: calcd, 313.1352; found, 313.1358.

3-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)-propionic Acid Ethyl Ester (21d). The title compound was obtained as oil (0.383 g; 37%) starting from 2,2-dimethyl-5-(2-phenyl-imidazo[1,2-*a*]pyridin-3-ylmethyl)-[1,3]dioxane-4,6-dione (**20d**; 1.218 g; 3.47 mmol) using the general procedure. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.62 (1H, dd, J = 9,2 Hz, H8), 7.18 (1H, ddd, J = 9, 7, 1.5 Hz, H7), 6.82 (1H, ddd, J = 7, 6.5, 2 Hz, H6), 8.04 (1H, dd, J = 6.5, 1.5 Hz, H5), 7.78 (2H, m, H2′ + H6′), 7.44 (2H, m, H3′ + H5′), 7.38 (1H, m, H4′), 3.44 (2H, t, J = 7 Hz, H3a″ + H3b″), 2.64 (2H, t, J = 7 Hz, H2a″ + H2b″), 4.13 (2H, q, J = 7 Hz, O−CH_2−CH_3), 1.22 (3H, t, J = 7 Hz, O−CH_2−CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.1 (O−CH_2−CH_3), 19.3 (C3″), 32.5 (C2″), 60.9 (O−CH_2−CH_3), 112.2 (C6), 118.6 (C8), 118.7 (C3), 123.0 (C5), 123.9 (C7), 127.6 (C4′), 128.2 (C3′ + C5′), 128.6 (C2′ + C6′), 134.7 + 142.9 (C2 + C1′), 144.7 (C9), 172.3 (*C*═O). IR (KBr) cm^{-1}: 2981, 1730, 1634, 1504, 1445, 1360, 1270, 1183, 1039, 752. HRMS: calcd, 295.1446; found, 295.1439.

3-(2-*p*-Tolylimidazo[1,2-*a*]pyridin-3-yl)-propionic Acid Ethyl Ester (21e). The title compound was obtained as oil (1.336 g; 71%) starting from 2,2-dimethyl-5-(2-p-tolyl-imidazo[1,2-*a*]pyridin-3-ylmethyl)-[1,3]dioxane-4,6-dione (**20e** 2.215 g; 6.1 mmol) using the general procedure. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.63 (1H, dd, J = 9, 2.2 Hz, H8), 7.17 (1H, ddd, J = 9, 7, 1 Hz, H7), 6.84 (1H, ddd, J = 7, 7, 2.2 Hz, H6), 8.04 (1H, dd, J = 7, 1 Hz, H5), 7.68 (2H, m, H2′ + H6′), 7.28 (2H, m, H3′ + H5′), 2.41(3H, s, Me), 3.44 (2H, t, J = 6.5 Hz, H3a″ + H3b″), 2.67 (2H, t, J = 6.5 Hz, H2a″ + H2b″), 4.13 (2H, q, J = 7 Hz, O−CH_2−CH_3), 1.22 (3H, t, J = 7 Hz, O−CH_2−CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.1 (O−CH_2−CH_3), 19.3 (C3″), 32.5 (C2″), 60.8 (O−CH_2−CH_3), 112.1 (C8), 117.7 (C6), 118.3 (C3), 122.9 (C7), 123.7 (C5), 128.0 + 129.3 (C2′ + C3′ + C5′ + C6′), 131.7 (C4′), 137.4 + 142.9 (C2 + C1′), 144.6 (C9), 172.3 (*C*═O). IR (KBr) cm^{-1}: 2922, 1731, 1633, 1502, 1358, 1269, 1182, 1038, 825, 751. HRMS: calcd, 309.1603; found, 309.1611.

3-(6-Bromo-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)-3-(4-fluorophenyl)-propionic Acid Ethyl Ester (21i). The title compound was obtained as oil (0.38 g; 61%) starting from 5-[(6-bromo-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)-(4-fluoro-phenyl)-methyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (**20i**; 0.70 g; 1.3 mmol) using the general procedure. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.95 (3H, t, O−CH_2−CH_3), 2.36 (3H, s, CH_3), 3.14 (1H, dd, J = 16 + 9 Hz, H2a″), 3.37 (1H, dd, J = 16 + 9 Hz, H2b″), 3.88 (2H, q, O−CH_2−CH_3), 5.30 (1H, t, J = 9 Hz, H1″), 7.10 (2H, m, H3‴ + H5‴), 7.16 (2H, m, H2‴ + H6‴), 7.20 (2H, m, H3′ + H5′), 7.31 (1H, dd, J = 9 +2 Hz, H7), 7.40 (2H, m, H2′ + H6′), 7.52 (1H, d, J = 9 Hz, H8), 8.55 (1H, d, J = 2 Hz, H5). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.6, 20.7, 35.5, 36.4, 60.0, 106.1, 115.4 (2C), 118.1, 124.4, 125.7, 127.2, 128.6 (2C), 128.7 (2C), 128.8 (2C), 128.9, 129.1, 131.8, 135.5, 137.3, 161.1, 170.6. IR (KBr) cm^{-1}: 2980, 1728, 1604, 1510, 1225, 1158, 825, 802. HRMS: calcd, 481.0927; found, 481.0921.

General Procedure for Preparing 3-Imidazo[1,2-*a*]-pyridin-3-yl-propionic Acids (16a−l and 22b−h). 3-Imidazo[1,2-*a*]pyridin-3-yl-propionic acid ethyl ester derivative (**15** and **21**) was dissolved in ethanol/water (10/1 v/v; 6 mL/mmol ester), and KOH (2.0 molar equivalent) was added while the reaction was cooled in an ice water bath. The coolant was removed, and the stirring was continued at room temperature for an hour. The ethanol was evaporated, and the residue was taken up in water. The basic aqueous solution was extracted with diethyl ether in order to remove the nonacidic impurities. The dissolved diethyl ether was removed from the aqueous phase under reduced pressure. The pH of the solution was adjusted to ∼4 by the portion-wise addition of 10% aq HCl solution.

Workup methods. Method A. If solid precipitation occurred, the solid product was filtered off and washed several times with diethyl ether, diisopropyl ether, and hexane. The so-obtained target was finally dried under ambient conditions.

Method B. If no precipitation occurred, the acidic aqueous solution was extracted 3 times with chloroform. The combined organic fraction was dried over $MgSO_4$ and was evaporated to dryness. The residue was triturated and solidified with diethyl ether. The resulting solid was filtered off and dried under ambient conditions.

Method C. When the product could not be extracted with chloroform, then water was removed under reduced pressure. The residue was digested with ethanol in several cycles. The collected ethanolic layers were combined and evaporated to

dryness, and the residue was solidified with diethyl ether. The resulting solid was filtered and dried under ambient condition.

3-Imidazo[1,2-*a*]pyridin-3-yl-propionic Acid (16a). The title compound was obtained as a light brown solid (0.397 g; 52%), starting from 3-imidazo[1,2-*a*]pyridin-3-yl-propionic acid ethyl ester (**15a**; 0.873 g; 4.00 mmol) by the general procedure using the work up method C. mp: 211−214 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 8.08 (1H, d, J = 8 Hz, H8), 7.95 (1H, dd, J = 8, 7 Hz, H7), 7.50 (1H, dd, J = 7, 6.7 Hz, H6), 8.86 (1H, d, J = 6.7 Hz, H5), 7.90 (1H, s, H2), 3.30 (2H, t, J = 7.7 Hz, H3a″ + H3b″), 2.85 (2H, t, J = 7.7 Hz, H2a″ + H2b″), 3.60 (1H, s, COOH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 16.9, 29.5, 111.0, 115.3, 118.2, 124.6, 125.0, 130.8, 137.9, 171.3. IR (KBr) cm^{-1}: 1726, 1658, 1527, 1410, 1169, 761. HRMS: calcd, 191.0820; found, 191.0807.

3-Imidazo[1,2-*a*]pyridin-3-yl-3-*o*-tolylpropionic Acid (16e). The title compound was obtained as a light brown solid (1.115 g; 60%), starting from 3-imidazo[1,2-*a*]pyridin-3-yl-3-*o*-tolylpropionic acid ethyl ester (**15e**; 2.063 g; 6.68 mmol) by the general procedure using the work up method B. mp: 211−213 °C (sintered at 171 °C). ^{1}H NMR (DMSO-d_6) δ (ppm): 7.65 (1H, s, H2), 7.52 (1H, d, J = 8.8 Hz, H8), 7.18 (1H, dd, J = 8.8, 7.5 Hz, H7), 6.80 (1H, dd, J = 7.5, 6.2 Hz, H6), 7.86 (1H, d, J = 6.2 Hz, H5), 6.97 (1H, d, J = 8 Hz, H3‴), 7.05−7.13 (2H, m, H4‴ + H5‴), 7.20 (1H, d, J = 9 Hz, H6‴), 4.98 (1H, m, H3″), 2.96−3.19 (2H, m, H2a″ + H2b″), 2.42 (3H, s, Me), 3.40 (1H, s, COOH). ^{13}C NMR (DMSO-d_6) δ (ppm): 34.8 (C3″), 40.2 (C2″), 112.6 (C8), 118.0 (C6), 124.2 (C7), 124.4 + 127.0 + 127.2 + 127.4 (C2‴ + C3‴ + C4‴ + C5‴), 127.5 (C3), 131.4 (C5), 132.2 (C2), 132.3 (C6‴), 136.3 (C1‴), 139.4 (C9), 170.5 (C═O). IR (KBr) cm^{-1}: 1715, 1581, 1502, 1370, 1246, 1149, 747. HRMS: calcd, 281.1290; found, 281.1283.

3-(6-Bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-propionic Acid (22f). The title compound was obtained as a light brown solid (0.741 g; 85%), starting from 3-(6-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-propionic acid ethyl ester (**21f**; 0.820 g; 2.19 mmol) by the general procedure using the work up method A. mp: 238−240 °C (sintered at 168 °C). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 8.0−8.1 (2H, m, H6 + H7), 9.4 (1H, d, J = 2 Hz, H5), 7.80 (2H, m, H2′ + H6′), 7.60 (3H, m, H3′ + H4′ + H5′), 3.42 (2H, t, J = 6.5 Hz, H3a″ + H3b″), 2.70 (2H, t, J = 6.5 Hz, H2a″ + H2b″), 4.20 (1H, br. s, COOH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 18.1 (C3″), 31.5 (C2″), 111.2 (C3), 113.6 (C6), 122.5 (C8), 127.0 (C7), 127.2 (C4′), 128.5 (C2′ + C6′), 129.4 (C3′ + C5′), 130.3 (C4), 133.6 (C2), 135.2 (C1′), 138.3 (C9), 173.1 (*C*OOH). IR (KBr) cm^{-1}: 2868, 1712, 1656, 1518, 1499, 1186, 812, 771, 698. HRMS: calcd, 345.0239; found, 345.0226.

3-(6-Bromo-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)-3-(4-fluorophenyl)-propionic Acid (22i). The title compound was obtained as a light brown solid (0.152 g; 56%), starting from 3-[6-bromo-2-(4-methoxyphenyl)-imidazo[1,2-*a*]pyridin-3-yl]-propionic acid ethyl ester (**21i**; 0.290 g; 0.60 mmol) by the general procedure using the work up method A. mp: 256−258 °C (sintered at 225 °C). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.36 (3H, s, CH_3), 3.05 (1h, dd, J = 16 + 8 Hz, H2a″), 3.33 (1H, dd, J = 16 + 8 Hz, H2b″), 5.27 (1H, t, J = 8 Hz, H1″), 7.10 (2H, m, H3‴ + H5‴), 7.19 (2H, m, H2‴ + H6‴), 7.24 (2H, m, H3′ + H5′), 7.33 (1H, dd, J = 9 + 2 Hz, H7), 7.49 (2H, m, H2′ + H6′), 7.55 (1H, d, J = 9 Hz, H8), 8.29 (1H, d, J = 2 Hz, H5). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.7, 35.3, 36.5, 106.0, 115.3 (2C), 118.1, 121.9, 124.3, 127.1, 128.4 (2C), 128.6 (2C), 128.7 (2C), 131.8, 135.8, 137.2, 142.5, 144.3, 161.1, 172.1. IR (KBr) cm^{-1}: 2985, 1701, 1604, 1513, 1158, 950, 826, 800. HRMS: calcd, 453.0614; found, 453.0609.

General Procedure for the Robot-Assisted Parallel Amidation of Carboxylic Acids. Preparation of Stock Solutions. Solution A was the activated carboxylic acid solution, which was prepared as follows: The starting carboxylic acids (**16a**−**l** and **22b**−**h**) were strictly dried before use in a vacuum desiccator cabinet. The appropriate carboxylic acid was dissolved in DCE (SPS grade) and further diluted up to c = 0.5 mol/L final concentration. The resulting solution was mixed with 1.05 molar equiv of CDI in DCE (SPS grade; c = 0.5 mol/L) at room temperature and allowed to stand for 1.5 h at the same temperature under a moisture-free atmosphere. Solution B was prepared (c = 0.50 mol/L) from the appropriate amine reagent with DCE (SPS grade) in a volumetric flask.

Parallel Reactors. The reactor unit was an 8 × 12 matrix organized block. The reaction vessels were 1-mL standard PE wells. As a liquid dispenser, a Quadra 96 type 320 automatic pipettor system was used. The same instrument was used for the liquid−liquid extraction.

Amidation. The reactions were executed in a scale of 50 μmol referring to the carboxylic acid in solution A, whereas 1.20 equiv amines in solution B was used for the reactions. The stock solutions were pipetted into the vials (solution A (200 μL), followed by solution B (120 μL)). The vials were shaken vigorously at room temperature until completion of the reaction. The reactions with aromatic amines required elevated temperature (40 °C). The conversion was monitored by TLC and eluted with a typical solvent mixture of DCE/EtOH, 10:1 or 5:1.

Workup Procedure. The samples were diluted with chloroform (with ∼300 μL). The reaction mixture was washed first with 5% aq HCl (200 μL), water (200 μL), 5% aq Na_2CO_3 solution (200 μL), and water (200 μL). After a final TLC control, ethanol (500 μL) was measured into the vials containing the organic phases. Small samples were taken of the solutions (60 μL) for HPLC/MS analysis into a standard well plate. The remaining solutions were transferred into tared 800-μL standard glass vials and evaporated in a vacuum until their weight remained constant.

3-Imidazo[1,2-*a*]pyridin-3-yl-*N*-isobutyl-3-*o*-tolylpropionamide (23a, R = *o*-tolyl). Yield = 11.1 mg; 66%. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.70 (6H, d, −CH(CH_3)$_2$), 1.60, (1H, m, −C*H*(CH_3)$_2$), 2.44 (3H, s, CH_3), 2.82−3.06 (4H, m, 2*CH_2), 5.1 (1H, t, C*H*), 6.64 (1H, m, H7), 6.80−7.20 (5H, m, H2‴ + H3‴ + H4‴ + H5‴ + H6‴), 7.50 (1H, s, H2), 7.31 (1H, s, CO−N*H*), 7.55 (1H, m, H8), 7.70 (1H, m, H5). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.4 (CH_3), 19.8 (2*CH−(CH_3)$_2$), 28.2 (*C*H−(CH_3)$_2$), 34.2 (C3″), 41.8 + 47.0

(2*CH_2), 112.1 (C6), 117.5 (C8), 123.5 (C2), 123.9 (C4‴), 126.1 (C3), 126.5 (C7), 127.1 (C5), 128.4 (C5‴), 131.0 (C6‴), 133.6 (C3‴), 135.8 (C2‴), 138.5 (C1‴), 145.7 (C9), 170.3 (C1″). IR (KBr) cm^{-1}: 3050, 2956, 1662, 1636, 1556, 1504, 1357, 1287, 1147, 765. HRMS: calcd, 336.2076; found, 336.2081.

1-Pyrrolidin-1-yl-3-(2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)-propan-1-one (24g, $R^1 = R^3 = H$, R^2= *p*-tolyl). Yield = 7.0 mg; 42%. ^1H NMR ($CDCl_3$) δ (ppm): 1.80 (4H, m, CH_2-CH_2), 2.40 (3H, s, CH_3), 2.62 (2H, m, H1a″ + H1b″), 3.16 (2H, m, H2a″ + H2b″), 3.40−3.50 (4H, m, CH_2-N-CH_2), 6.81 (1H, m, H6), 7.15 (1H, m, H7), 7.23 (2H, m, H3′ + H5′), 7.61 (1H, m, H8), 7.69 (2H, m, H2′ + H6′), 8.17 (1H, m, H5). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.2 (C3″), 21.2 (CH_3), 24.3 + 25.8 (2*CH_2), 33.0 (C2″), 45.8 + 46.5 (2*N-CH_2), 111.9 (C6), 117.4 (C8), 119.4 (C3), 123.6 (C5 + C7), 127.9 (C2′ + C6′), 129.3 (C3′ + C5′), 131.9 (C1′), 137.3 (C4′), 142.5 (C9), 144.5 (C2), 170.1 (C1″). IR (KBr) cm^{-1}: 3086, 2962, 1641, 1499, 1443, 1242, 832, 757, 509. HRMS: calcd, 334.1919; found, 334.1911.

Quality Assurance and Evaluation. A multilevel quality control guaranteed the identity and purity of the final products. During the production stage, all carboxylic acid intermediates **16** and **22** were subjected to 100% HPLC/MS and NMR analysis. The accepted purity limit for the last intermediates before the full robotic derivatization was ≥90% (both HPLC and NMR). For the last step only, a selected portion (5−10%) of the final carboxamide set **23** and **24** was characterized by NMR methods. Total coverage purity checking of the final products was performed by HPLC/MS with the minimum limit of ≥85%.

In the case of the subjected 3-imidazo[1,2-*a*]pyridin-3-yl-propionic acid amide library, out of 3280 amidations started, 1910 final products met the above purity limit with the described workup procedure. Another portion of 560 amides with purity level between 70 and 85% can be subjected to preparative HPLC purification; the remaining part of the reactions was considered as unsuccessful (HPLC 0−70%).

Acknowledgment. This paper is dedicated to Prof. Károly Lempert (Budapest University of Technology and Economics) on the occasion of his 80th birthday. We are indebted to Tamás Karancsi and Richárd Lágner (ComGenex) for performing HPLC/MS analysis as well as to Péter Slégel (EGIS Pharma) for the HRMS experiments. We are also grateful to Ferenc Kálmán (ComGenex) for his contribution and support.

Supporting Information Available. The collection of experimental and analytical data for the remaining compounds detailed in this paper is available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC040101J