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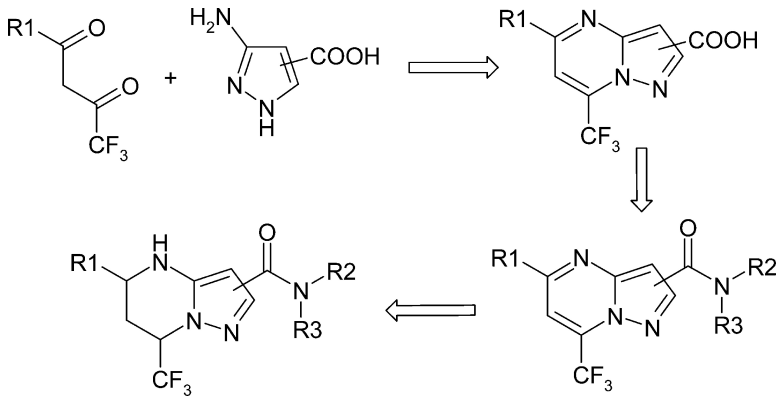

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Liquid-Phase Synthesis of Combinatorial Libraries Based on 7-Trifluoromethyl-Substituted Pyrazolo[1,5-*a*]Pyrimidine Scaffold

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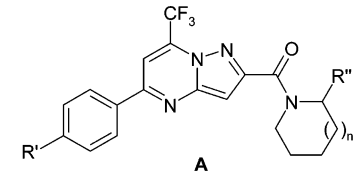
The parallel solution-phase synthesis of more than 2200 7-trifluoromethyl-substituted pyrazolo[1,5-*a*]-pyrimidine and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine carboxamides on a 50−100-mg scale has been accomplished. Key reactions include assembly of the pyrazolo[1,5-*a*]pyrimidine ring by condensation of 5-aminopyrazole derivatives with the corresponding trifluoromethyl-β-diketones. The libraries from libraries were then obtained in good yields and purities using solution-phase acylation and reduction methodologies. Simple manual techniques for parallel reactions using special CombiSyn synthesizers were coupled with easy purification procedures (crystallization from the reaction mixtures) to give high-purity final products. The scope and limitations of the developed approach are discussed.

Introduction

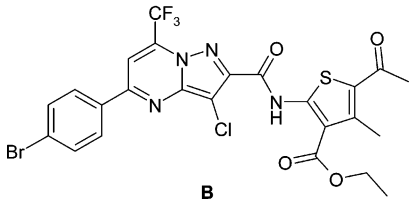
Combinatorial chemistry for the synthesis of a large number of organic compounds is recognized now as a key element of early drug discovery.[1] The primary advantage of the combinatorial technique is the speed at which different types of organic compounds can be synthesized, formulated, and tested for a particular application. In addition to speed, the amount of material needed for a combinatorial study is far less than that required for conventional methods, which makes combinatorial materials discovery more affordable when the materials are expensive.[2]

Among the broad range of templates, heterocyclic scaffolds represent the most promising molecules as lead structures for the discovery of novel synthetic drugs.[3] The development of new methods for the synthesis of heterocyclic compound libraries, both in solution and on solid phase, is an ever-expanding area in combinatorial chemistry. In particular, the pyrazolo[1,5-*a*]pyrimidine structural motif may be found in a large number of pharmaceutical agents with a diverse range of physiological activities, for example, antiepileptic agents,[4] anxiolytics,[5] antidepressants,[6] agents for treatment of sleep disorders[7] and oncolytics.[8] Recently, a series of antagonist of protease-activated PAR2 receptors were reported (structure A, Figure 1).[9] These compounds are expected to be useful for the treatment of arthritis, dermatitis, fever, asthma, bone resorption-related disorders, cardiovascular diseases, dysmenorrhea, nephritis, nephrosis, atherosclerosis, hypotension, shock, pain, neuroinflammation, cancer, and Alzheimer's disease, among other PAR2-mediated disorders. Compound B (Figure 1) has been described as an inhibitor of voltage-dependent sodium channels particularly useful for the treatment of pain, including inflammatory and neuropathic pain.[10]



A

R' = H, Cl; R" = H, Me, CO_2Et; n = 1,2



B

Figure 1. Examples of physiologically active 5-aryl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-2-ylcarboxamides.[9,10]

An interesting feature of compounds depicted in Figure 1 is the presence of a trifluoromethyl group in position 7 of the pyrazolo[1,5-*a*]pyrimidine ring. The trifuoromethyl group is one of the most attractive functional groups in organic chemistry, and efficient introduction of this group is a topic of growing interest in organofluorine chemistry.[11] The two latter examples are of particular interest for this article, because the physiologically active 5-aryl-7-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidin-2-ylcarboxamides shown in Figure 1 as well as a large variety of their analogues can be readily synthesized using the synthetic approaches described in the present work.

The shown recent examples highlight the high level of interest in variously substituted pyrazolo[1,5-*a*]pyrimidines and their modified analogues. However, although there is a wide range of methods available for the synthesis of

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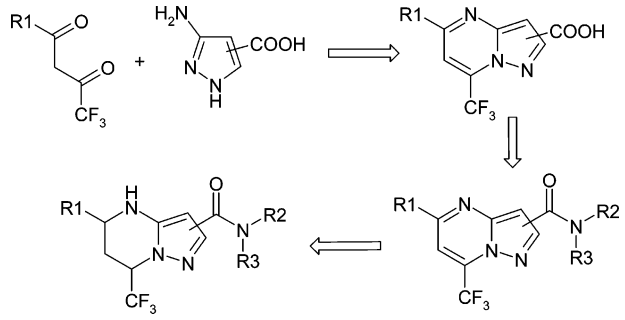
Scheme 1. General Scheme for Synthesis of Pyrazolo[1,5-*a*]pyrimidine Carboxylates and Their Amide Derivatives



pyrazolo[1,5-*a*]pyrimidines,[12] very few of these procedures have been developed in combinatorial chemistry, and there is a great need for new simple and facile procedures that can incorporate a number of points of structural diversity and a variety of substitution patterns in the target pyrazolopyrimidine library. In this paper, we report a successful solution-phase strategy for parallel synthesis of 7-trifluoromethyl-substituted pyrazolo[1,5-*a*]pyrimidine and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine carboxamides. The principal advantages, scope and limitations of the involved synthetic method are discussed.

The general synthetic approach is depicted in Scheme 1. The trifluoromethyl-β-diketones were treated with 5-aminopyrazolecarboxylic acid derivatives to provide the pyrazolo[1,5-*a*]pyrimidine carboxylates. The resulting acids were converted into the libraries of amides via the corresponding acid chlorides. Treatment with sodium borohydride afforded the libraries containing the reduced pyrimidine ring.

The key aminopyrazole intermediates can be obtained from commercial sources or synthetically. In this work, we used a modification of the recently reported procedure[13] for synthesis of 3-carboxy-5-aminopyrazole **5a** and its 4-chloro-substituted analogue **5b** (Scheme 2).

The commercially available 5-methyl-1*H*-pyrazole **1** (Scheme 1) was used as a starting compound. The nitropyrazole **2** was obtained in 38% yield by reaction of **1** with concentrated nitrous acid in acetic acid under reflux. The 4-chloro-substituted derivative **3** was obtained in high yield (90%) by reaction of **2** with SO_2Cl_2 in chloroform. Methyl groups of **2** and **3** were oxidized under treatment with sodium dichromate in concentrated HCl. Finally, a nickel-catalyzed reduction of the nitro group with hydrazine afforded 3-carboxy-5-aminopyrazoles **5a**,**b** in good yields (50−63%).

4-Etoxycarbonyl-5-aminopyrazole used as an alternative 5-aminopyrazole component for assembly of the pyrazolo-[1,5-*a*]pyrimidine moiety was obtained from Aldrich.

The synthetic approach for assembly of the pyrazolo[1,5-*a*]pyrimidine ring system is depicted in Scheme 3. A total of 14 different trifluoromethyl-β-diketones **6**{*1*−*14*} were synthesized as reported[14] and used in this work (Scheme 3). The choice of these particular β-diketones was determined by their synthetic accessibility. Compounds **6**{*1*−*14*} were treated with 5-aminopyrazolecarboxylic acid derivatives **5a**−**c** in the mixture of acetic acid and aqueous HCl under reflux. The initially formed imine intermediates underwent a facile cyclization to provide the corresponding pyrazolo-[1,5-*a*]pyrimidine 3- and 4-carboxylates **7**{*1*−*14*}, **8**{*1*−*14*}, and **9**{*1*−*14*}. These acids were purified by direct crystallization from the reaction mixtures. The final yields of these reactions were generally good, ranging from 60 to 90%. Only in the case of chloro-substituted derivatives **8**{*1*−*14*} were the yields slightly reduced (40−70%), mainly due to formation of 5-trifluoromethyl isomers (up to 20%). The resulting mixtures were difficult to separate in the high-throughput format using standard recrystallization techniques. To obtain the pure chloro-substituted reagents for further conversions, we recrystallized the mixtures of the corresponding acid chlorides.

The resulting combinatorial libraries of acids **7**{*1*−*14*}, **8**{*1*−*14*}, and **9**{*1*−*14*} were converted into the corresponding chlorides **10**{*1*−*14*}, **11**{*1*−*14*}, and **12**{*1*−*14*} by reaction with thionyl chloride in boiling CCl_4. Table 1 contains the yields of pure acids and acid chlorides belonging to these combinatorial sets. The structures and purity of all these compounds were established using ^{1}H NMR and LC/MS analyses.

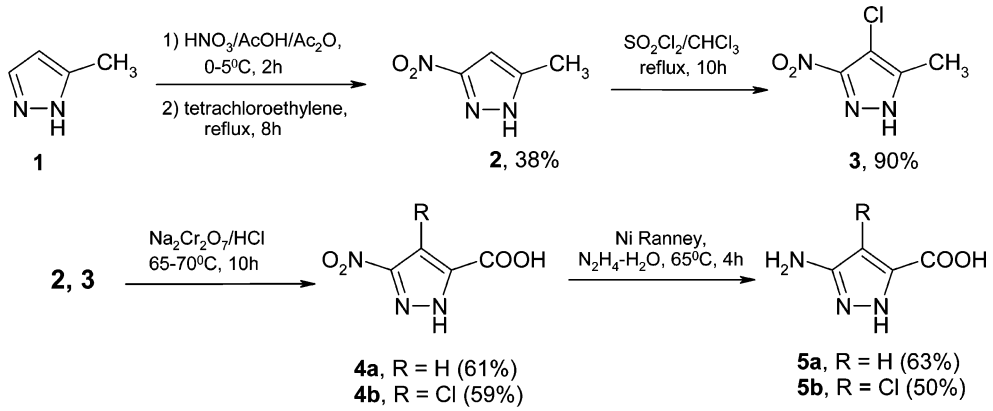
All the obtained chlorides **10**{*1*−*14*}, **11**{*1*−*14*}, and **12**{*1*−*14*} could be easily converted in good to high yields (50−90%) to the corresponding amide derivatives using conventional treatment with 450 diverse primary and secondary amines in acetonitrile (Scheme 4). With respect to amine component, we evaluated various aliphatic and aromatic amines, such as substituted anilines and benzylamines, heteroarylamines, cyclic and acyclic aliphatic amines, and nitrogen-containing compounds, which were tolerated without any limitations. Representative examples of the used amines are shown in Scheme 4. The yields as well as reaction and purification conditions slightly varied according to the nature of the amine (Table 2).

The resulting combinatorial libraries **14**{*1*−*662*}, **15**(*1*−*355*}, and **16**{*1*−*420*} include over 1400 novel 5-substituted 7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine 3- and 4-carboxamides.

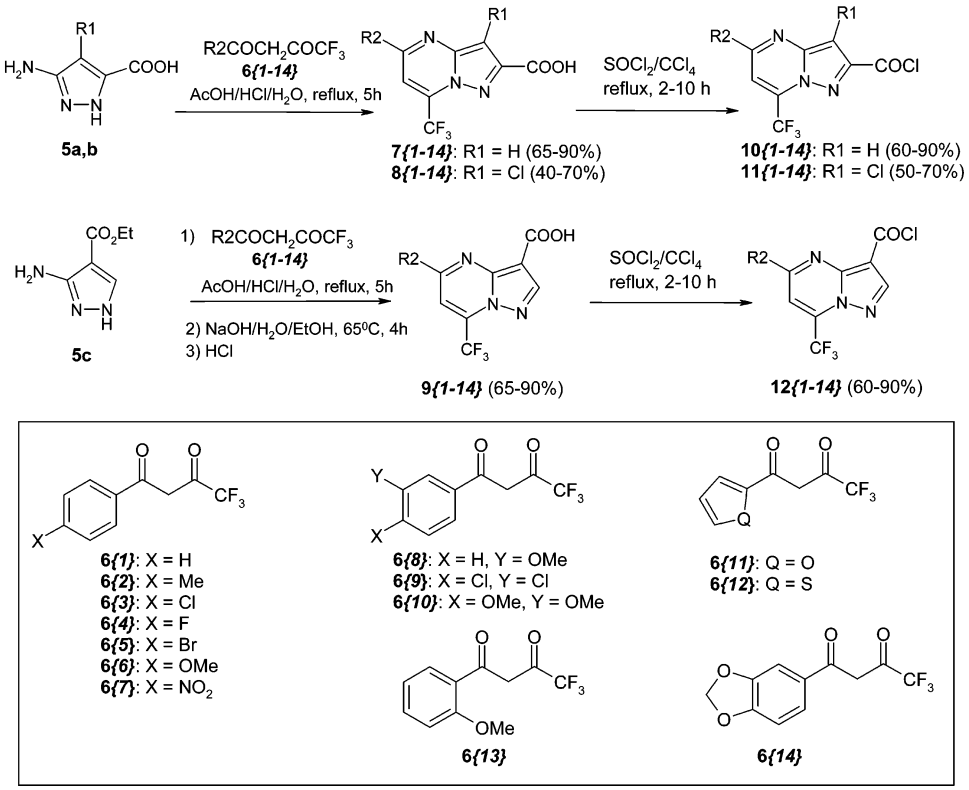
Different reduction techniques are of great importance in classical organic chemistry. However, their use in the combinatorial synthesis is often limited, mainly due to unselective reactions, resulting in complex mixtures of products whose separation is problematic in high-throughput format. In this work, we developed a successful approach to efficient selective reduction of the pyrimidine ring within the pyrazolo[1,5-*a*]pyrimidine scaffold. This method is based on a mild sodium borohydride reduction of pyrazolo[1,5-*a*]pyrimidines **14**{*1*−*662*}, **15**(*1*−*355*}, and **16**{*1*−*420*} in ethanol at room temperature. In most cases, this method allows almost quantitative conversion of the initial compounds into the corresponding 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine carboxamides **17**{*1*−*450*}, **18**(*1*−*196*}, and **19**{*1*−*215*}, which can be easily separated from the reaction mixture using a simple precipitation in water. The yields of the pure products are usually in the range of 80−90%.

The developed reduction with $NaBH_4$ is interesting with regard to its chemoselectivity (pyrimidine ring reduced in preference over pyrazole, amide, and ester groups) and its stereoselectivity. On the basis of ^{1}H NMR spectra and chromatographic data, the reduction leads to only one pair

Scheme 2. Synthesis of 3-Carboxy-5-aminopyrazoles



Scheme 3. Synthesis of Pyrazolo[1,5-*a*]pyrimidine Carboxylates and Their Chloride Derivatives



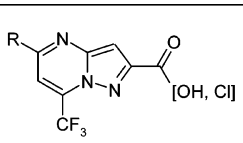
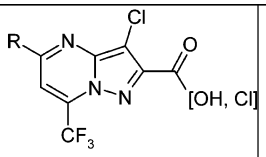
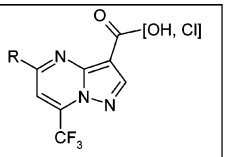
of enantiomers having identical proton shifts and that are indistinguishable using standard separation techniques which do not use the chiral reagents. We can suggest a two-step reduction mechanism depicted in Scheme 5. At the first step, the N1═C7 enamine bond is reduced to afford the dihydropyrimidine enantiomeric intermediates. The C5═C6 double bond of this intermediate is further reduced due to the influence of adjacent electron-withdrawing groups. The preferred mode of borohydride attack on this double bond is determined by the position of the bulky phenyl substituent and likely leads to 2,4-syn isomers. As a result, two enantiomers, (5*S*,7*R*) and (5*R*,7*S*) are formed. Similar stereoselective reactions of sterically hindered molecular fragments with borohydride complexes are described in a number of publications.[15]

There are two principal limitations of the described reduction method. First, it leads to a mixture of enantiomers, which could not be separated using conventional laboratory techniques. It is recognized now that screening mixtures of compounds can often complicate or mask bioassay results in the early stages of drug discovery. Sometimes, chiral compounds active as a single isomer can exhibit little or no activity as stereomixtures. This could be because the inactive isomer(s) are present in larger quantities or to the opposing effects of the stereoisomers, which effectively cancel each other out. The latter situation often results in wasting potentially valuable leads. The second limitation is related to the fact that the treatment with sodium borohydride is incompatible with substitutents containing ketone groups. In such cases, the reaction results in a complex mixtures of products, which are difficult to separate in the high-throughput combinatorial mode.

For illustration, 24 arbitrary compounds synthesized according to Scheme 4 are shown in Figure 2.

All pyrazolo[1,5-*a*]pyrimidines within these combinatorial series were characterized by ^{1}H NMR and LC/MS analysis.

Table 1. Structures and Yields of Carboxylic Acids and Acid Chlorides Belonging to Combinatorial Sets **7**{*1*−*14*}−**12**{*1*−*14*}

R	 **7**{*1-14*}, **10**{*1-14*}	 **8**{*1-14*}, **11**{*1-14*}	 **9**{*1-14*}, **12**{*1-14*}
	yield, % (acids/chlorides from the corresponding 5-aminopyrazoles)		
phenyl	90/81	80/56	55/47
4-methylphenyl	85/77	75/43	57/48
4-chlorophenyl	71/64	61/34	66/54
4-fluorophenyl	68/61	68/31	63/51
4-bromophenyl	70/56	60/44	62/47
4-methoxyphenyl	80/72	55/33	64/55
3-methoxyphenyl	83/75	73/55	51/40
2-methoxyphenyl	75/68	69/56	56/46
3,4-dichlorophenyl	64/58	57/43	64/55
3,4-dimethoxyphenyl	95/86	75/54	64/53
4-nitrophenyl	92/83	76/55	61/52
1,3-benzodioxol-5-yl	93/84	70/44	69/59
2-furyl	60/54	65/32	54/44
2-thienyl	62/56	61/26	66/58

The ^{1}H NMR spectra were clean, and LC/MS mass spectral data were also satisfactory.

The characteristic signals from protons of the pyrazolo[1,5-*a*]pyrimidine ring can be used for identification of the corresponding structures (Table 3). The pyrazolo[1,5-*a*]-pyrimidine protons H-2, H-3, and H-6 in acids **7**{*1*−*14*}, **8**{*1*−*14*}, and **9**{*1*−*14*} are sometimes concealed by other signals, but are usually clearly observed as singlets in the range of δ 8.50−8.65 ppm (H-2), δ 6.96−7.21 ppm (H-3), and δ 7.99−8.31 ppm (H-6). The same protons have resonances at δ 8.61−8.78, 6.88−7.11, and 8.02−8.32 ppm in the case of carboxamides **14**{*1*−*662*}, **15**(*1*−*355*}, and **16**{*1*−*420*}. Reduction of the pyrimidine ring leading to structures **17**{*1*−*450*}, **18**(*1*−*196*}, and **19**{*1*−*215*} usually causes a definite upfield shift for the H-2 ($\Delta\delta$ 0.65−0.70 ppm) and H-3 ($\Delta\delta$ 0.45−0.50 ppm) signals. As expected, the aromatic H-6 singlet disappears in the spectra of reduced compounds.

The preparation of such a significant number of compounds required utilization of a special laboratory equipment. Thus, all the described parallel solution-phase reactions were performed using laboratory synthesizers CombiSyn-012-3000.[16] The use of synthesizers of the CombiSyn family for efficient high-throughput solution-phase combinatorial synthesis is reported in a series of our recent papers.[17] All the workup, isolation, purification, and analytic procedures were carried out using a proprietary technology platform, which includes all the equipment required for parallel synthesis of large combinatorial libraries.[18]

Conclusion

An efficient synthetic route was developed for the combinatorial synthesis of pyrazolo[1,5-*a*]pyrimidine libraries in solution. In all of the reactions investigated, the corresponding libraries were generated with low levels of impurities using a simple crystallization from the reaction mixtures. The developed method uses readily available starting materials in mild and high yielding reactions that display a relatively high substituent tolerance and, therefore, is ideally suited for rapid synthesis of diverse libraries. Product yields varied according to reactant structures, but in most cases, the desired products were obtained in good to high yields, even using bulky side chain substituents with various functional groups. One disadvantage of the described strategy is that it requires relatively lengthy synthesis, leading to templates for the library generation steps. Biological evaluation of these pyrazolo[1,5-*a*]pyrimidines is currently in progress with respect to a number of GPCR and protein kinase biotargets and may lead to the design and synthesis of analogues possessing interesting physiological activity. The results

Scheme 4. Synthesis of Amide Libraries

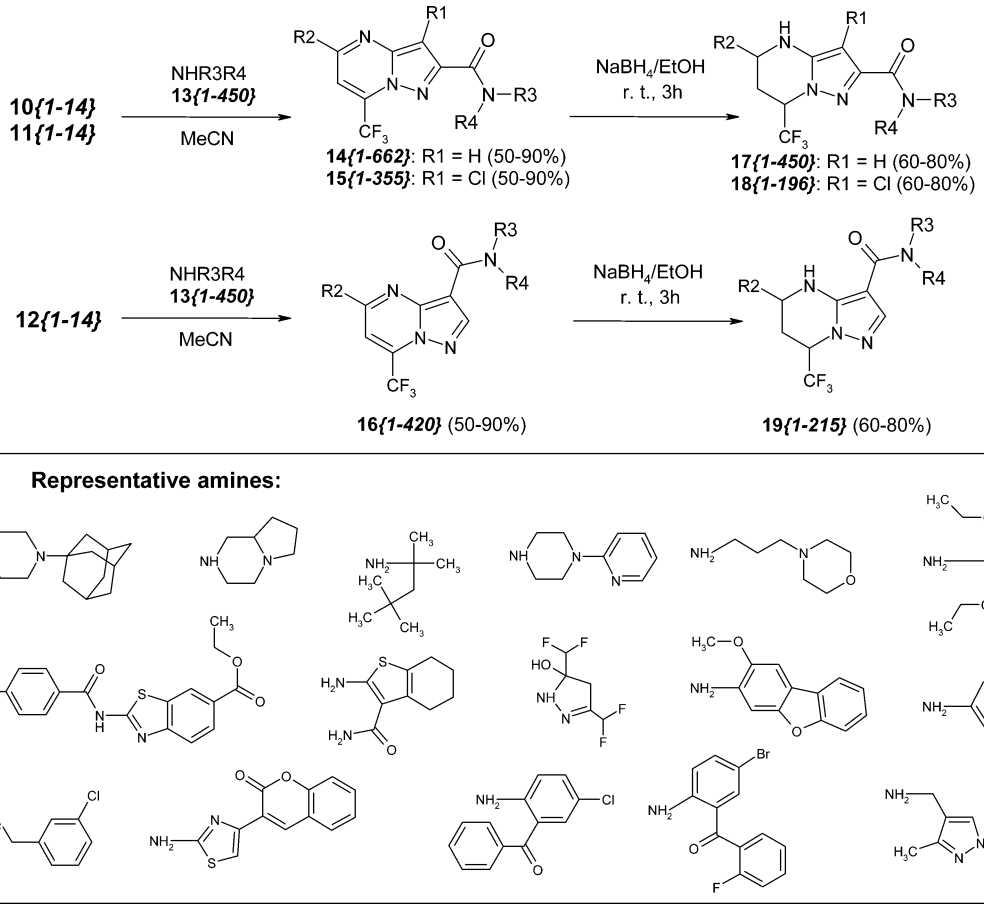


Table 2. Synthesis of Carboxamide Libraries **14**{*1*−*662*}, **15**(*1*−*355*}, and **16**{*1*−*420*} from Acid Chlorides **10**{*1*−*14*}, **11**{*1*−*14*}, **12**{*1*−*14*} and Different Types of Amines

	primary and secondary amines, benzylamines, *ortho*-methylaniline	substituted anilines, heteroarylamines	amine hydrochlorides
reaction conditions	2 mol equiv of amine, solvent MeCN, 20 min at 20 °C	1.05 mol equiv of amine, solvent MeCN, 5 min under reflux, then 12 h at 20 °C	1.05 mol equiv of amine hydrochloride, 2 mol equiv of Et_3N, solvent MeCN, 12 h at 20 °C
purification	crystallization from the reaction mixture, recrystallization from EtOH	crystallization from the reaction mixture, recrystallization from MeCN	crystallization from the reaction mixture, recrystallization from EtOH
yield	60−90%	80−90%	60−90%

provide confirmation of the scope and generality of the applied approach to pyrazolo[1,5-*a*]pyrimidines.

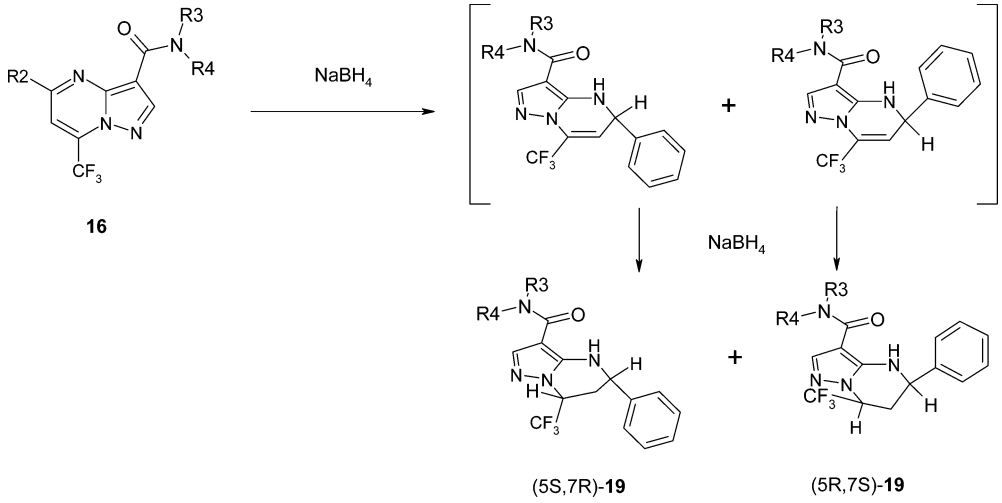
Experimental Section

General Information. Melting points (°C) were measured with Koeffler melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-400 and Varian spectrometers in DMSO-d_6 using TMS as an internal standard (chemical shifts in parts per million). LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a C_{18} column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. According to LC/MS data, all the synthesized compounds have purity >95%.

All solvents and reagents were obtained from commercial sources and were used without purification. 4-Ethoxycarbonyl-5-aminopyrazole **5c** was purchased from Aldrich. Other reagents were purchased from Acros Organics, Aldrich, or ChemDiv. The trifluoromethyl-β-diketones **6**{*1*−*14*} were obtained as reported.[14] 5-Amino-3-pyrazolecarboxylic acid **5a** and 5-amino-4-chloro-3-pyrazolecarboxylic acid **5b** were synthesized from 3-methylpyrazole using a modification of the reported procedure.[13] The parallel solution-phase syntheses of compounds **14**{*1*−*662*}, **15**(*1*−*355*}, and **16**{*1*−*420*} were accomplished using a laboratory synthesizer, CombiSyn-012-3000, on the 50−100-mg scale.

General Procedure for Synthesis of 2-Carboxy-7-trifluoromethylpyrazolo[5.1-a]pyrimidines 7{***1*−*14***} **and 2-Carboxy-3-chloro-7-trifluoromethylpyrazolo[5.1-a]pyrimidines 8**{***1*−*14***}**.** A suspension of amino acid **5a** or **5b**

Scheme 5



(1 mol) and diketone **6**{*1*−*14*} in acetic acid/aqueous 2 N HCl (1:1) (600 mL) was heated at reflux for 7 h. After cooling to room temperature, the formed precipitate was filtered off and recrystallized from MeCN to give pure **7**{*1*−*14*} in 60−90% yields. Acids **8**{*1*−*14*} prepared using this method contain up to 20% of the corresponding 5-trifluoromethyl isomers. The separation of pure 7-isomers can be achieved using recrystallization from the mixtures containing the corresponding acid chlorides **11**{*1*−*14*} synthesized at the next step.

5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic Acid 7{*1*}. mp 240−242 °C; ^{1}H NMR (500 MHz): δ 3.0−4.0 (s, 1H, COOH), 7.21 (s, 1H, ArH), 7.5 (d, J = 7.4 Hz, 3H, ArH), 8.05 (s, 1H, ArH), 8.25 (d, J = 7.5 Hz, 2H, ArH); ^{13}C NMR (125 MHz): δ 162.49 (COOH), 120.44 (CF_3), 2 × 127.59, 2 × 129.20, 131.46, 133.12 (phenyl), 100.26, 107.07, 135.03, 148.96, 149.21, 156.10 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 308 (M + 1).

5-Thien-2-yl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic Acid 7{*2*}. mp 255−257 °C; ^{1}H NMR (500 MHz): δ 3.1−4.2 (s, 1H, COOH), 7.20 (s, 1H, ArH), 7.29 (t, J = 5.4 Hz, 1H, ArH), 7.65 (d, J = 5.4 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 8.14 (d, J = 5.4 Hz, 1H, ArH); ^{13}C NMR (125 MHz): δ 164.31 (COOH), 120.46 (CF_3), 129.22, 141.82, 133.11, 134.21 (thiophene), 100.33, 107.11, 131.88, 148.99, 149.11, 152.76 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 314 (M + 1).

5-(4-Methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic Acid 7{*3*}. mp 250−251 °C; ^{1}H NMR (500 MHz): δ 3.83 (s, 3H, OCH_3), 7.02 (d, J = 8.4 Hz, 2H, ArH), 7.19 (s, 1H, ArH), 8.06 (s, 1H, ArH), 8.22 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (125 MHz): δ 162.98 (COOH), 120.42 (CF_3), 55.23, 2 × 114.62, 2 × 129.22, 133.43, 162.02 (4-methoxyphenyl), 100.02, 106.65, 127.87, 148.66, 149.23, 155.54 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 338 (M + 1).

5-(4-Fluorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-2-carboxylic Acid 7{*4*}. mp 218−220 °C; ^{1}H NMR (500 MHz): δ 2.75−3.38 (s, 1H, COOH), 7.21 (s, 1H, ArH), 7.25 (d, J = 8.2 Hz, 2H, ArH), 8.19 (s, 1H, ArH), 8.39 (m, 2H, ArH); ^{13}C NMR (125 MHz): δ 165.93 (COOH), 119.76 (CF_3), 162.43, 2 × 116.06, 2 × 129.99, 133.11 (4-fluorophenyl), 100.52, 107.10, 132.11, 149.06, 149.25, 155.54 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 326 (M + 1).

5-(4-Methylphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-2-carboxylic Acid 7{*5*}. mp 296−297 °C; ^{1}H NMR (500 MHz): δ 2.48 (s, 3H, CH_3), 7.20 (s, 1H, ArH), 7.31 (d, J = 7.8 Hz, 2H, ArH), 8.06 (s, 1H, ArH), 8.23 (d, J = 7.8 Hz, 2H, ArH); ^{13}C NMR (125 MHz): δ 162.98 (COOH), 120.42 (CF_3), 21.45, 2 × 127.52, 2 × 130.09, 133.40, 133.72 (4-methylphenyl), 100.12, 107.13, 142.07, 149.23, 149.56, 156.14 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 322 (M + 1).

5-(4-Chlorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-2-carboxylic Acid 7{*6*}. mp 223−225 °C; ^{1}H NMR (500 MHz): δ 2.4−3.5 (s, 1H, COOH), 7.21 (s, 1H, ArH), 7.51 (d, J = 8.4 Hz, 2H, ArH), 8.22 (s, 1H, ArH), 8.33 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (125 MHz): δ 164.53 (COOH), 119.69 (CF_3), 2 × 129.16, 2 × 129.29, 133.72, 134.54 (4-chlorophenyl), 100.92, 107.15, 136.71, 149.20, 149.25, 155.41 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 342 (M + 1).

3-Chloro-5-thien-2-yl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic Acid 8{*1*}. mp 250−251 °C; ^{1}H NMR (500 MHz): δ 3.0−4.0 (s, 1H, COOH), 7.20 (d, J = 7.6 Hz, 1H, ArH), 7.78 (d, J = 7.6 Hz, 3H, ArH), 8.2 (s, 1H, ArH), 8.22 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (125 MHz): δ 161.56 (COOH), 120.62 (CF_3), 129.23, 141.07, 133.21, 133.89 (thiophene), 101.57, 107.66, 132.22, 143.21, 145.56, 152.75 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 348 (M + 1).

3-Chloro-5-(4-methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic Acid 8{*2*}. mp 274−275 °C; ^{1}H NMR (500 MHz): δ 3.8 (s, 1H, OCH_3), 7.1 (d, J = 8.6 Hz, 2H, ArH), 8.18 (s, 1H, ArH), 8.29 (d, J = 8.6 Hz, 2H, ArH); ^{13}C NMR (125 MHz): δ 162.99 (COOH), 120.31 (CF_3), 55.76, 2 × 114.71, 2 × 129.98, 133.33, 162.55 (4-methoxyphenyl), 102.11, 108.32, 127.75, 143.86, 145.82, 156.24 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 372 (M + 1).

3-Chloro-5-(3,4-dimethoxyphenyl)-7-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine-2-carboxylic Acid 8{*3*}. mp 289−291 °C; ^{1}H NMR (500 MHz): δ 3.1−3.4 (s, 1H,

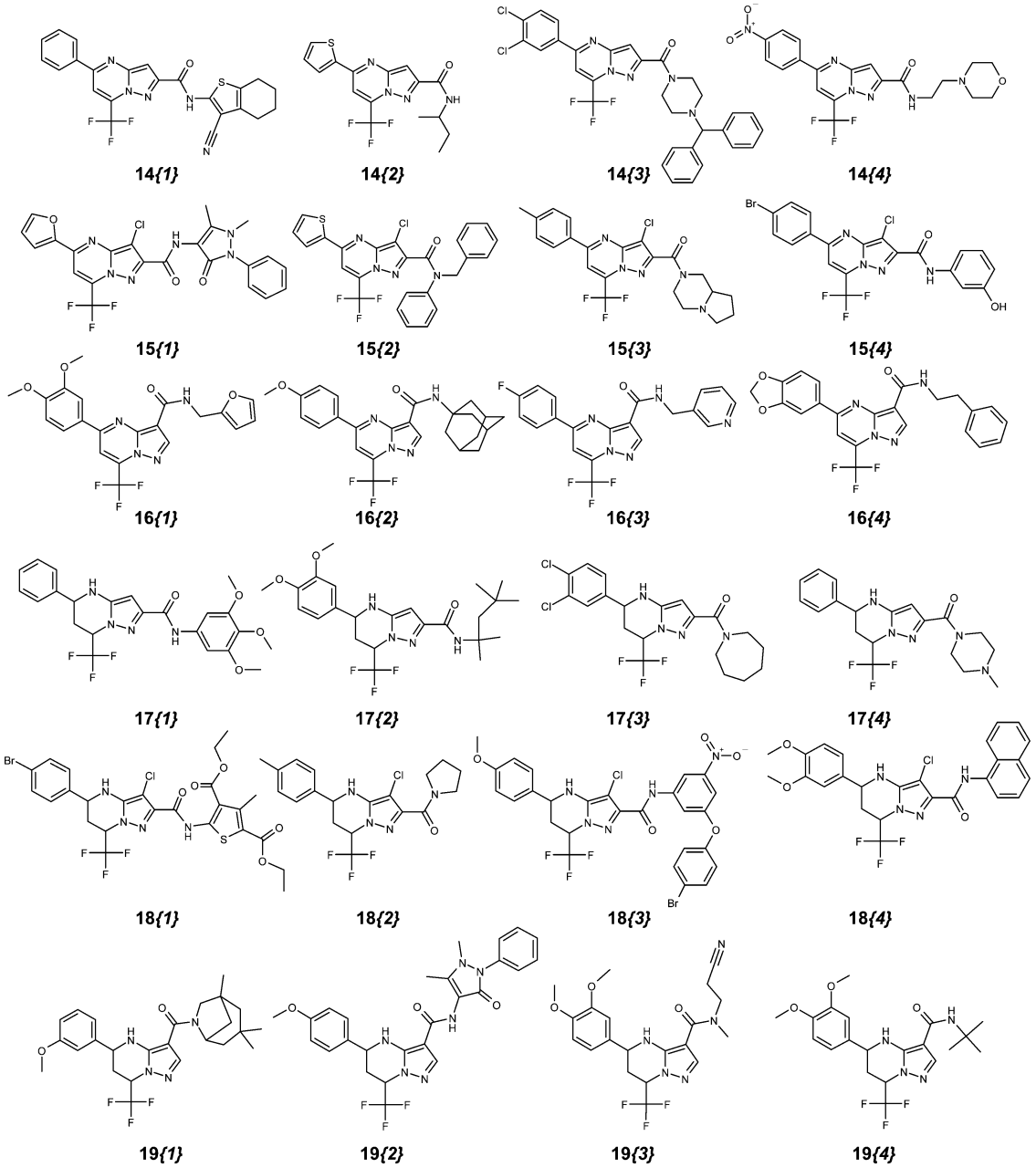


Figure 2. Examples of pyrazolo[1,5-*a*]pyrimidines synthesized in this work.

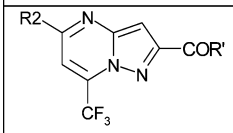
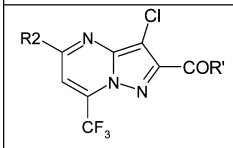
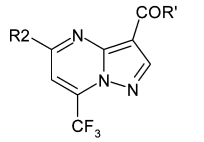
COOH), 3.9 (s, s, 6H, 2(OCH_3)), 7.12 (d, J = 8.8 Hz, 1H, ArH), 7.82 (s, 1H, ArH), 8.02 (d, J = 8.8 Hz, 1H, ArH), 8.28 (s, 1H, ArH); ^{13}C NMR (125 MHz): δ 161.97 (COOH), 119.55 (CF_3), 2 × 55.76, 110.12, 111.88, 122.35, 133.54, 149.25, 152.51 (3,4-dimethoxyphenyl), 102.01, 108.12, 127.15, 143.85, 145.32, 156.25 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 402 (M + 1).

General Procedure for Synthesis of 3-Carboxy-7-trifluoromethylpyrazolo[5.1-a]pyrimidines 9{*1*−*14*}. A solution of amino acid **5c** (1 mol) and diketone **6**{*1*−*14*} in acetic acid (500 mL) was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was poured onto ice (1.5 kg). The formed precipitate was filtered off, washed with water, and dried. The resulting ethyl carboxylate was added to a mixture of NaOH (56 g, 1.4 mol) in EtOH/water (1:3) (1200 mL), and the reaction mixture was kept at 60−70 °C for 4 h. The mixture was cooled to room temperature and acidified with concentrated HCl until pH 1 was reached. The formed precipitate was filtered off, washed with water, and recrystallized from MeCN to give pure **9**{*1*−*14*} in 50−70% yields.

5-(4-Fluorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-3-carboxylic Acid 9{*1*}. mp 252−253 °C; ^{1}H NMR (500 MHz): δ 2.35−2.55 (s, 1H, COOH), 7.25 (d, J = 8.2 Hz, 2H, ArH), 8.2 (s, 1H, ArH), 8.5 (m, 2H, ArH), 8.52 (s, 1H, ArH); ^{13}C NMR (125 MHz): δ 166.23 (COOH), 120.16 (CF_3), 163.41, 2 × 116.12, 2 × 130.27, 133.73 (4-fluorophenyl), 104.21, 106.33, 132.10, 145.66, 148.31, 155.14 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 326 (M + 1).

5-Thien-2-yl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid 9{*2*}. mp 272−273 °C; ^{1}H NMR (500 MHz): δ 2.8−3.2 (s, 1H, COOH), 7.23 (d, J = 7.4 Hz, 1H, ArH), 7.71 (d, J = 7.4 Hz, 1H, ArH), 8.21 (s, 1H,

Table 3. Characteristic ^{1}H NMR Signals (δ, ppm) of the Synthesized Compounds

Structure	R′=OH				R′=NR3R4			
	NN	H-2	H-3	H-6	NN	H-2	H-3	H-6
	**7***{1-14}*	–	6.96 - 7.21	8.05 - 8.31	**14***{1-662}*	–	6.88 - 7.11	8.02 - 8.32
	**8***{1-14}*	–	–	7.99 - 8.25	**15***{1-355}*	–	–	8.01 - 8.27
	**9***{1-14}*	8.50 - 8.65	–	8.01 - 8.29	**16***{1-410}*	8.61 - 8.78	–	8.11 - 8.26

ArH), 8.32 (d, J = 7.4 Hz, 1H, ArH), 8.53 (s, 1H, ArH); ^{13}C NMR (125 MHz): δ 162.51 (COOH), 120.23 (CF_3), 129.12, 141.82, 133.11, 134.21 (thiophene), 100.33, 107.11, 132.25, 148.99, 149.11, 152.76 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 314 (M + 1).

5-(4-Bromophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-3-carboxylic Acid 9{***3***}**.** mp 254−256 °C; ^{1}H NMR (500 MHz): δ 2 31−2.58 (s, 1H, COOH), 7.27 (d, J = 8.6 Hz, 2H, ArH), 8.24 (s, 1H, ArH), 8.51 (d, J = 8.6 Hz, 2H, ArH), 8.54 (s, 1H, ArH); ^{13}C NMR (125 MHz): δ 166.23 (COOH), 120.23 (CF_3), 126.15, 2 × 139.22, 2 × 130.27, 132.33 (4-fluorophenyl), 104.22, 106.33, 134.12, 147.71, 148.20, 157.22 (pyrazolo[1,5-*a*]pyrimidine); LC/MS *m*/*z* 387 (M+1).

General Procedure for Synthesis of Acid Chlorides 10{***1−14***}**, 11**{***1−14***}**, and 12**{***1−14***}**.** A suspension of acid **7**{*1−14*}, **8**{*1−14*}, or **9**{*1−14*} (1 mol) and $SOCl_2$ (1.5 mol) in CCl_4 (5 l) was heated at reflux until complete dissolution of the initial acid was reached (2−10 h). The mixture was cooled overnight at −20 °C, and the formed precipitate was filtered off and dried to afford pure chlorides **10**{*1−14*} and **12**{*1−14*}. The mother solution was concentrated in vacuo, and the crystallization procedure was repeated to furnish an additional amount of pure products. Combined yield 85−90%. Chlorides **11**{*1−14*} were additionally recrystallized from CH_2Cl_2 to give pure products in 50−70% yields.

General Procedure for Synthesis of Amide Libraries 14{***1−662***}**, 15(***1−355***}, and 16**{***1−420***}**. Method A (for Primary and Secondary Amines, Benzylamines, *ortho*-Methylaniline).** A solution of chloride **10**{*1−14*}, **11**{*1−14*}, or **12**{*1−14*} (1 mmol) and amine **13**{*1−450*} (2 mmol) in MeCN (10 mL) was stirred at room temperature for 20 min. The reaction mixture was poured into water (50 mL). The formed precipitate was filtered off and washed with water, aqueous ammonia, and EtOH. The recrystallization from EtOH affords pure amides in 60−90% yield.

Method B (for Substituted Anilines, Heteroarylamines). A solution of chloride **10**{*1−14*}, **11**{*1−14*}, or **12**{*1−14*} (1 mmol) and amine **13**{*1−450*} (1 mmol) in MeCN (10 mL) was heated at reflux for 5 min, cooled to room temperature, and stirred for 12 h. The reaction mixture was poured into water (20 mL). The formed precipitate was filtered off and washed with water, aqueous ammonia, and EtOH. The recrystallization from MeCN affords pure amides in 80−90% yield.

Method C (for Amine Hydrochlorides). A solution of chloride **10**{*1−14*}, **11**{*1−14*}, or **12**{*1−14*} (1 mmol), amine **13**{*1−450*} (1 mmol), and Et_3N (2 mmol) in MeCN (10 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water (50 mL). The formed precipitate was filtered off and washed with water, aqueous ammonia, and EtOH. The recrystallization from EtOH affords pure amides in 60−90% yield.

N′*-(Cyclopentylcarbonyl)-5-phenyl-7-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine-2-carbohydrazide 14**{1***}**.** ^{1}H NMR (500 MHz): δ 1.6 (m, 2H), 1.7−1.9 (m, 6H), and 2.75 (m, 1H) − cyclopentane, 7.2 (s, 1H, ArH), 7.5−7.63 (m, 3H, ArH), 8.1 (s, 1H, ArH), 8.26 (d, J = 7.5 Hz, 2H, ArH), 9.9 (s, 1H, NH), 10.09 (s, 1H, NH); LC/MS *m*/*z* 418 (M + 1).

N′*-(1,3-Benzodioxol-5-ylcarbonyl)-5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carbohydrazide 14**{2***}**.** ^{1}H NMR (500 MHz): δ 6.05 (s, 2H, CH_2), 6.85 (d, J = 7.2 Hz, 1H, ArH), 7.25 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.51−7.78 (m, 3H, ArH), 7.6 (d, 1H, ArH), 8.02 (s, 1H, ArH), 8.23 (d, J = 7.2 Hz, 2H, ArH); LC/MS *m*/*z* 470 (M + 1).

Methyl 2-({[5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-2-yl]carbonyl}amino)benzoate 14{***3***}**.** ^{1}H NMR (500 MHz): δ 3.85 (s, 3H, CH_3), 7.1 (t, J = 7.6 Hz, 1H, ArH), 7.3−7.7 (m, 4H, ArH), 8.06 (d, J = 7.4 Hz, 1H, ArH), 8.12 (s, 1H, ArH), 8.51 (d, J = 7.2 Hz, 2H, ArH), 8.70 (s, 1H, ArH), 8.69 (d, J = 7.4 Hz, 1H, ArH), 11.9 (s, 1H, NH); LC/MS *m*/*z* 441 (M + 1).

N*-[(1,5-Dimethyl-1*H*-pyrazol-4-yl)methyl]-5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide 14**{4***}**.** ^{1}H NMR (500 MHz): δ 2.25 (s, 3H, CH_3), 3.74

(s, 3H, NCH_3), 4.4 (d, $J = 5.2$ Hz, 2H, CH_2), 7.3 (s, 1H, ArH), 7.61 (m, 3H, ArH), 8.01 (t, $J = 7.6$ Hz, 1H, ArH), 8.19 (s, 1H, ArH), 8.21 (d, $J = 7.4$ Hz, 2H, ArH), 8.58 (s, 1H, ArH); LC/MS *m*/*z* 415 (M + 1).

5-(4-Bromophenyl)-*N*-butyl-3-chloro-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide 15{*1*}. ^{1}H NMR (500 MHz): δ 1.05 (d, $J = 7.2$ Hz, 3H, CH_3), 1.27−1.7 (2m, 4H, $(CH_2)_2$), 3.35 (m, 2H, CH_2), 7.68 (d, $J = 8.2$ Hz, 2H, ArH), 8.2 (s, 1H, ArH), 8.34 (d, $J = 8.2$ Hz, 2H, ArH); LC/MS *m*/*z* 476 (M + 1).

3-Chloro-5-(4-methoxyphenyl)-*N*-(3-morpholin-4-ylpropyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide 15{*2*}. ^{1}H NMR (500 MHz): δ 1.8 (t, $J = 6.4$ Hz, 2H, CH_2), 2.3−2.5 (m, 6H, $N(CH_2)_3$), 3.41 (d, $J = 6.2$ Hz, 2H, $NHCH_2$), 3.61 (m, 4H, $O(CH_2)_2-$), 7.02 (d, $J = 8.4$ Hz, 2H, ArH), 8.09 (s, 1H, ArH), 8.31 (d, $J = 8.4$ Hz, 2H, ArH); LC/MS *m*/*z* 498 (M + 1).

Methyl 2-({[3-chloro-5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-2-yl]carbonyl}amino)benzoate 15{*3*}. ^{1}H NMR (500 MHz): δ 4.01 (s, 3H, $-CH_3$), 7.15, 7.5−7.65 (t, $J = 7.4$ Hz, m, 5H, ArH), 8.01 (d, $J = 7.5$ Hz, 1H, ArH), 8.17 (s, 1H, ArH), 8.35 (d, $J = 7.5$ Hz, 2H, ArH), 8.91 (d, $J = 7.5$ Hz, 1H, ArH), 12.2 (s, 1H, NH); LC/MS *m*/*z* 475 (M + 1).

***N*-[2-(Benzylamino)ethyl]-5-phenyl-7-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine-3-carboxamide 16{*1*}.** ^{1}H NMR (500 MHz): δ 2.32 (s, 3H, $-CH_3$), 1.71, (t, $J = 5.7$ Hz, 2H, NCH_2), 3.60 (m, 4H, $(CH_2)_2$), 7.01 (m, 3H, ArH), 7.2 (d, $J = 7.5$ Hz, 2H, ArH), 7.38−7.5 (m, 3H, ArH), 8.18 (s, 1H, ArH), 8.3 (d, $J = 7.5$ Hz, 2H, ArH), 8.6 (s, 1H, ArH); LC/MS *m*/*z* 440 (M + 1).

***N*-Allyl-5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide 16{*2*}.** ^{1}H NMR (500 MHz): δ 4.12 (t, $J = 5.7$ Hz, 2H, $C{=}CH_2$), 5.1, 5.25 (2d, $J = 5.0$ Hz, 2H, NCH_2-), 6.0 (m, 1H, $CH{=}C$), 7.6 (m, 3H, ArH), 8.21 (s, 1H, ArH), 8.31 (d, $J = 7.5$ Hz, 2H, ArH), 8.6 (s, 1H, ArH); LC/MS *m*/*z* 347 (M + 1).

General Procedure for Synthesis of 4,5,6,7-Tetrahydropyrazolo[1,5-*a*]pyrimidine Carboxamides 17{*1*−*450*}, 18(*1*−*196*}, and 19{*1*−*215*}. $NaBH_4$ (3 mmol) was slowly added to a solution of amide **14**{*1*−*14*}, **15**{*1*−*14*}, or **16**{*1*−*14*} (1 mmol) in EtOH (5 mL) at room temperature. The reaction mixture was heated at reflux for 20 min, cooled, and kept at room temperature for 12 h. The excess of $NaBH_4$ was decomposed by addition of acetic acid. The reaction mixture was poured into water (25 mL). The formed precipitate was filtered off, washed with water, and dried. The recrystallization from EtOH affords pure amides **17**{*1*−*450*}, **18**(*1*−*196*}, and **19**{*1*−*215*} in 60−90% yield.

5-(3-Methoxyphenyl)-7-(trifluoromethyl)-*N*-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-2-carboxamide 17{*1*}. ^{1}H NMR (500 MHz): δ 2.21 and 2.53 (q, $J = 6.6$ Hz, d, $J = 6.1$ Hz, 2H, CH_2), 3.6, 3.76 (2s, 12H, CH_3), 4.64 (d, $J = 9.5$ Hz, 1H, CHPh), 5.1 (m, 1H, $CHCF_3$), 6.61 (s, 1H, NH), 6.81 (d, $J = 7.4$ Hz, 1H, ArH), 7.02 (s, 1H, ArH), 7.06 (d, $J = 7.4$ Hz, 1H, ArH), 7.1 (s, 2H, ArH), 7.3 (t, $J = 7.6$ Hz, 1H, ArH), 8.1 (s, 1H, ArH), 9.25 (s, 1H, NHCO); LC/MS *m*/*z* 421 (M + 1).

***N*-(4-Chlorophenyl)-5-(3-methoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-2-carboxamide 17{*2*}.** ^{1}H NMR (500 MHz): δ 2.20 and 2.52 (q, $J = 6.7$ Hz, d, $J = 6.2$ Hz, 2H, CH_2), 3.81 (s, 3H, CH_3), 4.63 (d, $J = 9.4$ Hz, 1H, CHPh), 5.13 (m, 1H, $CHCF_3$), 6.81 (d, $J = 7.4$ Hz, 1H, ArH), 7.02 (s, 1H, ArH), 7.04 (d, $J = 7.4$ Hz, 1H, ArH), 7.18 (d, $J = 8.4$ Hz, 2H, ArH), 7.27 (t, $J = 7.6$ Hz, 1H, ArH), 7.7 (d, $J = 8.4$ Hz, 2H, ArH), 8.08 (s, 1H, ArH), 9.5 (s, 1H, NHCO); LC/MS *m*/*z* 451 (M + 1).

***N*-(4-Chloro-2,5-dimethoxyphenyl)-5-(3-methoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-2-carboxamide 17{*3*}.** ^{1}H NMR (500 MHz): δ 2.15 and 2.61 (q, $J = 6.7$ Hz, d, $J = 6.2$ Hz, 2H, CH_2), 3.8, 3.86 (2s, 9H, CH_3), 4.66 (d, $J = 9.5$ Hz, 1H, CHPh), 5.11 (m, 1H, $-CHCF_3$), 6.81 (d, $J = 7.2$ Hz, 1H, ArH), 6.90 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.04 (d, $J = 7.2$ Hz, 1H, ArH), 7.26 (t, $J = 7.5$ Hz, 1H, ArH), 7.82 (s, 1H, ArH), 8.0 (s, 1H, ArH), 9.4 (s, 1H, NHCO); LC/MS *m*/*z* 511 (M + 1).

5-(3-Methoxyphenyl)-7-(trifluoromethyl)-*N*-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-2-carboxamide 17{*4*}. ^{1}H NMR (500 MHz): δ 2.14 and 2.60 (q, $J = 6.7$ Hz, d, $J = 6.3$ Hz, 2H, CH_2), 3.82 (s, 3H, CH_3), 4.69 (d, $J = 9.4$ Hz, 1H, CHPh), 5.10 (m, 1H, $CHCF_3$), 6.81 (d, $J = 7.4$ Hz, 1H, ArH), 7.02 (s, 1H, ArH), 7.04 (d, $J = 7.4$ Hz, 1H, ArH), 7.22 (d, $J = 7.4$ Hz, 1H, ArH), 7.28 (t, $J = 7.6$ Hz, 1H, ArH), 7.4 (t, $J = 7.6$ Hz, 1H, ArH), 7.92 (d, $J = 8.4$ Hz, 1H, ArH), 8.02 (s, 1H, ArH), 8.13 (d, $J = 8.4$ Hz, 1H, ArH), 9.7 (s, 1H, NHCO); LC/MS *m*/*z* 485 (M + 1).

3-Chloro-5-(4-methylphenyl)-2-(pyrrolidin-1-ylcarbonyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine 18{*2*}. ^{1}H NMR (500 MHz): δ 2.05 (m, 4H) and 3.37 (m, 4H) − pyrrolidine, 2.52 (s, 3H, CH_3), 2.12 and 2.59 (q, $J = 6.5$ Hz, d, $J = 6.2$ Hz, 2H, CH_2), 3.80 (s, 3H, CH_3), 4.5 (d, $J = 9.5$ Hz, 1H, CHPh), 5.11 (m, 1H, $CHCF_3$), 7.61 (d, $J = 7.4$ Hz, 2H, ArH), 8.11 (d, $J = 7.4$ Hz, 2H, ArH), 7.04 (s, 1H, ArH), 9.7 (s, 1H, NH); LC/MS *m*/*z* 413 (M + 1).

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Supporting Information Available. ^{1}H NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385−15444.

(2) (a) Devlin, J. P. *High Throughput Screening: The Discovery of Bioactive Substances*; Marcel Dekker: New York, 1997. (b) Gordon, E. M.; Kerwin, J. F., Jr. *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Wiley: New York, 1998.

(3) (a) An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311−3340. (b) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214.

(4) Tomcufcik, A. S.; Albright, J. D.; Dusza, J. P. U.S. Patent 4654347, 1987; *Chem. Abstr*. **1985**, *25*, 220889m.

(5) (a) Chen, Y. L. JP Patent 2000502723; *Chem. Abstr*. **1998**, *17*, 20490s. (b) Dusza, J. P.; Albright, J. D.; Tomcufcik, A. S. U.S. Patent 5538977, 1996; *Chem. Abstr*. **1996**, *13*, 168011c.
(6) Boes, M.; Stadler, H.; Riemer, C. U.S. Patent 6194410, 2001; *Chem. Abstr*. **1999**, *16*, 214304z.
(7) O'Donnell, P. B.; Thiele, W. J. U.S. Patent 6384221, 2002; *Chem. Abstr*. **2001**, *15*, 212744f.
(8) (a) Kendall, R. L.; Rubino, R.; Rutledge, R.; Bilodeau, M. T.; Fraley, M. E.; Thomas, K. A., Jr.; Hungate, R. W. U.S. Patent 6235741, 2001; *Chem. Abstr*. **1999**, *4*, 033028w. (b) Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebben, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2767−2770.
(9) Inoue, T.; Kawarai, Y.; Ogawa, S. JP Patent 2003286171, 2003; *Der. Abstr*. **2004**, 12780.
(10) Van Rhee, M. A.; Atkinson, R. N.; Gross, M. F. WO Patent 0337900, 2003.
(11) For recent reviews, see: Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613−7632. Prakash, G. K. S.; Yudin, A. K. *Chem. Rev*. **1997**, *97*, 757−786. Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757−1777. Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189−276.
(12) (a) Emelina, E. E.; Petrov, A. A.; Firsov, A. V. *Russ. J. Org. Chem.* **2001**, *37*, 852−858. (b) Chern, J.-W.; Lee, C.-C.; Liaw, Y.-C. W.; Andrew H.-J. *Heterocycles* **1992**, *34*, 1133−1145. (c) Balicki, R. *Pol. J. Chem.* **1983**, *57*, 1251−1261. (e) Auzzi, G.; Costanzo, A.; Bruni, F.; Clauser, M.; Guerrini, G.; Selleri, S.; Pecori Vettori, L. *Farmaco* **1990**, *45*, 1193−1205. (f) Bruni, F.; Chimichi, S.; Cosimelli, B.; Costanzo, A.; Guerrini, G.; Selleri, S. *Heterocycles* **1990**, *31*, 1141−1149. (g) Elnagdi, M. H.; Erian, A. W. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1854−1856. (h) Abdelrazek, F. M. *J. Prakt. Chem.* **1989**, *331*, 475−478. (i) Hussain, S. M.; El-Reedy, A. M.; El-Sharabasy, S. A. *Tetrahedron* **1988**, *44*, 241−246. (j) Ried, W.; Aboul-Fetouh, S. *Tetrahedron* **1988**, *44*, 7155−7162. (k) Ho, Y.-W. *J. Chin. Chem. Soc.* (*Taipei*) **1999**, *46*, 955−962.
(13) (a) Shevelev, S. A.; Dalinger, I. L. *Zhurn. Org. Khim.* (*Russ. J. Org. Chem.*) **1998**, *34*, 1127−1136. (b) Shevelev, S. A.; Vinogradov, V. M.; Dalinger, I. L.; Cherkasova, T. I. *Izv. Akad. Nauk Khim.* (*Proc. Rus. Acad. Sci. Chem.*) **1993**, *11*, 1945−1948.
(14) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, *11*, 1321−1324.
(15) For examples, see: (a) Gribble, G. W. *Chem. Soc. Rev*. **1998**, *27*, 395−404. (b) Enders, D.; Thiebes, C. *Pure Appl. Chem*. **2001**, *73*, 573−578. (c) Windey, G.; Seper, K.; Yamamoto, J. H. *PharmaChem* **2002**, *9*, 15−18.
(16) Baru, M.; Ivachtchenko, A. Russian Patent 2,180,609, 2002; Patent PCT WO 02/087740 A1, 2002; *Chem. Abstr.* **2003**, *138*, 014907f.
(17) (a) Ivachtchenko, A. V.; Kovalenko, S. M.; Drushlyak, O. G. *J. Comb. Chem*. **2003**, *5*, 775−788. (b) Ivachtchenko, A.; Kovalenko, S.; Drushlyak, O. *Heterocycl. Commun*. **2002**, *8*, 233−236. (c) Ivachtchenko, A. V.; Il'yin, A. P.; Kobak, V. V.; Zolotarev, D. A.; Guro, L. V.; Trifilenkov, A. S.; Ugoleva, D. M. *J. Comb. Chem.* **2002**, *4*, 419−428.
(18) For a description of this equipment, see: Technology Platform. In *Custom Chemistry*; Chemical Diversity Labs, Inc.: San Diego, CA, 2002; p 5. Available at http://www.chemdiv.com.

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