Approach to the Library of Fused Pyridine-4-carboxylic Acids by Combes-Type Reaction of Acyl Pyruvates and Electron-Rich Amino Heterocycles

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A library of fused pyridine-4-carboxylic acids (including pyrazolo[3,4-*b*]pyridines, isoxazolo[5,4-*b*]pyridines, furo[2,3-*b*]pyridines, thieno[2,3-*b*]pyridines, and pyrido[2,3-*d*]pyrimidines) was generated by Combes-type reaction of acyl pyruvates and electron-rich amino heterocycles followed by hydrolysis of the ester. The library members were also demonstrated to undergo the standard combinatorial transformations including amide coupling and esterification, as well as less common heterocyclizations to 1,2,4-triazoles and 1,2,4-oxadiazoles.

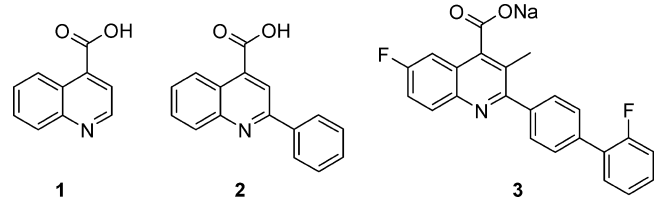
Introduction

Although solid-phase synthesis has been considered as a mainstream approach to drug discovery and lead optimization in the combinatorial chemistry over the past decades, the solution-phase methodology seems to be gaining momentum recently.[1] This approach is particularly efficient for generating libraries of compounds derived from heterocyclic scaffolds, which undeniably dominate in medicinal chemistry.[2] Derivatives of 4-quinolinecarboxylic (cinchoninic) acid (**1**) were used in drug discovery since the beginning of the 20th century when Cinchophen **2** was introduced as an analgestic drug, which was later abandoned because of undesirable side effects (Figure 1).[3] One of the most remarkable cinchoninic acid derivatives is represented by Brequinar sodium **3** which was originally discovered as an anticancer agent,[4] and later was found to display potent and selective immunosuppressive activity.[5] Other examples include compounds possessing antipsychotic,[6] antiallergic,[7] antiarthritic,[8] and anxiolytic activities.[9]

To diversify the chemical space covered by the libraries of cinchoninic acid derivatives, replacement of the benzene ring in molecule **1** with a heterocyclic (e.g., five-membered) core can be proposed. Introducing additional heteroatoms to the molecule of the cinchoninic acid analogue might increase affinity of the potential drug candidate to the biological target and improve its absorption, distribution, metabolism, and excretion (ADME) properties. This idea was recently used in the design of NK3 receptor ligands,[10] protein chaperone HSP 90 inhibitors,[11] and various kinases inhibitors.[12]

Several distinct approaches to the synthesis carboxylic acids of the general formula **4** have been reported in the literature, including three-component condensation of 5-aminopyrazoles, pyruvic acid and aldehydes,[13] reaction of β-acylacrylates and 6-aminopyrimidines,[14] rearrangement of oxa-bridged polyheterocycles[15] or reaction of *N*-(3-benzo[*b*-]thienyl)iminophosphoranes with α,β-unsaturated carbonyl compounds.[16] Understanding the ongoing demand on a general procedure allowing large libraries of the compounds **4** to be generated, we focused our attention on the methods employing the Combes-type condensation of electron-rich amino heterocycles **5** and acyl pyruvates **6** (Figure 2, Scheme 1). To the best of our knowledge, only single instances illustrating this concept were described in an open literature to date.[10a,17] As both amino heterocycles (**5**) and acyl pyruvates (**6**) are readily available compounds, the high diversity of the libraries obtained by their condensation is ensured.

Herein we wish to report the synthesis of the library of fused pyridine-4-carboxylic acids **4** by the solution-phase reaction of acyl pyruvates **6** and electron-rich amino heterocycles including aminopyrazoles **5**(1−11) and **5**(12−25),



1 2 3

Figure 1. Cinchoninic acid and its derivatives.

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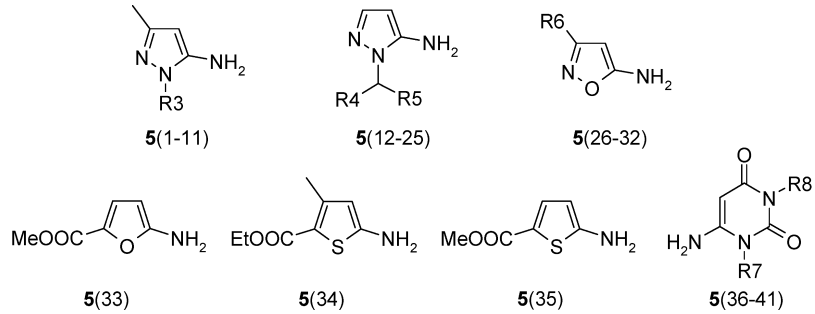
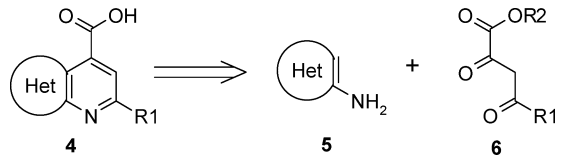
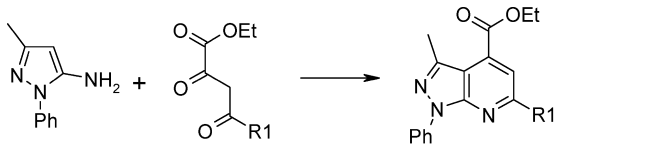


Figure 2. Subtypes of the amino heterocycles used in the synthesis of the library **4**.

Scheme 1



Scheme 2



aminooxazoles **5**(26−32), aminofuran **5**(33), aminothiophenes **5**(34,35), and aminouracils **5**(36−41). The library is generated using a two-step reaction sequence including Combes-type heterocyclization and hydrolysis steps.

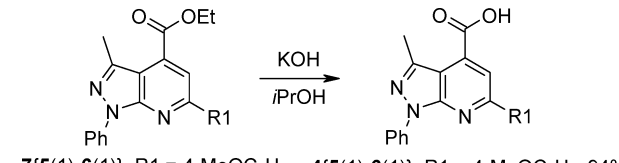
Results and Discussion

First of all, an optimization of the conditions was performed for the target two-step reaction sequence. 1-Phenyl-5-methylpyrazole **5**(1), ethyl 2,4-dioxo-4-(methoxyphenyl)butyrate **6**(1), and ethyl 2,4-dioxovalerate **6**(2) were used as model compounds in this part of the study. It has been found that the most appropriate procedure for the heterocyclization step includes refluxing of the starting compounds in acetic acid for several hours; this result is in accordance with those previously reported by our group for the reaction of thifluoromethyl β-diketones. In the case of ethyl 2,4-dioxo-4-(methoxyphenyl)butyrate **6**(1) and ethyl 2,4-dioxovalerate **6**(2), the formation of the compounds **7**{**5**(1)−**6**(1,2)} proceeded in a regioselective manner (Scheme 2), which is also consistent with our previous results.[18]

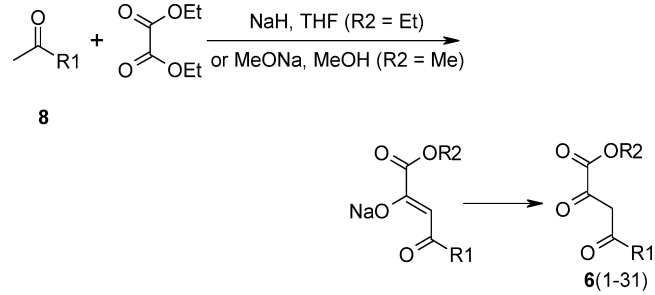
Since it is often preferable to handle, purify, and store the compounds **6** as their sodium salts, the latter were also checked in the heterocyclization reaction with pyrazole **5**(1). It was revealed that this modification of the procedure does not give a drop in the yield of the reaction; obviously, compounds **6** were rapidly generated in situ from the corresponding salts and acetic acid.

For the hydrolysis of the compounds **7**{**5**(1)−**6**(1,2)}, the optimized procedure included refluxing with 2 equiv of potassium hydroxide in 2-propanol for 2−5 h. After acidifying the reaction mixture with acetic acid and dilution with water, carboxylic acids **4**{**5**(1)−**6**(1,2)} were formed as

Scheme 3



Scheme 4



crystalline solids easily separated by filtration (Scheme 3). It has been revealed that special conditions were necessary for drying the compounds **4**{**5**(1)−**6**(1,2)}, that is, prolonged heating in vacuo over phosphorus pentoxide; otherwise, the samples were unsuitable for most of the further reactions because of high water content.

As it could be concluded from the above considerations, the procedures developed for both steps of the synthesis of fused pyridine-4-carboxylic acids **4** were compatible with solution-phase combinatorial techniques. The next part of the study included the synthesis of the library of compounds **4** using these optimized reaction conditions. The acyl pyruvates **6**(1−31) used in the synthesis are available commercially; they can be also obtained by Claisen condensation of the corresponding ketones **8** and diethyl oxalate,[19] thus introducing the first diversity point of the library (Scheme 4).

To increase the diversity of the library, several chemotypes of the aminoheterocycles were involved in the synthesis. In particular, two sets of aminopyrazoles **5**(1−11) and **5**(12−25) were used (Figures 3, 4), which can be prepared by two distinct approaches: one starting from hydrazines **9** and 3-aminocrotonitrile **10**,[20] another employing the reaction of ketones **11** and hydrazine **12**[21] (Scheme 5). It has been revealed that the standard procedure is applicable for the synthesis of carboxylic acids **4**{**5**(1−25)−**6**(1−31)} starting from pyrazoles **5**(1−25) and acyl pyruvates **6**; hence, the second diversity point was introduced successfully for these

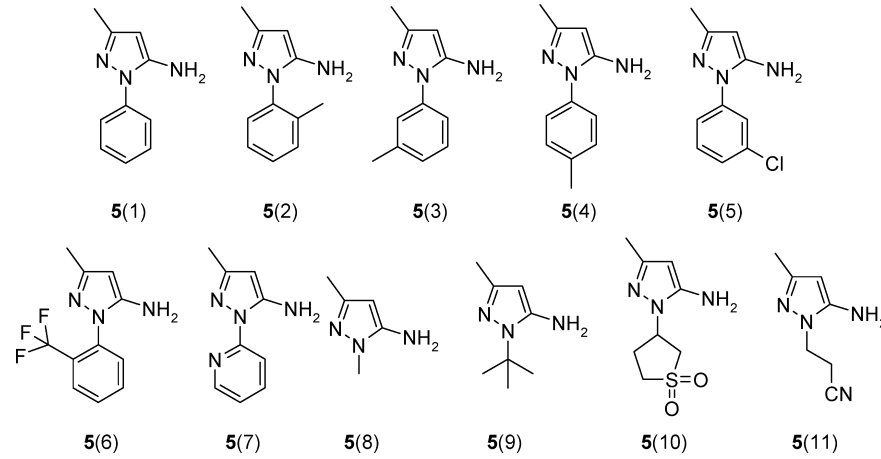


Figure 3. Diversity reagents **5**(1−11).

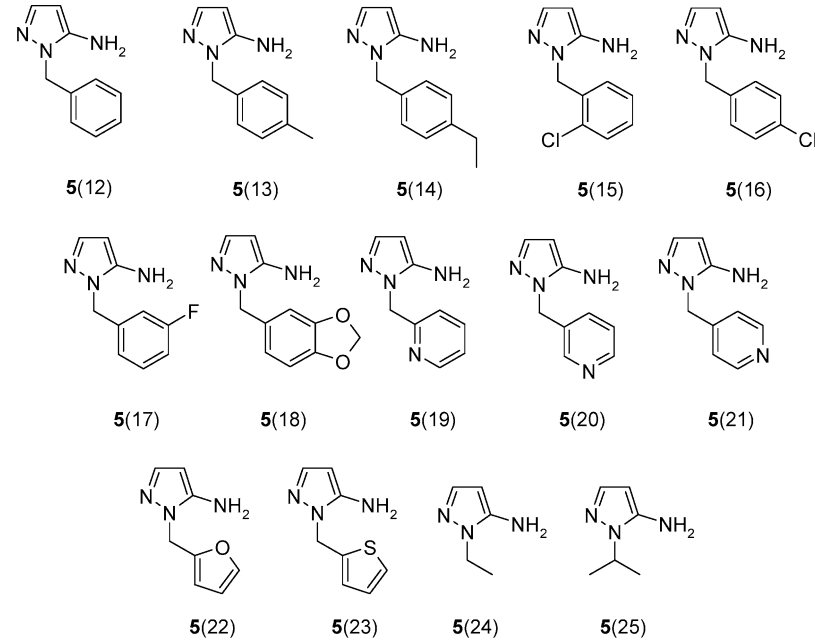
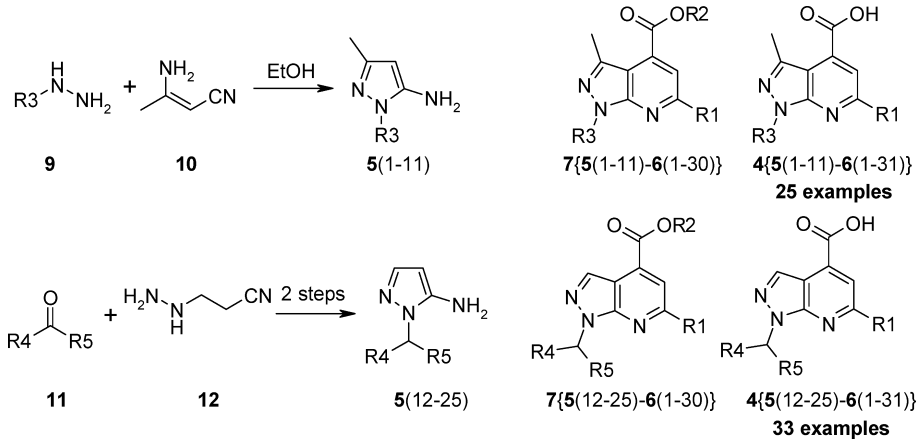


Figure 4. Diversity reagents **5**(12−25).

Scheme 5



library members (Figure 5, Scheme 5). However, the method failed in the case of aminopyrazoles **5**(10,11) because of the hydrolysis step, as the substituent R3 in the pyrazole moiety was sensitive to potassium hydroxide. To diminish the influence of strong alkalis at this step of the synthesis, milder conditions were developed for the hydrolysis of the chemset **7**{**5**(10,11)−**6**(1−31)} including stirring with a stoichiometric quantity of lithium hydroxide in methanol.

The procedures for the synthesis of carboxylic acids **4**{**5**(1−25)−**6**(1−31)} from aminopyrazoles **5**(1−25) described above allowed also chemset **4**{**5**(26−32)−**6**(1−31)} to be obtained, starting from aminooxazoles **5**(26−32)

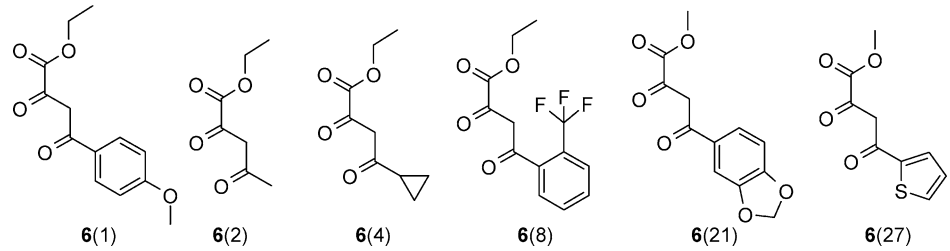


Figure 5. Diversity reagents **6**(1−31) (for the complete list, see the Supporting Information).

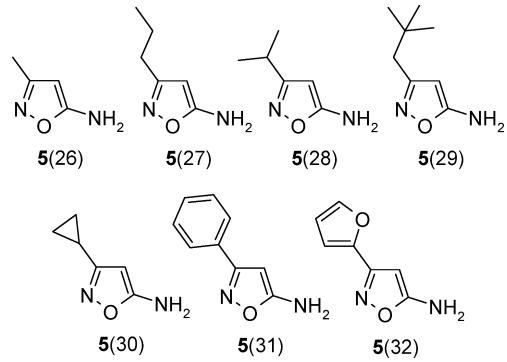
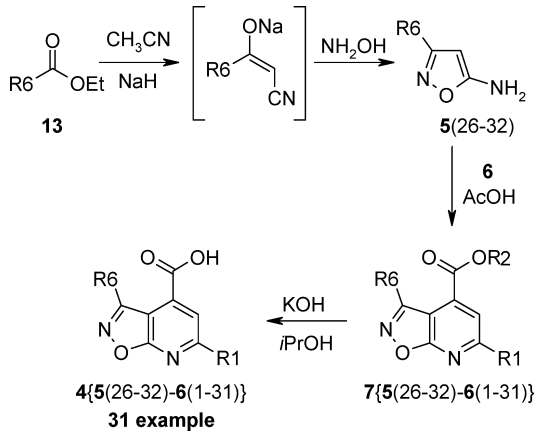


Figure 6. Diversity reagents **5**(26−32).

Scheme 6



(Figure 6). The latter can be prepared from esters **13** in two steps (Scheme 6).[22,23]

Reaction of acyl pyruvates **6** with aminofuran **5**(33)[24] was also performed in refluxing acetic acid, although the yield of the products **7**{**5**(33)−**6**(6,11,21,28)} were diminished because of decomposition of the starting compound **5**(33). Hydrolysis of the library members **7**{**5**(33)−**6**(6,11,21,28)} (KOH/*i*PrOH) resulted in the formation of dicarboxylic acid **14**{**5**(33)−**6**(6,11,21,28)} as both ester moieties present in the molecules of **7**{**5**(33)−**6**(6,11,21,28)} took part in the transformation (Scheme 7).

When the conditions described above were applied to the aminothiophene **5**(34),[25] no reaction with acyl pyruvates **6** occurred. After the prolonged reaction time, a complex mixture of unidentified products was formed. To obtain library members **7**{**5**(34)−**6**(16,17)}, the reaction was performed using chlorotrimethylsilane−DMF as a condensing reagent.[26] It should be noted that partial hydrolysis of the COOMe moiety occurred when this procedure was used; thus **7**{**5**(34)−**6**(16,17)} was contaminated with **4**{**5**(34)−**6**(16,17)}. The complete selective hydrolysis of the methyl ester moiety in the molecules of **7**{**5**(34)−**6**(16,17)} was possible as methyl esters **6**(16,17) were used as the starting material. Under more drastic hydrolysis conditions, dicarboxylic acid **14**{**5**(34)−**6**(16,17)} was obtained (Scheme 8).

In the case of aminothiophene **5**(35), both methods mentioned above were appropriate to obtain library members **7**{**5**(35)−**6**(16,27)}. Hydrolysis of **7**{**5**(35)−**6**(16,27)} resulted in the formation of the library members **14**{**5**(35)−**6**(16,27)} (Scheme 8).

Aminouracils **5**(36−41) (Figure 7) necessary for the synthesis of the next subset of the library **4** can be prepared by reaction of ureas **15** and ethylcyanoacetate.[27] Both procedures for the library synthesis (i.e., acetic acid/reflux or chlorotrimethylsilane−DMF/100 °C) succeeded in the reaction of **5**(36−41) with acyl pyruvates **6**, thus allowing a chemset **7**{**5**(36−41)−**6**(1−31)} to be obtained. Hydrolysis of **7**{**5**(36−41)−**6**(1−31)} was performed by standard protocol described above (Scheme 9).

As in the case of compounds **7**{**5**(1)−**6**(1,2)}, synthesis of the library members **7**{**5**(1−41)−**6**(1−31)} proceeded in a regioselective manner. The regiochemistry of the reaction was confirmed by Nuclear Overhauser Effect (NOE) experiments for the compounds **7**{**5**(12)−**6**(1)}, **7**{**5**(25)−**6**(16)}, **7**{**5**(23)−**6**(31)} and **7**{**5**(33)−**6**(6)}, as well as by ^{13}C patterns of other library members.

Carboxylic acids **4** were shown to undergo the standard combinatorial transformations including amide coupling and esterification, as well as less common heterocyclizations to 1,2,4-triazoles and 1,2,4-oxadiazoles (Scheme 10). Therefore, the library **4** can be used to generate more multifarious libraries possessing three diversity points.

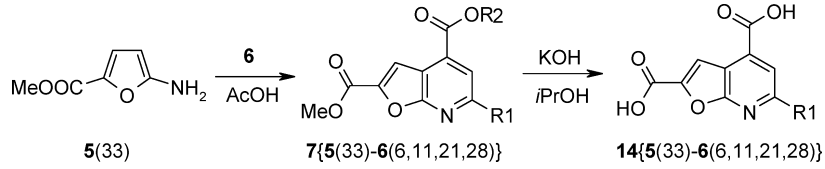
Conclusions

A library of fused pyridine-4-carboxylic acids of general formula **4** was generated using the high-yield two-step solution-phase combinatorial reaction sequence, namely, Combes-type heterocyclization and hydrolysis (Table 1). The library includes pyrazolo[3,4-*b*]pyridine, isoxazolo[5,4-*b*]pyridine, furo[2,3-*b*]pyridine, thieno[2,3-*b*]pyridine, and pyrido[2,3-*d*]pyrimidine derivatives. Using the developed procedures, 168 carboxylic acids **4** and **14** and 5830 of their derivatives were synthesized (Figures 8, 9, and 10). The overall virtual chemical space covered by the library includes 614736 members.[28]

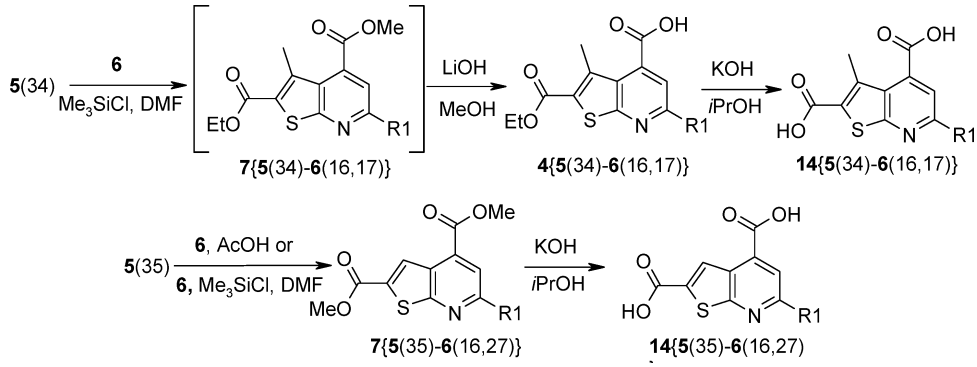
Experimental Section

General Procedures. 3-Hydrazinopropanenitrile **12** was prepared by the method reported in the literature.[29] All other chemicals were obtained from commercially available sources (Aldrich, Fluka, Enamine Ltd., and UkrOrgSyntez) and used

Scheme 7



Scheme 8



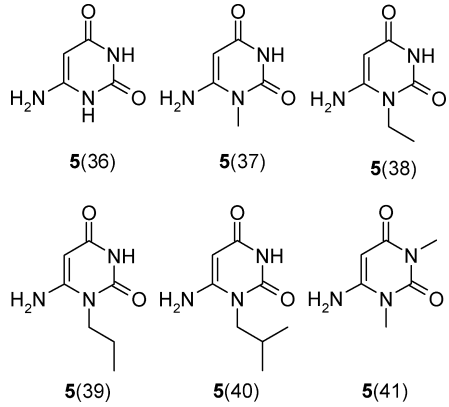
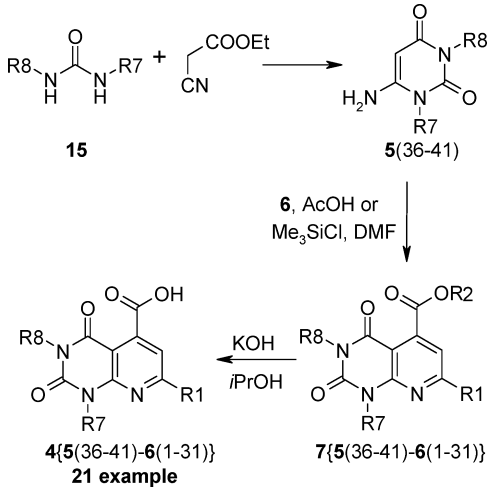


Figure 7. Diversity reagents **5**(36−41).

Scheme 9



without further purification. All the solvents for the reactions (DMF, acetic acid, 2-propanol, ethanol, *n*-butanol, benzene) were distilled and dried by standard methods. All solvents for the recrystallization were used as acquired. Monitoring the water concentration was performed using Mettler Toledo DL31 KF titrator. Melting points were measured on MPA100 OptiMelt automated melting point system. Elemental analyses were performed on Elementar Vario MICRO Cube CHNS/O analyzer. ^{1}H, ^{13}C, and all 2D NMR spectra were recorded on a Bruker Avance 500 and Varian Unity Plus 400 spectrometers using DMSO-d_6 as a solvent and TMS as an internal standard. LC/MS spectra were recorded using chromatography/mass spectrometric system consisting of Agilent 1100 Series high-performance liquid chromatograph equipped with Agilent LCMSD SL diode-matrix and mass-selective detector. The parameters of HPLC/MS analysis: column, Zorbax SB-C18, 1.8 μm, 4.6 × 15 mm; eluent, A: MeCN-water with 0.1% of TFA (95:5) and B: water with 0.1% of TFA; flow rate, 3 mL·s^{-1}; volume of the sample injected, 1 μL; UV detectors operating wavelengths, 215, 254, and 265 nm; ionization method, chemical ionization under atmospheric pressure (APCI); ionization mode, simultaneous scanning of positive and negative ions in the *m*/*z* range of 80−1000. All the synthesized compounds are more than 95% purity by HPLC/MS.

1-(4-Ethylphenyl)methyl-1*H*-pyrazol-5-amine 5(14), hydrochloride. To 4-ethylbenzaldehyde **11**(14) (150 g, 1.12 mol), hydrazine **12** (95 g, 1.12 mol) is added dropwise upon stirring at 20 °C (external cooling). The resulting mixture was stirred overnight, then dissolved in 450 mL of benzene, dried over sodium sulfate and evaporated in vacuo to give the corresponding hydrazone in almost quantitative yield. The product was added to a solution of sodium (5.5 g) in *n*-butanol (450 mL), and the mixture was refluxed for 7−10 h, then cooled and evaporated in vacuo. The residue was triturated with ether (700 mL), then 12 N HCl (110 mL) was added carefully, and the resulting mixture was stirred for 15 min. The precipitate formed was filtered and washed with ether (3 × 50 mL) to give 1-(4-ethylphenyl)-1*H*-pyrazol-5-amine **5**(14) hydrochloride (180 g, 0.76 mol, 68%). MS (*m*/*z*): 202 (MH^+), 119. Anal. Calcd for $C_{12}H_{16}ClN_3$ C 60.63, H 6.78, Cl 14.91, N 17.68. Found C 61.72, H 6.41, Cl 15.07, N 17.91. ^{1}H NMR (DMSO-d^6) δ 7.92 (d, J = 3.0 Hz, 1H, 3-C*H*), 7.33 (d, J = 7.8 Hz, 2H, C_6H_4), 7.17 (d, J = 7.8 Hz, 2H, C_6H_4), 5.73 (d, J = 3.0 Hz, 1H, 4-C*H*), 5.47 (s, 2H, NCH_2), 2.55 (q, J = 7.4 Hz, 2H, CH_2CH_3), 1.17 (t,

Scheme 10

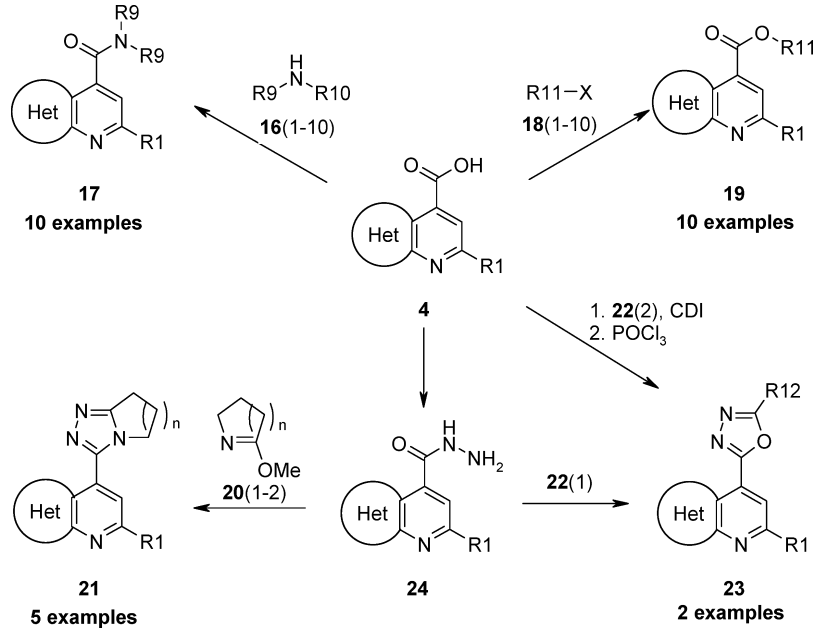


Table 1. Chemical Yields in the Synthesis of the Libraries **4** and **14**

			average yield[a], %		
entry no.	chemset	parent heterocycle	step 1	step 2	overall
1	**4**{**5**(1−25)−**6**(1−30)}	pyrazolo[3,4-*b*]pyridine	90	93	84
2	**4**{**5**(26−32)−**6**(1−30)}	isoxazolo[5,4-*b*]pyridine	92	95	87
3	**14**{**5**(33)−**6**(1−30)}	furo[2,3-*b*]pyridine	86	95	82
4	**14**{**5**(34−35)−**6**(1−30)}	thieno[2,3-*b*]pyridine	84	93	78
5	**4**{**5**(36−41)−**6**(1−30)}	pyrido[2,3-*d*]pyrimidine	93	94	87

[a] Most of the yield values are kept within ±5% range of the average value.

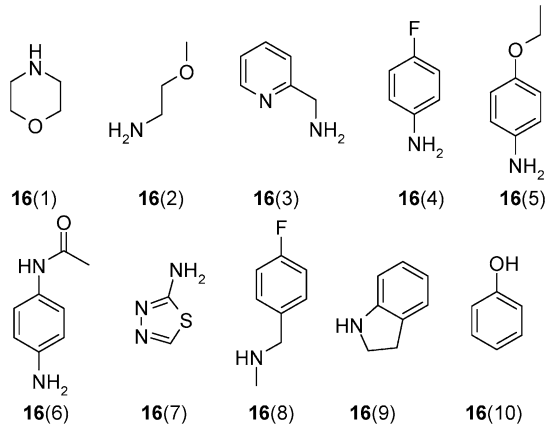


Figure 8. Diversity reagents **16**(1−10).

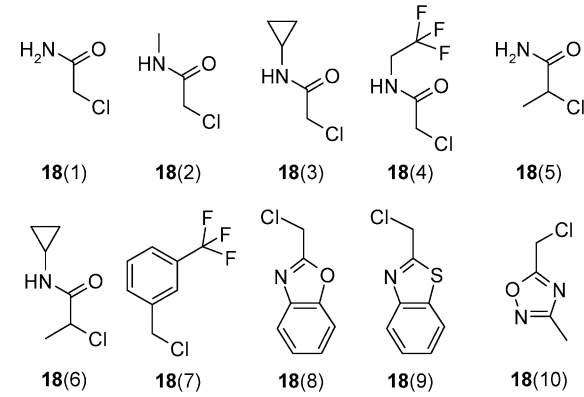


Figure 9. Diversity reagents **18**(1−10).

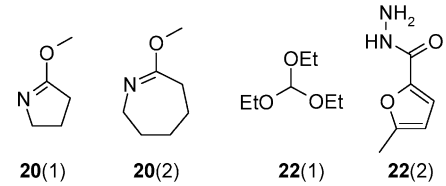


Figure 10. Diversity reagents **20**(1,2) and **22**(1,2).

J = 7.4 Hz, 3H, CH_2CH_3). All N*H* protons are exchanged with HDO. ^{13}C NMR (DMSO-d^6), δ 147.2, 143.0, 138.5, 135.9, 128.1, 127.8, 88.6, 50.1, 28.3, 16.9.

General Procedure for the Synthesis of Esters 7. Method A. A solution of amino heterocycle **5** (3 mmol) and acyl pyruvate **6** (or its sodium salt) (3 mmol) in acetic acid (15 mL) was refluxed for 2−4 h The solvent was removed in vacuo, the residue was triturated with water, filtered, and recrystallized from 2-propanol (in most cases).

Method B. Amino heterocycle **5** and acyl pyruvate **6** (or its sodium salt) (2 mmol) were placed in 15 mL pressure tube and dissolved in DMF (2−4 mL). Chlorotrimethylsilane (0.87 g, 8 mmol) was added dropwise to the solution. The tube was sealed thoroughly and heated on a water bath for 4−8 h. After cooling, the flask was opened (**Caution!** *Excessive pressure inside*), the reaction mixture was poured into water (10 mL) and then sonicated at 20 °C for 1 h. The precipitate formed was filtered and washed with *i*PrOH or Et_2O (2 mL).

General Procedure for the Synthesis of Carboxylic Acids 4. Method A. A solution of ester **5** (1 mmol) and potassium hydroxide (2 mmol) in 2-propanol (15 mL) was refluxed for 2−5 h, then cooled, diluted with water (15 mL), and neutralized with acetic acid. The precipitate was collected by filtration and dried in vacuo over phosphorus pentoxide.

Method B. The method was used for the synthesis of library members **4**{**5**(10,11)−**6**(1−30)}. A solution of ester **5** (1 mmol) and lithium hydroxide (1 mmol) in methanol (15 mL) was stirred overnight, then diluted with water (15 mL) and neutralized with acetic acid. The precipitate was collected by filtration, recrystallized from ethanol, and dried in vacuo over phosphorus pentoxide.

General Procedure for the Synthesis of Amides 17. Method A. A mixture of acid **4** (2 mmol), amine **16**(1−10) (2 mmol), diisopropylethylamine (5.8 mmol), and 1-methyl-2-chloropyridinium iodide (2.9 mmol) in dry acetonitrile (3 mL) was stirred at reflux for 1−4 h. The reaction mixture was diluted with water (10 mL). The precipitate was filtered off and washed with 5% aqueous sodium bicarbonate solution (10 mL) and ethanol (2 mL).

Method B. Carbonyldiimidazole was added to a solution of acid **4** in dry DMF (2 mL), and the reaction mixture was brought to 60 °C and stirred at this temperature for 2 h. Then amine was added to the reaction mixture in one portion. The reaction mixture was sonicated at 60 °C for 12 h. The reaction mixture was diluted with water (10 mL). The precipitate was filtered off and washed with 5% aqueous sodium bicarbonate solution (10 mL) and EtOH (2 mL).

General Procedure for the Synthesis of Esters 19. A mixture of acid **4** (2 mmol), alkylating agent (2 mmol), and diisopropylethylamine (2 mmol) in DMF (2 mL) was heated at 60 °C for 4 h. The reaction mixture was diluted with water (10 mL). The precipitate was filtered and washed with 2-propanol (2 mL).

General Procedure for the Synthesis of Hydrazides 24. A solution of the corresponding ester **7** (1 mmol) and hydrazine hydrate (5 mmol) in 2-propanol (15 mL) was refluxed for 2−5 h. After cooling, the precipitate was filtered and washed with 2-propanol (2 mL).

General Procedure for the Synthesis of 1,2,4-Triazoles 21. A solution of hydrazide **24** (3 mmol) and compound **20** (3 mmol) in 2-propanol (20 mL) was refluxed for 2 h. The solvent was removed in vacuo, the residue was refluxed in acetic acid for 4 h. The solvent was removed in vacuo, the residue was triturated with water, filtered, and recrystallized from ethanol (in most cases).

General Procedure for the Synthesis of 1,2,4-Oxadiazoles 23. Method A. (used for the synthesis of **23**{**5**(1)−**6**(27)−**22**(1)}). A mixture of hydrazide **24** (2 mmol) and ethyl orthoformate **22**(1) (2 mmol) was stirred at 100 °C for 12 h. The precipitate was filtered off and washed with Et_2O (2 mL).

Method B. (used for the synthesis of **23**{**5**(1)−**6**(27)−**22**(2)}). Carbonyldiimidazole (1 mmol) was added to a solution of acid **4** in dry DMF (2 mL), the reaction mixture was brought to 60 °C, and stirred at this temperature for 2 h. Then hydrazide **22**(2) was added to the reaction mixture in one portion. The reaction mixture was sonicated at 60 °C for 12 h. The reaction mixture was diluted with water (10 mL). The precipitate was filtered, washed with 5% aqueous sodium bicarbonate solution (10 mL) and EtOH (2 mL) to give the corresponding acyl hydrazide. A mixture of acyl hydrazide (2 mmol) and 5 mL of phosphorus oxychloride was refluxed with stirring for 4 h. The reaction mixture was poured onto ice (20 g), and the precipitate was filtered off and washed with 2-propanol (2 mL).

Supporting Information Available. Figures and compound/library member characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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