Diversification of the Three-Component Coupling of 2-Aminoheterocycles, Aldehydes, and Isonitriles: Efficient Parallel Synthesis of a Diverse and Druglike Library of Imidazo- and Tetrahydroimidazo[1,2-*a*] Heterocycles

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Due to their diverse range of biological activities, imidazoheterocycles are recognized as privileged structures making these structural motifs attractive targets for library preparation. We report herein the synthesis of a sizable collection of imidazo[1,2-*a*]heterocycle scaffolds well-suited for divergent library preparation by virtue of amine functional handles with diverse positioning and connectivities. Partial reduction of imidazo[1,2-*a*]pyrazines to the tetrahydroimidazo[1,2-*a*]pyrazines and regiospecific Mannich-type bond formation at the C-3 of imidazo[1,2-*a*]pyridine under mild conditions achieved additional topological and connective diversity within the scaffold collection. Subsequent parallel reaction of the functionalized imidazoheterocycles with polystyrene-tetrafluorophenol esters and sulfonates produced a 7500 compound library in high purity.

Introduction

The imidazoheterocyclic scaffold represents a promising area for identification of lead structures towards the discovery of novel synthetic drugs. Several launched drugs (Figure 1), such as the sedative Zolpidem,[1] the heart failure drug Olprinone,[2] the clinical antiulcer compound Soraprazan[3] (phase II), and many other compounds in biological testing and preclinical evaluation, exemplify the wide therapeutic spectrum and active interest in this class of drug scaffolds.

Recent advances in high-throughput screening combined with the continual need for pharmaceutically attractive leads have placed an ever-increasing demand on the ability to synthesize a large number of compounds with adequate diversity and purity. To meet this challenge, new high-speed synthetic methodologies have evolved over the past decade that utilize both solid supported and solution phase chemistries.[4]

During our ongoing efforts to rapidly create diverse collections of biologically relevant molecules for lead identification, we sought to utilize these high-speed methodologies to synthesize libraries from reactable heterocyclic scaffolds and to expeditiously conduct subsequent structure–activity relationship (SAR) studies from identified leads. Ideally, these scaffolds should be synthesized by highly efficient chemical transformations that would not only tolerate a broad range of substrates but would also be flexible towards the incorporation of reactive functional handles for use in parallel synthesis. Lastly, we desired to engineer the library not only to exhibit a high degree of diversity but also to maximize its druglike properties, including those described by Lipinski in his well known rule-of-five criteria.[5] As such, the virtual library arising from our parallel reaction inputs were analyzed in silico prior to synthesis in order to assess their druglike properties and help focus the library towards these goals.[6] These predictive properties and their desired target ranges included minimization of the number of nearest neighbors, a molecular weight range of 400–450, a polar surface area[7] of 100–110, a ClogP[8] of 3.5–4.0, a number of rotatable bonds between 5 and 9, and greater than 90% overall rule-of-five compliance.

With these requirements in mind, the recently discovered three-component coupling (3-CC) of 2-aminoheterocycles, aldehydes, and isonitriles[9] (Scheme 1) proved attractive not only for the synthetic efficiency associated with modern multicomponent coupling reactions[10] but also for the precedented biological activity that the fused imidazole products have over a broad range of therapeutic targets.[1–3,11] In particular, imidazo[1,2-*a*]pyrazine and pyridine, as well as the tetrahydro variants, were ideally suited for our screening

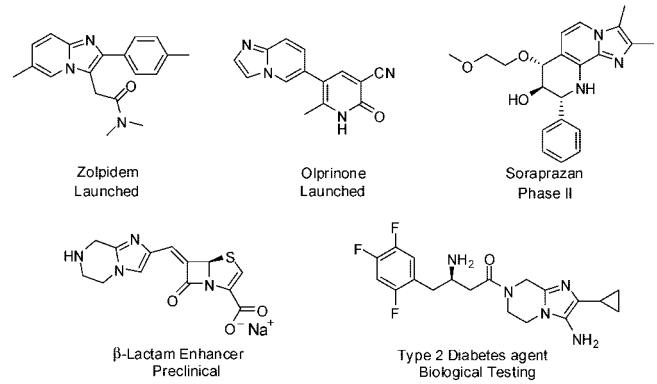

Figure 1. Examples of imidazoheterocyclic-containing therapeutics.

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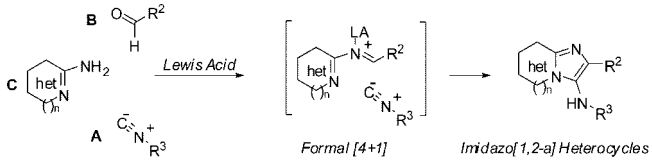
Scheme 1. Imino-isonitrile [4+1] Cycloaddition (3-CC).



interests. Optimal diversity around these heterocyclic cores was envisioned by synthesizing all three permutations of the 3-CC reaction where one component possesses the appropriate functionalization: $A^{FG}BC$, $AB^{FG}C$, ABC^{FG} (where A = isonitrile, B = aldehyde, C = aminoheterocycle, and FG = protected functional group).

Results and Discussion

Our efforts initiated with the synthesis of a diverse set of isonitriles bearing pendant, masked amines. Along these lines, a set of *N*-Boc amino isonitriles **1–3** (Figure 2) were prepared in high yield over two steps from a set of aryl and alkyl monoprotected diamines substrates. These isonitriles were obtained by *N*-formylation followed by dehydration of the resulting formamides with $POCl_3$ utilizing known procedures.[12] In a similar fashion, select groups of monofunctional isonitriles **4–12** were prepared for use in type $AB^{FG}C$ and ABC^{FG} reactions in order to introduce diversity beyond the limited commercial set of isonitriles. The reaction of isonitriles **1–12** in the central 3-CC reaction was optimally executed using catalytic $Sc(OTf)_3$ at room temperature in 2:1 CH_2Cl_2–CH_3OH, and high product purity was obtained in most cases by simple elution through a SiO_2 plug or by recrystallization. For 3-CC products derived from isonitriles **1–3**, liberation of the amine by Boc deprotection using HCl in dioxane–CH_2Cl_2 furnished the amine scaffold hydrochloride salts in high overall yield (Scheme 2 and **13–16** in Figure 3). Overall, 27 scaffolds of type $A^{FG}BC$ were synthesized in 90% minimum purity with an average two-step yield of 72%.

For use in $AB^{FG}C$ reactions, amino aldehyde components were prepared utilizing *N*-Boc amino acid precursors and partial reduction of the corresponding Weinreb amides[14] that were, in turn, prepared by mixed anhydride activation.[15] In contrast to reported procedures[16] that use diisobutylaluminum hydride (DIBAL-H), the sensitive partial reduction was best achieved using $LiAlH_4$ in THF[17] at 0 °C. Under these

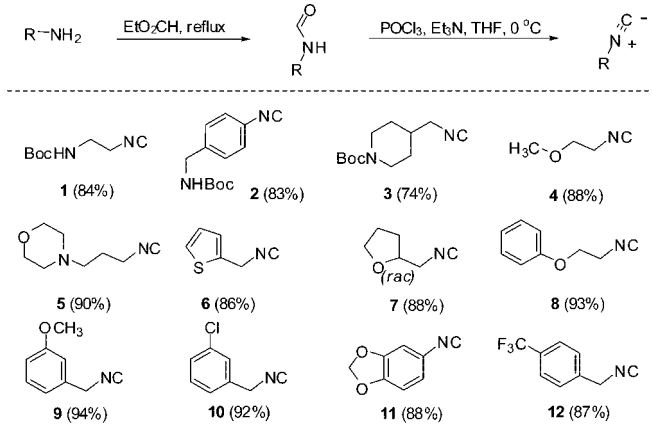
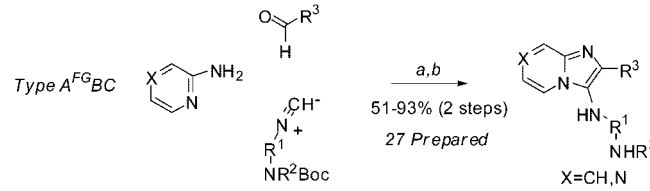


Figure 2. Synthesis of mono- and difunctional isonitriles.[13]

Scheme 2. Type $A^{FG}BC$ 3-CC Reactions[a]



[a] Reagents and conditions: (a) 5 mol % $Sc(OTf)_3$, CH_2Cl_2–CH_3OH, rt; (b) HCl, dioxane–CH_2Cl_2, rt.

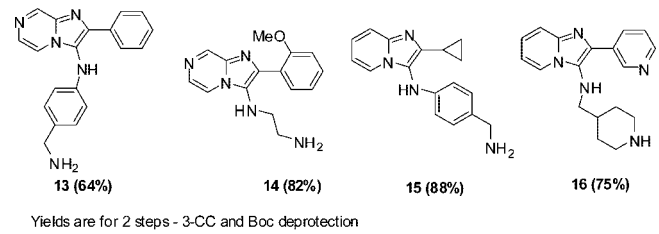


Figure 3. Representative $A^{FG}BC$ imidazo[1,2-*a*]heterocycle scaffolds.[13]

conditions, natural amino acid residues **19–21**, as well as unnatural **17** and **18**, were readily converted into the corresponding aldehyde in high yield with no over-reduction observed (Figure 4). Included in the set was *N*-Boc-glycinal **22**, which was acquired from a commercial source.

Type $AB^{FG}C$, 3-CC of these aldehydes proceeded smoothly under the aforementioned $Sc(OTf)_3$-catalyzed conditions creating 24 scaffolds with amine handles derived from component B in high overall yield (Scheme 3 and **23–26** in Figure 5). For scaffolds involving aldehyde **21**, both the *N*-Boc and *tert*-butyl ether groups were cleaved during treatment with HCl following the 3-CC reaction.

Completion of the 3-CC permutations was carried out on a limited set of functionalized amino heterocycles. Inclusion of 4-(*N*-Boc-aminoethyl)-2-aminothiazole **27**[18] in ABC^{FG} couplings provided imidazo[1,2-*a*]thiazoles in moderate yield, which exhibited an amine functional group appended to the thiazole portion of the scaffold (Scheme 4). Additional entries into this ABC^{FG} scaffold class were generated upon borane reduction[19] of the carboxamide within the heterocycle products derived from 2-aminopyridine-5-carboxamide as the

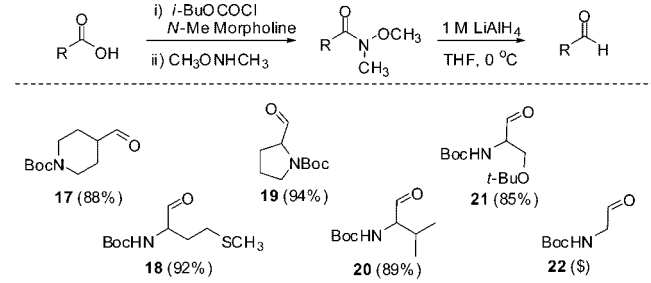
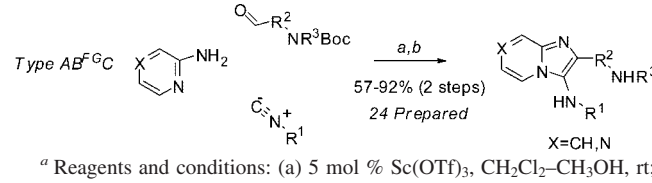


Figure 4. Representative *N*-protected amino aldehydes.[13]

Scheme 3. Type $AB^{FG}C$ 3-CC Reactions[a]



[a] Reagents and conditions: (a) 5 mol % $Sc(OTf)_3$, CH_2Cl_2–CH_3OH, rt; (b) HCl, dioxane–CH_2Cl_2, rt.

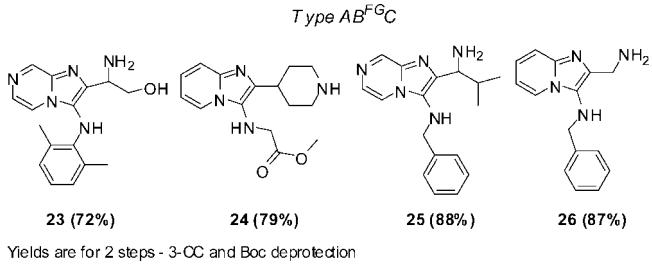
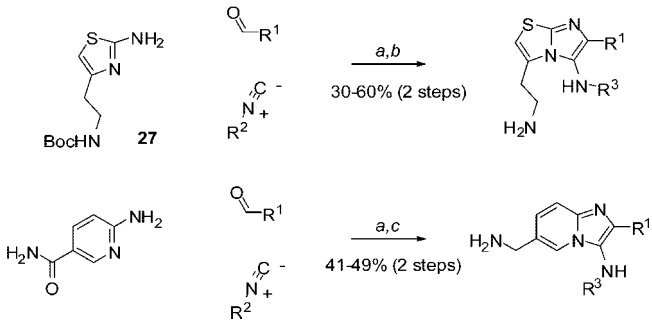


Figure 5. Representative AB^{FG}C imidazo[1,2-*a*]heterocycle scaffolds.[13]

Scheme 4. Type ABC^{FG} 3-CC Reactions[a]



[a] Reagents and conditions: (a) 5 mol % Sc(OTf)$_3$, CH_2Cl_2–CH_3OH, rt; (b) HCl, dioxane–CH_2Cl_2, rt; (c) BH_3, THF, 0 °C to rt.

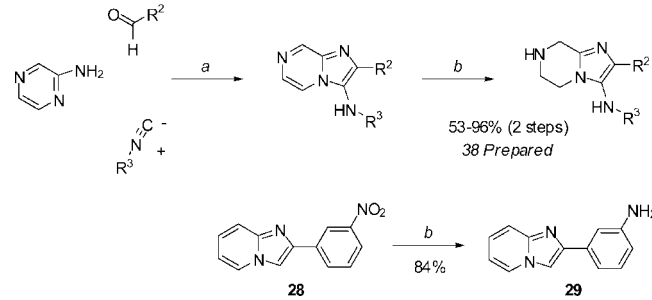
C component. However, difficulty in cleanly cleaving the reduced products from borane complexation resulted in low isolated yields, thus restricting the number of scaffolds in this group.

Having synthesized imidazo[1,2-*a*]heterocycles with various modes of functional group connectivity, we next sought to further the topological diversity of the scaffold collection to include nonplanar tetrahydro derivatives. It has been documented that imidazo[1,2-*a*]pyrazines undergo regioselective partial reduction either by hydrogenation,[20] reaction with $LiBH_4$, or under reductive amination conditions using $NaBH_3CN$[22] to provide tetrahydro[1,2-*a*]imidazopyrazines. Thus, exposure of prepared imidazopyrazines to catalytic PtO_2 in dry ethanol under an atmosphere of hydrogen gas resulted in clean reduction of the pyrazine nucleus (Scheme 5). Representative tetrahydro[1,2-*a*]imidazopyrazines products **30**–**34** are shown in Figure 6.

Furthermore, 3-(4-nitrophenyl)-imidazole[1,2-*a*]pyridine[23] **28** (Scheme 5) underwent nearly exclusive reduction of the nitro functionality under these conditions to provide the corresponding aniline scaffold **29** in 84% isolated yield.[24]

Prior to transforming the set of amine scaffolds into a library through parallel chemistry techniques, additional diversity around the imidazoheterocycle periphery was incorporated through regiospecific Mannich reaction at the C-3 position of the imidazo[1,2-*a*]pyridine. Although this site-specific transformation has been documented in the literature, the desired products are usually obtained in low to moderate yields through the use of either strongly acidic, thermal conditions[25] (excess HOAc or HCl, heat) or preformed iminium salts.[26] These harsh conditions and poor yields prompted us to seek alternative conditions that would tolerate the use of labile substrates. Li and co-workers[27] have recently shown that *N*-protected pyrroles undergo Mannich additions catalyzed by Y(OTf)$_3$ in aqueous formaldehyde.

Scheme 5. Partial Reduction of Imidazo[1,2-*a*]pyrazines[a]



[a] The reagents and conditions were the following: (a) 5 mol % Sc(OTf)$_3$, CH_2Cl_2–CH_3OH, rt; (b) H_2, 7 mol % PtO_2, EtOH, rt.

This work prompted us to investigate group IIIA and lanthanide triflates as catalysts in our systems. With only minimal experimentation, it was found that addition of imidazo[1,2-*a*]pyridine to *N*-Boc-piperazine and aqueous formaldehyde (3.00 equiv) in the presence of 10 mol % Sc(OTf)$_3$ cleanly afforded the desired Boc-protected Mannich adduct in 95% yield (80% after deprotection) at room temperature in CH_3CN (Scheme 6). These conditions[28] were subsequently applied towards the efficient synthesis of scaffolds bearing a variety of diamine subunits (**35**–**38**). Combined with the aforementioned methodologies, a total of 93 imidazo[1,2-*a*]heterocyclic scaffolds[13] were prepared for use in parallel synthesis.

Since one of the main objectives was to synthesize a library of high purity, we decided to utilize recently reported polystyrene-bound tetrafluorophenol (TFP) esters and sulfonyl esters.[29] Our attraction to these solid phase reagents was based on the several advantageous features that these reagents had over conventional acylating and sulfonylating agents. The use of excess TFP reagent did not require any supplementary quenching step, as isolation of the final product only required filtration. Additionally, the TFP reagents could be easily synthesized on a large scale with high loading capacity, and they can be stored for long periods of time at ambient temperature. Finally, a wide range of functionality could be introduced, since we could draw upon the commercial pool of carboxylic acids and sulfonic acids as inputs. Thus, a collection of 96 polystyrene-bound TFP (PS-TFP) ester and sulfonate ester inputs (Scheme 7) was prepared according to published procedures,[29] and the extent of loading was determined by ^{19}F NMR analysis. To ensure diversity within the TFP collection, alkyl, aryl, and heteroaryl acids were employed in the loading reactions (Figure 7).

Final production of a library of amides and sulfonamides was carried out on the scaffolds at an 80 μmol scale using 1.4 equiv of preloaded TFP esters. The scaffold stock solutions were prepared by treating a suspension of scaffold HCl salt in dry *N*,*N*-dimethylacetamide (DMA) with 2–3 excess equiv of *N*,*N*-diisopropylethylamine (DIEA). The mixture was sonicated until a homogenous solution was obtained, and additional DMA was added to bring the final solution concentration to 0.08 M. A 48 tube Bohdan reaction block was charged with one TFP-bound reagent per tube, followed by the addition of excess macroporous (MP) carbonate as an HCl scavenger (Scheme 8). To each tube was added additional dry DMA, and the resin was allowed

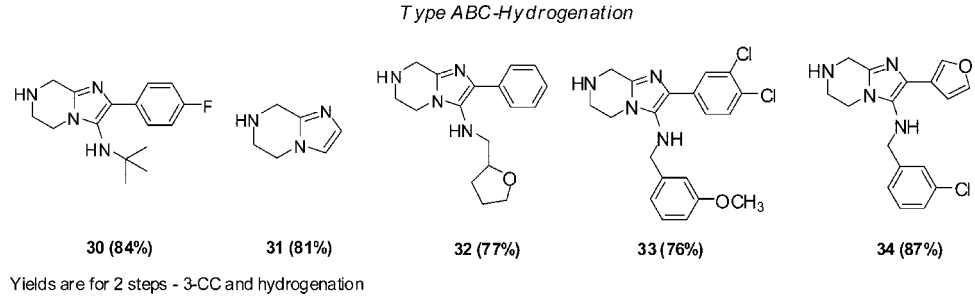
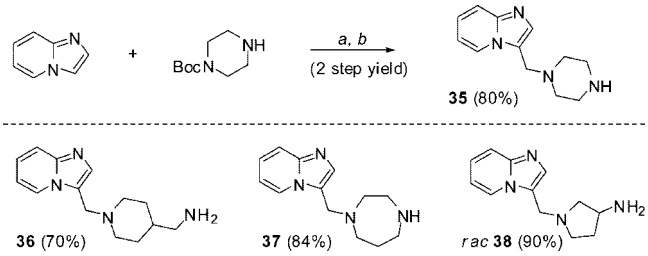


Figure 6. Representative ABC-hydrogenation scaffolds.[13]

Scheme 6. C-3 Mannich Reactions[a]

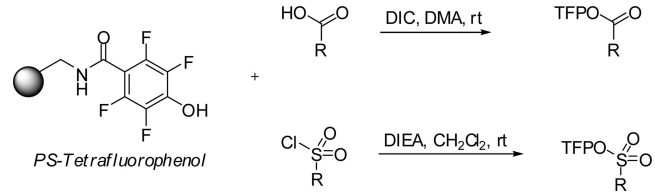


[a] Reagents and conditions: (a) 10 mol % $Sc(OTf)_3$, CH_2O(aq), CH_3CN–H_2O, rt; (b) HCl, dioxane–CH_3OH.

to swell for 5 min. The scaffold stock solution was then added to each well, after which the blocks were sealed and mixed on a platform shaker for 48 h at room temperature (rt). The supernatant solution was collected by vacuum suction into a collection plate, and the resins were sequentially washed with two wash cycles (DMA, CH_2Cl_2, and CH_3CN), for which each cycle was collected into a separate collection plate. The mother plate and the two wash plates were combined, concentrated, and aliquoted into a 96-well microtiter plate for analytical testing. These plates containing 80 compounds were serially diluted to a final theoretical product concentration of 1–2 mM. Each well was then analyzed by LCMS using UV and evaporative light scattering detection (ELSD) detection. Representative results depicting purity and mass analysis of the final compounds from the parallel synthesis of type $A^{FG}BC$ (**14**), $AB^{FG}C$ (**26**), and ABC-hydrogenation (**30**) scaffolds are summarized in Table 1.

A variety of alkyl, substituted alkyl, aryl, and heterocyclic TFP ester and sulfonyl ester inputs were used in the parallel step. Generally, acylation of the reactive amine handle provided final compounds of exceptionally high purity (>95%). The sulfonyl TFP esters, such as **39{8}** and **39{11}** (Figure 7), also gave excellent results, albeit in slightly diminished purity. A further extension of the parallel chemistry was the introduction of masked secondary amines **39{19}** and amino acids in the TFP input, such as **39{20}** and **39{21}** (Figure 7). The resulting acylated compounds could be cleanly deprotected by treatment with TFA to generate the final products with a free amine in >95% purity.[30] Overall the TFP inputs provided final compounds of exceptional purity with little or no observable bisacylation or bis-sulfonylation by LCMS analysis. In order to confirm these observations, a small set of compounds taken from each scaffold class (Figure 8) underwent NMR analysis, which was found to be in good agreement with both proposed structure and purity.

Scheme 7. TFP-Input Synthesis



Since our overall emphasis was to synthesize a screening library of high purity and owing to the magnitude of the library, individual compound yields were not determined. Instead, the overall yield for each individual core was calculated based on the mass recovery of the final plates containing 80 compounds each. The plate yield was calculated by dividing the observed mass recovery by the theoretical product mass for the entire plate. In general, the mass recoveries ranged from a low of 44% to a high of 96%, with an average of 72%.

In total, 8560 final compounds were synthesized and all were tested for analytical purity. Individual compounds were characterized by LCMS with mass analysis of the major chromatographic peak. In order to be eligible for biological testing, a compound had to achieve pass status. A compound was designated as a pass if both the observed MS correlated with that of the target and if the overall purity by area was greater then 80%. The analysis of the final library gave a total of 7465 passed compounds with an average purity of 93%[31] and 1095 failed compounds. A large portion of the compounds (682 in total) that failed the purity criteria were found to originate from scaffolds containing a cyclopropane, benzyl, isopropyl, isobutyl, or 4-*N*-dimethyl aniline in the R2 position (Figure 9). Reaction of these scaffolds frequently led to a complex mixture of products.[32] Additionally, 92 compounds were designated as failed, due to insufficient UV absorption arising from an inadequate compound concentration.

In silico screening of the final library demonstrated that we were able to prejudice the physical characteristics of the library within the prescribed parameters in order to maximize their druglike properties (Table 2). All computed values fell within their designated ranges: calculated mean polar area of 108.49 (target range of 100–110), calculated mean ClogP of 3.91 (target range of 3.5–4.0), calculated mean molecular weight of 432 (target range of 400–450), and finally the calculated mean number of rotatable bonds of 6.94 (target

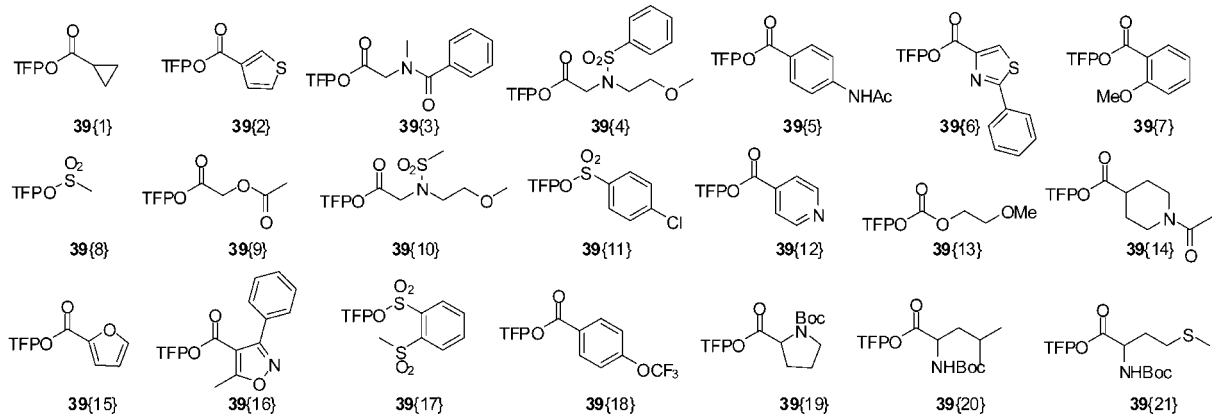
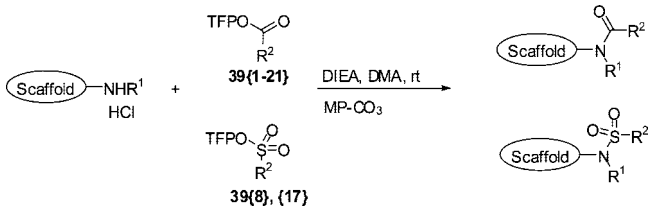


Figure 7. Select PS-TFP ester and sulfonate inputs used in parallel synthesis.[13]

Scheme 8. Production Scheme



range of 5–9). Overall, we were able to achieve an excellent rule-of-five compliance.

Conclusions

By expanding the scope of the 3-CC of aldehydes, 2-aminoheterocycles, and isonitriles through the efficient preparation of amino isonitriles and amino aldehyde inputs, we were able to synthesize a large collection of highly pure imidazo[1,2-*a*]heterocycles, incorporating diversity that was previously unobtainable. Global diversity around these heterocycles was further enhanced in two ways: first through regioselective partial reduction of imidazo[1,2-*a*]pyrazines to afford the tetrahydro variants and second through development of novel and extremely mild conditions for Mannich bond formation at the C-3 position of imidazo[1,2-*a*]pyridines. Lastly, through in silico evaluation of the druglike properties of the final library derived from TFP inputs, we were able to achieve a high value screening library of approximately 7500 compounds with a 92% rule-of-five compliance.

Experimental Section

General Methods. Unless otherwise stated, all reactions were carried out under an atmosphere of dry nitrogen. Reaction solvents were EM Science DriSolv solvents and were used without additional purification or drying. Silica gel plug filtrations and silica gel column chromatography were performed using Merck silica gel 60. Scandium trifluoromethanesulfonate [$Sc(OTf)_3$] and 1 M $LiAlH_4$ in THF were purchased from Aldrich Fine Chemicals and were used without additional purification. Platinum oxide (PtO_2) was purchased from Engelhard Corp. ^{1}H and ^{13}C NMR spectra were acquired using a Varian 400 MHz instrument.

General Method for Synthesis of *N*-Boc Amino Isonitriles. A solution of the primary amine (100 mmol) in fresh ethyl formate (200 mL) was heated at reflux for 18 h. Upon cooling to room temperature, the reaction mixture was concentrated under reduced pressure to furnish the corresponding formamide, which was used directly in the next step. A solution of the crude formamide (100 mmol) and triethyl amine (69.7 mL, 500 mmol) in dry THF (300 mL) was cooled to 0 °C, and phosphorous oxychloride (10.3 mL, 110 mmol) in THF (25 mL) was added over 45 min. The reaction was stirred at 0 °C for 2 h and for 1 h at rt. The reaction mixture was poured into cold H_2O (2× reaction volume), the organic layer was separated, and the remaining aqueous portion was extracted with Et_2O (3×). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude isonitrile was eluted through a silica gel plug (1:1 EtOAc–hexanes for elution) to furnish pure isonitrile.

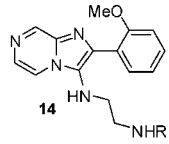
(2-Isocyano-ethyl)-carbamic Acid *tert*-Butyl Ester (1). IR (neat) υ 3335, 2960, 2147, 1699, 1518, 1168 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 3.51 (s, 2H), 3.37 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 155.8, 80.3, 42.2, 40.0, 28.5. HRMS (ESI) *m*/*z*: calcd for $C_8H_{14}N_2O_2$ (M + Na^+) 193.0947; found 193.0962.

(4-Isocyano-benzyl)-carbamic Acid *tert*-Butyl Ester (2). IR (neat) υ 2978, 2110, 1679, 1502, 1251, 1156 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 4H), 5.07 (s, 1H), 4.28 (d, J = 2.0 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 156.1, 141.1, 128.4, 126.7, 125.7 (t, J = 6.0 Hz), 80.0, 44.1, 28.6. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{16}N_2O_2$ (M + Na^+) 255.1103; found 255.1087.

4-Isocyanomethyl-piperidine-1-carboxylic Acid *tert*-Butyl Ester (3). IR (neat) υ 2960, 2147, 1690, 1411, 1355, 1162, 1128 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (bs, 2H), 3.27 (d, J = 7.0 Hz, 2H), 2.67 (dd, J = 11.2, 11.2 Hz, 2H), 1.71–1.81 (m, 3H), 1.42 (s, 9H), 1.24–1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (t, J = 5.3 Hz), 154.8, 79.8, 47.3 (t, J = 6.4 Hz), 43.4, 36.1, 29.3, 28.6. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{20}N_2O_2$ (M + Na^+) 247.1416; found 247.1433.

General Method for Synthesis of Isonitriles. A solution of the primary amine (400 mmol) in fresh ethyl formate (800 mL) was heated at reflux for 18 h. Upon cooling to room temperature, the reaction mixture was concentrated under reduced pressure to furnish the corresponding formamide, which was used directly in the next step. A solution of the crude formamide (400 mmol) and triethyl amine (223 mL,

Table 1. Representative Purity and Mass Analysis of Final Production Compounds



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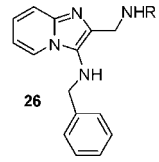

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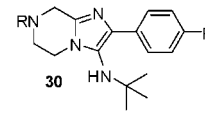


30

entry	purity (%)[a]	M + H	entry	purity (%)[a]	M + H	entry	purity (%)[a]	M + H
14{1}	100	352.179	**26{1}**	100	321.119	**30{1}**	100	357.194
14{2}	96	394.131	**26{2}**	98	363.071	**30{2}**	100	399.174
14{3}	100	459.196	**26{3}**	98	428.148	**30{3}**	96	464.224
14{4}	94	539.236	**26{4}**[b]	91	508.166	**30{4}**	97	544.22
14{5}	96	445.195	**26{5}**	100	414.12	**30{5}**	92	450.228
14{6}	92	471.166	**26{6}**	91	440.085	**30{6}**	100	476.116
14{7}	100	418.162	**26{7}**	100	387.113	**30{7}**	96	423.224
14{8}	96	362.147	**26{8}**	86	331.07	**30{8}**	85	367.189
14{9}[b]	92	384.151	**26{9}**	100	353.097	**30{9}**	86	389.211
14{10}	96	477.218	**26{10}**	100	446.13	**30{10}**	100	482.223
14{11}	96	458.134	**26{11}**	97	427.029	**30{11}**	97	463.164
14{12}	97	389.175	**26{12}**	100	358.142	**30{12}**	100	394.21
14{13}	100	370.175	**26{13}**	94	339.127	**30{13}**	97	391.199
14{14}[b]	98	437.222	**26{14}**[c]	98	406.205	**30{14}**[c]	95	442.224
14{15}	100	378.164	**26{15}**	100	347.098	**30{15}**	100	383.16
14{16}	100	469.178	**26{16}**	100	438.118	**30{16}**	97	474.205
14{17}	100	502.173	**26{17}**	82	471.037	**30{17}**	93	507.15
14{18}[b]	100	424.186	**26{18}**[b]	98	441.091	**30{18}**	96	477.166
14{19}[f]	94	381.88	**26{19}**[f]	100	350.138	**30{19}**[c]	100	386.165
14{20}[f]	96	397.224	**26{20}**[f]	95	366.173	**30{20}**[f]	100	402.18
14{21}[f]	100	415.166	**26{21}**[f]	96	384.15	**30{21}**[f]	100	420.155
average pass purity[d]	96			98			98	
plate yield[e]	91			56			73	

[a] Purity based on HPLC area percent at 254 nm unless otherwise noted. [b] Purity based on HPLC area percent at 220 nm. [c] Purity based on HPLC area percent using ELSD. [d] Average pass purity was calculated from all library compounds of >80% purity derived from that scaffold. [e] Plate yield was calculated by dividing the observed mass recovery by the theoretical mass recovery of the total plate. [f] Purity and mass identification is based on the TFA deprotected material.

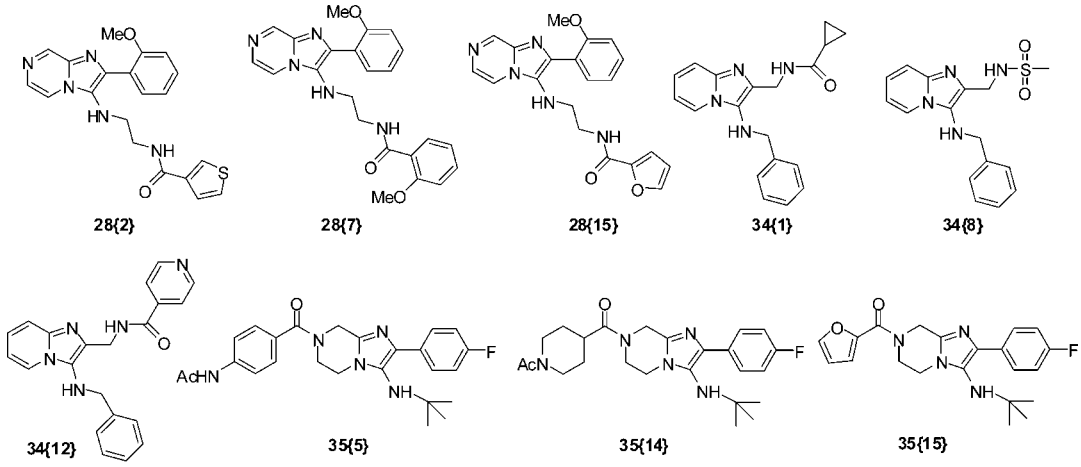
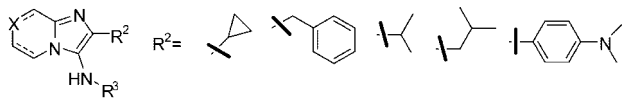


Figure 8. Representative final production compounds.



X = NH for saturated or unsaturated core
= CH for pyrimidine core

Figure 9. Scaffolds that generated low purity final compounds.

1600 mmol) in dry THF (1000 mL) was cooled to 0 °C, and phosphorous oxychloride (41.0 mL, 440 mmol) in THF (100 mL) was added over 45 min. The reaction was stirred at 0 °C for 2 h and for 1 h at rt. The reaction mixture was poured into cold H_2O (1500 mL), the organic layer was separated, and the remaining aqueous portion was extracted with Et_2O (3×). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude isonitrile was eluted through a silica gel plug (Et_2O for elution) to furnish the pure isonitrile.

1-Isocyano-2-methoxy-ethane (4). IR (neat) υ 2933, 2150, 1680, 1443, 1322, 1121, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.50–3.54 (m, 4H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (t, $J = 6.6$ Hz), 69.9, 59.2, 41.8 (t, $J = 7.1$ Hz). HRMS (EI) *m/z*: calcd for $C_4H_7NO^+$ 85.0522; found 85.0522.

2-Isocyanomethyl-thiophene (6). IR (neat) υ 2974, 2149, 1437, 1368, 1220, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, $J = 5.2$, 1.2 Hz, 1H), 7.07 (d, $J = 3.6$ Hz, 1H),

Table 2. Library Characteristics

library size	7465
average purity	93%[a]
median # of nearest neighbors	13
mean polar surface area	108.49
poor permeability	2.88%[b]
mean ClogP	3.91
mean MW	432
mean # of rotatable bonds	6.94
rule-of-five compliance	92%

[a] Area percent from HPLC analysis at 254 nM, 220 nM, or ELSD. [b] A compound was considered to have poor permeability if the computed, polar surface area exceeded 200.[7,33]

6.99 (dd, $J = 3.6$, 3.6 Hz, 1H), 4.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (t, $J = 5.3$ Hz), 134.6, 127.3, 127.2, 126.6, 40.8 (t, $J = 6.6$ Hz). HRMS (EI) *m/z*: calcd for C_6H_5NS 123.0137; found 123.0138.

2-Isocyanomethyl-tetrahydro-furan (7). IR (neat) υ 2979, 2875, 2152, 1440, 1080, 922 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (dddd, $J = 4.0$, 4.0, 4.0, 2.0 Hz, 1H), 3.95 (ddd, $J = 6.4$, 6.4, 1.6 Hz, 1H), 3.81 (ddd, $J = 6.4$, 6.4, 1.6 Hz, 1H), 3.43–3.54 (m, 2H), 2.04–2.14 (m, 1H), 1.91–2.04 (m, 2H), 1.74–1.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (t, $J = 6.1$ Hz), 76.0, 69.2, 45.9 (t, $J = 7.4$ Hz), 28.9, 25.9.

(2-Isocyano-ethoxy)-benzene (8). IR (neat) υ 2936, 2359, 2152, 1597, 1495, 1244 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, $J = 7.2$, 7.2 Hz, 2H), 7.00 (dd, $J = 7.2$, 7.2 Hz, 1H), 6.91 (d, $J = 7.2$ Hz, 2H), 4.16 (t, $J = 5.6$ Hz, 2H), 3.77 (t, $J = 5.6$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (t, $J = 4.5$ Hz), 158.9, 130.8, 122.9, 115.9, 66.4, 42.4 (t, $J = 7.6$ Hz). HRMS (EI) *m/z*: calcd for C_9H_9NO 147.0678; found 147.0683.

1-Isocyanomethyl-3-methoxy-benzene (9). IR (neat) υ 2939, 2147, 1600, 1493, 1432, 1258 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, $J = 8.0$, 8.0 Hz, 1H), 6.87–6.92 (m, 3H), 4.61 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 157.9 (t, $J = 5.4$ Hz), 134.0, 130.3, 119.0, 114.1, 112.4, 55.5, 45.6 (t, J= 7.6 Hz). HRMS (EI) *m/z*: calcd for C_9H_9NO 147.0678; found 147.0675.

1-Chloro-3-isocyanomethyl-benzene (10). IR (neat) υ 2138, 1471, 1426, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.35 (m, 3H), 7.22–7.26 (m, 1H), 4.63 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (t, $J = 5.3$ Hz), 130.0, 129.1, 125.3, 123.7, 121.8, 119.7, 40.0 (t, $J = 7.6$ Hz). HRMS (EI) *m/z*: calcd for C_8H_6ClN 151.0183; found 151.0197.

5-Isocyano-benzo[1,3]dioxole (11). IR (neat) υ 2916, 2126, 1499, 1487, 1255, 922, 848, 805 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.83 (d, $J = 2.0$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.03 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 148.6, 148.2, 121.1, 120.1 (t, $J = 3.7$ Hz), 108.6, 107.4, 102.4. HRMS (EI) *m/z*: calcd for $C_8H_5NO_2$ 147.0314; found 147.0301.

1-Isocyanomethyl-4-trifluoromethyl-benzene (12). IR (neat) υ 2151, 1416, 1328, 1164, 1118, 1064 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, $J = 8.0$ Hz, 2H), 7.49 (d, $J = 8.0$ Hz, 2H), 4.72 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (t, $J = 5.3$ Hz), 136.3, 130.9 (q, $J = 32.2$ Hz), 127.1, 126.3, 124.0 (q, $J = 270.2$ Hz), 45.3 (t, $J = 7.2$ Hz). HRMS (EI) *m/z*: calcd for $C_9H_6F_3N$ 185.0446; found 185.0465.

General Method for Synthesis of *N*-Boc Amino Aldehydes. A solution of the *N*-Boc amino acid (100 mmol) and triethylamine (41.8 mL, 300 mmol) in dry THF (75 mL) was cooled to 0 °C, and isobutyl chloroformate (15.6 mL, 120 mmol) was added over 5 min. The reaction was allowed to stir at 0 °C for 30 min, followed by 3 h at rt. *N,O*-Dimethylhydroxylamine–HCl (11.7 g, 120 mmol) was added, and the reaction was stirred for 12 h at rt. The reaction mixture was diluted with 1 N HCl, the organic layer was removed, and the remaining aqueous layer was extracted with EtOAc (3×). The combined organic fractions were washed with saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated to give the desired Weinreb amide as a clear oil, which was used without further purification. A solution of the Weinreb amide in THF (75 mL) was cooled to 0 °C, and 1 M $LiAlH_4$ in THF (50.0 mmol, 50.0 mL) was added dropwise over 10 min. The reaction was stirred at 0 °C for 10 min, after which the reaction was cooled to −40 °C and quenched by the careful addition of 1 M $KHSO_4$. The reaction mixture was warmed to rt and was diluted with EtOAc. The mixture was treated with 1 M HCl until the aqueous layer became homogenous. The EtOAc layer was removed, and the remaining aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give the desired aldehyde in greater than 90% purity as indicated by ^{1}H NMR analysis and matched literature characterizations for **17**,[34] **18**,[35] **19**,[36] **20**,[37] and **21**.[38] The aldehydes were used without further purification in the 3-CC reaction.

General Method for the Imino-isonitrile Formal [4+1] Cycloaddition (3-CC). The following constitutes the general procedure used for the three-component coupling of 2-aminoheterocycles, aldehydes, and isonitriles: To a solution of the 2-aminoheterocycle (25.0 mmol) and aldehyde (26.3 mmol) in 2:1 CH_2Cl_2–CH_3OH (85 mL) was added $Sc(OTf)_3$ (615 mg, 1.25 mmol), and the mixture was stirred at rt for 30 min. The isonitrile (27.5 mmol) was added in one portion, and the reaction mixture was stirred for 18 h at room temperature. The reaction was directly filtered through a silica gel plug elution with ethyl acetate to provide the crude imidazo[1,2-*a*]heterocycle. In most cases, the crude material was of ample purity (85–90% by HPLC) for direct use in the next synthetic step. When required, additional purification was achieved via chromatography on silica gel (40% EtOAc/hexanes then EtOAc for elution) or by recrystallization from 50% EtOAc/hexanes.

General Method for *N*-Boc Deprotection. Removal of the *N*-Boc protecting groups from 3-CC products was carried out as follows: A solution of the *N*-Boc imidazoheterocycle (20.0 mmol) in 2:1 dioxane–CH_2Cl_2 (100 mL) was cooled to 0 °C, and anhydrous 4 M HCl–dioxane (160 mmol, 40 mL) was added with vigorous stirring. The mixture was allowed to slowly reach rt over 1 h and was stirred for 16 h at rt. The reaction mixture was concentrated, and the residual solid was washed thoroughly with dry Et_2O to furnish the desired scaffold–HCl salt as a powder after drying in vacuo.

(4-Aminomethyl-phenyl)-(2-phenyl-imidazo[1,2-*a*]pyrazin-3-yl)-amine (13). ^{1}H NMR (400 MHz, D_2O) δ 9.18 (s, 1H), 8.30 (dd, J = 5.2, 1.2 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.73–7.76 (m, 2H), 7.31–7.33 (m, 3H), 7.12 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 3.90 (s, 2H). ^{13}C NMR (100 MHz, D_2O) δ 143.3, 142.8, 135.4, 134.1, 130.7, 129.2, 128.8, 127.7, 125.6, 125.1, 123.2, 119.5, 115.3, 42.8. HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{17}N_5$ (MH+) 316.1556; found 316.1557.

***N*-[2-(2-Methoxy-phenyl)-imidazo[1,2-*a*]pyrazin-3-yl]-ethane-1,2-diamine (14).** ^{1}H NMR (400 MHz, D_2O) δ 8.94 (s, 1H), 8.35 (dd, J = 5.2, 1.2 Hz, 1H), 7.85 (d, J = 5.2, Hz, 1H), 7.42–7.48 (m, 2H), 7.03–7.10 (m, 2H), 3.73 (s, 3H), 3.20 (t, J = 6.0 Hz, 2H), 2.8 (t, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, D_2O) δ 157.1, 136.2, 134.2, 133.6, 132.7, 132.3, 131.5, 122.4, 121.5, 118.3, 117.5, 112.1, 55.9, 42.1, 39.2. HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{17}N_5O$ (MH+) 284.1505; found 284.1510.

(4-Aminomethyl-phenyl)-(2-cyclopropyl-imidazo-[1,2-*a*]pyridin-3-yl)-amine (15). ^{1}H NMR (400 MHz, D_2O) δ 8.09 (dd, J = 6.8, 1.2 Hz, 1H), 7.71 (dd, J = 6.8, 6.8 Hz, 1H), 7.62 (dd, J = 9.2, 0.8 Hz, 1H), 7.19 (dd, J = 6.8, 6.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 8.4 Hz, 2H), 3.91 (s, 2H), 1.88–1.95 (m, 1H), 0.91–0.99 (m, 2H), 0.78–0.81 (m, 2H). ^{13}C NMR (100 MHz, D_2O) δ 145.4, 137.2, 134.3, 133.4, 130.8, 124.6, 124.2, 120.5, 117.0, 114.1, 111.7, 42.8, 6.9, 5.1. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{19}N_4$ P(MH+) 279.1604; found 279.1605.

Piperidin-4-ylmethyl-(2-pyridin-3-yl-imidazo[1,2-*a*]-pyridin-3-yl)-amine (16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, J = 2.0 Hz, 1H), 8.81 (ddd, J = 8.4, 2.0, 2.0 Hz, 1H), 8.76 (d, J = 6.4 Hz, 1H), 8.51 (d, J = 6.4 Hz, 1H), 8.08 (dd, J = 8.4, 6.4 Hz, 1H), 7.83–7.87 (m, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.39 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 3.26 (d, J = 12.8 Hz, 2H), 2.88 (d, J = 6.8 Hz, 2H), 2.79 (ddd, J = 12.8, 12.8, 2.8 Hz, 2H), 1.86 (d, J = 12.8 Hz, 2H), 1.66–1.74 (m, 1H), 1.20–1.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 140.7, 139.0, 136.2, 133.0, 128.4, 125.9, 125.4, 123.3, 117.6, 115.6, 110.4, 50.3, 41.8, 32.4, 24.3. HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{22}N_5$ (MH+) 308.1869; found 308.1870.

2-Amino-2-[3-(2,6-dimethyl-phenylamino)-imidazo-[1,2-*a*]pyrazin-2-yl]-ethanol (23). ^{1}H NMR (400 MHz, D_2O) δ 8.89 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.51 (d, J = 5.6 Hz, 1H), 7.08 (s, 3H), 3.95 (t, J = 9.6 Hz, 1H), 3.55 (bs, 2H), 1.99 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 136.2, 135.0, 134.8, 134.4, 133.0, 132.8, 129.2, 129.1, 127.4, 118.5, 117.7, 62.6, 60.9, 49.7, 17.4. HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{20}N_5O$ (MH+) 298.1662; found 298.1667.

(2-Piperidin-4-yl-imidazo[1,2-*a*]pyridin-3-ylamino)-acetic Acid Methyl Ester (24). ^{1}H NMR (400 MHz, D_2O) δ 8.45 (d, J = 6.8 Hz, 1H), 7.72 (ddd, J = 9.2, 6.8, 0.8 Hz, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.28 (ddd, J = 9.2, 6.8, 0.8 Hz, 1H), 3.82 (s, 2H), 3.57 (s, 3H), 3.42–3.53 (m, 3H), 3.09 (ddd, J = 13.2, 13.2, 4.0 Hz, 2H), 2.04–2.08 (m, 2H), 1.95 (ddd, J = 13.2, 13.2, 4.0 Hz, 2H). ^{13}C NMR (100 MHz, D_2O) δ 171.2, 137.2, 133.4, 129.7, 126.6, 125.2, 116.8, 111.6, 52.7, 48.6, 43.9, 29.7, 27.4. HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{21}N_4O_2$ (MH+) 289.1659; found 289.1661.

[2-(1-Amino-2-methyl-propyl)-imidazo[1,2-*a*]pyrazin-3-yl]-benzyl-amine (25). ^{1}H NMR (400 MHz, D_2O) δ 8.91 (s, 1H), 8.28 (dd, J = 5.6, 0.8 Hz, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.17–7.22 (m, 5H), 4.42 (s, 2H), 4.17 (d, J = 8.0 Hz, 1H), 2.13 (dddd, J = 11.6, 5.8, 5.8, 5.8 Hz, 1H), 1.70 (m, 1H), 0.84 (d, J = 5.8 Hz, 3H), 0.60 (d, J = 5.8 Hz, 3H). ^{13}C NMR (100 MHz, D_2O) δ 139.9, 138.6, 135.4, 135.0, 133.6, 129.3, 128.2, 127.6, 118.8, 68.0, 53.6, 49.0, 32.1, 25.1, 18.1, 17.4. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{21}N_5$ (MH+) 296.1869; found 296.1872.

[2-Aminomethyl-imidazo[1,2-*a*]pyridin-3-yl)-benzyl-amine (26). ^{1}H NMR (400 MHz, D_2O) δ 8.34 (d, J = 6.8 Hz, 1H), 7.79 (dd, J = 7.2, 7.2 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.29 (dd, J = 7.2, 7.2 Hz, 1H), 7.20–7.22 (m, 3H), 7.08–7.11 (m, 3H), 4.11 (s, 2H), 3.82 (s, 2H). ^{13}C NMR (100 MHz, D_2O) δ 138.4, 137.8, 134.8, 130.4, 129.1, 128.7, 128.3, 125.3, 118.7, 117.4, 112.3, 51,2, 32.0. HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{17}N_4$ (MH+) 253.1447; found 253.1442.

General Method for the Partial Hydrogenation of Imidazo[1,2-*a*]pyrazines. To a solution of the imidazo[1,2-*a*]pyrazine (20.0 mmol) in absolute EtOH (80 mL) was added PtO_2 (318 mg, 1.40 mmol), and the flask was purged with H_2 gas. The mixture was stirred at rt under a balloon atmosphere of hydrogen until total consumption of substrate was observed by thin-layer chromatography (TLC) analysis (18–48 h). During the course of reaction, additional PtO_2 (227 mg, 1.00 mmol) was added if the reaction was not complete after 18 h. *Note: A nitrogen purging of the reaction flask prior to the addition of fresh catalyst was performed in order to prevent ignition.* After completion, the reaction was purged with nitrogen, diluted with Et_2O (100 mL), and treated with activated charcoal. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification of the crude material was carried out via silica gel chromatography (EtOAc then 20% (9:1 NH_4OH/MeOH)/EtOAc for elution).

***tert*-Butyl-[2-(4-fluoro-phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl]-amine (30).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (ddd, J = 8.8, 8.8, 2.0 Hz, 2H), 7.02 (dd, J = 8.8, 8.8 Hz, 2H), 4.10 (s, 2H), 3.81 (dd, J = 6.8, 6.8, 2H), 3.19 (dd, J = 6.8, 6.8, 2H), 2.71 (bs, 1H), 2.20 (bs, 1H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.5, 139.9, 132.8, 132.2, 132.1, 129.1, 129.0, 128.9, 115.3, 115.0, 55.5, 45.1, 43.4, 43.3, 30.5. HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{22}FN_4$ (MH+) 289.1823; found 289.1822.

5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyrazine (31). ^{1}H NMR (400 MHz, D_2O) δ 7.41 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 4.71 (s, 2H), 4.43 (t, J = 6.0 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, D_2O) δ 136.3, 121.9, 120.2, 42.1, 40.4, 39.2. HRMS (ESI) *m*/*z*: calcd for $C_6H_9N_3$ (MH+) 124.0869; found 124.0868.

(2-Phenyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrazin-3-yl)-(tetrahydro-furan-2-ylmethyl)-amine (32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0, 2H), 7.36 (dd, J = 7.6, 7.6 Hz, 2H), 7.16 (dd, J = 7.6, 7.6 Hz, 1H), 4.07 (s, 2H), 3.99–4.03 (m, 1H), 3.75–3.89 (m, 4H), 3.32 (bs, 1H), 3.24 (dd, J = 5.2, 5.2 Hz, 2H), 2.92–3.08 (m, 2H), 1.86–1.96

(m, 4H), 1.54–1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 135.1, 132.6, 128.6, 128.0, 125.9, 125.6, 78.3, 68.2, 53.4, 45.0, 43.1, 42.4, 28.9, 26.1. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{23}N_4O$ (MH+) 299.1866; found 299.1868.

[2-(3,4-Dichloro-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2-*a*]pyrazin-3-yl]-(3-methoxy-benzyl)-amine (33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 8.4, 2.0 Hz, 1H), 7.35–7.39 (m, 2H), 7.22–7.26 (m, 1H), 6.80–6.86 (m, 3H), 4.04–4.07 (m, 4H), 3.77 (s, 3H), 3.57–3.60 (m, 2H), 3.12–3.15 (m, 2H), 3.08 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 140.7, 139.7, 135.2, 132.7, 132.6, 130.5, 130.0, 129.4, 128.6, 127.3, 127.2, 124.8, 120.6, 113.9, 113.3, 55.5, 53.6, 45.0, 43.1, 42.5. HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{21}Cl_2N_4O$ (MH+) 403.1086; found 403.1082.

(3-Chloro-benzyl)-(2-furan-3-yl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrazin-3-yl)-amine (34). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.26–7.27 (m, 2H), 7.16–7.17 (m, 1H), 6.74 (s, 1H), 4.06–4.07 (m, 4H), 3.58 (t, J = 6.5 Hz, 2H), 3.15 (t, J = 6.5 Hz, 2H), 3.05 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 141.4, 139.5, 138.4, 134.7, 130.8, 130.1, 128.5, 128.0, 126.6, 123.6, 119.7, 108.8, 53.1, 44.7, 43.0, 42.8. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{17}CLN_4O$ (MH+) 329.1163; found 329.1158.

General Method for Mannich Reaction with Imidazo[1,2-*a*]pyridine. A solution of the mono-Boc diamine (22.0 mmol) and formaldehyde (5.00 mL, 60.0 mmol, 37% in H_2O) in 6:1 CH_3CN–H_2O (70 mL) was stirred at rt for 15 min. Imidazo[1,2-*a*]pyridine (2.03 mL, 20.0 mmol) and $Sc(OTf)_3$ (984 mg, 2.00 mmol) were added sequentially, and the reaction was stirred at rt for 24 h. The reaction mixture was poured into 1 M K_2CO_3 (150 mL), and the mixture was extracted with EtOAc (3×). The combined extracts were washed with half-saturated NaCl solution (2×), brine, dried over $MgSO_4$, and eluted through a plug of silica gel (EtOAc elution) to provide the Mannich adduct in pure form. The Mannich product was dissolved in MeOH (150 mL), and 4 M HCl–dioxane (50.0 mL, 200 mmol) was added. After stirring for 6 h, the mixture was concentrated in vacuo and the resulting solids were washed thoroughly with dry Et_2O. Additional drying in vacuo afforded the desired scaffold–HCl salt as a white solid. If required, additional purification was achieved by washing the salt with *i*PrOH.

3-Piperazin-1-ylmethyl-imidazo[1,2-*a*]pyridine (35). ^{1}H NMR (400 MHz, D_2O) δ 8.75 (d, J = 6.8 Hz, 1H), 8.12 (s, 1H), 7.81–7.91 (m, 2H), 7.44 (ddd, J = 6.8, 6.8, 1.2 Hz, 1H), 4.75 (s, 2H), 3.40–3.45 (m, 8H). ^{13}C NMR (100 MHz, D_2O) δ 141.0, 135.1, 127.0, 126.1, 118.2, 116.3, 112.8, 48.5, 48.3, 41.4, 40.5. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{16}N_4$ (MH+) 217.1447; found 217.1446.

(1-((*H*-Imidazo[1,2-*a*]pyridin-3-yl)methyl)piperidin-4-yl)-methanamine (36). ^{1}H NMR (400 MHz, D_2O) δ 8.75 (d, J = 6.8 Hz, 1H), 8.17 (s, 1H), 7.85–7.95 (m, 2H), 7.48 (dd, J = 6.8, 6.8 Hz, 1H), 4.82 (s, 2H), 3.58 (d, J = 12.0 Hz, 2H), 3.13 (dd, J = 12.0, 12.0 Hz, 2H), 2.84 (d, J = 6.0 Hz, 2H), 1.96 (m, 3H), 1.46 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ 141.2, 135.0, 126.3, 118.4, 118.3, 115.6, 113.0, 51.8, 47.5, 43.3, 31.3. HRMS (ESI) *m*/*z*: calcd for $C_{14}H_{20}N_4$ (MH+), 245.1760; found, 245.1764.

3-[1,4]Diazepan-1-ylmethyl-imidazo[1,2-*a*]pyridine (37). ^{1}H NMR (400 MHz, D_2O) δ 8.77 (d, J = 5.8 Hz, 1H), 8.18 (s, 1H), 7.85–7.95 (m, 2H), 7.48 (dd, J = 5.8, 1.2 Hz, 1H), 4.88 (s, 2H), 3.71 (dd, J = 4.4, 4.4 Hz, 2H), 3.55 (dd, J = 4.4, 4.4 Hz, 2H), 3.47 (dd, J = 5.6, 5.6 Hz, 2H), 3.37 (dd, J = 5.6, 5.6 Hz, 2H), 2.15 (dddd, J = 5.6, 5.6, 5.6, 5.6 Hz, 2H). ^{13}C NMR (100 MHz, D_2O) δ 141.1, 135.2, 126.8, 126.6, 118.3, 116.3, 112.9, 54.2, 50.3, 48.6, 44.5, 41.1, 21.2. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{18}N_4$ (MH+) 231.1604; found 231.1604.

1-Imidazo[1,2-*a*]pyridin-3-ylmethyl-pyrrolidin-3-yl-amine (38). ^{1}H NMR (400 MHz, D_2O) δ 8.77 (d, J = 5.8 Hz, 1H), 8.20 (s, 1H), 7.85–7.95 (m, 2H), 7.48 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 4.98 (s, 2H), 4.14 (dddd, J = 3.0, 3.0, 2.0, 2.0 Hz, 1H), 3.91 (dd, J = 12.8, 8.4 Hz, 1H), 3.48–3.65 (m, 3H), 2.54 (dddd, J = 4.0, 2.0, 2.0, 2.0 Hz, 1H), 2.13 (dddd, J = 4.0, 2.0, 2.0, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, D_2O) δ 141.1, 135.3, 126.7, 126.0, 118.4, 116.6, 112.9, 55.6, 52.9, 47.9, 45.7, 28.1. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{16}N_4$ (MH+) 217.1447; found 217.1446.

General Method for Parallel Synthesis. Production of the library was carried out utilizing 48 tube Bohdan blocks in conjunction with a Packard liquid handler and Bohdan platform shakers. The scaffold stock solutions were prepared as follows: The corresponding scaffold–HCl (8.80 mmol) was placed into a volumetric bottle containing anhydrous DMA (80.0 mL). A minimum of 1 equiv excess of DIEA was added to free base and dissolve the scaffold (i.e., 1 HCl salt–2 equiv DIEA; 3 HCl salt–4 equiv DIEA). Additional DMA was added to bring the total volume to 110 mL (0.08 M solution). The Bohdan blocks were charged with one TFP-bound reagent (120 μmol, 1.50 equiv) per tube followed by the addition of MP carbonate (3.00 equiv minimum). To each tube was added anhydrous DMA (800 μL), and the resin was allowed to swell for 10 min. The scaffold solution (1.00 mL, 80.0 μmol, 0.08 M) was then added to each tube, after which the blocks were sealed and vortexed on a platform shaker for 48 h at rt. The supernatant solution was collected into an appropriate collection plate, and the resins were sequentially washed with two 1.8 mL wash cycles (600 μL each of DMA, DCM, and CH_3CN), for which each cycle was collected into a separate collection plate. The mother plate and the two wash plates were concentrated, combined, and daughtered for analytical testing.

***N*-(2-(2-(2-Methoxyphenyl)imidazo[1,2-*a*]pyrazin-3-ylamino)ethyl)thiophene-3-carboxamide. 14{2}.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.96 (d, J = 4.4 Hz, 1H), 7.82–7.84 (m, 2H), 7.59 (s, 1H), 7.42 (dd, J = 8.0, 8.0 Hz, 1H), 7.27–7.31 (m, 1H), 7.14–7.18 (m, 2H), 6.97 (d, J = 8.0 Hz, 1H), 6.04 (bs, 1H), 4.35 (dd, J = 6.4, 6.4 Hz, 1H), 3.80 (s, 3H), 3.26–3.30 (m, 2H), 3.17–3.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 156.3, 143.6, 137.3, 137.1, 135.5, 132.0, 130.3, 129.1, 128.8, 128.4, 126.6, 126.2, 122.9, 122.2, 115.4, 112.2, 56.6, 46.5, 40.1. LRMS (APCI) *m*/*z*: calcd for $C_{20}H_{19}N_5O_2S$ (MH+) 394.1; found 394.2.

2-Methoxy-*N*-(2-(2-(2-methoxyphenyl)imidazo[1,2-*a*]-pyrazin-3-ylamino)ethyl)benzamide. 14{7}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.15 (dd, J = 0.8, 0.8 Hz, 1H), 7.99 (dd, J = 0.8, 8.0 Hz, 1H), 7.92 (bs, 1H), 7.79–7.81

(m, 2H), 7.46 (ddd, J = 8.0, 8.0, 0.8 Hz, 1H), 7.36 (ddd, J = 8.0, 8.0, 0.8 Hz, 1H), 7.08–7.12 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.34 (bs, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.51 (dd, J = 6.0, 6.0 Hz, 2H), 3.16 (dd, J = 6.0, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.5, 156.3, 143.6, 137.2, 135.4, 133.1, 132.4, 131.9, 130.0, 129.5, 129.0, 122.9, 121.8, 121.6, 121.4, 115.4, 111.8, 111.5, 56.4, 56.1, 47.3, 40.4. LRMS (APCI) *m*/*z*: calcd for $C_{23}H_{23}N_5O_3$ (MH+) 418.2; found 418.1.

***N*-(2-(2-(2-Methoxyphenyl)imidazo[1,2-*a*]pyrazin-3-ylamino)ethyl)furan-2-carboxamide. 14{15}.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.95 (dd, J = 4.8, 0.8 Hz, 1H), 7.82–7.84 (m, 2H), 7.57 (dd, J = 2.8, 0.8 Hz, 1H), 7.43 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.30–7.32 (m, 1H), 7.14–7.19 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 5.87 (bs, 1H), 4.35 (dd, J = 6.4, 6.4 Hz, 1H), 3.80 (s, 3H), 3.25–3.28 (m, 2H), 3.18–3.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 155.0, 142.5, 136.1, 135.9, 134.4, 130.8, 129.2, 127.9, 127.5, 127.2, 125.5, 124.9, 121.7, 121.1, 114.2, 111.0, 55.4, 45.2, 38.9. LRMS (APCI) *m*/*z*: calcd for $C_{20}H_{19}N_5O_3$ (MH+) 378.17; found 378.1.

***N*-((3-(Benzylamino)imidazo[1,2-*a*]pyridine-2-yl)methyl)bicyclopropanecarboxamide 26{1}.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 6.4 Hz, 1H), 7.69 (bs, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.22–7.29 (m, 4H), 7.10 (ddd, J = 6.8, 6.8, 1.2 Hz, 1H), 6.74 (dd, J = 6.4, 6.4 Hz, 1H), 4.78 (dd, J = 6.4, 6.4 Hz, 1H) 4.11–4.14 (m, 4H), 1.39 (ddd, J = 4.4, 4.4, 4.4 Hz, 1H), 1.26 (dd, J = 7.2, 7.2 Hz, 1H), 0.89–0.93 (m, 2H), 0.63–0.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 141.4, 139.6, 134.7, 128.7, 128.6, 127.6, 127.5, 123.8, 122.9, 117.1, 111.7, 52.8, 36.3, 14.7, 7.3. LRMS (APCI) *m*/*z*: calcd for $C_{19}H_{20}N_4O$ (MH+) 321.16; found 321.2.

***N*-((3-(Benzylamino)imidazo[1,2-*a*]pyridine-2-yl)methyl)methanesulfonamide 26{8}.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 6.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.15–7.35 (m, 6H), 6.80 (dd, J = 6.4, 6.4 Hz, 1H), 6.29 (bs, 1H), 4.12 (d, J = 6.4 Hz, 2H), 4.05 (d, J = 5.6 Hz, 2H), 3.90 (dd, J = 6.4, 6.4 Hz, 1H) 3.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.1, 132.8, 128.9, 128.6, 128.0, 126.9, 126.6, 125.6, 123.0, 117.0, 112.7, 52.9, 41.4, 39.1. LRMS (APCI) *m*/*z*: calcd for $C_{16}H_{18}N_4O_2S$ (MH+) 331.12; found 331.1.

***N*-((3-(Benzylamino)imidazo[1,2-*a*]pyridine-2-yl)methyl)isonicotinamide 26{12}.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (bs, 1H), 8.57 (dd, J = 2.0, 4.8 Hz, 2H), 8.05 (d, J = 7.2 Hz, 1H), 7.63 (dd, J = 2.0, 4.8 Hz, 2H), 7.24–7.31 (m, 5H), 7.17 (d, J = 8.8 Hz, 1H), 7.05 (dd, J = 2.0. 8.8 Hz, 1H), 6.78 (dd, J = 2.0, 12.4 Hz, 1H) 4.94 (dd, J= 6.8, 6.8 Hz, 1H), 4.31 (d, J = 6.8 Hz, 2H), 4.20 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.5, 141.4, 141.3, 139.4, 133.7, 128.7, 128.6, 128.0, 127.7, 124.4, 123.0, 121.3, 112.0, 76.8, 52.8, 36.4. LRMS (APCI) *m*/*z*: calcd for $C_{21}H_{19}N_5O$ (MH+) 358,17; found 358.2.

***N*-(4-(3-*(tert*-Butylamino-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-7-crabonyl)phenylacetamide 30{5}.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (bs, 1H), 7.57–7.64 (m, 4H), 7.40–7.42 (m, 2H), 7.04 (dd, J = 8.0, 8.0 Hz, 2H), 4.82 (m, 2H), 3.94–4.07 (m, 4H), 2.14 (s, 3H), 2.08 (s, 1H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 155.0, 142.5, 136.2, 135.9, 134.4, 130.8, 129.1, 127.9, 127.5, 127.2, 125.4, 124.9, 121.7, 121.1, 114.2, 111.0, 76.0, 55.4, 45.2, 38.9, 29.3. LRMS (APCI) *m*/*z*: calcd for $C_{25}H_{28}FN_5O_2$ (MH+) 450.23; found 450.1.

1-(4-(3-*(tert*-Butylamino-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-7-carbonyl)piperidin-1-yl)ethanone 30{14}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 2H), 7.06 (dd, J = 8.0, 8.0 Hz, 2H), 4.82 and 4.75 (s, rotomer, 2H), 4.64 (d, J = 10.0 Hz, 1H), 3.88–3.98 (m, 4H), 3.20–3.61 (m, 5H), 2.10 and 2.21 (s, rotomer, 3H), 1.78–1.82 (m, 2H), 1.25 (bs, 2H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 170.0, 169.1, 163.0, 160.6, 136.8, 136.6, 133.8, 133.7, 131.7, 129.6, 129.5, 128.9, 128.8, 115.5, 115.4, 115.2, 115.2, 76.9, 55.6, 45.9, 45.5, 44.8, 44.0, 42.3, 42.0, 41.8, 41.0, 39.8, 39.2, 39.1, 30.4, 29.8, 28.7, 28.2, 21.8, 21.6. LRMS (APCI) *m*/*z*: calcd for $C_{24}H_{32}FN_5O_2$ (MH+) 442.31; found 442.3.

(3-(*tert*-Butylamino-2-(4-fluorophenyl)-5,6,-dihydroimidazo[1,2-*a*]pyrazin-7(8H)-yl)(furan-2-yl)methanone 30{15}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 3.2, 3.2 Hz, 2H), 7.54 (s, 1H), 7.14 (d, J = 3.2 Hz, 1H), 7.05 (dd, J = 8.4, 8.4 Hz, 2H), 6.53 (dd, J = 1.6, 1.6 Hz, 1H), 5.12 (bs, 2H), 4.12 (s, 2H), 4.00 (s, 2H), 2.81 (bs, 1H), 1.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.6, 159.6, 147.2, 144.6, 137.3, 133.8, 131.8, 131.7, 129.4, 128.9, 128.8, 117.9, 115.4, 115.2, 111.9, 76.9, 55.6, 30.4. LRMS (APCI) *m*/*z*: calcd for $C_{21}H_{23}FN_5O_2$ (MH+) 383.19; found 383.2.

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Supporting Information Available. Analytical spectra (^{1}H NMR, ^{13}C NMR, and LCMS) for exemplified compounds and LCMS for exemplified library compounds **14{1–21}**, **26{1–21}**, and **30{1–21}**. Also included are complete lists of all aldehydes and isonitriles used in the 3-CC, synthesized scaffolds and TFP inputs used in final library production. This material is available free of charge via the Internet at http://pubs.acs.org.

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