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Rapid Assembly of Polyfunctional Structures Using a One-Pot Five- and Six-Component Sequential Groebke–Blackburn/Ugi/Passerini Process

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Sequential addition of up to six components under well-defined conditions results in the formation of novel structures with amino acid, peptide, and heterocyclic components. This process forms up to eight new bonds under very mild conditions and tolerates a broad spectrum of functional groups. An orthogonal union of the Groebke–Blackburn three-component reaction with the Ugi four-component or Passerini three component reaction was adopted to synthesize polyfunctionalized heterocycles. In terms of diversity oriented synthesis, 10 positions on the basic polycyclic structure can be varied. Straightforward batch splitting provides a simple and efficient method for preparing structurally complex analogs.

Introduction

The development of efficient synthetic strategies that lead to molecular diversity plays an important role in the success of drug discovery.[1–3] With such a procedure, an enormous number of complex small molecules can be prepared for evaluation of biological activity such as perturbation of protein function.[4] The challenge for synthetic chemists is therefore to improve the overall efficiency through the development of economic procedures that proceed with high yield and selectivity.[5]

Among approaches to therapeutic discovery, diversity-oriented synthesis has played a prominent role by concentrating on employing efficient reactions that tolerate a broad substrate scope. In this regard, one of the most

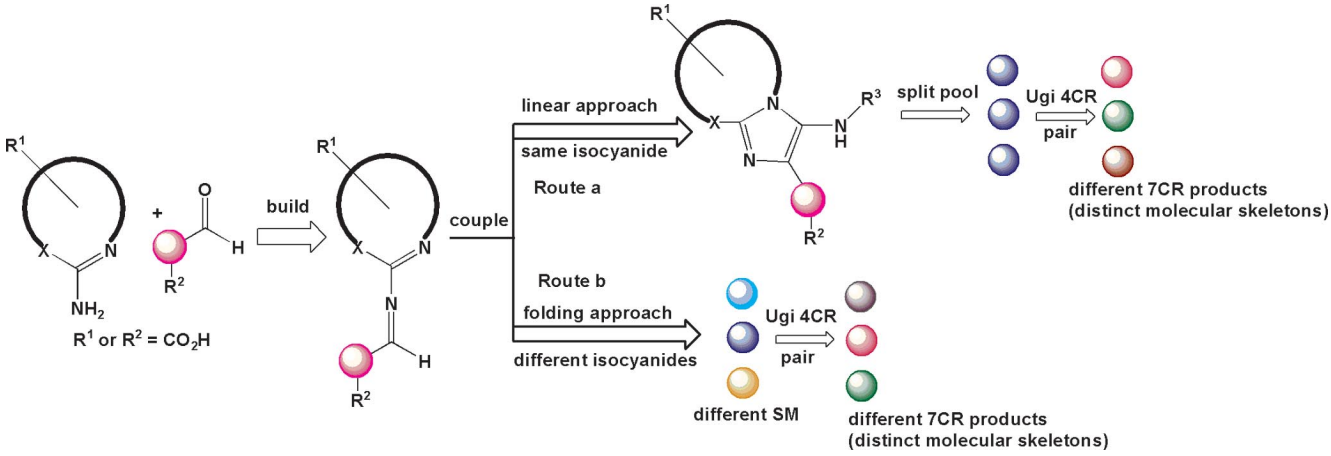

Figure 1. Sequential MCR strategies employed.

powerful approaches is the union of two multicomponent reactions (MCRs) in which a set of reagents is sequentially and predictably brought together. Such an approach requires a functional group that is unreactive in the initial stage but reactive in a subsequent reaction (Figure 1). In an ideal case, reactions are efficiently combined in a single flask to yield a higher-order MCR. Central to this union of MCRs[4,5] is the orthogonal reactivity of functional groups combined in one molecule to be deployed in different reactions. Such strategies avoid the use of protecting groups and increase efficiency in organic synthesis. Many research groups have utilized the Ugi four-component reaction

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(4CR) followed by cycloaddition reactions, metathesis strategies, and sequential additive transformations to assemble complex structures.[5–7]

An approach to engendering efficient assembly of variably substituted structures requires the use of MCRs in which a set of simple components is brought together. This straightforward approach, however, is not easily implemented.[8–11] Reactions often have experimental limitations including the inflexibility of the substitution pattern of the starting materials, the need for protection/deprotection of intermediates, and solvent incompatibilities between the subsequent reaction steps. To avoid complex mixtures, components must react selectively and predictably. To this end, few elegant contributions have been reported wherein six components or more were brought together.[6]

Two notable multicomponent reactions are the Groebke–Blackburn and Ugi reactions. Both of these reactions take advantage of the isocyanide functionality that is capable of forming two new bonds to carbon.[4,12,9,13] The Groebke–Blackburn reaction is an acid-mediated addition of an isocyanide to a 2-iminopyridine, yielding a fused pyridine–imidazole product. Similarly, the Ugi reaction is the four-component assembly of an isocyanide, acid, and imine to produce a skeletally diverse dipeptide. If these named reactions could be combined efficiently in a tandem fashion, this would give rise to molecular diversity and rapid construction of libraries of structurally related compounds.

As part of an ongoing program of natural product synthesis and the preparation of medicinally important structures,[14] we report herein a tandem process that combines two successive MCRs in one pot, a higher-order MCR for the construction of imidazopyridine, -pyrazine, and -pyrimidine derivatives with unprecedented possibilities for complexity generation and diversification. Recent studies implicate a role for these scaffolds in addressing many of the most common human diseases including diabetes,[15] cancer,[16] infection by microorganisms,[17] and an array of neurological syndromes.[18]

Results and Discussion

Efficiently sequencing these two named reactions would ideally involve a single-flask reaction without the need for any intermediate isolation steps. Positioning the Groebke–Blackburn reaction before the Ugi reaction was the most straightforward because the former could carry with it an unprotected carboxylic acid group. We therefore began by investigating conditions for the tandem combination of these two reactions. An important element of this concept was the independent reactivity of the functional groups resident on the key substrate.[8] Such a process would involve a functional group in the first MCR that does not participate in the reaction but does react as one of the essential components in the second MCR (e.g., the carboxylic acid group in these MCRs, Figure 1).

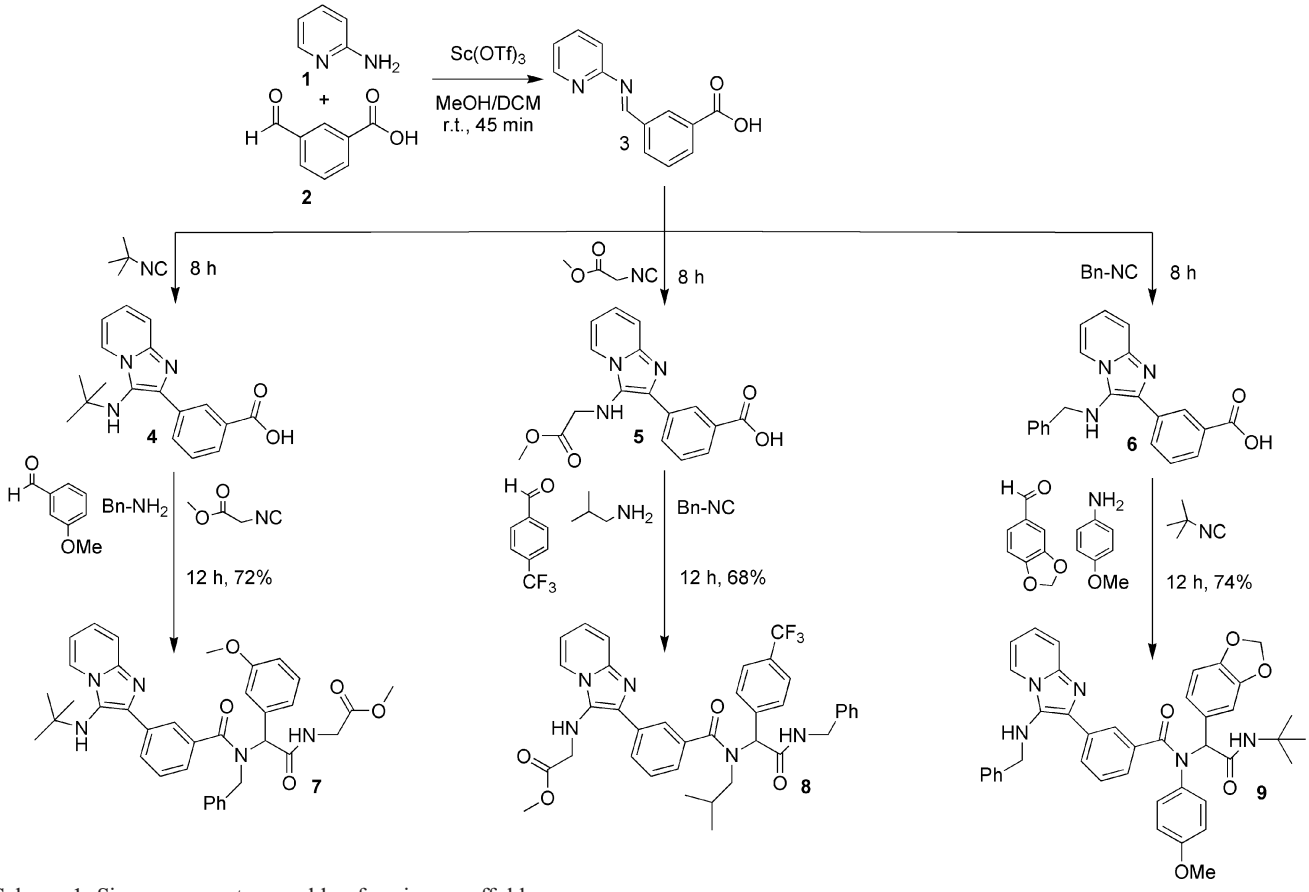
A Six-Component Reaction Sequence

Before presenting applications of our strategy as outlined in Figure 1, several appropriate comments are in order. Unlike the respected Ugi and other multicomponent reactions, the components in our process must be combined in a sequential process due to the reactivity of the different functional groups in the initial components. The first stage of the process involves formation of imine **I**; this intermediate may or may not be isolated in crude form. For example, the aldehyde and amine may be condensed in the presence of $Sc(OTf)_3$ (5 mol-%) in methanol/dichloromethane (2:3) to give a solution of imine **I**. This solution may then be used directly in the next [4+1] cycloaddition step to give a variety of bicyclic azole scaffolds **II** (Figure 1, route a) bearing a carboxylic acid on one side or the other of the resulting heterocycle. This pendant acid moiety provides a linkage for subsequent union of Ugi 4CR or Passerini 3CR (Figure 1). This product can then be split and used in a different MCR (Figure 1, route a; and Scheme 2). Alternatively, the crude imine solution could be distributed into different reaction flasks charged with different isocyanides (Figure 1, route b). The products from this route could be used directly in the next MCRs or each product could be split again to multiply the number of skeletally diverse heterocyclic products. The majority of the reactions presented herein were conducted in a single flask without intermediate isolation, as outlined Scheme 1; the crude imines were directly coupled with the desired isocyanide and then the resulting bicyclic [4+1] cycloaddition product was split and subjected to a second MCR to generate a library of complex heterocyclic scaffolds. It should be noted, however, that the conditions were not always optimized for the formation of intermediate imines **I** or for their subsequent conversion into adducts **II**. Nevertheless, ^1H NMR spectroscopic analysis of the crude imidazopyridine carboxylic acid derivatives resulting from the first 3CR product indicated quantitative conversion.

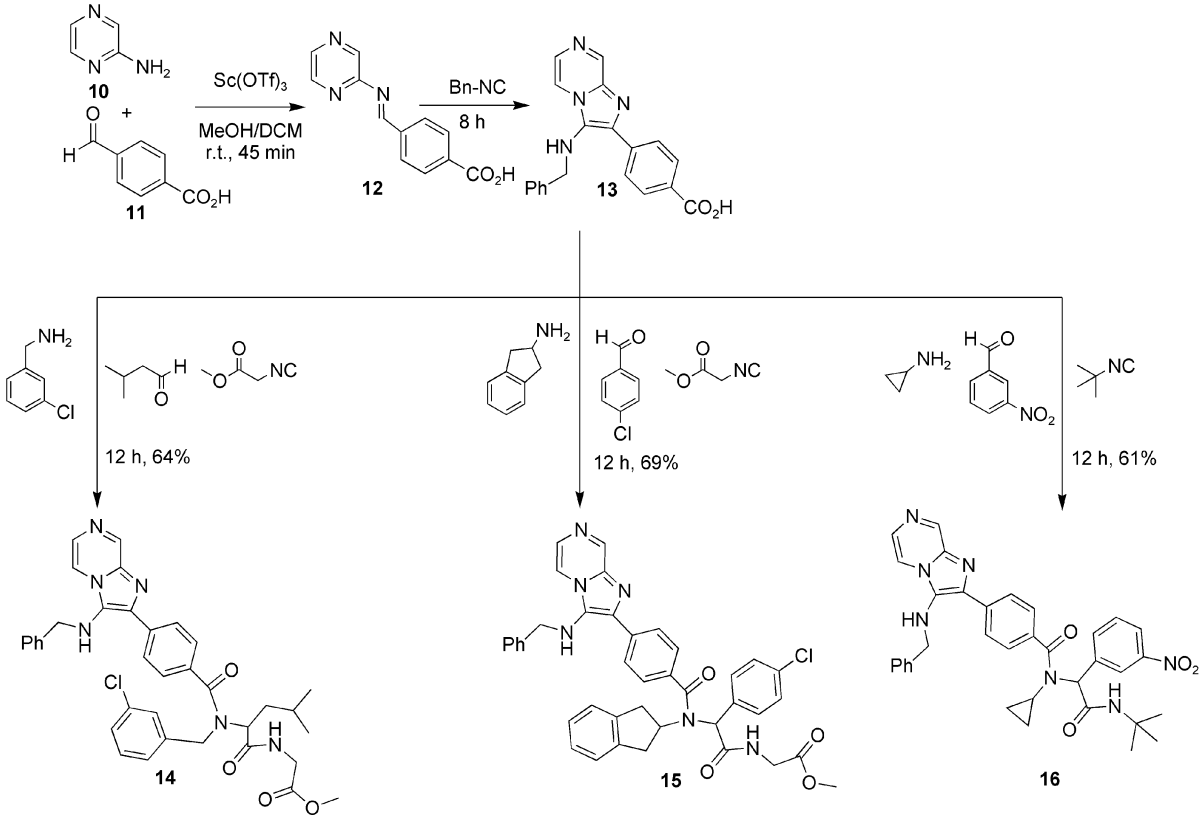
Split-Pool Synthesis

Having established a protocol for the facile synthesis of intermediates **I** and **II** (Figure 1) a number of post-cycloaddition reactions including the Ugi 4CR and Passerini 3CR was examined to generate diverse heterocyclic scaffolds. To achieve this goal and to broaden the scope of this approach, we explored the possibility of accessing different heterocyclic systems by varying the nature of the nucleophilic amines, the aldehydes, isocyanides, and/or the position of the carboxylic acid handle. As described below, our strategy followed three different routes for the union of both MCRs.

To verify the plan contemplated in Figure 1, we started our synthesis by using the split-pool synthesis approach with the intermediate imine (Scheme 1) and by splitting the initial MCR [4+1] cycloaddition product (Scheme 2). To this end, we treated 2-aminopyridine (**1**) with 3-carboxybenzaldehyde (**2**) in the presence of $Sc(OTf)_3$ (5 mol-%) to deliver imine **3**. Without isolation, the latter product was distributed into three reaction vials. To each vial a different



Scheme 1. Six-component assembly of various scaffolds.



Scheme 2. Different variants of six sequential MCR.

isocyanide was added as indicated in Scheme 1. After 8 h, the Groebke–Blackburn reaction protocol proceeded smoothly and intermediates **4**, **5**, and **6** were produced. Subsequently these products were subjected to the second MCR Ugi reaction. Therefore, different aldehydes, amines, and isocyanides were added to deliver, after 12 h, polyfunctionalized imidazopyridines **7**, **8**, and **9** in 72, 68, and 74% yield, respectively.

In the alternative route, 2-aminopyrazine (**10**) was condensed with 4-carboxybenzaldehyde (**11**) under the same reaction conditions as mentioned above to deliver imine **12** (Scheme 2), which was directly subjected to the Groebke–Blackburn reaction with benzyl isocyanide to produce [4+1] cycloaddition product **13**. Without isolation, product **13** was distributed into three vials and to each of these vials was added an amine, an aldehyde, and an isocyanide as indicated in Scheme 2. As a result, Ugi reaction products **14**, **15**, and **16** were isolated by flash column chromatography in 64, 69, and 61% yield, respectively.

Variations of the Primary Amine Input

Having successfully demonstrated the underlying utility of this strategy for the rapid preparation of complex heterocycles, the next task was to apply this approach to the synthesis of more complex heterocyclic scaffolds with different branching patterns by utilizing various amines for the initial condensation. Thus, 1-aminoisoquinoline (**17**) and 2-aminothiazole (**21**) were separately treated with 3-carboxybenzaldehyde (**2**) to afford intermediates **18** and **22**, respectively. These intermediates were then subjected to the Groebke–Blackburn reaction conditions with *tert*-butyl isocyanide to give polycyclic compounds **19** and **23**, respectively. These intermediates were then subjected to reaction with isobutylamine, piperonal, and two isocyanides under the Ugi reaction conditions as shown in Scheme 3 to deliver polyfunctional heterocyclic diamides **20** and **24** in 55 and 61% yield, respectively.

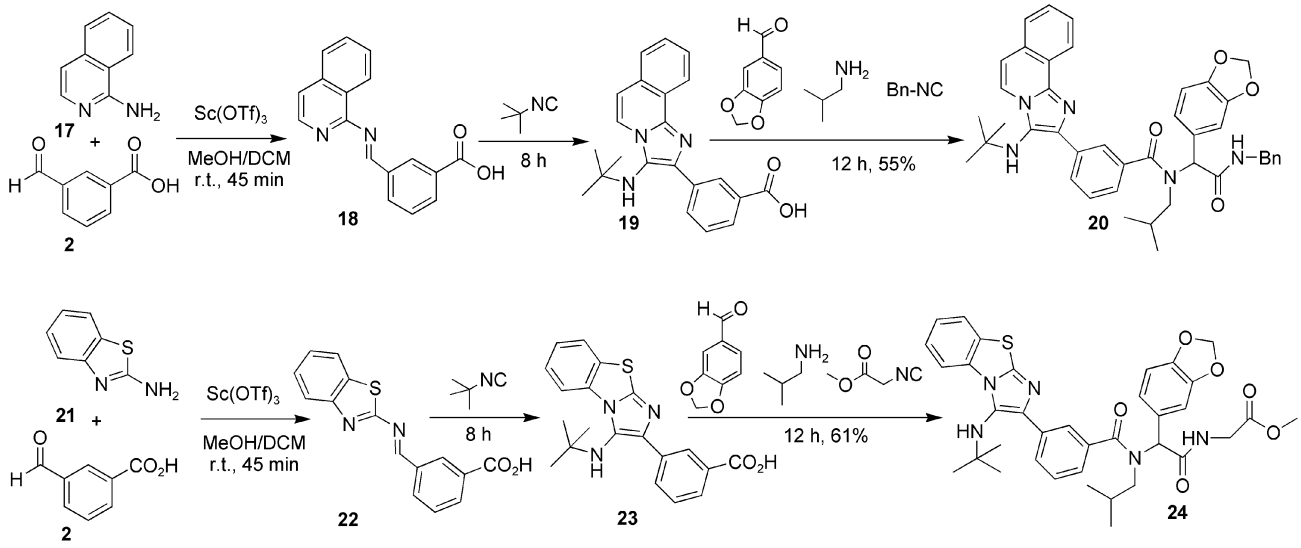
Positional Variation of the Carboxylic Acid Handle

To evaluate the scope of this tandem process we investigated varying the position of the carboxylic acid group, the cornerstone of the protocol. Thus, the acid functionality was placed on the heterocyclic amine instead of the aldehyde component for the initial condensation reactions (compare Schemes 1 and 4). To achieve this goal, 5-carboxy-2-aminopyridine (**25**) was condensed with benzaldehyde (**26**) in the presence of $Sc(OTf)_3$ (5 mol-%) to deliver imine **27** (Scheme 4). Reaction of **27** with benzyl isocyanide gave intermediate **28**. This product was divided among three reaction vials and each vial was subjected to different Ugi reaction conditions to produce polysubstituted imidazopyridines **29**, **30**, and **31** in good yields (65, 70, and 73%, respectively).

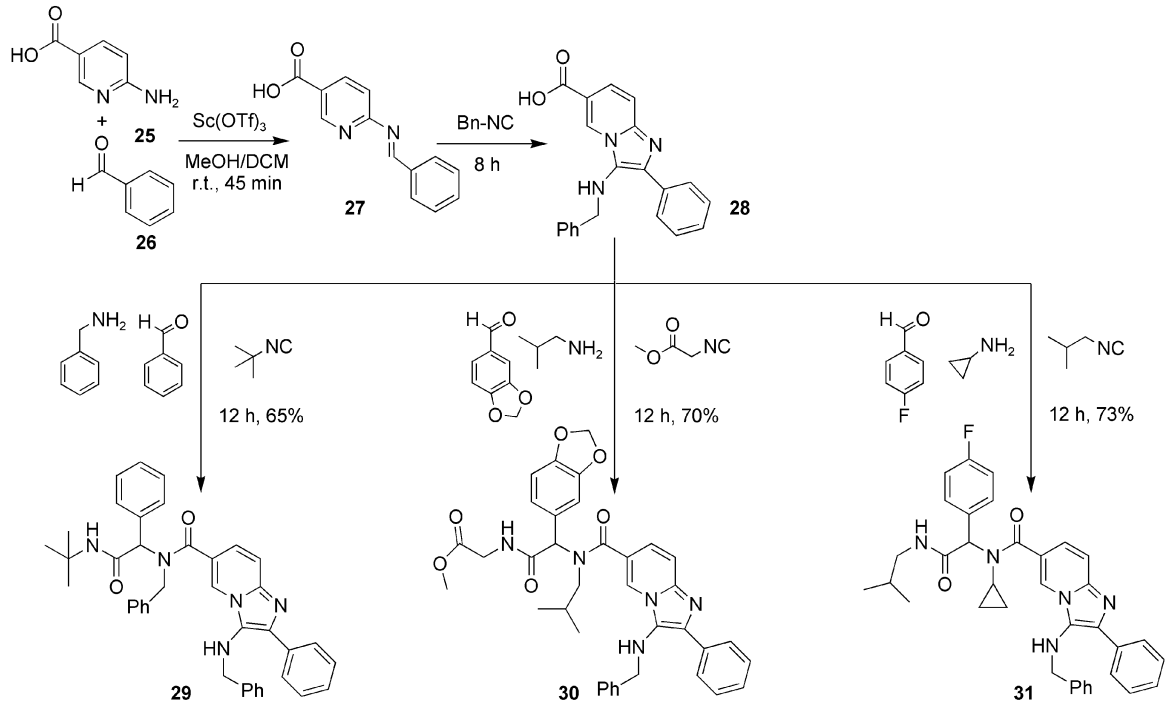
The applicability of these variations was also tested with 5-carboxy-2-aminobenzothiazole (**32**; Scheme 5). Thus, reaction of **32** with 2-thiophencarboxaldehyde (**33**) followed by application of our 6CR procedure as described above gave compound **36** in 67% yield after flash chromatography.

Groebke–Blackburn/Passerini Five-Component Protocol

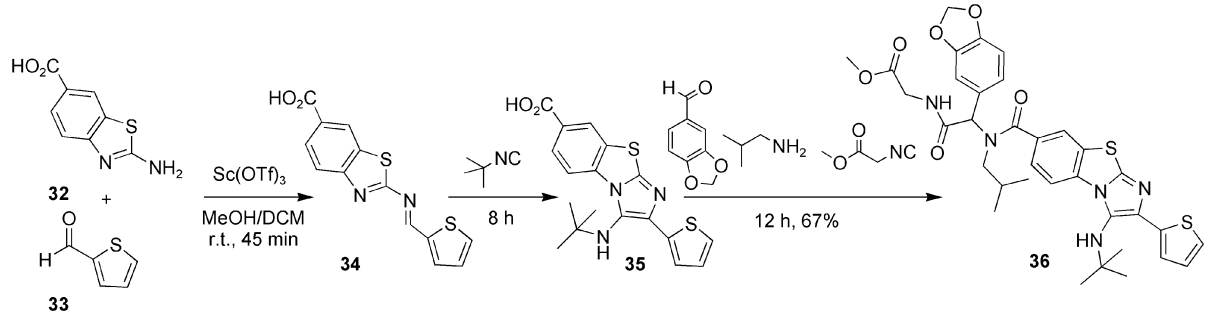
With successful illustration of our combined Groebke–Blackburn/Ugi sequence, we tested the expansion of this strategy to include an alternative MCR. For this purpose we selected the Passerini 3CR. Incorporation of this reaction followed the same sequence for the reaction union described above. To this end, a Groebke–Blackburn 3CR was achieved by applying the standard condensation of 2-aminopyrimidine (**37**) with 3-carboxybenzaldehyde (**2**) to produce imine **38**, which was further treated with benzyl isocyanide to give imidazopyrimidine **39** (Scheme 6). To each of three reaction vials containing compound **39** was added aldehydes and isocyanides to afford smoothly multisubstituted heterocyclic structures **40**, **41**, and **42** in 78, 69, and 57% yield, respectively (Scheme 6).



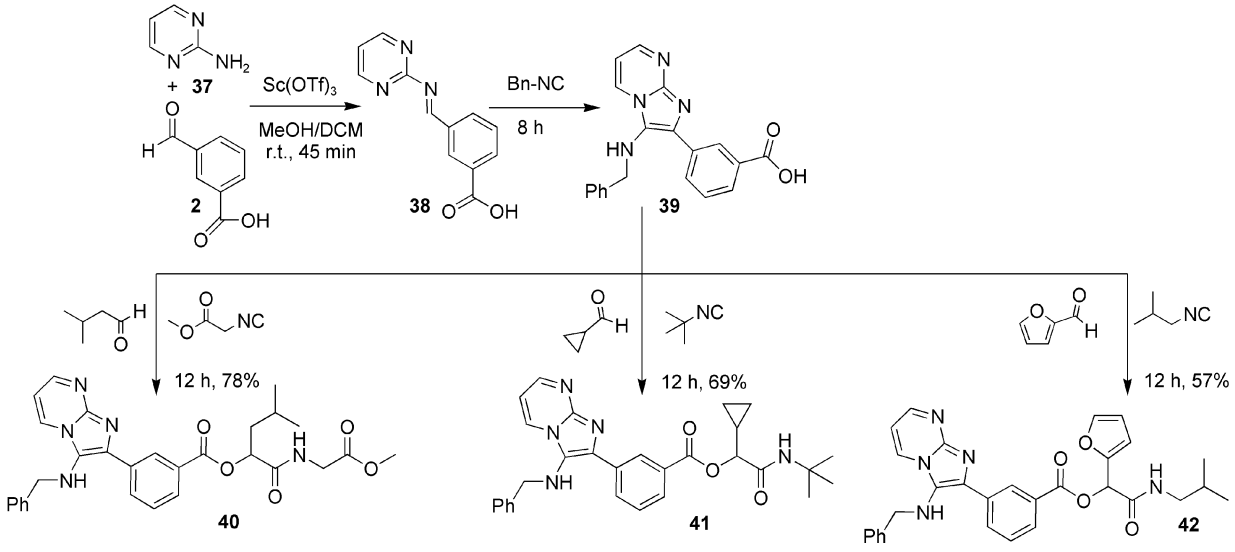
Scheme 3. Variation of the amine input in the primary MCR.



Scheme 4. Variation of the position of the carboxylic acid arm in the primary MCR sequence.



Scheme 5. Six-component sequential union with different inputs.



Scheme 6. Five-component assembly products.

The aldehydes used for these sequences are aromatic and contain a carboxylic acid group paired with reagents for a subsequent Ugi 4CR or Passerini 3CR. Incorporation of other functionalities into the starting aldehydes and/or aromatic amines can be envisioned to enable the formation of alternative cyclic manifolds.[13,18] For example, starting with heteroarylamines and aldehydes bearing carboxylic acids in the [4+1] cycloaddition processes, followed by union with Ugi and Passerini MCRs would produce structurally unique products. It should also be mentioned that given the known scope of the Groebke–Blackburn, Ugi, and Passerini MCRs the chemistry presented here should work for all possible functional groups typically used in such MCRs.[13]

Conclusions

In summary, we have developed several new examples of 5- and 6CRs with the formation of up to 8 new bonds and up to 10 points of diversity. The approach described here allows the construction of complex, diverse sets of drug-like compounds in a single, economic, and facile operation. The reaction is remarkably efficient (>55% per bond formation) and constitutes an economic approach for 5- and 6CRs. These representative examples clearly establish the merits of this new strategy for the synthesis of diverse nitrogen heterocycle collections. Significantly, these scaffolds bear orthogonal functionality that may be selectively exploited for further manipulation and diversification to create novel sets of compounds having substructures found in biologically active and clinically useful drugs. Further applications of the concepts outlined in Figure 1 for the synthesis of diverse collections of scaffolds that are endowed with reactive sites or handles are in progress in our laboratories.

Experimental Section

General Information: All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven-dried or flamed graduated vessels. Solvents were dried and purified by conventional methods prior to use. Flash column chromatography was performed with Silica gel 60, 0.040–0.063 mm (230–400 mesh). Aluminum-backed plates precoated with silica gel 60 (UV254) were used for thin-layer chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (δ = 7.27 ppm, 1 H; 77.16 ppm, middle peak, ^{13}C). Elemental analysis was carried out at the University of Jordan. High- and low-resolution mass spectrometric analyses were conducted at the University of Jordan by using positive ion electrospray ionization (ESI+). The samples were dissolved in acetonitrile, diluted in spray solution [methanol/water (1:1) + 0.1% formic acid] and infused by using a syringe pump with a flow rate of 2 μL/min. External calibration was conducted by using arginine cluster in a mass range m/z = 175–871.

General Experimental Procedure A: A mixture of aminopyridine (3.0 mmol) in MeOH/DCM (2:3, 15.0 mL) and aldehyde (3.0 mmol) containing $Sc(OTf)_3$ (5 mol-%) in a graduated test tube was stirred for 45 min at room temperature. The resulting imine was divided into three graduated test tubes and to each tube was added the desired isocyanide (3 mmol), and the mixture was stirred for another 8 h. Without workup, to each vial was added the desired aldehyde (3.0 mmol), amine (3.0 mmol), and isocyanide (3.0 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure, washed with hexane/EtOAc (5:1, 3 × 30 mL), and triturated with EtOAc/hexane. The crude product was purified by flash chromatography (0–30% EtOAc/hexanes) to give the desired product as an amorphous solid.

General Experimental Procedure B: A mixture of aminopyridine (3.0 mmol) in MeOH/DCM (2:3, 15.0 mL) and aldehyde (3.0 mmol) containing $Sc(OTf)_3$ (5 mol-%) in a graduated test tube was stirred for 45 min at room temperature followed by the addition of the desired isocyanide (3.15 mmol), and the mixture was stirred for another 8 h. Without workup, the resulting iminopyridine product was divided equally into three reaction vials. To each vial was added the desired aldehyde (3.0 mmol), amine (3.0 mmol), and isocyanide (3.0 mmol), and the resulting solution was then stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, washed with EtOAc/hexane (5:1, 3 × 30 mL), and triturated with EtOAc/hexane. The crude product was purified by flash chromatography (0–30% EtOAc/hexanes) to give the desired product as an amorphous solid.

General Experimental Procedure C: A mixture of aminopyridine (1.0 mmol) in MeOH/DCM (2:3, 5.0 mL) and aldehyde (1.0 mmol) containing $Sc(OTf)_3$ (5 mol-%) in a graduated test tube was stirred for 45 min at room temperature followed by the addition of the desired isocyanide (1.05 mmol), and the mixture was stirred for another 8 h. Without workup, to the resulting iminopyridine product was added the desired aldehyde (1.0 mmol), amine (1.0 mmol), and isocyanide (1.0 mmol), and the mixture was then stirred at room temperature for 12 h. The resulting reaction mixture was concentrated under reduced pressure, washed with hexane/EtOAc (5:1, 3 × 15 mL), and triturated with EtOAc/hexane. The crude product was purified by flash chromatography (0–30% EtOAc/hexanes) to give the desired product as an amorphous solid.

Methyl 2-[2-(*N*-Benzyl-3-{3-(*tert*-butylamino)imidazo[1,2-*a*]pyridin-2-yl}benzamido)-2-(3-methoxyphenyl)acetamido]acetate (7): According to general procedure A; yield: 456 mg, 72%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.20 (s, 9 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 4.03 (s, 2 H), 4.79 (d, $J_{H,H}$ = 9.6 Hz, 1 H), 4.86 (d, $J_{H,H}$ = 9.6 Hz, 1 H), 6.44 (s, 1 H), 6.84 (m, 2 H), 6.98 (m, 2 H), 7.18 (t, $J_{H,H}$ = 10.2 Hz, 1 H), 7.42 (m, 5 H), 7.70 (m, 1 H), 7.83 (d, $J_{H,H}$ = 6.6 Hz, 1 H), 7.96 (m, 2 H), 8.77 (d, $J_{H,H}$ = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 172.8, 171.0, 169.0, 154.6, 143.2, 141.8, 136.5, 134.0, 133.7, 132.5, 128.8, 128.4, 128.2, 127.5, 127.2, 126.9, 126.0, 115.6, 115.5, 115.4, 105.2, 69.6, 60.2, 56.9, 48.5, 43.5, 34.1, 30.7 ppm. HRMS (ESI): calcd. for $C_{37}H_{39}N_5O_5Na$ $[M + Na]^+$ 656.2849; found 656.2894.

Methyl 2-{2-(3-[{2-Benzylamino-2-oxo-1-[4-(trifluoromethyl)phenyl]-ethyl}(isobutyl)carbamoyl]phenyl)imidazo[1,2-*a*]pyridin-3-ylamino}-acetate (8): According to general procedure A; yield: 457 mg, 68%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.04 (d, $J_{H,H}$ = 7.2 Hz, 6 H), 1.98 (m, 1 H), 3.01 (s, 2 H), 3.62 (s, 3 H), 4.14 (s, 2 H), 4.39 (m, 2 H), 4.45 (d, $J_{H,H}$ = 6.3 Hz, 1 H), 6.04 (s, 1 H), 6.11 (s, 1 H), 6.83 (d, $J_{H,H}$ = 8.1 Hz, 1 H), 7.17 (m, 6 H), 7.52 (m, 3 H), 7.60 (m, 3 H), 7.93 (m, 3 H), 8.88 (d, $J_{H,H}$ = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 174.3, 170.4, 165.5, 144.8, 135.2, 130.9, 128.9, 127.9, 127.4, 126.9, 126.7, 126.3, 123.9, 123.7, 123.6, 119.9, 110.5, 104.4, 60.3, 52.7, 46.2, 41.0, 26.2, 19.8 ppm. HRMS (ESI): calcd. for $C_{37}H_{36}F_3N_5OH$ $[M + H]^+$ 672.2798; found 672.2789.

***N*-{1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(*tert*-butylamino)-2-oxoethyl}-3-{3-(benzylamino)imidazo[1,2-*a*]pyridin-2-yl}-*N*-(4-methoxyphenyl)-benzamide (9):** According to general procedure A; yield: 504 mg, 74%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34 (s, 9 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 4.72 (d, $J_{H,H}$ = 7.6 Hz, 1 H), 5.92 (s, 2 H), 6.33 (d, $J_{H,H}$ = 7.8 Hz, 1 H), 6.6.81 (m, 3 H), 7.40–7.17 (m, 10 H), 8.03–7.74 (m, 5 H), 8.88 (d, $J_{H,H}$ = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 170.2, 161.7, 158.3, 149.3, 146.1, 144.8, 141.4, 134.2, 132.6, 130.7, 128.2, 127.7, 127.5, 127.2, 126.9, 123.7, 121.1, 120.2, 114.8, 112.6, 110.4, 109.4, 103.0, 101.0, 69.6, 55.2, 49.9, 49.4, 28.6 ppm. HRMS (ESI): calcd. for $C_{41}H_{39}N_5O_5Na$ [M + Na]$^+$ 704.2849; found 704.2851.

Methyl 2-{2-[4-{3-(Benzylamino)imidazo[1,2-*a*]pyrazin-2-yl}-*N*-(3-chlorobenzyl)benzamido]-4-methylpentanamido}acetate (14): According to general procedure B; yield: 418 mg, 64%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.87 (d, $J_{H,H}$ = 7.3 Hz, 6 H), 1.51 (m, 3 H), 3.71 (s, 3 H), 4.03 (s, 2 H), 4.72 (s, 2 H), 5.28 (m, 1 H), 7.55–7.12 (m, 9 H), 7.91 (s, 1 H), 8.29 (m, 4 H), 8.56 (d, $J_{H,H}$ = 8.4 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 172.9, 171.0, 168.2, 143.0, 141.7, 136.4, 133.4, 132.6, 129.6, 128.6, 127.8, 125.9, 121.6, 115.6, 115.2, 114.0, 55.4, 52.0, 50.7, 50.0, 38.3, 36.2, 25.4, 20.7 ppm. HRMS (ESI): calcd. for $C_{36}H_{37}ClN_6O_4H$ [M + H]$^+$ 653.2643; found 653.2650.

Methyl 2-{2-[4-{3-(Benzylamino)imidazo[1,2-*a*]pyrazin-2-yl}-*N*-(2,3-dihydro-1*H*-inden-2-yl)benzamido]-2-(4-chlorophenyl)acetamido}-acetate (15): According to general procedure B; yield: 482 mg, 69%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.87 (m, 2 H), 3.35 (m, 2 H), 3.72 (s, 3 H), 4.03 (s, 2 H), 4.72 (s, 2 H), 5.06 (m, 1 H), 6.46 (d, $J_{H,H}$ = 10.8 Hz, 1 H), 7.43–6.98 (m, 16 H), 8.25 (m, 1 H), 8.30 (m, 1 H), 8.53 (d, $J_{H,H}$ = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 173.0, 169.0, 167.9, 141.5, 136.2, 135.8, 135.0, 128.6, 128.1, 127.5, 127.0, 126.0, 124.1, 122.2, 117.3, 115.0, 67.8, 60.2, 55.1, 52.2, 43.6, 38.4, 36.3 ppm. HRMS (ESI): calcd. for $C_{40}H_{35}ClN_6O_4H$ [M + H]$^+$ 699.2487; found 699.2482.

4-{3-(Benzylamino)imidazo[1,2-*a*]pyrazin-2-yl}-*N*-[2-(*tert*-butylamino)-1-(3-nitrophenyl)-2-oxoethyl]-*N*-cyclopropylbenzamide (16): According to general procedure B; yield: 377 mg, 61% amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.88 (m, 4 H), 1.34 (s, 9 H), 3.14 (m, 1 H), 4.74 (s, 2 H), 6.23 (s, 1 H), 6.34 (s, 1 H), 7.40–7.07 (m, 8 H), 7.75 (m, 1 H), 8.52–8.23 (m, 5 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 173.2, 167.0, 149.7, 146.6, 142.5, 142.2, 137.6, 136.4, 131.2, 129.8, 129.2, 128.5, 128.2, 127.5, 126.1, 120.8, 63.4, 49.9, 49.4, 45.8, 28.6, 6.9 ppm. HRMS (ESI): calcd. for $C_{35}H_{35}N_7O_4H$ [M + H]$^+$ 618.2829; found 618.2831.

***N*-{1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(benzylamino)-2-oxoethyl}-3-{3-(*tert*-butylamino)imidazo[2,1-*a*]isoquinolin-2-yl}-*N*-isobutyl-benzamide (20):** According to general procedure C; yield: 375 mg, 55%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.05 (d, $J_{H,H}$ = 7.3 Hz, 6 H), 1.20 (s, 9 H), 1.97 (m, 1 H), 3.02 (m, 2 H), 4.37 (d, $J_{H,H}$ = 12.6 Hz, 1 H), 4.43 (d, $J_{H,H}$ = 12.6 Hz, 1 H), 5.92 (s, 2 H), 6.20 (s, 1 H), 6.63 (d, $J_{H,H}$ = 8.4 Hz, 1 H), 6.80 (d, $J_{H,H}$ = 8.7 Hz, 1 H), 6.94 (s, 1 H), 7.11 (m, 1 H), 7.22 (m, 5 H), 7.30 (m, 1 H), 7.71–7.40 (m, 3 H), 7.90 (m, 2 H), 8.41 (m, 1 H), 8.75 (d, $J_{H,H}$ = 7.2 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 170.4, 165.5, 147.3, 146.4, 145.4, 139.4, 134.5, 131.8, 131.3, 129.7, 128.9, 127.9, 126.9, 126.2, 126.0, 122.7, 119.9, 110.2, 108.5, 108.1, 101.0, 68.8, 60.2, 52.2, 41.0, 31.1, 26.2, 19.8 ppm. HRMS (ESI): calcd. for $C_{42}H_{43}N_5O_4Na$ [M + Na]$^+$ 704.3213; found 704.3206.

Methyl *N*-{1,3-Benzodioxol-5-yl[(3-{3-(*tert*-Butylamino)imidazo[2,1-*b*][1,3]benzothiazol-2-yl}benzoyl)(isobutyl)amino]acetyl}glycinate (24): According to general procedure C; yield: 427 mg, 61%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.07 (d, $J_{H,H}$ = 7.1 Hz, 6 H), 1.1 (s, 9 H), 1.96 (m, 1 H), 3.04 (m, 2 H), 3.72 (s, 3 H), 4.03 (s, 2 H), 5.92 (s, 2 H), 6.42 (m, 2 H), 6.81 (d, $J_{H,H}$ = 8.7 Hz, 1 H), 6.93 (s, 1 H), 7.12 (d, $J_{H,H}$ = 10.2 Hz, 1 H), 7.22 (d, $J_{H,H}$ = 7.8 Hz, 1 H), 7.54 (m, 2 H), 7.91 (m, 2 H), 8.08 (d, $J_{H,H}$ = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 169.8, 165.5, 149.6, 147.3, 146.4, 143.3, 138.7, 134.8, 131.3, 129.7, 127.3, 127.0, 126.2, 125.7, 122.8, 122.5, 119.9, 113.7, 108.5, 108.1, 101.0, 67.5, 60.3, 54.6, 51.9, 38.4, 31.1, 26.2, 19.8 ppm. HRMS (ESI): calcd. for $C_{36}H_{39}N_5O_6SNa$ [M + Na]$^+$ 692.2519; found 692.2523.

***N*-Benzyl-3-(benzylamino)-*N*-[2-(*tert*-butylamino)-2-oxo-1-phenylethyl]-2-phenylimidazo[1,2-*a*]pyridine-6-carboxamide (29):** According to general procedure B; yield: 404 mg, 65%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34 (s, 9 H), 4.72 (s, 2 H), 4.80 (d, $J_{H,H}$ = 9.3 Hz, 1 H), 4.86 (d, $J_{H,H}$ = 9.3 Hz, 1 H), 6.03 (s, 1 H), 7.07–7.49 (m, 20 H), 8.40 (t, $J_{H,H}$ = 2.1 Hz, 1 H), 9.71 (s, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 170.3, 157.7, 148.4, 143.0, 132.3, 130.4, 129.7, 128.8, 128.6, 128.2, 127.7, 127.5, 126.9, 126.2, 115.4, 113.7, 67.8, 52.0, 49.9, 49.4, 28.6 ppm. HRMS (ESI): calcd. for $C_{40}H_{39}N_5O_2H$ [M + H]$^+$ 622.3182; found 622.3182.

Methyl 2-{2-(Benzo[*d*][1,3]dioxol-5-yl)-2-(3-benzylamino-*N*-isobutyl-2-phenylimidazo[1,2-*a*]pyridine-6-carboxamido)acetamido}acetate (30): According to general procedure B; yield: 453 mg, 70%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.04 (d, $J_{H,H}$ = 7.2 Hz, 6 H), 1.1 (s, 9 H), 1.95 (m, 1 H), 3.03 (m, 2 H), 3.72 (s, 2 H), 4.03 (s, 2 H), 4.72 (s, 2 H), 5.93 (s, 2 H), 6.40 (m, 1 H), 6.81 (d, $J_{H,H}$ = 8.7 Hz, 1 H), 6.92 (d, $J_{H,H}$ = 3.1 Hz, 1 H), 7.50–7.30 (m, 12 H), 8.37 (t, $J_{H,H}$ = 2.1 Hz, 1 H), 9.70 (s, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 169.8, 158.0, 148.4, 147.3, 146.4, 143.0, 141.4, 131.6, 128.7, 128.2, 127.5, 127.2, 126.9, 126.7, 126.2, 122.1, 115.7, 115.1, 110.4, 108.5, 101.0, 66.3, 60.8, 51.9, 50.0, 38.4, 34.0, 28.4, 25.4, 20.9 ppm. HRMS (ESI): calcd. for $C_{37}H_{37}N_5O_6Na$ [M + Na]$^+$ 670.2642; found 670.2650.

3-Benzylamino-*N*-cyclopropyl-*N*-[1-(4-fluorophenyl)-2-(isobutylamino)-2-oxoethyl]-2-phenylimidazo[1,2-*a*]pyridine-6-carboxamide (31): According to general procedure B; yield: 430 mg, 73%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.86 (m, 4 H), 0.91 (d, $J_{H,H}$ = 6.6 Hz, 6 H), 1.08 (m, 1 H), 3.15 (m, 2 H), 4.72 (s, 2 H), 5.82 (s, 1 H), 6.10 (s, 1 H), 6.34 (s, 1 H), 6.63 (m, 2 H), 7.45–7.30 (m, 10 H), 7.60 (t, $J_{H,H}$ = 12.0 Hz, 2 H), 8.47 (t, $J_{H,H}$ = 5.7 Hz, 1 H), 981 (s, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 169.5, 164.9, 161.4, 156.7, 143.0, 141.4, 137.2, 132.3, 132.2, 131.6, 128.2, 127.5, 127.2, 126.9, 126.7, 126.2, 118.7, 116.4, 116.0, 108.3, 63.0, 49.9, 49.3, 44.6, 28.4, 20.1, 7.7 ppm. HRMS (ESI): calcd. for $C_{36}H_{36}FN_5O_2H$ [M + H]$^+$ 590.2931; found 590.2926.

Methyl *N*-{1,3-Benzodioxol-5-yl[({3-(*tert*-butylamino)-2-thien-2-ylimidazo[2,1-*b*][1,3]benzothiazol-7-yl}carbonyl)(isobutyl)amino]-acetyl}glycinate (36): According to general procedure C; yield: 453 mg, 67%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.03 (d, $J_{H,H}$ = 7.2 Hz, 6 H), 1.20 (s, 9 H), 1.97 (m, 1 H), 3.04 (m, 2 H), 3.73 (s, 3 H), 4.01 (s, 2 H), 5.92 (s, 2 H), 6.42 (m, 1 H), 6.83 (d, $J_{H,H}$ = 8.5 Hz, 1 H), 6.93 (s, 1 H), 7.13 (d, $J_{H,H}$ = 10.2 Hz, 1 H), 7.50 (dd, $J_{H,H}$ = 4.8, 9.3 Hz, 1 H), 7.80 (d, $J_{H,H}$ = 8.7 Hz, 1 H), 7.98 (d, $J_{H,H}$ = 4.8 Hz, 1 H), 8.28 (d, $J_{H,H}$ = 8.7 Hz, 1 H), 9.20 (s, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 169.8, 166.4, 147.3, 147.0, 146.4, 145.4, 135.6, 132.3, 131.1, 127.7, 127.2, 126.8, 126.3, 124.1, 121.0, 119.9, 111.8, 108.5, 108.1, 101.0, 67.5, 60.3, 54.6, 51.9, 38.4, 31.1, 26.2, 19.8 ppm. HRMS (ESI): calcd. for $C_{34}H_{37}N_5O_6S_2H$ [M + H]$^+$ 676.2264; found 676.2274.

1-(2-Methoxy-2-oxoethylamino)-4-methyl-1-oxopentan-2-yl 3-{3-(Benzylamino)imidazo[1,2-*a*]pyrimidin-2-yl}benzoate (40): According to general procedure B; yield: 413 mg, 78%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.05 (d, $J_{H,H}$ = 7.1 Hz, 6 H), 1.13 (m, 1 H), 1.74 (m, 1 H), 2.13 (m, 1 H), 3.73 (s, 3 H), 3.92 (s, 2 H), 4.72 (s, 2 H), 5.15 (t, $J_{H,H}$ = 9.3 Hz, 1 H), 6.23 (s, 1 H), 6.74 (d, $J_{H,H}$ = 4.2 Hz, 1 H), 7.40–7.14 (m, 6 H), 7.80 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 8.07 (d, $J_{H,H}$ = 9.6 Hz, 1 H), 8.44 (s, 1 H), 8.50 (d, $J_{H,H}$ = 9.0 Hz, 1 H), 8.90 (s, 1 H), 9.32 (d, $J_{H,H}$ = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 172.3, 170.5, 162.8, 151.3, 149.4, 142.0, 134.6, 132.3, 130.6, 129.0, 128.5, 128.2, 128.0, 127.8, 127.5, 126.9, 110.2, 71.5, 52.0, 49.9, 42.0, 39.8, 23.2, 22.3 ppm. HRMS (ESI): calcd. for $C_{29}H_{31}N_5O_5H$ $[M + H]^+$ 530.2403; found 530.2412.

2-(*tert*-Butylamino)-1-cyclopropyl-2-oxoethyl 3-{3-(Benzylamino)-imidazo[1,2-*a*]pyrimidin-2-yl}benzoate (41): According to general procedure B; yield: 343 mg, 69%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.68 (m, 4 H), 1.35 (s, 9 H), 1.60 (m, 1 H), 4.72 (s, 2 H), 4.87 (d, $J_{H,H}$ = 8.1 Hz, 1 H), 6.73 (t, $J_{H,H}$ = 4.2 Hz, 1 H), 7.43–7.14 (m, 5 H), 8.80 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 8.05 (s, 1 H), 8.45 (dd, $J_{H,H}$ = 4.3, 9.1 Hz, 1 H), 8.90 (s, 1 H), 9.32 (d, $J_{H,H}$ = 3.9 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 172.5, 161.4, 151.3, 149.4, 142.0, 134.6, 133.7, 130.9, 130.6, 130.3, 128.8, 128.2, 127.5, 126.9, 110.2, 78.0, 49.9, 48.1, 28.7, 15.1, 14.1, 12.4 ppm. HRMS (ESI): calcd. for $C_{29}H_{31}N_5O_3Na$ $[M + Na]^+$ 520.2325; found 520.2325.

1-(Furan-2-yl)-2-(isobutylamino)-2-oxoethyl 3-{3-(Benzylamino)-imidazo[1,2-*a*]pyrimidin-2-yl}benzoate (42): According to general procedure B; yield: 298 mg, 57%; amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.92 (d, $J_{H,H}$ = 6.9 Hz, 6 H), 1.79 (m, 1 H), 3.03 (d, $J_{H,H}$ = 6.9 Hz, 2 H), 4.72 (s, 2 H), 5.73 (s, 2 H), 6.14 (d, $J_{H,H}$ = 4.2 Hz, 1 H), 6.21 (d, $J_{H,H}$ = 1.5 Hz, 1 H), 6.39 (s, 1 H), 6.74 (d, $J_{H,H}$ = 4.2 Hz, 1 H), 7.32–7.14 (m, 4 H), 7.83 (m, 1 H), 8.05 (m, 1 H), 8.47 (m, 2 H), 8.90 (s, 1 H), 9.32 (d, $J_{H,H}$ = 3.9 Hz, 1 H) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$, 25 °C): δ = 169.0, 159.1, 155.6, 151.3, 149.4, 142.0, 137.5, 134.6, 132.3, 130.6, 129.5, 129.0, 128.8, 127.5, 126.9, 111.4, 110.2, 107.6, 71.9, 49.9, 45.9, 28.4, 20.1 ppm. HRMS (ESI): calcd. for: $C_{30}H_{29}N_5O_4Na$ $[M + Na]^+$ 546.2117; found 546.2108.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra.

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