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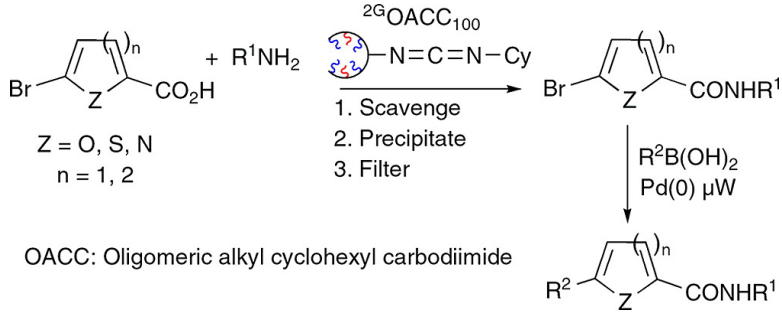


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# Studies Towards the Synthesis of Methionine Aminopeptidase Inhibitors: Diversification Utilizing a ROMP-Derived Coupling Reagent

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Efforts to synthesize potential methionine aminopeptidase inhibitors is described. Preliminary SAR and docking studies served as a guide to design the compound libraries. "Chromatography-free" synthesis of various heterocyclic amides was realized by using a high-load, soluble coupling reagent derived via ring-opening metathesis polymerization (ROMP). Subsequent microwave-assisted Suzuki reactions with ortho-substituted arylboronic acids, followed by chromatographic purification afforded a 55-member library in high yields and purities. While the biological testing was not satisfactory, concurrent X-ray crystallography studies revealed key structural features essential for inhibition of methionine aminopeptidase, which directed fruitful results reported in the accompanying manuscript. In addition, *in silico* Lipinksi profiles and ADME properties of the library are also reported.

## Introduction

Methionine aminopeptidase (MetAP) is a ubiquitous metalloenzyme that removes N-terminal methionine residue from newly synthesized polypeptide in both eukaryotic and prokaryotic cells.[1] The removal of N-terminal methionine residues is critical for protein maturation and posttranslational modifications and deletion of the genes encoding MetAP has been reported to be lethal to *Escherichia coli*[2] or *Salmonella typhimurium.*[3] Therefore, MetAPs are essential for cell growth and proliferation and are potential targets for developing antibacterial and antifungal drugs. MetAP can be activated in vitro by several divalent metal ions including Co(II), Mn(II), Ni(II), Zn(II), and Fe(II).[4] However, the importance of each metal in vivo is not established. Moreover, relatively few nonpeptidic MetAP inhibitors are known, and they either show poor selectivity among different metalloforms tested in vitro[5] or have not been tested on metalloforms other than the Co(II) form. New metalloform-selective MetAP inhibitors are therefore warranted, which could serve as valuable tools for probing the identity of physiological metals for MetAP activation, as well as leads for development of new therapeutic agents.

Solid-phase organic chemistry (SPOC) is an established technique for chemical library syntheses. It is employed in discovery of active compounds in pharmaceutical research and development and has been the primary driving force in the combinatorial revolution. Despite advances in this area, issues continue to surface, including purification of compound libraries[6] and validation-time in conversion of solution-phase protocols to solid-phase, as well as obtaining compounds in adequate quantities for biological interrogation. In this context, solution-phase methods have emerged as an enabling technique for library-generation in drug discovery,[7] whereby a paradigm shift in SPOC has occurred by placing scaffolds in solution, along with immobilized reagents, scavengers, and catalysts. This approach offers several advantages over traditional SPOC methods, including (i) decreased validation-time, (ii) favorable reaction kinetics, (iii) convenient reaction monitoring,[8,9] and (iv) fortuitous scale-up for resynthesis of active compounds. In this context, an array of polymer-bound reagents and scavengers[10] have appeared, effectively streamlining synthetic methods to simple mix, filter, and evaporate protocols. The hallmark of these methods is avoiding the use of insoluble polymers during synthesis, yet retaining the virtues of both solution- and solid-phase approaches.

Despite advances in this area, limitations in reaction homogeneity (nonlinear reaction kinetics), low resin-load capacities, and means of distributing reagents continue to

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warrant development of designer polymers. To address these limitations, a number of strategies have been developed including fluorous-phase,[11,12] soluble-supported catalysts,[13] and ionic liquids[14] to name a few. In the course of these developments, pioneering work by Barrett and others[15,16] has led to the general use of ring-opening metathesis (ROM) polymerization for generating high-load, immobilized reagents, while advances in ROMP-immobilized catalysts were simultaneously championed by Buchmeiser[17] and Bolm.[18] As part of our continued efforts toward the development of high-load ROMP-derived reagents, scavengers, and soluble supports,[19] we now report extensive implementation of our previously reported high-load, soluble oligomeric reagent ($^{2G}$OACC$_n$).[20] This versatile reagent offers flexible oligomer design, favorable reaction kinetics, diverse solubility profile, and displays wide applicability with a variety of coupling partners.[21]Ultimately, oligomers derived via ROM polymerization have emerged as an attractive platform circumventing many of the problems associated with conventional immobilized/soluble reagents. In this report, we use these attributes en route to the production of a library of potential methionine aminopeptidase inhibitors. To the best of our knowledge, this is the first application of a high-load soluble ROMP-derived coupling reagent and opens up new avenues and possibilities for application of this reagent for parallel synthesis.

## Library Design

High-throughput screening led to several novel structural classes of inhibitors that are potent and metal-selective with **1** emerging as the lead compound for study (Figure 1).[22] An assortment of diverse analogues was designed with different heterocyclic acids serving as the core structure. Key design elements included replacing the central furan ring with isosteric pyridine ring, substituting the carboxylic acid with amides and sulfonamides, and placing different substituents on the phenyl ring. Initial testing on lead compounds suggested a requirement of noncoplanar conformation between the two aromatic rings for inhibitory activity, which was introduced by placing an ortho-substituent on the phenyl ring. Figures 2−4 represent the core acids, amines, sulfonamides, and the arylboronic acids that were used in the library production.

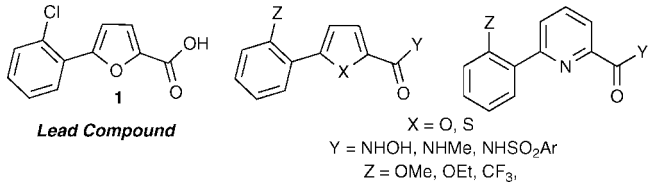


**Figure 1.** Structures of analogues of lead compound **1**.

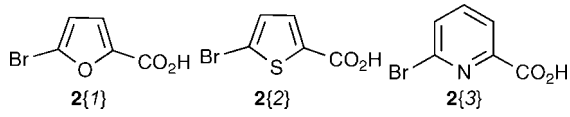


**Figure 2.** Heterocyclic core acids for library synthesis.

## Results and Discussion

Initial efforts toward library production of potential MetAP inhibitors relied on use of the aforementioned ROMP-derived

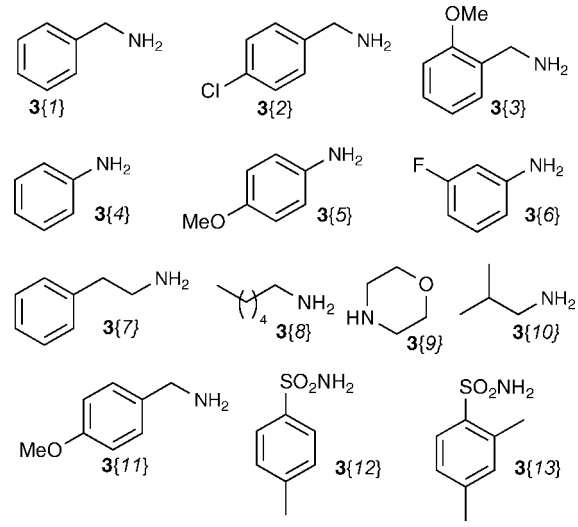


**Figure 3.** Amines and aryl sulfonamides chosen for coupling reactions.

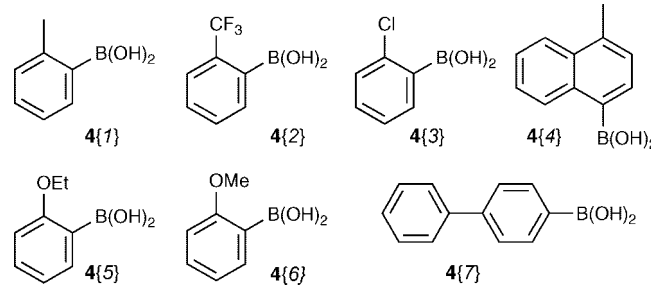


**Figure 4.** ortho-Substituted arylboronic acids used as building blocks.

oligomeric alkyl cyclohexyl carbodiimide (OACC) in the production of disubstituted furans containing both a C(2)-carboxamide group providing a binding motif and an ortho-substituted aromatic group at the C(5) position. First, commercially available 5-bromofuroic acid was coupled with a variety of benzyl, alkyl, and aromatic amines using $^{2G}$OACC$_{100}$ and DMAP as a catalyst to provide corresponding amides in good yields and excellent purities.[18] Excess of amine and DMAP were scavenged from the reaction mixture with Amberlyst A-15 ion-exchange resin followed by precipitation/filtration, which served as the sole purification protocol (Scheme 1). These reactions were performed in parallel on 100 mg scale, and the products were subsequently subjected to Suzuki coupling reactions as described below.

The Suzuki reaction was investigated with different catalysts and solvents under conventional heating and microwave irradiation. The optimal conditions were found to be microwave irradiation for 15 min in DME using $Pd(PPh_3)_2Cl_2$. Treatment of the crude reaction mixture with aqueous NaOH (0.5 M, 1 mL), followed by filtration through a SPE cartridge packed with a 1:1 mixture of $MgSO_4$/silica provided the crude products, which were purified on a high-performance flash-purification system[23] to produce a 28-member library in good yield and high purity (Table 1).

We next set out to design and prepare a library possessing surrogate acid replacements. We performed molecular modeling and computational prescreening on a variety of scaffolds of inhibitors of MetAP, which are summarized in Figure

**Scheme 1**

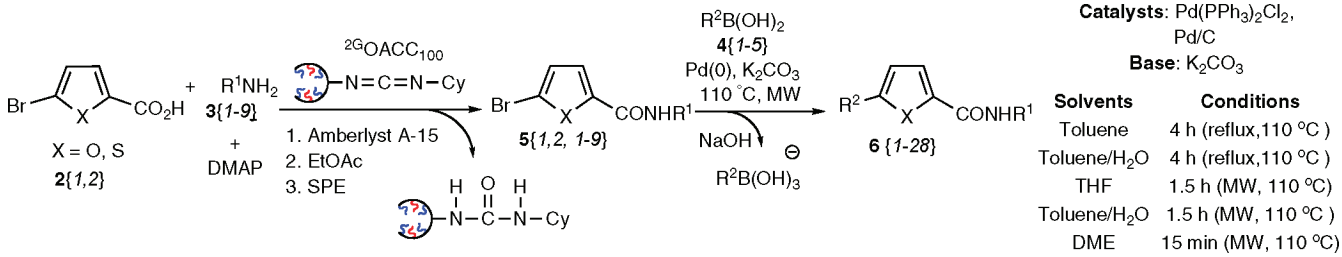


**Table 1.**

| entry | $R^1$ | $R^2$ | product | yield (%) | purity (%)[b] |
|---|---|---|---|---|---|
| | | X = S | | | |
| amide-1 | benzyl | | **5**{*2,1*} | 57 | 93 |
| amide-2 | 4-methoxyphenyl | | **5**{*2,5*} | 63 | 98 |
| amide-3 | morpholino | | **5**{*2,9*} | 88 | 94 |
| | | X = O | | | |
| 1 | benzyl | 2-trifluoromethylphenyl | **6**{*1*} | 70 | 99 |
| 2 | benzyl | 4-methylnapthyl | **6**{*2*} | 83 | 99 |
| 3 | benzyl | 2-ethoxyphenyl | **6**{*3*} | 19[a] | 100 |
| 4 | benzyl | 2-methylphenyl | **6**{*4*} | 80 | 96 |
| 5 | 4-chlorobenzyl | 2-chlorophenyl | **6**{*5*} | 40 | 97 |
| 6 | 4-chlorobenzyl | 2-trifluoromethylphenyl | **6**{*6*} | 98 | 99 |
| 7 | 4-chlorobenzyl | 4-methylnapthyl | **6**{*7*} | 70 | 92 |
| 8 | 2-methoxybenzyl | 2-trifluoromethylphenyl | **6**{*8*} | 62 | 100 |
| 9 | 2-methoxybenzyl | 2-chlorophenyl | **6**{*9*} | 17[a] | 99 |
| 10 | phenyl | 2-chlorophenyl | **6**{*10*} | 72 | 98 |
| 11 | phenyl | 2-trifluoromethylphenyl | **6**{*11*} | 67 | 99 |
| 12 | phenyl | 4-methylnapthyl | **6**{*12*} | 46 | 99 |
| 13 | 4-methoxyphenyl | 2-chlorophenyl | **6**{*13*} | 65 | 82 |
| 14 | 4-methoxyphenyl | 2-trifluoromethylphenyl | **6**{*14*} | 53 | 97 |
| 15 | 4-methoxyphenyl | 4-methylnapthyl | **6**{*15*} | 63 | 96 |
| 16 | 3-fluorophenyl | 2-chlorophenyl | **6**{*16*} | 66 | 90 |
| 17 | 3-fluorophenyl | 2-trifluoromethylphenyl | **6**{*17*} | 38 | 93 |
| 18 | 3-fluorophenyl | 4-methylnapthyl | **6**{*18*} | 66 | 98 |
| 19 | 3-fluorophenyl | 2-methylphenyl | **6**{*19*} | 43 | 100 |
| 20 | phenethyl | 2-chlorophenyl | **6**{*20*} | 72 | 98 |
| 21 | phenethyl | 2-trifluoromethylphenyl | **6**{*21*} | 17[a] | 99 |
| 22 | phenethyl | 4-methylnapthyl | **6**{*22*} | 50 | 92 |
| 23 | hexyl | 2-chlorophenyl | **6**{*23*} | 82 | 93 |
| 24 | hexyl | 4-methylnapthyl | **6**{*24*} | 46 | 94 |
| 25 | hexyl | 2-trifluoromethyl | **6**{*25*} | 67 | >95[c] |
| | | X = S | | | |
| 26 | benzyl | 2-trifluoromethylphenyl | **6**{*26*} | 8[a] | 100 |
| 27 | 4-methoxyphenyl | 2-trifluoromethylphenyl | **6**{*27*} | 29[a] | 99 |
| 28 | morpholino | 2-Chlorophenyl | **6**{*28*} | 6[a] | 99 |

[a] These compounds have been purified via mass directed fractionation. [b] Purities were determined by RP HPLC-MS-UV at 215 nm. [c] Purities were determined from NMR.

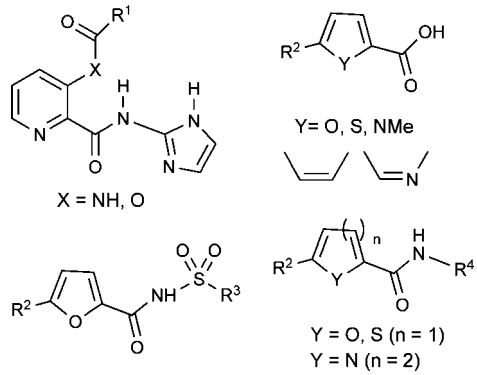


**Figure 5.** Scaftitlefolds examined via molecular docking to MetAP. The R groups include a variety of primarily hydrophobic constructs.

5. The receptor model for our calculations was constructed from the MetAP crystal structure cocrystallized with compound **1**.[19] A collection of molecules (361 in total) assembled from the scaffolds (Figure 5) were docked into the MetAP receptor via AutoDock[24] using the Lamarckian genetic algorithms search technique and requesting 50 poses per molecule. All parameters were left at their default values, except for Mn interaction parameters that were specified according to the form we devised for Mn ions in adenylyl cyclase.[25] Initial redocking of the cocrystallized inhibitor **1** validated the methodology by predicting a bound-state conformation in the same orientation relative to the crystallographic reference structure (root mean squared atomic displacement of only 0.94 Å; well within the 1.52 Å crystallographic resolution).

The predicted docking score of −10.19 kcal/mol corresponds to the **1** submicromolar inhibitor, thus agreeing reasonably well with our screening results. Inhibition of MetAP by **1** seems to be driven primarily by electrostatic attraction between the ligand's carboxylate and the $Mn^{2+}$ centers at the base of the receptor and lipophilic interactions with adjacent hydrophobic residues (Tyr 62, Tyr 65, and Trp

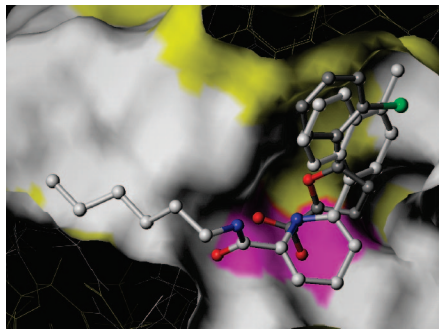

**Figure 6.** Docked conformers **1** and our top-scoring pyridine-based inhibitor (Figure 7) within the MetAP binding site. Hydrophobic MetAP surfaces are yellow; the two $Mn^{2+}$ ions are magenta, and all other surfaces are rendered in white. The inhibitors are both rendered according to standard CPK coloring, except the pyridine-based inhibitor is tinted relative to **1** for visual contrast.

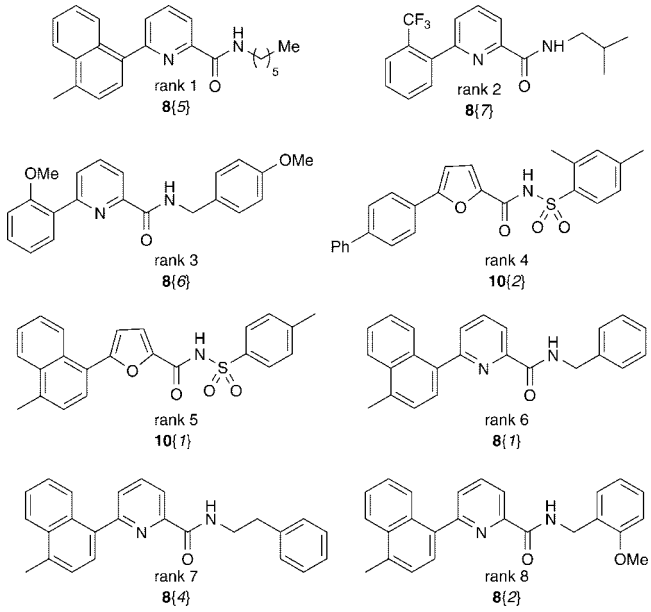


**Figure 7.** Structures and rank orders of *in silico* inhibitors.

221). These two features tend to be very well preserved through all of the strongly binding inhibitors in our set of 361 molecules, many of which are predicted to be substantially better inhibitors than **1**. The top three molecules all belonged to the picolinamide-based scaffold (see Figure 7), wherein the pyridine N and the adjacent amide carbonyl (in lieu of a carboxyl) couple with the $Mn^{2+}$ ions. The top scoring ligand ($\Delta G_{dock} = -16.11$ kcal/mol) is shown also in Figure 6 in its MetAP binding conformation relative to **1**. These molecules occupy very similar regions in the receptor; however it appears that the pyridine-based inhibitor improves on **1** by also binding an aliphatic tail to the mildly lipophilic gorge wall (relevant residues are Cys 169, Gly 170, and the nonpolar portion of His 171 and Val 183). This feature is maintained consistently among the top-scoring inhibitors. We next planned to prepare the eight top-ranked compounds shown in Figure 7. Although prior results[19] showed that the methyl ester and the amide of **1** do not yield tangible MetAP inhibition, the insight derived from the modeling study led us to explore whether the monosubstituted amides in Figure 7 (rank 1–3, 6–8) possess the predicted potent activity.

**Scheme 2**

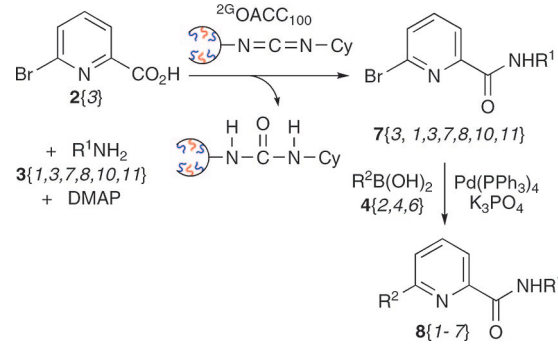


**Table 2.**

| entry | $R^1$ | $R^2$ | product | yield (%) | purity (%)[b] |
|---|---|---|---|---|---|
| 1 | benzyl | | **7**{*3,1*} | 83 | 98 |
| 2 | 2-methoxybenzyl | | **7**{*3,3*} | 48 | >95 |
| 3 | phenethyl | | **7**{*3,7*} | 64 | 98 |
| 4 | hexyl | | **7**{*3,8*} | 14[a] | 93 |
| 5 | isobutyl | | **7**{*3,10*} | 40[a] | >95 |
| 6 | 4-methoxybenzyl | | **7**{*3,11*} | 60 | 97 |
| 7 | benzyl | 4-methylnapthyl | **8**{*1*} | 53 | 99 |
| 8 | 2-methoxybenzyl | 4-methylnapthyl | **8**{*2*} | 57 | 99 |
| 9 | 4-methoxybenzyl | 4-methylnapthyl | **8**{*3*} | 40 | 91 |
| 10 | phenethyl | 4-methylnapthyl | **8**{*4*} | 50 | 96 |
| 11 | hexyl | 4-methylnapthyl | **8**{*5*} | 18 | 96 |
| 12 | 4-methoxybenzyl | 2-methoxyphenyl | **8**{*6*} | 28 | 100 |
| 13 | isobutyl | 2-trifluoromethylphenyl | **8**{*7*} | 50 | 100 |

[a] The requisite amides were made using EDC and DMAP, which after scavenging with Amberlyst resin and aqueous work up, gave acceptable yields and purities. [b] Purities for all compounds were determined by RP HPLC-MS-UV except for **7**{*3,3*}and **7**{*3,10*} which were determined from NMR.

6-Bromopicolinamides were generated, employing similar conditions as above, using $^{2G}OACC_{100}$ in moderate to good yields (Scheme 2). Subsequent Suzuki reactions provided the desired compounds in moderate yields and high purities (Table 2).

Facile amidation was accomplished with arylsulfonamides **3**{*12,13*} with $^{2G}OACC_{75}$ and an excess of DMAP, which served as both a catalyst and a base (Scheme 3). Subsequent Suzuki reaction, followed by purification, provided the desired products in moderate yields and excellent purities (Table 3).

The potency of compounds in Tables 1–3 were tested against recombinant *E. coli* MetAP1, which was purified as an apoenzyme as reported previously,[4b] and were found to be inactive with $IC_{50}$ values above 25 $\mu$M. Concurrent studies at that time involving cocrystallization of the enzyme with substituted furoic acid **1**[22] revealed that two oxygen atoms coordinate with Mn(II), an essential element for activity/inhibition, and confirmed the importance of the free carboxylate group for activity.[22]

The failure of our initial structure-based modeling work to produce viable inhibitors suggests that MetAP inhibition is likely contingent on dynamic/entropic effects (possibly receptor conformational mobility) that are not well represented in the AutoDock scoring function. Given an increasingly sizable body of screening data for the MetAP enzyme, our plan is to train a comparative binding energy (COMBINE) type model to specifically represent the idiosyncrasies of the MetAP inhibitor structure–activity

**Scheme 3**

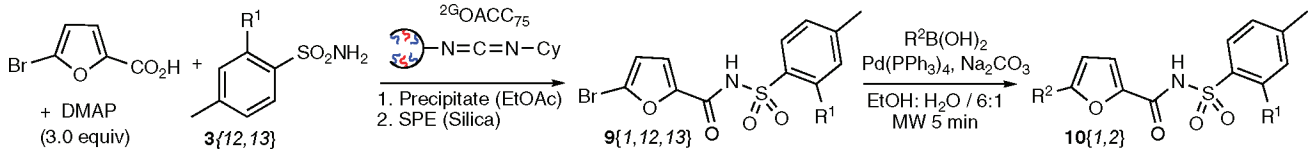


**Table 3.**

| entry | $R^1$ | $R^2$ | productt | yield (%) | purity (%)[b] |
|---|---|---|---|---|---|
| 1 | H | | **9**{*1*,*12*} | 90 | 89 |
| 2 | Me | | **9**{*1*,*13*} | 86 | 100 |
| 3 | H | 4-methylnapthyl | **10**{*1*} | 75 | 93 |
| 4 | Me | 4-biphenyl | **10**{*2*} | 30[a] | 97 |

[a] This compound was purified via mass directed fractionation. [b] Purites were determined by RP HPLC-MS-UV.

relationship. We have previously found this to be highly successful in studies of other complex receptors such as acetylcholinesterase[26] and adenylyl cyclase.[27]

The compounds reported herein were evaluated *in silico* according to standard oral availability and absorption−distribution−metabolism−excretion (ADME) criteria, using SYBYL[28] and VolSurf[29] programs. These compounds are Lipinski-compliant, are predicted to have good CACO2 permeability, moderate-to-good albumin transport properties, moderate-to-good tissue distribution, borderline metabolic stability, and are typically not expected to be hERG blocking threats. Predictions also suggest that they may tend toward BBB permeability (a possible problem) and may have some aqueous and DMSO solubility problems. As evaluated relative to the PubChem collection via DiverseSolutions,[30] the collection appears to contain some pockets of relative chemical diversity, although most of the compounds are in relatively well-populated chemical space. In essence, the collection appears to be reasonably druglike, however some efforts would be expended in any subsequent lead-refinement stage toward improving polar solvation capacity and perhaps introducing BBB impermeable functionality.

## Conclusion

We have demonstrated the synthetic utility and potential of a high-load soluble ROMP-generated oligomer for a diverse set of building blocks and successfully applied this reagent to library-generation. Furthermore, this library synthesis integrates various facilitated protocols such as parallel solution-phase synthesis using supported reagents, microwave-assisted synthesis, and high-throughput chemical library purification, which are amendable to automation. While initial testing of these compounds have not been satisfactory, computational studies indicate they are Lipinski compliant and reasonably druglike. These compounds have been added to the KU-CMLD collection and are currently being evaluated against a number of targets at the MLSMR.

## Experimental Section

**General Experimental Methods.** All air- and moisture-sensitive reactions were carried out in flame- or oven-dried glassware under an argon atmosphere using standard gastight syringes, cannulaes, and septa. Stirring was achieved with oven-dried magnetic stir bars. Microwave reactions were done in Emrys' microwave reactor, and the vials (0.2–0.5 mL) were purchased from Biotage. All solvents that were used for Suzuki reactions, such as DMF, DME, absolute EtOH, and water, were degassed with argon before use. Toluene, $Et_2O$, THF, and $CH_2Cl_2$ were purified bypassage through the Solv-Tek purification system employing activated $Al_2O_3$.[31] All chromatographic purifications were done on the Biotage Horizon HPFC system. Olefin metathesis catalysts were acquired from Materia and used without further purification. Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. $^1H$ and $^{13}C$ spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 and 100 MHz, respectively; or a Bruker Avance operating at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million (ppm) downfield from TMS (0 ppm). Data are reported as follows: chemical shift, multiplicity (app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad), coupling constants, and integration. HPLC analyses were carried out at the KU-CMLD Core C laboratory using a Xterra MS C-18 column (5um, 4.6 × 150 mm) and a gradient elution (10% CAN-water to 100% ACN) on a Waters Mass Directed Fractionation instrument using a Waters 2767 sample manager, Waters 2525 HPLC pump, a 2487 dual $\lambda$ absorbance detector, and Waters/Micromass ZQ (quadrupole) MS ELSD detector (Sedex 85) connected to a PC with MassLynx workstation. High-resolution mass spectra (HRMS) [ESI+] were obtained using Waters/Micromass LCT Premier (TOF instrument).

**Enzyme Inhibition Assays.** Recombinant *E. coli* MetAP1 was purified as an apoenzyme as reported previously.[4] All compounds were placed on 384-well flat-bottom polystyrene microplate in 12 concentrations in 2-fold dilutions starting from 50 $\mu$M (final concentration). Serial dilutions were performed by Precision 2000 automated microplate pipetting system (BioTek Instruments Inc., Winooski, VT). The assay mixture (80 $\mu$L final volume) contains 20 $\mu$L of compound, 50 mM MOPS (pH 7.0), 1.0 $\mu$M apo-*Ec*MetAP, 200 $\mu$M Met-AMC (Bachem Bioscience Inc., King of Prussia, PA), and 100 $\mu$M $MnCl_2$. Enzymatic activity of MetAP was monitored by a fluorescence kinetic assay using Met-AMC as a fluorogenic substrate on a SpectraMax Gemini XS microplate fluorescence reader (Molecular Devices Corp., Sunnyvale, CA) ($\lambda_{ex}$ = 360 nm, $\lambda_{em}$ = 460 nm). 2.5% DMSO was used as a negative control, while compound **1** was used as a positive control. The $IC_{50}$ values were obtained from nonlinear curve fitting of the plot of percent inhibition versus inhibitor concen-

tration [*I*] by using the equation, %inhibition = 100/{1 + ($IC_{50}$/[*I*])*k*}, where *k* is the Hill coefficient.

**General Procedure for Amidation using $^{2G}OACC_n$.** To a mixture of acid **2**{*1–3*}, amine **3**{*1–9*,*11*} (1.0–1.5 equiv), and DMAP (10 mol %) at room temperature was added dropwise a solution of $^{2G}OACC_n$ (1.5–2.0 equiv, n = 75, 100) in $CH_2Cl_2$ (2 mL), and the reaction mixture was stirred overnight. After completion of the reaction (TLC), the excess of amine and DMAP were scavenged using Amberlyst A-15 ion-exchange resin (purchased from Aldrich, load = 4 mmol/g). Precipitation of the spent oligomer and any excess OACC with EtOAc (or MeOH), followed by filtration through a short SPE ($SiO_2$) cartridge and concentration under reduced pressure, provided the corresponding amides in good to excellent yields and purities.

**General Procedure for Preparation of 9{*1*,*12*,*13*}.** To a mixture of arylsulfonamide **3**{*12*,*13*} (1.0 equiv), acid **2**{*1*} (1.5 equiv), and DMAP (3 equiv) at room temperature was added dropwise a solution of $^{2G}OACC_{75}$ (2.0 equiv) in $CH_2Cl_2$ (0.1 M), and the reaction mixture was stirred overnight. After completion of the reaction (TLC), the excess of DMAP was scavenged using Amberlyst A-15 ion-exchange resin (purchased from Aldrich, load = 4 mmol/g). Precipitation of the spent oligomer and any excess OACC with EtOAc (or MeOH), followed by filtration through a short SPE ($SiO_2$) cartridge and concentration under reduced pressure, provided the corresponding sulfon amides in good-to-excellent yields and purities.

**General Procedure for Library Members 6{*1–28*}.** An oven-dried microwave vial was charged with the required amide **5**{*1*,*2*,*1–9*}, the boronic acids **4**{*1–5*} (2 equiv), $Pd(PPh_3)_2Cl_2$ (1 mol%), $K_2CO_3$ (3 equiv), and dimethoxyethane (0.5 mL). The reaction vial was sealed, flushed with argon, and heated at 110 °C for 15 min. To this crude reaction mixture, aqueous NaOH (0.5 M, 1 mL) was added, and the resulting mixture was stirred for 0.5 h, followed by filtration through a short SPE cartridge packed with a 1:1 mixture $MgSO_4$/silica, to give the crude products, which were further purified on a Biotage HPFC system (eluting with hexane/EtOAc = 2:1) to provide the coupled products **6**{*1–28*} in moderate–good yields and high purities.

**General Procedure for Library Members 8{*1–7*}.** An oven-dried microwave vial was charged with the required picolinamide **7**{*3*,*1*,*3*,*7*,*8*,*10*,*11*}, the boronic acids **4**{*2*,*4*,*6*} (2 equiv), $Pd(PPh_3)_4$ (3–4 mol%), $K_3PO_4$ (2 equiv), and DMF (0.5 mL). The reaction vial was sealed, flushed with argon, and heated at 150 °C for 5–15 min. To this crude reaction mixture, aqueous NaOH (0.5 M, 1 mL) was added, and the resulting mixture was stirred for 0.5 h, followed by filtration through a short SPE cartridge packed with a 1:1 mixture $MgSO_4$/silica, to give the crude products, which were further purified on a Biotage purification system to provide the coupled products **8**{*1–7*}, in moderate yields.

**General Procedure for Synthesis of Library Members 10{*1*,*2*}.** An oven-dried microwave vial was charged with the required sulfonamide **9**{*12*,*13*}, the boronic acids **4**{*4*,*7*} (2 equiv), $Pd(PPh_3)_4$ (4 mol%), $Na_2CO_3$ (5 equiv), and EtOH/$H_2O$ (6:1, 0.15 M). The reaction vial was sealed, flushed with argon and heated at 150 °C for 5–15 min. To this crude reaction mixture, aqueous NaOH (0.5 M, 1 mL) was added, and the mixture was stirred for 0.5 h, followed by filtration through an SPE cartridge packed with a 1:1 mixture $MgSO_4$/silica, to give the crude products, which were further purified on a Biotage high-performance flash purification system.

**Spectroscopic and Analytical Data. *N*-Benzyl-5-(4-methylnaphthalen-1-yl)furan-2-carboxamide 6{*2*}.** Yield: 83%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.25 (dd, $J_{HH}$ = 8.5, 1.9 Hz, 1H), 8.06 (dd, $J_{HH}$ = 8.2, 1.8 Hz, 1H), 7.61–7.53 (m, 3H), 7.38–7.25 (m, 7H), 6.75 (d, $J_{HH}$ = 3.4 Hz, 2H), 4.66 (d, $J_{HH}$ = 3.4 Hz, 2H), 2.73 (s, 3H).$^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.4, 155.1, 147.1, 138.1, 136.3, 132.8, 130.5, 128.7, 127.9, 127.6, 126.9, 126.6, 126.1, 125.9, 125.5, 124.7, 116.2, 111.5, 43.2, 19.8. HRMS Calcd for $C_{23}H_{19}N_2O$: $(M + H)^+$ 342.1485. Found: 342.1485.

***N*-Benzyl-5-(2-ethoxyphenyl)furan-2-carboxamide 6{*3*}.** Yield: 19%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.82 (d, $J_{HH}$ = 7.2 Hz, 1H), 7.40–7.27 (m, 7H), 7.10 (d, $J_{HH}$ = 3.5 Hz, 1H), 7.03–6.96 (m, 2H), 6.72 (br s, 1H), 4.70 (d, $J_{HH}$ = 5.9 Hz, 2H), 4.18 (q, $J_{HH}$ = 6.9 Hz, 2H), 1.55 (t, $J_{HH}$ = 6.8 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 156.6, 153.6, 150.2, 143.6, 136.2, 127.4, 126.8, 126.6, 126.0, 125.6, 124.3, 118.5, 116.5, 114.9, 110.2, 109.2, 62.0, 41.2, 12.9. HRMS Calcd for $C_{20}H_{19}ClNO_3$: $(M + H)^+$ 322.1443. Found: 322.1427.

**5-(2-Chlorophenyl)-*N*-(2-methoxybenzyl)furan-2-carboxamide 6{*9*}.** Yield: 17%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (dd, $J_{HH}$ = 7.7, 1.7 Hz, 1H), 7.45 (dd, $J_{HH}$ = 7.9, 1.3 Hz, 1H), 7.34–7.20 (m, 5H), 7.10 (d, $J_{HH}$ = 3.6 Hz, 1H), 6.98 (m, 3H), 4.65 (d, $J_{HH}$ = 6.0 Hz, 2H), 3.90 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 156.0, 155.6, 149.5, 145.2, 129.1, 129.0, 127.9, 127.3, 127.0, 126.4, 126.3, 125.0, 124.0, 118.8, 113.9, 110.8, 108.4, 53.4, 37.1. HRMS Calcd for $C_{19}H_{16}ClNO_3$: $(M + H)^+$ 342.0897. Found: 342.0895.

**5-(2-Chlorophenyl)-*N*-phenylfuran-2-carboxamide 6{*10*}.** Yield: 72%. Purity: 90%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.08 (br s, 1H), 7.85 (dd, $J_{HH}$ = 7.8, 1.6 Hz, 1H), 7.67 (dd, $J_{HH}$ = 8.0, 0.8 Hz, 2H), 7.50 (dd, $J_{HH}$ = 7.9, 1.1 Hz, 1H), 7.41–7.31 (m, 5H), 7.25–7.21 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.1, 151.9, 146.7, 137.3, 131.1, 131.0, 129.6, 129.1, 128.6, 128.1, 127.0, 124.4, 120.0, 117.6, 117.0, 114.6, 113.2. HRMS Calcd for $C_{17}H_{12}ClNO_2$: $(M + H)^+$ 298.0635. Found: 298.0636.

**5-(4-Methylnaphthalen-1-yl)-*N*-phenylfuran-2-carboxamide 6{*12*}.** Yield: 46%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.28 (dd, $J_{HH}$ = 4.0, 3.8 Hz, 1H), 8.15 (br s, 1H), 8.10 (d, $J_{HH}$ = 8.1 Hz 1H), 7.67–7.57 (m, 5H), 7.42–7.36 (m, 4H), 7.14 (t, $J_{HH}$ = 7.3 Hz, 1H), 6.79 (dd, $J_{HH}$ = 3.2, 1.0 Hz, 1H), 2.76 (s, 3H).$^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 156.2, 155.6, 147.1, 137.4, 136.6, 132.9, 130.7, 129.1, 127.1, 126.8, 126.2, 126.1, 125.8, 125.5, 124.8, 124.5, 120.0, 117.0, 111.8, 19.8. HRMS Calcd for $C_{22}H_{17}NO_2$: $(M + H)^+$ 328.1337. Found: 328.1338.

***N*-(4-Methoxyphenyl)-5-(2-(trifluoromethyl)phenyl)furan-2-carboxamide 6{*14*}.** Yield: 53%. Purity: 97%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.07 (s, 1H), 7.83 (d, $J_{HH}$ = 7.9 Hz, 1H), 7.51 (d, $J_{HH}$ = 7.7 Hz, 1H), 7.65 (t, $J_{HH}$ = 7.6, Hz, 1H), 7.58–7.52 (m, 3H), 7.30 (dd, $J_{HH}$ = 3.5, 1.1 Hz,

1H), 6.92 (s, 2H), 6.80 (d, $J_{HH}$ = 3.0 Hz, 1H), 3.81 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.5, 154.7, 151.4, 146.9, 131.0, 129.4, 129.3, 128.0, 127.2, 126.2, 126.1, 125.9, 121.8, 120.7, 120.4, 115.3, 113.2, 110.9, 54.4. HRMS Calcd for $C_{19}H_{14}F_3NO_3$: $(M + H)^+$ 362.1004. Found: 362.1002.

***N*-(4-Methoxyphenyl)-5-(4-methylnaphthalen-1-yl)furan-2-carboxamide 6{*15*}.** Yield: 63%. Purity: 96%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.29 (br d, $J_{HH}$ = 6.5 Hz, 1H), 8.12 (br d, $J_{HH}$ = 6.2 Hz, 1H), 8.07 (s, 1H), 7.68 (d, $J_{HH}$ = 7.2 Hz, 1H), 7.65–7.58 (m, 4H), 7.44–7.41 (m, 2H), 6.93–6.91 (m, 2H), 6.81 (dd, $J_{HH}$ = 3.5, 1.1 Hz, 1H), 3.83 (s, 3H), 2.78 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 155.4, 155.3, 154.8, 145.9, 135.3, 131.6, 129.4, 129.2, 125.7, 125.5, 125.0, 124.9, 124.8, 124.6, 124.3, 123.5, 123.3, 120.5, 115.6, 113.3, 110.8, 54.2, 12.9. HRMS: Calcd for $C_{23}H_{19}NO_3$: $(M + H)^+$ 358.1443. Found: 358.1433.

**5-(2-Chlorophenyl)-*N*-(3-fluorophenyl)furan-2-carboxamide 6{*16*}.** Yield: 66%. Purity: 90%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.12 (s, 1H), 7.83 (d, $J_{HH}$ = 7.7 Hz, 1H), 7.64 (d, $J_{HH}$ = 10.9 Hz, 1H), 7.5 (d, $J_{HH}$ = 7.8 Hz, 1H), 7.39–7.31 (m, 4H), 7.17 (d, $J_{HH}$ = 3.6 Hz, 1H), 6.85 (br s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 164.0, 162.0, 155.9, 152.3, 146.4, 138.8, 131.3, 131.1, 130.1, 129.7, 128.0, 127.0, 117.4, 115.2, 113.2, 111.4, 107.8. HRMS Calcd for $C_{17}H_{11}ClFNO_2$: $(M + H)^+$ 316.0540. Found: 316.0533.

***N*-(3-Fluorophenyl)-5-*o*-tolylfuran-2-carboxamide 6{*19*}.** Yield: 64%. Purity: 100%.$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.11 (s, 1H), 7.70–7.63 (m, 2H), 7.36–7.27 (m, 5H), 6.87–6.82 (m, 2H), 6.68 (d, $J_{HH}$ = 3.6 Hz, 1H), 2.53 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 163.9, 161.9, 156.0, 155.6, 146.0, 138.8, 135.4, 131.3, 130.0, 128.9, 128.8, 127.8, 126.1, 117.3, 115.3, 111.2, 107.4, 21.6. HRMS Calcd for $C_{18}H_{14}FNO_2$: $(M + H)^+$ 296.1089. Found: 296.1089.

**5-(2-Chlorophenyl)-*N*-phenethylfuran-2-carboxamide 6{*20*}.** Yield: 72%. Purity: 98%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.70 (dd, $J_{HH}$ = 7.7, 1.7 Hz, 1H), 7.46 (dd, $J_{HH}$ = 7.7, 1.3 Hz, 1H), 7.36–7.26 (m, 7H), 7.20 (dd, $J_{HH}$ = 7.7, 1.7 Hz, 1H), 7.12 (d, $J_{HH}$ = 3.6 Hz, 1H), 6.45 (br s, 1H), 3.72 (dd, $J_{HH}$ = 13.1, 6.9 Hz, 2H), 2.94 (t, $J_{HH}$ = 6.9 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.2, 151.5, 146.9, 138.7, 131.0, 130.9, 129.2, 128.9, 128.3, 128.2, 128.7, 126.9, 126.6, 115.8, 112.7, 40.3, 35.8. HRMS Calcd for $C_{19}H_{16}ClNO_2$: $(M + H)^+$ 326.0948. Found: 326.0934.

**5-(4-Methylnaphthalen-1-yl)-*N*-phenethylfuran-2-carboxamide 6{*22*}.** Yield: 50%. Purity: 93%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.23 (br d, $J_{HH}$ = 7.6 Hz, 1H), 8.07 (d, $J_{HH}$ = 8.0 Hz, 1H), 7.59–7.54 (m, 3H), 7.38–7.23 (m, 7H), 6.73 (d, $J_{HH}$ = 3.4 Hz, 1H), 6.48 (br s, 1H), 3.71 (dd, $J_{HH}$ = 6.9, 6.2 Hz, 2H), 2.93 (t, $J_{HH}$ = 6.9 Hz, 2H), 2.78 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.5, 155.1, 147.3, 138.8, 136.3, 132.9, 130.5, 128.8, 128.7, 126.8, 126.7, 126.6, 126.1, 125.9, 125.5, 124.7, 115.8, 111.3, 40.4, 35.9, 19.8. HRMS Calcd for $C_{24}H_{21}NO_2$: $(M + H)^+$ 356.1650. Found: 356.1647.

**5-(2-Chlorophenyl)-*N*-hexylfuran-2-carboxamide 6{*23*}.** Yield: 82%. Purity: 93%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.80 (d, $J_{HH}$ = 8.0 Hz, 1H), 7.47 (d, $J_{HH}$ = 8.0 Hz, 1H), 7.37–7.26 (m, 2H), 7.20 (dd, $J_{HH}$ = 3.6, 1.2 Hz, 1H), 7.12 (dd, $J_{HH}$ = 3.6, 1.2 Hz, 1H), 6.40 (br s, 1H), 3.45 (dd, $J_{HH}$ = 13.6, 6.8 Hz, 2H), 1.66–1.59 (m, 2H), 1.41–1.25 (m, 6H), 0.89 (t, $J_{HH}$ = 6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.1, 151.3, 147.0, 130.9, 129.3, 128.4, 128.2, 127.8, 116.5, 112.7, 42.8, 39.2, 31.5, 29.6, 26.5, 22.6, 13.9. HRMS Calcd for $C_{17}H_{20}ClNO_2$: $(M + H)^+$ 306.1261. Found: 306.1265.

***N*-Hexyl-5-(4-methylnaphthalen-1-yl)furan-2-carboxamide 6{*24*}.** Yield: 46%. Purity: 94%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.26 (dd, $J_{HH}$ = 6.9, 2.5 Hz, 1H), 8.08 (dd, $J_{HH}$ = 6.9, 2.8 Hz, 1H), 7.62 (m, 3H), 7.38 (d, $J_{HH}$ = 7.2 Hz, 1H), 7.28 (d, $J_{HH}$ = 3.4 Hz, 1H), 6.73 (d, $J_{HH}$ = 3.5 Hz, 1H), 3.45 (dd, $J_{HH}$ = 13.6, 6.6 Hz, 2H), 2.75 (s, 3H), 1.67–1.57 (m, 3H), 1.37–1.25 (m, 6H), 0.88 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 158.5, 154.9, 147.5, 136.2, 132.9, 130.6, 126.8, 126.6, 126.2, 126.1, 126.0, 125.8, 124.4, 115.7, 111.4, 39.2, 31.5, 29.7, 26.5, 22.5 19.8, 14.0. HRMS Calcd for $C_{22}H_{25}NO_2$: $(M + H)^+$ 336.1963. Found: 336.1953.

***N*-Benzyl-6-bromopicolinamide 7{*3,1*}.** Yield: 83%. Purity: 98%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.21 (d, $J_{HH}$ = 7.2 Hz, 1H), 8.18 (br s, 1H), 7.65 (app t, $J_{HH}$ = 8.0, 7.6 Hz, 1H), 7.62 (br d, $J_{HH}$ = 7.6, 1H), 7.38–7.28 (m, 5H), 4.68 (d, $J_{HH}$ = 6.2 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 161.7, 149.8, 139.5, 138.6, 136.8, 131.8, 130.7, 128.5, 127.1, 120.0, 42.5. HRMS Calcd for $C_{13}H_{11}BrN_2O$: $(M + H)^+$ 291.0133. Found: 291.0137.

**6-Bromo-*N*-phenethylpicolinamide 7{*3,7*}.** Yield: 64%. Purity: 98%.$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.15 (d, $J_{HH}$ = 7.2 Hz, 1H), 7.92 (br s, 1H), 7.70 (app t, $J_{HH}$ = 8.0, 7.6 Hz, 1H), 7.59 (d, $J_{HH}$ = 7.6 Hz, 1H), 7.34–7.24 (m, 5H), 3.70 (app q, $J_{HH}$ = 8.8, 6.4, 5.6 Hz, 2H), 2.94 (t, $J_{HH}$ = 7.4, Hz, 2H).$^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 162.8, 151.0, 140.5, 140.2, 139.7, 138.7, 132.2, 130.6, 128.8, 127.7, 126.5, 121.25, 40.9, 33.7. HRMS Calcd for $C_{14}H_{13}BrN_2O$: $(M + H)^+$ 305.0289. Found: 305.0294.

***N*-Benzyl-6-(4-methylnaphthalen-1-yl)picolinamide 8{*1*}.** Yield: 53%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.49 (br s, 1H), 8.29 (dd, $J_{HH}$ = 8.0, 0.8 Hz, 1H), 8.10–7.19 (m, 3H), 7.70 (dd, $J_{HH}$ = 7.6, 1.0 Hz, 1H), 7.56 (dt, $J_{HH}$ = 7.7, 1.3 Hz, 1H), 7.50–7.40 (m, 3H), 7.34–7.22 (m, 5H), 4.67, (s, 1H), 4.66 (s, 1H), 2.76 (s, 3H).$^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 163.3, 156.9, 148.4, 137.2, 136.8, 135.0, 134.7, 131.8, 129.9, 127.5, 126.8, 128.6, 126.5, 126.3, 126.0, 125.1, 125.0, 124.9, 123.4, 119.4, 42.3, 18.7. HRMS Calcd for $C_{24}H_{20}N_2O$: $(M + H)^+$ 353.1654. Found: 353.1642.

***N*-(2-Methoxybenzyl)-6-(4-methylnaphthalen-1-yl)picolinamide 8{*2*}.** Yield: 57%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.68 (br s, 1H), 8.25 (d, $J_{HH}$ = 7.6 Hz, 1H), 8.09 (d, $J_{HH}$ = 9.2 Hz, 2H), 7.96 (t, $J_{HH}$ = 7.8 Hz, 1H), 7.68 (d, $J_{HH}$ = 7.6 Hz, 1H), 7.49 (app t, $J_{HH}$ = 15.2, 7.2 Hz, 1H) 7.48–7.41 (m, 3H), 7.33 (d, $J_{HH}$ = 6.8 Hz, 1H), 7.26–7.21 (m, 1H), 6.90 (t, $J_{HH}$ = 8.0 Hz, 1H), 6.82 (d, $J_{HH}$ = 8.0 Hz, 1H), 4.65 (d, $J_{HH}$ = 8.0 Hz, 2H), 3.69 (s, 3H), 2.77 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 164.1, 157.9, 157.5, 149.7, 137.8, 136.1, 135.7, 132.9, 131.0, 129.3, 128.6, 127.3, 126.3, 126.2, 126.1, 125.8, 124.5, 120.5, 120.4, 110.2, 55.1, 39.1, 19.7. HRMS Calcd for $C_{25}H_{22}N_2O_2$: $(M + H)^+$ 383.1756. Found: 383.1756.

**6-(4-Methylnaphthalen-1-yl)-*N*-phenethylpicolinamide 8{*4*}.** Yield: 53%. Purity: 99%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.24 (d, $J_{HH}$ = 7.6 Hz, 2H), 8.11 (d, $J_{HH}$ = 8.0 Hz, 1H),

8.02–7.95 (m, 2H), 7.69 (d, $J_{HH}$ = 8.0 Hz, 1H), 7.58 (t, $J_{HH}$ = 7.4 Hz, 1H), 7.49–7.42 (m, 3H), 7.29–7.15 (m, 5H), 3.69 (q, $J_{HH}$ = 6.8, Hz, 2H), 2.9 (t, $J_{HH}$ = 7.4 Hz, 2H), 2.78 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 164.3, 157.9, 149.5, 138.9, 137.8, 136.1, 135.7, 132.9, 131.0, 128.8, 128.5, 127.5, 127.3, 126.5, 126.4, 126.2, 126.1, 125.9, 124.5, 120.3, 40.8, 35.9, 19.8. HRMS Calcd for $C_{25}H_{22}N_2O$: $(M + H)^+$ 367.1810: Found: 367.1811.

***N*-Hexyl-6-(4-methylnaphthalen-1-yl)picolinamide 8{*5*}.** Yield: 18%. Purity: 96%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.25 (d, $J_{HH}$ = 7.6 Hz, 1H), 8.14–8.05 (m, 3H), 7.97 (t, $J_{HH}$ = 8.0 Hz, 1H), 7.69 (d, $J_{HH}$ = 8.0 Hz, 1H), 7.58 (dd $J_{HH}$ = 7.6, 2.0 Hz, 1H), 7.51–7.43 (m, 3H), 3.44 (q, $J_{HH}$ = 6.8 Hz, 2H), 2.78, (s, 3H), 1.64–1.54 (m, 2H), 1.35–1.28 (m, 6H), 0.86 (br s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 164.3, 157.9, 149.6, 137.8, 136.1, 135.7, 132.9, 131.0, 128.2, 127.4, 127.0, 126.2, 126.1, 124.5, 121.0, 120.3, 39.4, 31.5, 29.7, 26.6, 22.5, 19.7, 14.1. HRMS Calcd for $C_{23}H_{26}N_2O$: $(M + H)^+$ 347.2121. Found: 347.2121.

**5-(Biphenyl-4-yl)-*N*-(2,4-dimethylphenylsulfonyl)furan-2-carboxamide 10{*2*}.** Yield: 30%. Purity: 97%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.01 (s, 1H), 7.86 (br s, 1H), 7.78–7.41 (m, 2H), 7.62 (d, $J_{HH}$ = 7.6 Hz, 1H), 7.50–7.39 (m, 5H), 7.31–7.28 (m, 2H), 7.17 (d, $J_{HH}$ = 7.6 Hz, 1H), 7.12 (d, $J_{HH}$ = 3.6 Hz, 1H), 6.31 (d, $J_{HH}$ = 3.6 Hz, 1H), 2.58 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 157.1, 154.2, 143.5, 141.7, 140.3, 136.3, 134.8, 134.4, 132.9, 132.3, 131.6, 131.2, 129.3, 128.4, 128.1, 127.9, 127.3, 127.2, 127.1, 119.6, 111.0, 20.8, 20.0. HRMS Calcd for $C_{25}H_{21}NO_4S$: $(M + H)^+$ 432.1269. Found: 432.1251.

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**Supporting Information Available.** Characterization data for library members including HPLC/MS chromatograms, HRMS data, $^1$H and $^{13}$C NMR spectra, and Lipinski/ADME property table are given in the Supporting Information. This material is available free of charge via the Internet at http://acs.pubs.org/.

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