Pyrazolo[1,5-*a*]pyrimidines. Identification of the Privileged Structure and Combinatorial Synthesis of 3-(Hetero)arylpyrazolo[1,5-*a*]pyrimidine-6-carboxamides

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The pyrazolo[1,5-*a*]pyrimidine class of compounds has been identified as a privileged structure for library synthesis on the basis of several key characteristics of the core molecule. A chemical set in excess of 400 compounds was synthesized to give 3,6,7-substituted pyrazolo[1,5-*a*]pyrimidinecarboxamides **9**. To facilitate the rapid preparation of this library, a preparative strategy included the synthesis of activated *p*-nitrophenyl esters, followed by subsequent scavenging of the *p*-nitrophenol leaving group. Excess reagents were also removed using scavenging reagents that were found to be compatible with the synthetic methodology and that afforded target compounds in acceptable purity and yields.

Introduction

Since its introduction by Evans[1] in 1988, the concept of privileged structures has had a tremendous impact on modern drug discovery. Privileged structures, which by definition are "certain select structures [that] are able to provide high affinity ligands for more than one type of receptor", have been successfully used to design a variety of clinical candidates.[2a−c] This strategy was extensively used with heterocyclic scaffolds, including 1,4-benzodiazepin-2-ones,[1] dihydropyridines,[3] isoxazoles,[4] indoles,[2a,5a,b] and tetrazoles.[6] It was further used for the development of natural-product-like heterocyclic combinatorial libraries.[7a,b]

Privileged structures (PS) are typically rigid polycyclic heteroatomic systems, which orient diverse substituents in well-defined 3-dimensional space. Several such fused [5 + 6], [6 + 6], and [7 + 6] ring systems have recently been identified. Privileged [5 + 6] bicyclic ring systems are usually limited to *benzo*-annulated structures and include indoles, benzimidazoles, benzofurans, and benzothiophenes.[8] However, heterocyclic bicyclic [5 + 6] ring systems are also of interest and are the focus of our work.

Given the important contribution of the privileged structure concept to medicinal chemistry, the identification of cores that are based on unique chemotypes is of great importance. These unique chemotypes, together with modern parallel synthetic chemistry techniques and rational diversity selection through computational chemistry input, offers a powerful tool to help identify new lead candidates. Herein, we report the selection of the pyrazolo[1,5-*a*]pyrimidine ring system (Figure 1) as a novel privileged structure. The development of a robust synthetic protocol that facilitated the development of a unique compound set using this structural motif was the primary goal of the investigation. A synthetic route to 3,6,7-substituted pyrazolo[1,5-*a*]pyrimidinecarboxamides **9** with two major points of diversity at positions 3 and 6 and the generation of 426-member compound library are presented.

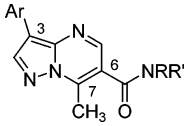

Figure 1. General substitution pattern of 3,6,7-substituted pyrazolo-[1,5-*a*]pyrimidinecarboxamide core scaffold.

Results and Discussion

Identification of the Privileged Structure. The advantage of a privileged structural subunit is the ability to synthesize an array of compounds based on the core scaffold and screen it against a variety of different targets. The ultimate success of this approach depends on the proper choice of the structural motif to be used as a library scaffold. The core scaffold should meet several key requirements: (i) activity toward diverse biological targets, (ii) a rigid ring system which presents substituents to target-binding sites in a well-defined fashion,[7a] (iii) the capacity to incorporate a variety of substituents as a diversity set, and (iv) obedience to the "Rule of 3" for core molecular weight and lipophilicity, allowing for broad variations on hit-to-lead and lead-optimization steps. A literature search of pyrazolo[1,5-*a*]-pyrimidines uncovered biological studies targeted on corticotropin-releasing factor (CRF),[9a−d] GABA and GABAA receptors,[10a−j] peripheral benzodiazepine receptor,[11a−d] 5HT receptors,[12] potassium channel,[13a,b] and histamine-3 receptor[14] ligands. Pyrazolo[1,5-*a*]pyrimidine compounds have the potential to be efficacious in therapeutic areas such as psychopharmacology (treatment of sleep disorders, anxiolytics, antidepressants)[10a,15a−c] and as analgesics,[14,16] fungicides,[17] antibacterial,[18] anti-inflammatory, antitumor, and antidiabetic agents.[14] Pyrazolo[1,5-*a*]pyrimidines with 5,6-, 6,7-, 3,7-, and 2,5,6-substitution patterns have been com-

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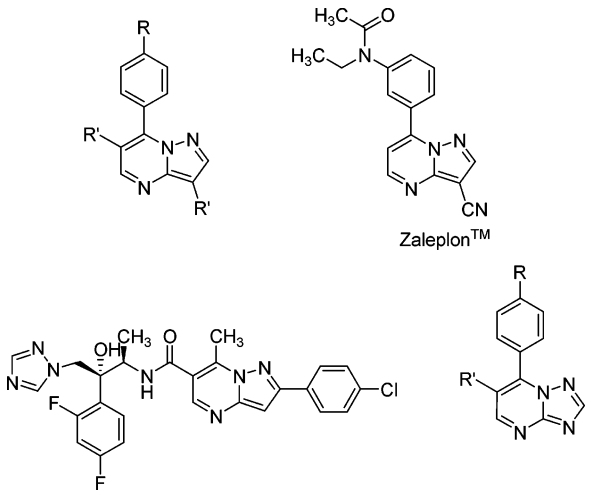


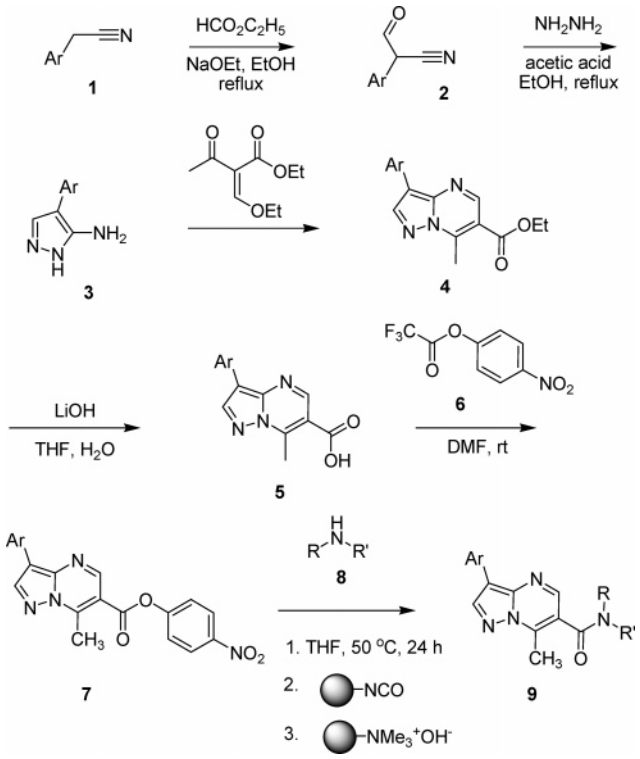
Figure 2. Analogs of pyrazolo[1,5-a]pyrimidines showing biological activity.

monly represented in the chemical literature (Figure 2).[19−22] *N*-[3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl-*N*-ethylacetamide, Zaleplon, is an approved pharmaceutical for treatment of insomnia.[23a−c] 3-Triazolyl-2-aryl-1-methylpropan-2-ol derivatives of 3-pyrazolo[1,5-*a*]pyrimidine-6-carboxamides have been reported as antifungals, and were proved to be superior to Fluconazole in murine models of candidosis, coccidioidomycosis, cryptococcosis, and histoplasmosis.[24a] Most recently, pyrazolo[1,5-*a*]pyrimidines were described as KDR kinase inhibitors[24b] with the emphasis on 3- and 6-substitution of the ring system. Further developments around this ring system have included 3,6,7-substituted derivatives and related 1,2,4-triazolo[1,5-*a*]- and imidazo-[1,2-*a*]-bioisosters[25] as structural analogues of Zaleplon, which were designed to selectively bind to the subtype BZ_1 benzodiazepine receptor.

Pyrazolo[1,5-*a*]pyrimidines represent a rigid bicyclic aromatic system which allows for structural modifications at positions 2, 3, and 5−7 during ring-construction and side-chain modification steps.[26] These structural characteristics, together with a molecular weight of 119 amu and *c* log *P* value of 0.5, give vast opportunities for scaffold modification and optimization within druglike chemical space. Therefore, we identified the pyrazolo[1,5-*a*]pyrimidine subunit containing the requirements for a privileged structure around which to elaborate a compound library that is likely to generate perspective chemical entities for drug discovery.

Scaffold Synthesis. We have specifically identified 3,6,7-substituted pyrazolo[1,5-*a*]pyrimidinecarboxamides **9** as our target core of interest for library diversification. The synthetic route used (Scheme 1) generates pyrazolo[1,5-*a*]pyrimidines with aryl substitution at the 3-position, substituted carboxamide moieties at the 6-position, and a methyl group in the 7-position. Specifically, aryl-substituted acetonitriles (Scheme 1) were treated with ethylformate in toluene in the presence of sodium methoxide to give the corresponding α-formylarylacetonitriles (**2**{*1*−*9*}) which were used without purification. Key intermediates, 4-aryl-2*H*-pyrazol-3-ylamines **3**{*1*−*9*}, were prepared by the treatment of **2**{*1*−*9*} with hydrazine and glacial acetic acid as described in the literature.[27a−f] Ethyl 2-ethoxymethylene-3-oxobutyrate, prepared according to a known procedure,[28] was used as the dielectrophile for the pyrimidine ring-formation step. Subsequent saponification afforded acids **5**{*1*−*9*} which were characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as LRMS.

Scheme 1. General Synthetic Scheme Used in the Preparation of 3,6,7-Substituted Pyrazolo-[1,5-*a*]pyrimidinecarboxamides.



Library Synthesis. Initial attempts at standard carboxamide bond formation between intermediate **5** and amines using standard coupling reagents (EDC, DCC, or BOP) or carboxy group activation (acyl chloride) were unsuccessful because of the low solubility characteristic of **5**{*1*−*9*} in conventional solvents. Because this final step of the synthesis needed to be completed in a parallel high-throughput manner, we set out to identify an alternative strategy. Activated *p*-nitrophenyl esters **7**{*1*−*9*} were easily prepared from **5**{*1*−*9*} with *p*-nitrophenyltrifluoroacetate **6** and pyridine in solution with *N*,*N*-dimethylformamide as the solvent at 80 °C for 6 h.[29a−h] Activated scaffolds **7**{*3*−*9*} were characterized by ^{1}H NMR and LRMS, while scaffolds **7**{*1*} and **7**{*2*} were used directly without further purification. It is noteworthy to mention that intermediates **7**{*1*−*9*} proved to be very suitable reagents for parallel synthesis as they are stable, easy to handle, and of high solubility.

All parallel synthetic reactions were conducted in 96-well 1.2 mL polypropylene plates. Treatment of **7**{*1*−*9*} (200 μmol) with a 1.5-fold excess of amines **8**{*1*−*50*} (300 μmol) in the presence of triethylamine (300 μmol) was determined to give optimal conversion to the desired amides. The selection of amines **8**{*1*−*50*} included the variety of aliphatic, substituted benzyl, and phenethylamines (Figure 4).

Carboxamide bond formation was usually complete after 8−10 h at 50 °C; however to ensure reaction completion,

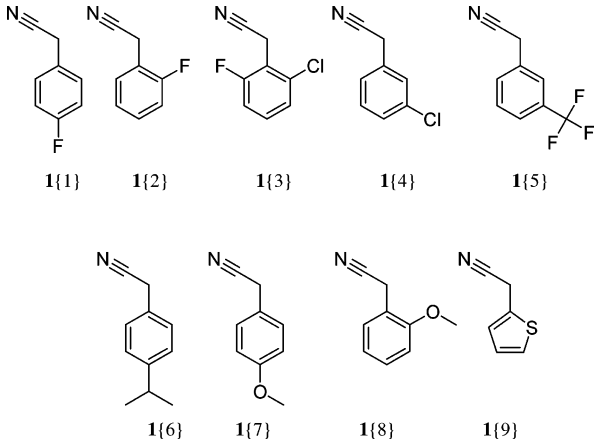


Figure 3. Reagent set of aryl-substituted acetonitriles used to incorporate diversity at the 3-substitution position of the 3,6,7-pyrazolo[1,5-*a*]pyrimidinecarboxamides **9**.

plates were agitated for 24 h. In most cases, LC/MS and TLC analysis of the crude reaction mixtures indicated that all starting activated esters **7** were converted to **9** and that the only other components of the reaction mixture were excess amine **8**, *p*-nitrophenol, and triethylamine. The workup and purification protocol (Scheme 1) included scavenging of *p*-nitrophenol with strongly basic Dowex 550A OH resin and the simultaneous removal of unreacted amines with isocyanate resin. Final purification was achieved by passing the resultant reaction mixture through pad of silica gel. This rapid purification synthetic strategy resulted in the preparation of a diverse library of 3,6,7-substituted pyrazolo-[1,5-*a*]pyrimidinecarboxamides **9**{*1*−*9, 1*−*50*}; 426 compounds (94.6%) were above 85% purity with an average HPLC purity (UV at 220 nm) of 97% and 35 mg weight. The purity and identity of compounds were confirmed by LC/MS analysis of all of the library products, as well as ^{1}H NMR analysis of 10% of the products. The library of substituted 3,6,7-pyrazolo[1,5-*a*]pyrimidinecarboxamides is likely to have good physicochemical properties on the basis

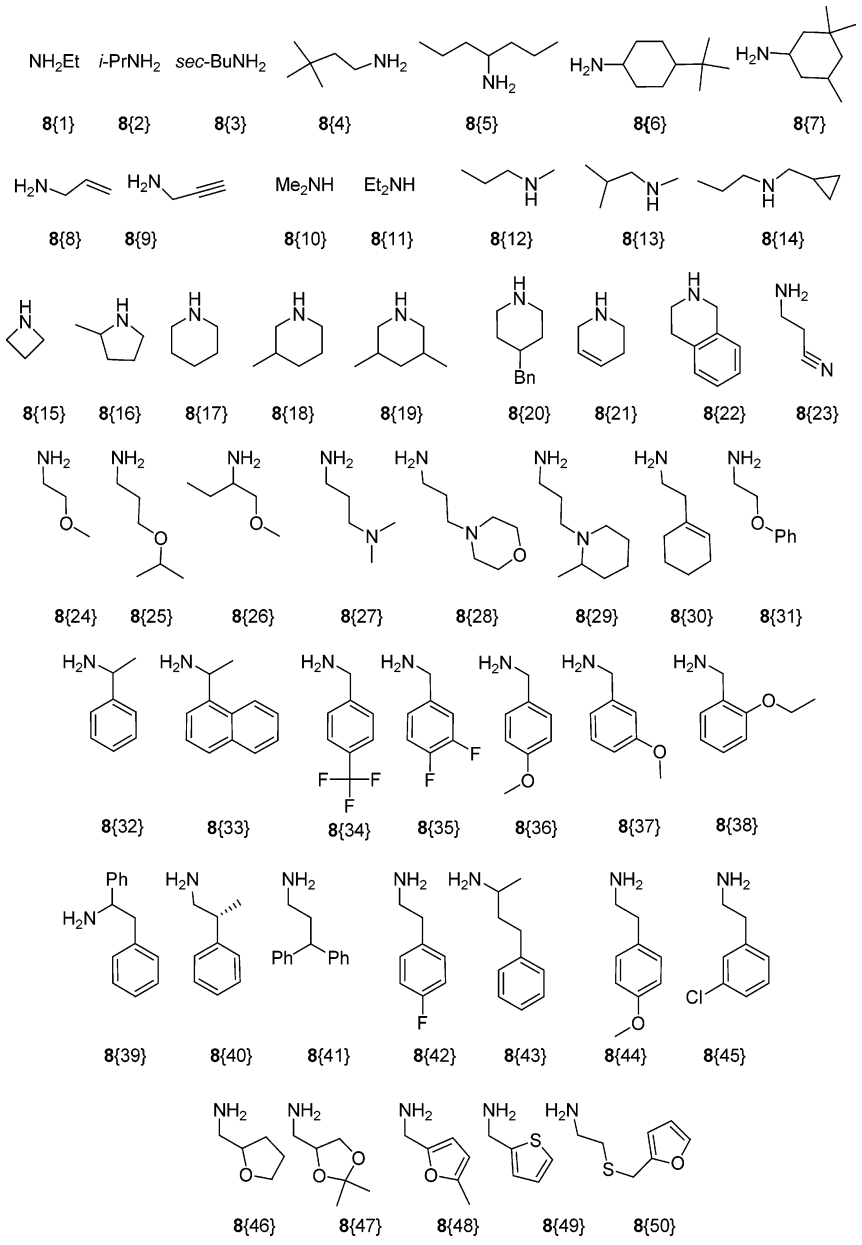


Figure 4. Reagent set of amines used to incorporate diversity at the 6-position of the 3,6,7-pyrazolo[1,5-*a*]pyrimidinecarboxamides **9**.

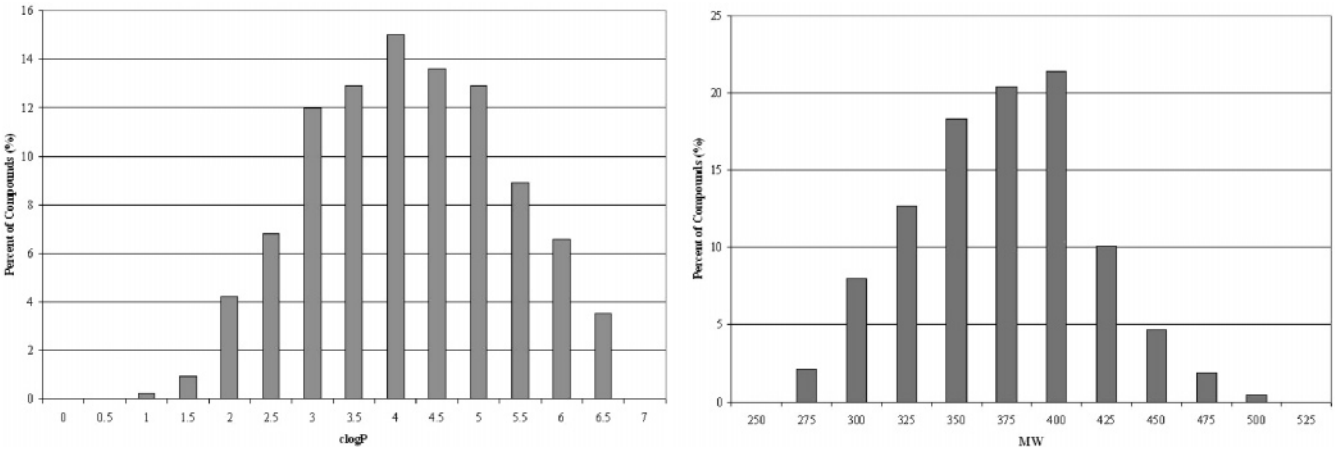


Figure 5. *c* log *P* and molecular weight distribution analysis of the 426 compounds composing the substituted 3,6,7-pyrazolo[1,5-*a*]-pyrimidinecarboxamides **9** library.

of the *c* log *P* distribution (2−5 units) and molecular weight distribution (325−500 amu) as depicted in Figure 5.

Conclusion

Numerous literature references cite the capability of pyrazolo[1,5-*a*]pyrimidine to bind to multiple receptors with high affinity, and by definition, this satisfies the term privileged structure that was first reported in 1988 by Evans et al.[1] Compounds based on this scaffold have the potential to be viable chemical entities for drug discovery. In summary, we have developed a robust solution-phase synthesis method for the preparation of 3,6,7-substituted pyrazolo[1,5-*a*]-pyrimidinecarboxamides **9** containing a methyl moiety in the 7-position, aryl substitution in the 3-position, and amides in the 6-position of the ring system. A key to the synthetic strategy to overcome the insoluble nature of the carboxylic acid-containing intermediates was the conversion to more synthetically amenable activated *p*-nitrophenylesters. Subsequent scavenging of the leaving group with basic resin and removal of excess reagent with PS-isocyanate resin afforded target compounds in high purity and yields.

Experimental Section

General Information. All solvents and reagents were obtained from commercial sources and used without further purification. Nitriles **1**{*1*−*9*} were purchased from Sigma-Aldrich Co. *p*-Nitrophenyl trifluoroacetate (**6**) was purchased from Sigma-Aldrich Co. and Lancaster; amines **8** were from Acros Organics and Sigma-Aldrich Co. Biorad AG-50W-X2 and DOWEX 550A OH resins were purchased from Sigma-Aldrich Co.

The LCMS data were recorded on a Perkin-Elmer Sciex single-quadropole mass-spectrometer with 254 nm detection using a Phenomenex Luna, 5 μm C8 column (100 × 4.60 mm). Two mobile phases (A 99.98% water, 0.02% TFA; B 99.98% acetonitrile, 0.02% TFA) were used as a gradient from 30 to 95% B in 4.0 min and 30% B for 2.0 min with a flow rate of 2.0 mL/min. ^{1}H NMR spectra were recorded in 5 mm tubes on a 300 MHz Bruker Avance in DMSO-d_6. Chemical shifts are reported in δ units (ppm) downfield from TMS as an internal standard. Pyrazolo[1,5-*a*]pyrimidine acids **5** were prepared according to known procedures,[27a−f] and they were characterized with ^{1}H and ^{13}C NMR and LRMS.

Synthesis of the library was performed in 96-well plates. The products were transferred into tared bar-coded vials using an Apogent Matrix 6-channel pipet (Portsmouth, NH) and weighed using the Mettler-Toledo Bohdan USP (Mt. Vernon, IL).

General Procedure for the Preparation of α-Formylarylacetonitriles 2. A fresh solution of sodium ethoxide was prepared by dissolution of sodium (2.73 g, 119 mmol) in ethanol (150 mL). The mixture was then cooled to 0 °C, and the appropriate acetonitrile (108 mmol) was added; then the mixture stirred for 5 min, followed by the addition of ethyl formate (20.0 g, 270 mmol). The reaction mixture was heated to reflux and stirred for 18 h, then cooled to room temperature, and concentrated in vacuo. The residue was diluted with water (100 mL), and the pH was adjusted to 3−4 using 1 N hydrochloric acid; then the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated to afford **2** (>95%), which was used without further purification.

General Procedure for the Preparation of 4-Aryl-2*H*-pyrazol-3-ylamines 3. Hydrazine hydrate (10.8 g, 216 mmol) was added to a stirred solution of **2** (108 mmol) in ethanol (100 mL), followed by acetic acid (10 mL). The reaction mixture was heated at reflux for 2 h, then cooled to room temperature, concentrated in vacuo, and then diluted with water (100 mL) and diethyl ether (200 mL). The organic layer was separated, washed with water (100 mL) and brine (2 × 100 mL), dried over sodium sulfate, filtered, and concentrated to afford **3** (90%) as a dark orange oil, which was used without further purification.

General Procedure for the Preparation of Ethyl 3-Aryl-7-methylpyrazolo[1,5-α]pyrimidine-6-carboxylate 4. Ethyl 2-ethoxymethylene-3-oxobutyrate[28] (18.0 g, 96.9 mmol) was added to a stirred solution of **3** (96.9 mmol) in ethanol (300 mL), and a thick precipitate was observed. The reaction mixture was heated to reflux, at which time all the solids had dissolved, and was maintained at reflux for 2.5 h. The reaction mixture was cooled, and upon cooling, **4** precipitated

from the reaction mixture. The solids were removed by filtration and washed with ethanol (2 × 50 mL). The filtrate was then reduced to ~1/2 the original volume, at which time additional **4** precipitated, which was then collected by filtration. The two batches were combined to afford **4** (35%) as a white solid.

General Procedure for the Preparation of 3-Aryl-7-methylpyrazolo[1,5-α]pyrimidine-6-carboxylic Acid 5. Lithium hydroxide (1.70 g, 40.2 mmol) was added to a stirred solution of **4** (33.5 mmol) in tetrahydrofuran (150 mL) and water (50 mL), and the mixture was stirred for 18 h. The volatile solvents were removed in vacuo; the resiude was then diluted with water (200 mL), acidified with 1 N hydrochloric acid, and then extracted with diethyl ether (200 mL), at which time some solids precipitated. The solids were removed by filtration, and the filtrate was then extracted with ethyl acetate (2 × 150 mL), dried over sodium sulfate, filtered, and concentrated to afford **5** (10.2 g, 95%) as a white solid.

General Procedure for the Preparation of 4-Nitrophenyl 3-Aryl-7-methylpyrazolo[1,5-α]pyrimidine-6-carboxylate 7. The stirred mixture of the corresponding acid **5** (50 mmol) and DMF (100 mL) was heated at 80 °C until a clear solution formed. Pyridine (4.4 mL, 55 mmol, 1.1 equiv) then was added, followed by the portion-wise addition of 4-nitrophenyl trifluoroacetate (12.5 g, 53 mmol, 1.06 equiv). The heat was removed, and the mixture was stirred for an additional 6 h. The resultant precipitate was collected, washed with ether (2 × 200 mL), and dried to give activated esters **7**.

General Procedure for the Preparation of 7-Methyl-3-aryl-pyrazolo[1,5-*a*]pyrimidine-6-carboxamides 9. A solution of the corresponding activated ester **7** (0.2 M in THF, 0.5 mL, 0.1 mmol) was added to each well across the rows of a 96-well plate. Solutions of amines (1 M in THF, 0.15 mL, 0.15 mmol) were added to each well down the corresponding columns. Triethylamine (0.2 mL, 0.15 mmol) was then added to all the wells in the plate. The plates were then capped and shaken at 50 °C for 24 h. Once the reactions had gone to completion, the plates were uncapped, and isocyanate resin (70 mg/well) and Dowex 550A OH resin (70 mg/well) were added to all the wells. The plates were then capped and shaken at room temperature overnight. After they were scavenged, the compounds were filtered through silica, and the silica was rinsed with THF. The compounds were then transferred to barcoded and tared vials and concentrated in vacuo.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra for novel compounds **2**{*3*}, **2**{*6*}, **3**{*3*}, **3**{*6*}, **5**{*3*}, and **5**{*6*} and representative ^{1}H NMR and LCMS spectra for chemset **9**{*1*−*9, 1*−*50*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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