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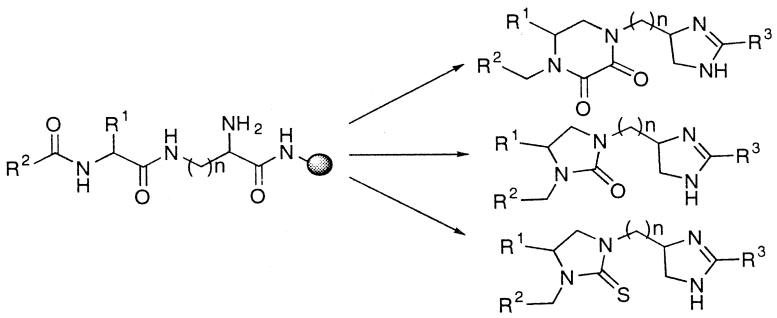

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Solid-Phase Synthesis of Substituted Imidazoline-Tethered 2,3-Diketopiperazines, Cyclic Ureas, and Cyclic Thioureas

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Efficient methods for the solid-phase synthesis of imidazoline-tethered 2,3-diketopiperazines, cyclic ureas, and cyclic thioureas are described. Following the exhaustive reduction of resin-bound dipeptides derived from orthogonally protected diamino acids, the primary amine of the resulting tetraamines was selectively protected with Dde. The compounds were then selectively cyclized via their secondary amines with three different diimidazole derivatives ($(COIm)_2$, $COIm_2$, $CSIm_2$). Upon Dde removal, the compounds were selectively N-acylated and dehydratively cyclized with $POCl_3$ to afford the imidazoline-tethered analogues in moderate yield and high purity. These procedures have been extended to prepare mixture-based combinatorial libraries. Details of the selection of building blocks for preparation of the positional scanning libraries based on the "libraries from libraries" approach are discussed.

Introduction

Heterocyclic compounds have long been known to exhibit remarkable biological and pharmacological properties.[1] Despite the exponential growth in the number of strategies appearing on the synthesis of heterocycles on solid support over the past few years, heterocycles prepared using peptides as starting materials have been less studied, thus prompting our exploration of this synthetic approach. Among these heterocycles, diketopiperazines (DKPs) have been extensively studied for their rigid scaffold, which is present in many natural products known to exhibit diverse biological properties. Examples of these activities include (i) inhibitors of the mammalian cell cycle and several enzymes,[2,3] (ii) inhibitors of mammalian DNA topoisomerase I and suppressors of tumor cell growth,[4] (iii) highly selective collagenase-I inhibitors and bradykinin antagonists,[5] (iv) modulators of the activity of human plasminogen activator inhibitors-1 (their high concentrations are considered a risk factor in thrombotic diseases and control of dopamine receptor activities[6]), and (v) opioid receptor agonists and antagonists.[7] Cyclic ureas and thioureas are reported to be useful in the construction of neutral hydrogen bonding receptors and show strong anion binding activities.[8,9] Cyclic ureas and cyclic thioureas are reported to be potent inhibitors of human immunodeficiency virus (HIV) protease and HIV replication.[10] Recent studies have also revealed that the imidazoline ring is a required pharmacophore for certain potent antihyperglycemic properties.[11] Imidazoline derivatives, such as midaglizole, deriglidole, and Efaroxan, have been identified as promising antihyperglycemic agents.[11] An imidazoline moiety has previously been incorporated into a known antihypertensive agent, clodine.[12] The striking biological properties of these heterocycles make the investigation of the synthetic approach of imidazoline-tethered heterocycles worthwhile.

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Several approaches have been reported for the solid-phase synthesis of DKPs,[13,14] cyclic ureas,[15] and cyclic thioureas.[15] Among these, the use of diimidazole derivatives, such as $(COIm)_2$, $COIm_2$, and $CSIm_2$ for cyclization of secondary amines to generate 2,3-diketopiperazines (DKPs), cyclic ureas, and cyclic thioureas, respectively, is believed to be a preferred approach for preparation of these heterocycles.[13,15a]

In a continuation of our efforts directed toward the solid-phase synthesis of low molecular weight heterocycles from amino acids and peptides and toward their use in the identification of active compounds from their combinatorial libraries, we describe, herein, an efficient strategy for the preparation of imidazoline-tethered heterocycles (DKPs, cyclic thioureas, and cyclic ureas) and their respective positional scanning libraries.[16] The use of different orthogonally protected diamino acids (amino acids having two amine functionalities) in the synthesis also permits variation of the tether carbon length.

Results and Discussion

Individual orthogonally protected diamino acids, N^{α}-(Fmoc)-N^{x}-(Boc)-diamino acids ($x = \beta$ and ϵ), were coupled to 4-methylbenzhydrylamine (MBHA) resin (Scheme 1). Deprotection of the Boc group using 50% trifluoroacetic acid (TFA) in dichloromethane (DCM) of the resin-bound N^{α}-(Fmoc)-N^{x}-(Boc)-diamino acids, followed by neutralization using 2% *N*,*N*′-diisopropylethylamine (DIEA) in DCM, generated compounds **1** having a primary amine. Boc amino acids were coupled to the primary amine of **1**, followed by deprotection of the Boc group, to generate the resin-bound dipeptides **2**. Following N-acylation with a range of carboxylic acids at the primary amine of the dipeptides **2**, the N^{α}-Fmoc group was removed. Exhaustive reduction of the amides of the N-acylated dipeptides **3** was performed by treatment with BH_3-THF,[17] resulting in tetraamines **4** having three secondary amines and a primary amine.

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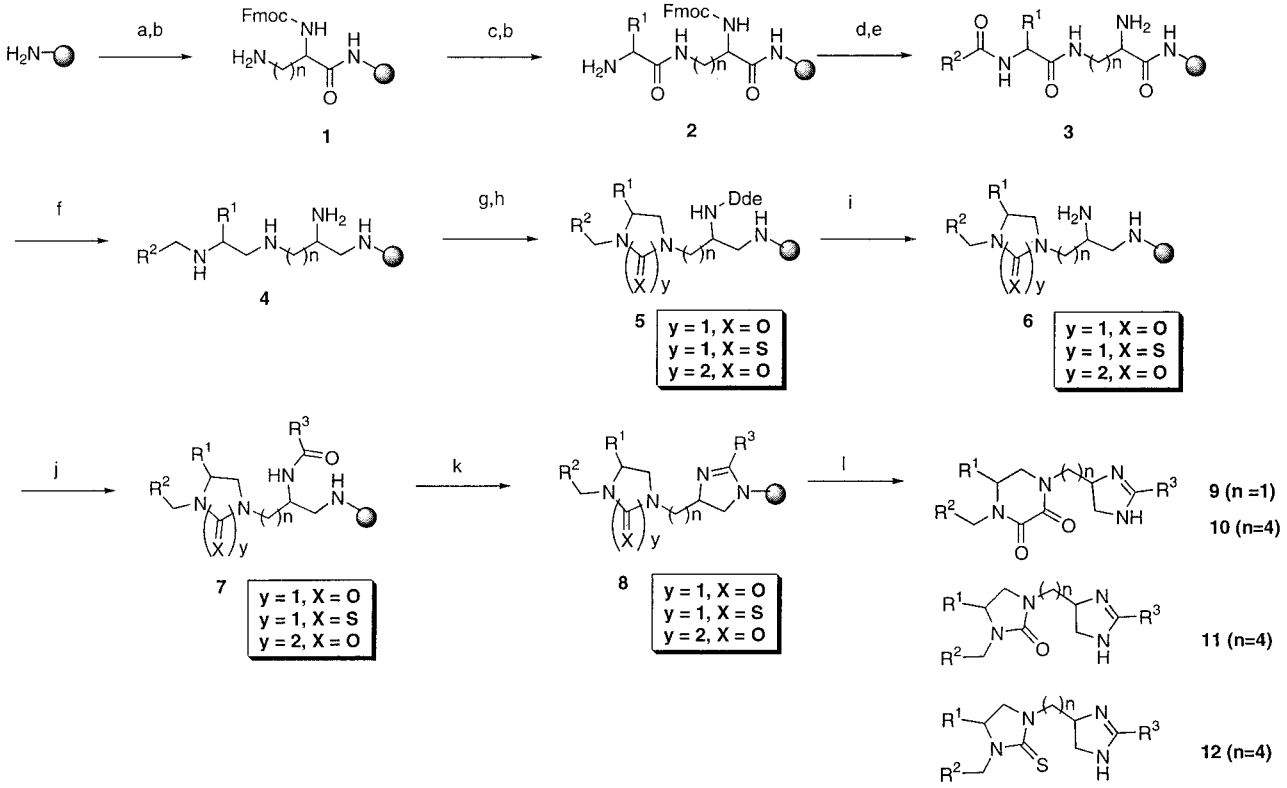
Scheme 1[a]

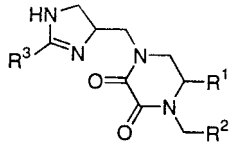


[a] (a) Fmoc-(Boc)-L-diamino Acids (2.5 equiv, 0.05 M in DMF), DIC (2.5 equiv), HOBt (2.5 equiv), room temp, overnight; (b) 55% TFA in 45% DCM, room temp, 30 min; (c) Boc-NHCH(R^1)CO_2H (6 equiv, 0.1 M in DMF), DIC (6 equiv), HOBt (6 equiv), room temp, 2 h; (d) R^2CO_2H (10 equiv, 0.1 M in DMF), DIC (10 equiv), HOBt (10 equiv), room temp, Overnight; (e) 20% piperidine in 80% DMF, room temp, 30 min; (f) (i) BH_3−THF, 65 °C, 4 days; (ii) piperidine, 65 °C, 20 h; (g) 2-acetyldimedone (Dde-OH) (1.5 equiv, 0.03 M in DMF), room temp, 3 h; (h) $(COIm)_2$ (7 equiv, 0.07 M in DMF)/$CSIm_2$ (10 equiv, 0.1 M in DCM)/$COIm_2$ (10 equiv, 0.1 M in DCM), room temp, overnight; (i) 2% NH_2NH_2 in DMF, 2 × 30 min, room temp; (j) R^3CO_2H (3 equiv, 0.06 M in DMF), HBTU (3 equiv), DIEA (6 equiv), room temp, 3.5 h; (k) $POCl_3$ (10 equiv, 0.09 M in dioxane), 2.5 h, 110 °C; (l) HF, anisole, 0 °C, 7 h. "*n*" denotes the tether carbon length.

Selective protection of the primary amine of the tetraamines **4** was tested with various protecting groups, such as triphenylmethyl chloride (Trityl-Cl),[18] 9-fluorenylmethyl chloroformate (Fmoc-Cl),[19] di-*tert*-butyl-dicarbonate (Boc),[20,21] and 2-acetyldimedone (Dde-OH).[21] Following cyclization with different diimidazole derivatives, the protecting groups were removed and the compounds were cleaved to determine their selectivity of protection. Uncyclized starting materials (>20%) were detected by LC−MS for compounds protected with Boc, Fmoc, or trityl protecting groups. These results indicate that neither the Boc nor the Fmoc protecting groups selectively protect the desired primary amine. In the case of trityl protection, steric factors are probably the reason mostly starting material was obtained. When Dde protection was used, the compounds were obtained in excellent yield and purity by LC−MS and reverse-phase (RP)-HPLC without any undesirable and/or uncyclized material. Therefore, Dde-OH was chosen to selectively protect the primary amine.

The primary amine of the tetraamines **4** was thus treated with Dde-OH to selectively protect the primary amine.[21] Cyclization was carried out through two secondary amines (those furthest from the solid support) with three different diimidazole derivatives ($(COIm)_2$, $COIm_2$, $CSIm_2$) to yield compounds of general structure **5**. Upon removal of the Dde group with 2% hydrazine in DMF,[21] the primary amine of **6** was selectively N-acylated using a range of carboxylic acids to generate amides of general structure **7**. Different coupling conditions[22] were examined [*N*,*N*′-diisopropylcarbodiimide (DIC), DIC and *N*-hydroxybenzotriazole (HOBt), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), and DIEA] to selectively N-acylate the primary amine of compounds of general structure **6**. Using either DIC or DIC in the presence of HOBt led to unwanted N-acylation at the secondary amine next to the solid support. The best results were achieved using low concentrations of the carboxylic acids (3 equiv, 0.03 M) in the presence of HBTU and DIEA in DMF for 3.5 h at room temperature. Negligible N-acylation (<1%) was observed at the secondary amine of **6** by LC−MS, although complete N-acylation of the primary amine was observed. On treatment with freshly distilled $POCl_3$ in dioxane at 110 °C, the resin-bound in situ generated imidoyl chlorides cyclized[23] to afford the resin-bound imidazoline-tethered heterocycles **8**. The final products were cleaved from the solid support using anhydrous HF and extracted with 95% acetic acid in water to yield the compounds **9**−**12**. Ten individual control compounds were prepared for each tethered derivative (**9**−**12**) in order to determine the generality of this synthetic approach. These controls were prepared by varying a common structure at the first (R^1) position of diversity with three amino acids (Ala, Phe, and Val), the second position (R^2) of diversity with three carboxylic acids (butyric acid, phenylacetic acid, and acetic acid), and the third (R^3) position of diversity with four carboxylic acids (butyric acid, phenylacetic acid,

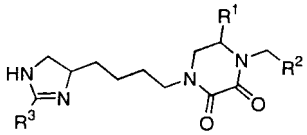
Table 1. RP-HPLC Purity and Masses Found for **9**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
9a	$-CH_3$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	356.5	357.4 ($M + H^+$)	86
9b	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	432.6	433.4 ($M + H^+$)	94
9c	$-CH(CH_3)C_2H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	398.5	399.4 ($M + H^+$)	94
9d	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$	384.5	385.4 ($M + H^+$)	88
9e	$-CH_2C_6H_5$	$-CH_3$	$-CH_2CH_2CH_3$	356.5	357.4 ($M + H^+$)	95
9f	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	480.6	481.4 ($M + H^+$)	89
9g	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CHCH_2$	430.5	431.4 ($M + H^+$)	86
9h	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_3$	404.5	405.4 ($M + H^+$)	85
9i	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CHCHC_6H_4(2-CF_3)$	560.6	561.4 ($M + H^+$)	87
9j	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-C(C_2H_5)CHCH_2CH_2CH_3$	486.6	487.5 ($M + H^+$)	87
9k	$-CH_2C_6H_5$	$-CH_2C_6H_4(3-OCH_3)$	$-CH_2CH_2CH_3$	462.6	463.4 ($M + H^+$)	88

[a] The yields obtained were greater than 60% in all cases with respect to the initial loading of the resin (1.15 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at $\lambda = 214$ nm.

Table 2. RP-HPLC Purity and Masses Found for **10**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
10a	$-CH_3$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	398.5	399.2 ($M + H^+$)	82
10b	$-CH_2CH(CH_3)_2$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	440.6	441.1 ($M + H^+$)	88
10c	$-CH_2CH_2CH_3$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	426.6	427.1 ($M + H^+$)	86
10d	$-CH_2C_6H_5$	$-CH(CH_3)C_2H_5$	$-CH_2CH_2CH_3$	440.6	441.1 ($M + H^+$)	86
10e	$-CH_2C_6H_5$	$-CH_3$	$-CH_2CH_2CH_3$	398.5	399.0 ($M + H^+$)	87
10f	$-CH_2C_6H_5$	$-C(CH_3)_3$	$-CH_2CH_2CH_3$	440.6	441.3 ($M + H^+$)	86
10g	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CHCHC_6H_4(2-CF_3)$	602.7	603.3 ($M + H^+$)	90
10h	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH(CH_3)_2$	474.6	475.2 ($M + H^+$)	89
10i	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C(CH_3)_3$	502.7	503.2 ($M + H^+$)	88
10j	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$	426.6	427.3 ($M + H^+$)	85
10k	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_{11}$	528.7	529.6 ($M + H^+$)	86

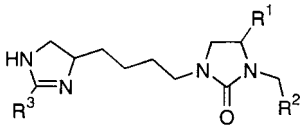
[a] The yields obtained were greater than 60% in all cases with respect to the initial loading of the resin (1.15 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm.

isovaleric acid, and vinylacetic acid). Complete cyclization was observed by LC−MS and RP-HPLC. The samples were purified by high-pressure long-column chromatography (HPLC) (see Tables 1−4) and were characterized by high-resolution mass spectra (HRMS), ^{1}H NMR, and ^{13}C NMR.

Two strong downfield proton signals at δ 9.9−10.3 ppm (DMSO-d_6) in the ^{1}H NMR spectra were found for all of the above imidazoline-tethered derivatives. The imidazoline moiety is protonated (p$K_a \approx 9.5$)[11] following purification using 0.05% TFA. Thus, the two downfield signals corresponded to the two NH protons of the protonated imidazoline moiety.[11] The two amide carbonyl carbon signals at δ 156−158 ppm in the ^{13}C NMR spectrum for the 2,3-diketopiperazine derivatives (DKPs) (**9** and **10**) were assignable to the carbonyls in the diketopiperazine moiety.[3] The carbon signals at $\delta \sim 160$ ppm in the ^{13}C NMR spectrum for all the imidazoline-tethered cyclic ureas (**11**) were assigned to the amide carbon of the cyclic urea moiety.[3] For imidazoline-tethered cyclic thioureas (**12**), the appearance of a carbon signal at $\delta \sim 181$ ppm in the ^{13}C NMR spectra corresponded to the thioamide carbon.[9] The ^{1}H NMR spectra of compounds derived from unsaturated carboxylic acids at the third (R^3) position of diversity, such as vinylacetic acid, crotonic acid, and 2-(trifluoromethyl)cinnamic acid, were examined to determine the susceptibility of the unsaturated sites to side reactions under the cyclodehydration conditions used. Appearance of proton signals at δ 6.08−6.12 ppm for vinylacetic acid (**9g** and **12g**), 6.06−6.09 ppm for crotonic acid (**11d**), and ~6.8 ppm for 2-(trifluoromethyl)cinnamic acid (**9i** and **10g**) in the ^{1}H NMR spectra for imidazoline-tethered derivatives indicated retention of these double bonds[2] during cyclodehydration.

It was found that a detectable amount (<5%) of the N^{α}-Fmoc group was removed during neutralization using 2% DIEA in DCM (i.e., following the N^{ϵ}-Boc group removal) from N^{α}-Fmoc-N^{ϵ}-Boc-lysine. This was most likely due to

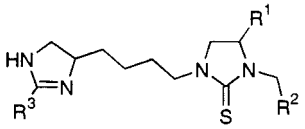
Table 3. RP-HPLC Purity and Masses Found for **11**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
11a	$-CH(CH_3)_2$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	398.6	399.1 ($M + H^+$)	82
11b	$-CH_2C_6H_5$	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$	398.6	399.1 ($M + H^+$)	83
11c	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2CH_2CH_3$	412.6	413.1 ($M + H^+$)	81
11d	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CHCHCH_3$	444.6	445.1 ($M + H^+$)	82
11e	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH(CH_3)_2$	446.6	447.2 ($M + H^+$)	81
11f	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	460.7	461.2 ($M + H^+$)	81
11g	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH(CH_3)_2$	474.7	475.2 ($M + H^+$)	80
11h	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_3$	418.6	419.1 ($M + H^+$)	82
11i	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	446.6	447.3 ($M + H^+$)	80
11j	$-CH_2C_6H_5$	$-CH_2CH_2C_5H_9$	$-CH_2CH_2CH_3$	452.7	453.4 ($M + H^+$)	80
11k	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-C_4H_7$	458.6	459.4 ($M + H^+$)	80

[a] The yields obtained were greater than 60% in all cases with respect to the initial loading of the resin (1.15 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm.

Table 4. RP-HPLC Purity and Masses Found for **12**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
12a	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	428.7	429.0 ($M + H^+$)	82
12b	$-CH_3$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	386.6	387.0 ($M + H^+$)	83
12c	$-CH(CH_3)C_2H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	428.7	429.1 ($M + H^+$)	80
12d	$-CH_2C_6H_5$	$-CH_2CH_2C_6H_{11}$	$-CH_2CH_2CH_3$	482.8	483.5 ($M + H^+$)	82
12e	$-CH_2C_6H_5$	$-CH_3$	$-CH_2CH_2CH_3$	386.6	387.1 ($M + H^+$)	81
12f	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH(CH_3)_2$	490.7	491.2 ($M + H^+$)	81
12g	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CHCH_2$	460.7	461.1 ($M + H^+$)	80
12h	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_3$	434.6	435.0 ($M + H^+$)	82
12i	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	462.7	463.2 ($M + H^+$)	80
12j	$-CH_2C_6H_5$	$-CH(CH_3)C_2H_5$	$-CH_2CH_2CH_3$	428.7	429.2 ($M + H^+$)	80
12k	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2CH_2CH_3$	428.7	429.1 ($M + H^+$)	80
12l	$-CH_2C_6H_5$	$-CH_2C_6H_3(3,4-OCH_3)_2$	$-CH_2CH_2CH_3$	522.7	523.3 ($M + H^+$)	81

[a] The yields obtained were greater than 60% in all cases with respect to the initial loading of the resin (1.15 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm.

the intramolecular base-promoted Fmoc deprotection by the N^{ϵ}-amino functionality following neutralization with DIEA. No detectable amount of N^{α}-Fmoc group deprotection was observed for other orthogonally protected diamino acids during neutralization at this step. The use of 1−2% DIEA in DCM for <1 min for neutralization following Boc removal (for N^{α}-Fmoc-N^{ϵ}-Boc-lysine) was found to minimize Fmoc removal at this step. The undesirable byproducts, most likely formation of bis derivatives during cyclization upon treatment with diimidazole derivatives, were cleaved during the $POCl_3$ treatment as explained below. This is evident from the moderate yield (>60%) and high purity (>80%) of the final compounds.

We obtained moderate yields (>60%) for all imidazoline-tethered derivatives. This was caused, as expected, by acidolytic cleavage that occurred because of generation of HCl during $POCl_3$ treatment.[24] It is important to maintain anhydrous conditions and to utilize pure $POCl_3$ during this reaction. Various cyclodehydrative conditions[23] were tested in order to obtain the final products in good yield and purity. The best conditions were obtained using 10 equiv excess of $POCl_3$ (0.09 M) in anhydrous dioxane for 2.5 h at 110 °C, yielding products in moderate yield (>60%) and good purity (>80%) (see Tables 1−4).

The possibility of racemization during BH_3−THF reduction, protection of the primary amine upon treatment with Dde-OH, cyclization by diimidazole derivatives, and/or cyclodehydration was determined. For each step, two diastereomers known not to coelute were prepared. Comparison of the RP-HPLC of the two enantiomers and ^1H NMR data showed that there was no detectable racemization (<1% racemization) either during exhaustive reduction of amides of the N-acylated dipeptides[17,18] or during cyclization using the diimidazole derivatives,[13,15a] in conformity with our earlier observations. Following protection of the primary amine of the tetraamines **4** with Dde, deprotection, and subsequent cleavage, no detectable racemization (<1%) was observed as indicated by RP-HPLC. Similarly, the final compounds obtained after $POCl_3$ treatment were found to be 99% chirally pure by ^1H NMR.

After optimization of the different reaction steps, we expanded the synthesis of individual control compounds using 40 different amino acids at the first (R^1) position of diversity and 48 carboxylic acids each at the second (R^2) and third (R^3) positions of diversity to determine their acceptability for inclusion in the synthesis of a positional scanning library.[16] It was found that *p*-NO_2-phenylalanine analogues were partially reduced during the exhaustive reduction step, resulting in undesirable byproducts in the final step.[15a] Serine and threonine analogues were not considered because of formation of undesirable byproducts occurring most likely during $POCl_3$ treatment. However, tyrosine analogues were included because of the high purities (>80%) of the crude compounds. Amino acids having either an extra amine functionality (e.g., arginine) or generating an extra amine functionality after reduction (e.g., glutamine) were not included at the first position (R^1) of diversity in the synthesis of the libraries because of formation of undesirable byproducts.

It was found that N-benzylic derivatives, obtained upon N-acylation using *m*-toluic acid at the second (R^2) position, were partially removed during the 7 h of HF cleavage of the resin-bound cyclic urea (**11**) and cyclic thiourea (**12**) derivatives. But this moiety was not cleaved at the same relative position of diversity for the diketopiperazine (**9** and **10**) derivatives. Thus, benzoic acid derivatives were excluded for N-acylation at the second (R^2) position of diversity. However, *m*-toluic acid, *p*-toluic acid, and 4-fluorobenzoic acid were included for N-acylation at the third (R^3) position of diversity because of the acceptable purity (>80%) of the final crude compounds of these derivatives. It was observed that the *N*-methylbiphenyl moiety, obtained upon N-acylation with biphenylcarboxylic acid or 4-ethyl-4′-biphenylcarboxylic acid at the second (R^2) position of diversity, was completely cleaved during HF cleavage for imidazoline-tethered cyclic urea (**11**) and cyclic thiourea (**12**) analogues. In contrast, these moieties were retained for imidazoline-tethered diketopiperazine (**9** and **10**) analogues during the 7 h of HF cleavage. Thus, these carboxylic acids were not considered for N-acylation at the second (R^2) position of diversity. However, these carboxylic acids were included for N-acylation at the third (R^3) position of diversity because of the high purity (>80%) of the crude control compounds. Unsaturated aromatic and aliphatic carboxylic acid derivatives, obtained upon N-acylation with 2-trifluorocinnamic acid, 2-hydroxycinnamic acid, 2-methoxycinnamic acid, crotonic acid, vinylacetic acid, 2-ethyl-2-hexenoic acid, gave undesirable byproducts of low purity (<40%) for N-acylation at the second (R^2) position of diversity. This is most likely due to the formation of borane complexes during reduction with BH_3-THF. These carboxylic acids were excluded for N-acylation at the second (R^2) position of diversity for synthesis of libraries. However, 2-trifluorocinnamic acid, crotonic acid, vinylacetic acid, and 2-ethyl-2-hexenoic acid were included for N-acylation at the third (R^3) position of diversity. 1-Adamantanecarboxylic acid, 2-hydroxycinnamic acid, and 4-nitrophenylacetic acid, obtained upon N-acylation at the third (R^3) position of diversity, were excluded for N-acylation at the third (R^3) position of diversity because of formation of undesirable byproducts and/or incomplete cyclization during $POCl_3$ treatment. This is most likely due to steric hindrance and/or formation of more basic imidoyl chloride intermediates that inhibit the cyclization or slowly transform these intermediates to quaternary derivatives hindering cyclization.[23] We ultimately selected only those building blocks that are compatible with the three imidazoline-tethered analogues, i.e., DKPs, cyclic ureas, and cyclic thioureas, because the libraries were prepared from the same starting resins of the general structure **4**.

The percent crude yield for each compound was determined from the final yield of the compound with respect to the theoretical loading of the resin (1.15 mequiv/g). The percent crude purity was determined from the relative peaks areas of the HPLC chromatograms at $\lambda = 214$ nm. From the different amino acids and carboxylic acids tested, those building blocks yielding purities of the crude compounds greater than 80% were selected for inclusion in the synthesis of the positional scanning libraries.[16] Thus, 34 amino acids at the first (R^1) position of diversity, 37 carboxylic acids at the second (R^2) position of diversity, and 45 carboxylic acids at the third (R^3) position of diversity were chosen for preparation of the positional scanning libraries of imidazoline-tethered DKPs (derived from N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid and N^{α}-Fmoc-N^{ϵ}-Boc-lysine), cyclic ureas, and cyclic thioureas derived from N^{α}-Fmoc-N^{ϵ}-Boc-lysine (included in the Supporting Information). Predetermined isokinetic ratios, for different Boc amino acids at the first (R^1) position of diversity and carboxylic acids for N-acylation at the second (R^2) position of diversity using DIC and HOBt, were used for coupling of the mixtures involved.[25] However, a different set of predetermined isokinetic ratios was used for coupling of mixtures of carboxylic acids (included in Supporting Information) in the selective N-acylation of the primary amine at the third (R^3) position of diversity using HBTU and DIEA. The final compounds were cleaved from the solid support using anhydrous HF and extracted with 95% acetic acid in water.

Conclusion

In summary, we report herein an efficient methodology for the synthesis of imidazoline-tethered 2,3-diketopiperazines, cyclic ureas, and cyclic thioureas. The solid-phase synthesis of these tethered compounds is straightforward, with moderate yields and high purity of the final compounds. The carbon spacer between the imidazoline moiety and 2,3-diketopiperazine, cyclic urea, or cyclic thiourea moieties was varied by employing different orthogonally protected diamino acids. Considering the known desirable biological properties of the DKPs, we have prepared separate positional scanning libraries of imidazoline-tethered DKPs derived from N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid and N^{α}-Fmoc-N^{ϵ}-Boc-lysine using the "libraries from libraries" approach.[16] We have also prepared the positional scanning libraries of the imidazoline-tethered cyclic ureas and cyclic thioureas derived from N^{α}-Fmoc-N^{ϵ}-Boc-lysine using the "libraies from libraries" concept.[16] Identification of individual active compounds through the use of these libraries will be reported elsewhere. We anticipate that, in due course, we will extend our

approach to the synthesis of other imidazoline-tethered analogues derived from N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid, N^{α}-Fmoc-N^{γ}-Boc-diaminobutyric acid, N^{α}-Fmoc-N^{δ}-Boc-ornithine, and N^{α}-Fmoc-N^{ϵ}-Boc-lysine.

Experimental Section

Boc-, Fmoc-diamino acid derivatives, 2-acetyldimedone (Dde-OH), di-*tert*-butyl-dicarbonate (tert-Boc)$_2$O, *N*-hydroxybenzotriazole (HOBt), and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA) and Bachem Bioscience Inc. (Philadelphia, PA). 4-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100−200 mesh, 1.15 mequiv/g substitution) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex International (Wood Dale, IL). Anhydrous hydrogen fluoride was purchased from Air Products (San Marcos, CA). All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). LC−MS (ESI and APCI) were recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at $\lambda = 214$ nm using a Betasil C18, 3 μm, 100 Å, 3 mm × 50 mm column. Preparative RP-HPLC was performed on a Waters Delta Prep preparative HPLC (Millipore) using a Vydac 218TP1022 C18 column (2.2 cm × 25 cm). High-resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Facility of the University of California at Riverside.

Typical Procedure for the Individual Synthesis of Imidazoline-Tethered DKPs, Cyclic Ureas, and Cyclic Thioureas. A polypropylene mesh packet consisting of 100 mg of MBHA resin (1.15 mequiv/g, 100−200 mesh) was sealed.[26] The resin was washed with dichloromethane (DCM) followed by neutralization with 5% *N*,*N*′-diisopropylethylamine (DIEA) in DCM and washed with DCM. Polypropylene bottles and 50 mL conical tubes (where necessary) were used for all the reactions.

(1) Coupling of Orthogonally Protected Diamino Acids to Resin (Scheme 1). Orthogonally protected diamino acids (N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid and N^{α}-Fmoc-N^{ϵ}-Boc-lysine) (2.5 equiv, 0.05 M in DMF, overnight) were coupled to MBHA resin using DIC and HOBt (2.5 equiv each) at room temperature. Following washes with DMF (four times), the Boc group was deprotected using 50% TFA in DCM for 30 min, followed by neutralization with 2% DIEA in DCM for 1 min (three times). Boc amino acids (6 equiv, 0.1 M in DMF) were coupled to the free amine using DIC and HOBt (6 equiv each) for 2 h at room temperature, followed by washes with DMF (three times) and DCM (three times). Deprotection of the Boc group, followed by neutralization, was carried out according to the same procedure described above. N-acylation at the free amine of the dipeptides was performed with a range of carboxylic acids (10 equiv, 0.1 M in DMF, overnight) using DIC and HOBt (10 equiv each). Following washes with DMF (four times) and DCM (three times), the Fmoc group was removed using 20% piperidine in DMF for 30 min at room temperature, followed by washes with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). Completeness of the coupling was verified by the ninhydrin test.[27]

(2) Exhaustive Reduction of Amide Groups of the N-Acylated Dipeptides by BH_3−THF. Exhaustive reduction of the N-acylated dipeptides was carried out in 50 mL glass conical tubes under nitrogen. The resin packet (0.115 mequiv of resin, i.e., 0.345 mequiv of amide) was added to each tube, followed by addition of boric acid (12 equiv, i.e., 4.14 mequiv) and trimethyl borate (12 equiv, i.e., 4.14 mequiv). Borane−THF complex (1 M, 40 equiv, i.e., 13.8 mequiv) was added slowly. After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 4 days, followed by decantation of the reaction solution and quenching with methanol (MeOH). The resin was washed with DMF and MeOH (four times), followed by treatment with piperidine at 65 °C for 20 h to disproportionate the borane complexes.[17] Following decantation of the piperidine−borane solution, the resin packet was washed with DMF (four times), DCM (four times), and MeOH (two times) and was dried.

(3) Formation of 2,3-Diketopiperazines (DKPs), Cyclic Ureas, and Cyclic Thioureas. Following neutralization of the resin-bound tetraamines with 5% DIEA in DCM, the primary amine of the tetraamines was protected using Dde-OH (1.5 equiv, 0.03 M in DMF) for 3 h at room temperature. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (3 times) and was dried. Completeness of the Dde protection was verified by the ninhydrin test.[27] The protected tetraamines were cyclized upon treatment with different diimidazole derivatives, i.e., $(COIm)_2$ (7 equiv, 0.07 M in DMF), $COIm_2$, and $CSIm_2$ (10 equiv each, 0.1 M in DCM), at room temperature overnight to form 2,3-diketopiperazines (DKPs), cyclic ureas, and cyclic thioureas, respectively. Following washes with DMF (four times for $(COIm)_2$, DCM (four times for $COIm_2$ and $CSIm_2$), IPA (two times), and DCM (three times), the Dde group was deprotected using 2% hydrazine in DMF (two times, 30 min each) at room temperature and washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times).

(4) Selective N-Acylation at the Primary Amine of Compounds of General Structure 6 (See Scheme 1). Following neutralization with 5% DIEA in DCM, N-acylation was performed with a range of carboxylic acids (3 equiv, 0.06 M in DMF) in the presence of HBTU (3 equiv) and DIEA (6 equiv) for 3.5 h. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). Completeness of the coupling was verified by the ninhydrin test.[27]

(5) Cyclization on Treatment with $POCl_3$. The cyclization of the N-acylated compounds was carried out in 50 mL conical tubes under nitrogen. To each tube was added the resin packet (0.115 mequiv resin, 100 mg of starting resin) and anhydrous dioxane, followed by $POCl_3$ (10 equiv, 0.09 M). The capped tubes were heated at 110 °C for 2.5 h followed by decantation of the reaction solution. The resin was washed with dioxane (two times), DMF, MeOH (four times each), DCM (two times), IPA (two times), and DCM (four times). The resin was cleaved by anhydrous HF in the presence of anisole at 0 °C for 7 h,[28] and the cleaved product was extracted with 95% acetic acid in H_2O and lyophilized.

5-Methyl-4-(2-phenylethyl)-1-[(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl]piperazine-2,3-dione (9a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (t, J = 7.24 Hz, 3H), 1.17−1.8 (d, J = 6.43 Hz, 3H), 1.59−1.64 (m, 2H), 2.42−2.46 (m, 2H), 2.82−2.87 (m, 2H), 3.17−3.37 (m, 3H), 3.57−3.61 (m, 2H), 3.71−3.82 (m, 3H), 3.90 (t, J = 11.4 Hz, 1H), 4.44−4.46 (m, 1H), 7.23−7.33 (5H), 10.09 (s, 2H).

5-Benzyl-4-(2-phenylethyl)-1-[(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl]piperazine-2,3-dione (9b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (t, 7.29, 3H), 1.58−1.62 (m, 2H), 2.40−2.44 (m, 2H), 2.76−2.96 (m, 5H), 3.04−3.13 (m, 3H), 3.55−3.59 (dd, J = 6.92 Hz, J = 11.5 Hz, 1H), 3.66−3.69 (m, 2H), 3.83−3.91 (m, 2H), 3.96−4.01 (dd, J = 7.2 Hz, J = 13.8 Hz, 1H), 4.39−4.40 (m, 1H), 7.19−7.33 (m, 10H), 10.07 (s, 1H), 10.09 (s, 1H). HRMS (DCI): m/z 433.2612 found ([M + H]$^+$), 433.2604 calculated for $C_{26}H_{33}N_4O_2$ ([M + H]$^+$).

5-*sec*-Butyl-4-(2-phenylethyl)-1-[(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl] piperazine-2,3-dione (9c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.74−0.75 (d, J = 6.84 Hz, 3H), 0.85 (t, J = 7.38 Hz, 3H), 0.93 (t, J = 7.50 Hz, 3H), 1.21−1.24 (m, 1H), 1.31−1.33 (m, 1H), 1.60−1.66 (m, 3H), 2.42−2.46 (m, 1H), 2.84−2.91 (m, 3H), 3.09−3.15 (m, 2H), 3.26−3.28 (m, 1H), 3.42−3.45 (d, J = 13.3 Hz, 1H), 3.53−3.58 (dd, J = 7.04 Hz, J = 11.5 Hz, 1H), 3.62−3.65 (dd, J = 4.54 Hz, J = 13.54 Hz, 1H), 3.87−4.01 (m, 3H), 4.42−4.44 (m, 1H), 7.21−7.33 (m, 5H), 10.09 (s, 1H), 10.11 (s, 1H).

5-Benzyl-4-butyl-1-[(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl]piperazine-2,3-dione (9d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87−0.92 (m, 6H), 1.24−1.29 (m, 2H), 1.48−1.61 (m, 4H), 2.40−2.42 (m, 2H), 2.77−2.83 (m, 2H), 2.95−2.99 (dd, J = 5.18 Hz, J = 13.6 Hz, 1H), 3.04−3.07 (dd, J = 5.26 Hz, J = 13.9 Hz, 1H), 3.15−3.18 (d, J = 12.1 Hz, 1H), 3.56−3.59 (dd, J = 6.83 Hz, J = 11.5 Hz, 1H), 3.62−3.67 (m, 1H), 3.77−3. 82 (m, 1H), 3.88 (t, J = 11.3 Hz, 1H), 3.98−4.02 (q, J = 7.66 Hz, J = 13.8 Hz, 1H), 4.38−4.39 (m, 1H), 6.53 (s, 1H), 7.23−7.34 (m, 5H), 10.06 (s, 2H).

5-Methyl-4-ethyl-1-[(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl]piperazine-2,3-dione (9e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (t, J = 7.19 Hz, 3H), 1.12 (t, J = 6.99 Hz, 3H), 1.57−1.61 (m, 2H), 2.39−2.42 (m, 2H), 2.79−2.83 (dd, J = 8.89 Hz, J = 13.5 Hz, 1H), 2.88−2.92 (m, 1H), 2.95−2.99 (dd, J = 5.16 Hz, J = 13.7 Hz, 1H), 3.02−3.06 (dd, J = 5.18 Hz, J = 13.9 Hz, 1H), 3.15−3.17 (d, J = 13.0 Hz, 2H), 3.55−3.59 (dd, J = 6.82 Hz, J = 11.5 Hz, 1H), 3.64−3.68 (m, 1H), 3.76−3.80 (dd, J = 4.07 Hz, J = 13.1 Hz, 1H), 3.86−3.90 (m, 1H), 3.99−4.04 (q, J = 7.70 Hz, J = 13.8 Hz, 1H), 4.38−4.42 (m, 1H), 7.23−7.34 (m, 5H), 10.05 (s, 2H).

5-Benzyl-1-[(2-benzyl-4,5-dihydro-1*H*-imidazol-4-yl)-methyl]-4-(2-phenylethyl)piperazine-2,3-dione (9f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.73−2.94 (m, 5H), 3.02−3.12 (m, 3H), 3.57−3.66 (m, 2H), 3.80−3.94 (m, 3H), 3.97−4.01 (q, J = 6.83 Hz, J = 13.9 Hz, 2H), 4.41−4.42 (m, 1H), 7.18−7.40 (m, 15H), 10.17 (s, 1H), 10.22 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.98, 33.36, 36.92, 47.15, 47.63, 49.46, 55.05, 55.56, 126.39, 126.73, 127.81, 128.45, 128.59, 128.67, 128.93, 128.96, 129.17, 132.57, 137.13, 138.78, 156.02, 157.50, 168.80.

1-[(2-Allyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl]-5-benzyl-4-(2-phenylethyl)piperazine-2,3-dione (9g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.98 (t, J = 5.61 Hz, 2H), 2.76−2.96 (m, 6H), 3.03−3.13 (m, 3H), 3.58−3.67 (m, 3H), 3.82−3.88 (m, 1H), 3.92 (t, J = 11.6 Hz, 1H), 3.98−4.03 (q, J = 6.93 Hz, J = 14.0 Hz, 1H), 4.41−4.44 (m, 1H), 6.08−6.12 (dd, J = 1.5 Hz, J = 15.8 Hz, 1H), 6.99−7.04 (m, 1H), 7.19−7.33 (m, 9H), 10.08 (s, 1H), 10.10 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.73, 33.30, 36.92, 47.19, 47.37, 47.63, 49.58, 54.55, 55.63, 113.76, 126.37, 126.74, 128.43, 128.59, 128.68, 129.19, 137.15, 138.80, 148.28, 156.00, 157.49, 162.77. HRMS (DCI): m/z 431.2455 found ([M + H]$^+$), 431.2447 calculated for $C_{26}H_{31}N_4O_2$ ([M + H]$^+$).

5-Benzyl-1-[(2-methyl-4,5-dihydro-1*H*-imidazol-4-yl)-methyl]-4-(2-phenylethyl)piperazine-2,3-dione (9h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.14 (s, 3H), 2.49−2.95 (m, 5H), 3.02−3.11 (m, 4H), 3.53−3.57 (dd, J = 7.11 Hz, J = 11.5 Hz, 1H), 3.64−3.66 (m, 2H), 3.95−3.99 (q, J = 7.09 Hz, J = 13.8 Hz, 1H), 4.36−4.38 (m, 1H), 7.19−7.33 (m, 10H), 10.03 (s, 1H), 10.07 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.30, 33.33, 36.94, 40.78, 42.15, 42.86, 46.92, 47.67, 49.34, 54.78, 55.60, 126.38, 126.73, 128.44, 128.60, 128.69, 129.18, 137.15, 138.81, 156.03, 157.49, 167.62.

5-Benzyl-4-(2-phenylethyl)-1-[(2-{(*E*)-2-[2-trifluoromethyl)phenyl]ethenyl}-4,5-dihydro-1*H*-imidazol-4-yl)-methyl]piperazine-2,3-dione (9i). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.78−2.83 (m, 2H), 2.87−2.88 (m, 2H), 2.94−2.97 (dd, J = 5.0 Hz, J = 13.7 Hz, 1H), 3.05−3.07 (m, 2H), 3.15−3.23 (m, 2H), 3.66−3.73 (m, 3H), 3.83−3.88 (m, 1H), 4.00−4.04 (m, 2H), 4.53−4.57 (m, 1H), 6.78−6.82 (d, J = 16.2 Hz, 1H), 7.15−7.34 (m, 8H), 7.72−7.74 (m, 1H), 7.81−7.88 (m, 2H), 7.93−7.99 (m, 2H), 10.49 (s, 2H). HRMS (DCI): m/z 561.2454 found ([M + H]$^+$), 561.2477 calculated for $C_{32}H_{32}F_3N_4O_2$ ([M + H]$^+$).

5-Benzyl-1-({2-[(1*E*)-1-ethylpent-1-enyl]-4,5-dihydro-1*H*-imidazol-4-yl}methyl)-4-(2-phenylethyl)piperazine-2,3-dione (9j). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88−0.96 (m, 5H), 1.42−1.46 (m, 2H), 2.24−2.26 (m, 2H), 2.30−2.36 (m, 2H), 2.77−2.97 (m, 5H), 3.04−3.15 (m, 4H), 3.61−3.64 (dd, J = 6.95 Hz, J = 11.7 Hz, 1H), 3.69−3.71 (m, 1H), 3.82−3.86 (m, 1H), 3.95 (t, J = 11.3 Hz, 1H), 4.00−4.05 (q, J = 6.58 Hz, J = 14.1 Hz, 1H), 4.40−4.44 (m, 1H), 6.53 (t, J = 7.2 Hz, 1H), 7.20−7.34 (m, 10H), 9.94 (s, 1H), 10.01 (s, 1H).

5-Benzyl-4-[2-(3-methoxyphenyl)ethyl]-1-[(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)methyl]piperazine-2,3-dione (9k). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90−0.93 (t, J = 7.48 Hz, 3H), 1.58−1.62 (m, 2H), 2.40−2.44 (m, 4H), 2.75−2.85 (m, 3H), 2.92−2.95 (dd, J = 4.96 Hz, J = 13.7 Hz, 1H), 3.03−3.13 (m, 3H), 3.55−3.59 (dd, J = 6.92 Hz, J = 11.5 Hz, 1H), 6.77−6.82 (m, 3H), 7.19−7.33 (m, 4H), 10.06 (s, 1H), 10.08 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.12, 18.81, 27.74, 33.45, 36.90, 47.46, 47.56, 49.47, 54.66, 54.96, 55.56, 111.91, 114.20, 120.90, 126.73, 126.73, 128.58, 129.18, 129.47, 137.18, 140.42, 156.05, 157.47,

159.35, 170.45. HRMS (DCI): *m*/*z* 463.2710 found ([M + H]$^+$), 463.2709 calculated for $C_{27}H_{35}N_4O_3$ ([M + H]$^+$).

5-Methyl-4-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (t, J = 7.5 Hz, 3H), 1.15−1.17 (d, J = 6.64 Hz, 3H), 1.19−1.32 (m, 2H), 1.47−1.65 (m, 6H), 2.43 (t, J = 7.37 Hz, 2H), 2.80−2.87 (m, 2H), 3.15−3.24 (m, 3H), 3.38−3.53 (m, 3H), 3.58−3.62 (dd, J = 4.01 Hz, J = 13.0 Hz, 1H), 3.81−3.84 (m, 1H), 3.90 (t, J = 11.3 Hz, 1H), 4.17−4.18 (m, 1H), 7.20−7.32 (m, 5H), 9.99 (s, 1H), 10.14 (m, 1H). HRMS (DCI): *m*/*z* 399.2745 found ([M + H]$^+$), 399.2760 calculated for $C_{23}H_{35}N_4O_2$ ([M + H]$^+$).

5-Isobutyl-4-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.80−0.82 (d, J = 6.63 Hz, 3H), 0.85−0.86 (d, J = 6.44 Hz, 3H), 0.90 (t, J = 7.24 Hz, 3H), 1.23−1.30 (m, 3H), 1.43−1.65 (m, 9H), 2.42 (t, J = 7.59 Hz, 2H), 2.81−2.88 (m, 2H), 3.03−3.09 (m, 1H), 3.19−3.25 (m, 3H), 3.37−3.54 (m, 2H), 3.88−3.95 (m, 2H), 4.15−4.19 (m, 1H), 7.21−7.32 (m, 5H), 9.94 (s, 1H), 10.10 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.07, 18.83, 21.17, 21.52, 23.24, 24.35, 26.12, 27.63, 33.38, 34.17, 45.69, 45.91, 47.39, 49.21, 52.28, 56.72, 126.38, 128.42, 128.73, 138.92, 156.32, 156.75, 169.91.

4-(2-Phenylethyl)-5-propyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, J = 7.03 Hz, 3H), 0.90 (t, J = 6.96 Hz, 3H), 1.21−1.31 (m, 4H), 1.43−1.51 (m, 4H), 1.54−1.63 (m, 5H), 2.42 (t, J = 7.37 Hz, 2H), 2.82−2.89 (m, 2H), 3.10−3.15 (m, 1H), 3.22−3.39 (m, 3H), 3.45−3.53 (m, 2H), 3.88−3.94 (m, 2H), 4.15−4.19 (m, 1H), 7.20−7.32 (m, 5H), 9.92 (s, 1H), 10.08 (s, 1H).

5-Benzyl-4-(2-methylbutyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.76−0.77 (d, J = 6.8 Hz, 3H), 0.81−0.89 (m, 7H), 1.01−1.11 (m, 1H), 1.23−1.33 (m, 3H), 1.47 − 1.48 (m, 1H), 1.54−1.62 (m, 5H), 1.71−1.76 (m, 1H), 2.40−2.53 (m, 2H), 2.79−2.82 (m, 1H), 2.97−3.00 (m, 1H), 3.07−3.11 (m, 1H), 3.23−3.25 (m, 1H), 3.38−3.42 (m, 1H), 3.46−3.60 (m, 2H), 3.75−3.77 (m, 2H), 3.90 (t, J = 11.2 Hz, 1H), 4.16−4.18 (m, 1H), 7.22−7.34 (m, 5H), 9.93 (s, 1H), 10.10 (s, 1H).

5-Methyl-4-ethyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88 (t, J = 7.77 Hz, 3H), 1.07 (t, J = 6.93 Hz, 3H), 1.21−1.25 (m, 1H), 1.31−1.35 (m, 1H), 1.44−1.48 (m, 2H), 1.54−1.63 (m, 4H), 2.41 (t, J = 7.59 Hz, 1H), 2.78−2.83 (m, 2H), 2.96−3.00 (dd, J = 5.73 Hz, J = 13.5 Hz, 1H), 3.05−3.08 (d, J = 13.8 Hz, 1H), 1.17−3.20 (m, 1H), 3.41−3.49 (m, 3H), 3.59−3.63 (m, 1H), 3.70−3.73 (dd, J = 4.28 Hz, J = 13.4 Hz, 1H), 3.85−3.92 (m, 2H), 4.16−4.18 (m, 1H), 7.23−7.34 (m, 5H), 9.91 (s, 1H), 10.06 (s, 1H).

5-Benzyl-4-neopentyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87−1.00 (m, 12H), 1.23−1.27 (m, 1H), 1.32−1.35 (m, 1H), 1.45−1.63 (m, 5H), 2.40−2.43 (m, 3H), 2.74−2.79 (dd, J = 9.02 Hz, J = 13.5 Hz, 1H), 2.99−3.02 (dd, J = 5.53 Hz, J = 13.6 Hz, 1H), 3.06−3.08 (d, J = 12.7 Hz, 1H), 3.22−3.27 (m, 1H), 3.38−3.44 (m, 2H), 3.46−3.50 (dd, J = 7.54 Hz, J = 11.2 Hz, 1H), 3.63−3.66 (d, J = 13.3 Hz, 1H), 3.71−3.74 (m, 1H), 3.82−3.85 (dd, J = 3.93 Hz, J = 13.4 Hz, 1H), 3.90 (t, J = 11.3 Hz, 1H), 4.17−4.20 (m, 1H), 7.22−7.34 (m, 5H), 9.96 (s, 1H), 10.12 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.05, 18.83, 21.60, 26.09, 27.61, 27.98, 33.76, 34.17, 36.94, 45.79, 46.28, 49.20, 56.05, 56.70, 56.73, 126.76, 128.60, 129.11, 137.27, 156.31, 157.40, 169.90.

5-Benzyl-4-(2-phenylethyl)-1-[(4-{(*E*)-2-[2-trifluoromethyl)phenyl]ethenyl}-4,5-dihydro-1*H*-imidazol-4-yl)-butyl]piperazine-2,3-dione (10g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.26−1.30 (m, 2H), 1.35−1.38 (m, 2H), 1.44−1.52 (m, 1H), 1.62−1.69 (m, 1H), 2.75−2.96 (m, 6H), 3.00−3.03 (d, J = 12.9 Hz, 1H), 3.20−3.25 (m, 2H), 3.52−3.55 (dd, J = 4.11 Hz, J = 13.3 Hz, 1H), 3.59 3.65 (m, 2H), 3.81−3.84 (m, 1H), 4.04 (t, J = 11.4 Hz, 1H), 4.29−4.32 (m, 1H), 6.77−6.80 (d, J = 16.4 Hz, 1H), 7.19−7.32 (m, 10H), 7.71 (t, J = 7.65 Hz, 1H), 7.81 (t, J = 7.55 Hz, 1H), 7.85−7.91 (dd, J = 7.8 Hz, J = 23.1 Hz, 1H), 7.99−8.02 (dd, 1H), 10.43 (s, 1H), 10.55 (s, 1H).

5-Benzyl-1-[4-(2-isopropyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-4-(2-phenylethyl)piperazine-2,3-dione (10h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.17−1.22 (m, 6H), 1.29−1.31 (m, 2H), 1.42−1.47 (m, 2H), 1.53−1.58 (m, 2H), 2.75−2.88 (m, 4H), 2.91−3.01 (m, 3H), 3.18−3.22 (m, 1H), 3.45−3.54 (m, 3H), 3.65 (m, 1H), 3.81−3.84 (m, 1H), 3.90 (t, J = 11.3 Hz, 1H), 4.16−4.18 (m, 1H), 7.18−7.33 (m, 10H), 9.90 (s, 1H), 10.02 (s, 1H).

5-Benzyl-1-[4-(2-neopentyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-4-(2-phenylethyl)piperazine-2,3-dione (10i). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92−0.97 (m, 9H), 1.22−1.26 (m, 2H), 1.29−1.33 (m, 2H), 1.42−1.50 (m, 1H), 1.55−1.60 (m, 1H), 2.31 (t, J = 14.4 Hz, 2H), 2.75−2.96 (m, 5H), 2.99−3.01 (d, J = 12.9 Hz, 1H), 3.18−3.21 (m, 1H), 3.35−3.39 (m, 1H), 3.49−3.54 (m, 2H), 3.63−3.64 (m, 1H), 3.80−3.84 (m, 1H), 3.93 (t, J = 11.2 Hz, 1H), 4.18−4.21 (m, 1H), 7.18−7.33 (m, 10H), 9.85 (s, 1H), 10.02 (s, 1H).

5-Benzyl-4-butyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]piperazine-2,3-dione (10j). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84−0.90 (m, 6H), 1.21−1.32 (m, 4H), 1.42−1.62 (m, 8H), 2.41 (t, J = 7.57 Hz, 2H), 2.67−2.70 (m, 1H), 2.78−2.83 (dd, J = 8.67 Hz, J = 13.6 Hz, 1H), 2.96−3.00 (dd, J = 5.75 Hz, J = 13.6 Hz, 1H), 3.05−3.08 (d, J = 13.2 Hz, 1H), 3.18−3.21 (m, 1H), 3.37−3.43 (m, 1H), 3.46−3.49 (dd, J = 7.49 Hz, J = 11.1 Hz, 1H), 3.58−3.63 (m, 1H), 3.71−3.74 (dd, J = 4.17 Hz, J = 13.4 Hz, 1H), 3.82 (m, 1H), 3.90 (t, J = 11.2 Hz, 1H), 4.16−4.19 (m, 1H), 7.23−7.34 (m, 5H), 9.94 (s, 1H), 10.09 (s, 1H).

5-Benzyl-1-{4-[2-(cyclomethyl)-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4-(2-phenylethyl)piperazine-2,3-dione (10k). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90−0.93 (m, 2H), 1.08−1.24 (m, 5H), 1.30−1.34 (m, 1H), 1.41−1.49 (m, 2H), 1.53−1.57 (m, 3H), 1.63 (m, 3H), 1.68−1.69 (m, 3H), 2.29−2.34 (m, 2H), 2.75−3.01 (m, 5H), 3.20−3.24 (m, 1H), 3.46−3.54 (m, 2H), 3.64 (m, 1H), 3.81−3.84 (m, 1H), 3.91 (t, J = 11.3 Hz, 1H), 4.16−4.18 (m, 1H), 7.19−7.33 (m, 10H), 9.93 (s, 1H), 10.10 (s, 1H). ^{13}C NMR (125 MHz, DMSO-

d_6): δ 21.65, 25.23, 25.39, 26.08, 31.93, 32.03, 33.18, 34.23, 35.03, 37.18, 46.03, 46.16, 47.68, 49.22, 55.36, 56.73, 126.33, 126.73, 128.38, 128.55, 128.70, 129.12, 137.27, 138.81, 156.26, 156.55, 168.90. HRMS (DCI): *m/z* 529.3561 found ($[M + H]^+$), 529.3543 calculated for $C_{33}H_{45}N_4O_2$ ($[M + H]^+$).

4-Isopropyl-3-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidin-2-one (11a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83−0.84 (d, J = 6.88 Hz, 3H), 0.90 (t, J = 7.07 Hz, 6H), 1.21−1.27 (m, 2H), 1.42−1.45 (m, 2H), 1.53−1.63 (m, 3H), 2.03−2.05 (m, 1H), 2.42 (t, J = 7.34 Hz, 2H), 2.61−2.66 (m, 2H), 2.78−2.82 (dd, J = 4.17 Hz, J = 9.1 Hz, 2H), 2.95−2.98 (m, 1H), 3.03−3.08 (m, 2H), 3.15 (t, J = 9.45 Hz, 1H), 3.44−3.51 (m, 2H), 3.90 (t, J = 11.2 Hz, 1H), 4.16−4.18 (m, 1H), 6.52 (s, 1H), 7.19−7.30 (m, 5H), 9.88 (s, 1H), 10.04 (s, 1H).

4-Benzyl-3-isobutyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidin-2-one (11b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.71−0.78 (d, J = 6.46 Hz, 3H), 0.83−0.85 (d, J = 6.68 Hz, 3H), 0.89 (t, J = 7.54 Hz, 3H), 1.14−1.21 (m, 2H), 1.33−1.36 (m, 2H), 1.48−1.63 (m, 4H), 1.85−1.90 (m, 1H), 2.41 (t, J = 7.41 Hz, 2H), 2.56−2.60 (dd, J = 8.77 Hz, J = 13.4 Hz, 1H), 2.84−2.88 (dd, J = 5.62 Hz, J = 13.9 Hz, 1H), 2.90−3.08 (m, 6H), 3.15 (t, J = 8.48 Hz, 1H), 3.40−3.46 (m, 1H), 3.88 (t, J = 11.2 Hz, 1H), 4.13−4.16 (m, 1H), 7.21−7.32 (m, 5H), 9.90 (s, 1H), 10.05 (s, 1H).

4-Benzyl-3-pentyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidin-2-one (11c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84−0.91 (m, 6H), 1.15−1.35 (m, 4H), 1.46−1.53 (m, 3H), 1.58−1.63 (m, 2H), 2.41 (t, J = 7.6 Hz, 2H), 2.58−2.62 (dd, J = 8.65 Hz, J = 13.5 Hz, 2H), 2.88−3.05 (m, 6H), 3.14 (t, J = 8.53 Hz, 2H), 3.43−3.46 (dd, J = 7.64 Hz, J = 11.2 Hz, 2H), 3.77−3.79 (m, 1H), 3.89 (t, J = 11.1 Hz, 1H), 4.13−4.17 (m, 1H), 6.52 (s, 1H), 7.23−7.32 (m, 5H), 9.86 (s, 1H), 10.01 (s, 1H).

4-Benzyl-3-(2-phenylethyl)-1-(4-{2-[(1E)-prop-1-enyl]-4,5-dihydro-1*H*-imidazol-4-yl}butyl) imidazolidin-2-one (11d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.16 (m, 2H), 1.21−1.23 (m, 2H), 1.34−1.36 (m, 2H), 1.51−1.57 (m, 3H), 1.93−1.95 (m, 3H), 2.54−2.59 (dd, J = 2.5 Hz, J = 8.4 Hz, 2H), 2.63−2.66 (m, 1H), 2.78−2.80 (m, 1H), 2.89 (t, J = 7.43 Hz, 1H), 2.95−3.04 (m, 2H), 3.09−3.19 (m, 2H), 3.46−3.75 (m, 1H), 3.93 (t, J = 11.2 Hz, 1H), 4.16−4.19 (m, 1H), 6.06−6.09 (dd, 1H), 7.02−7.07 (m, 1H), 7.17−7.32 (m, 9H), 9.95 (s, 1H), 10.07 (s, 1H).

4-Benzyl-1-[4-(2-isopropyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-3-(2-phenylethyl)imidazolidin-2-one (11e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13−1.22 (m, 6H), 1.32−1.37 (m, 2H), 1.49−1.56 (m, 2H), 2.54−2.58 (dd, J = 8.6 Hz, J = 13.4 Hz, 1H), 2.65−2.66 (m, 1H), 2.78−2.82 (m, 1H), 2.89 (t, J = 8.0 Hz, 1H), 2.96−3.05 (m, 3H), 3.10 (t, J = 8.72 Hz, 1H), 3.18−3.19 (m, 3H), 3.43−3.54 (m, 3H), 3.72−3.75 (m, 1H), 3.89 (t, J = 11.1 Hz, 1H), 4.13−4.16 (m, 1H), 7.17−7.32 (m, 10H), 9.86 (s, 1H), 9.97 (s, 1H).

4-Benzyl-1-[4-(2-isobutyl-4,5-dihydro-1*H*-imidazol-4-yl-)butyl]-3-(2-phenylethyl)imidazolidin-2-one (11f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90−0.92 (d, J = 6.62 Hz, 6H), 1.14−1.21 (m, 2H), 1.32−1.36 (m, 2H), 1.49−1.55 (m, 2H), 1.98−2.01 (m, 1H), 2.30−2.32 (d, J = 7.36 Hz, 2H), 2.54−2.58 (dd, J = 8.35 Hz, J = 13.2 Hz, 2H), 2.63−2.66 (m, 1H), 2.79−2.80 (m, 1H), 2.89 (t, J = 7.85 Hz, 1H), 2.94−3.04 (m, 3H), 3.10 (t, J = 8.52 Hz, 1H), 3.16−3.19 (m, 1H), 3.35−3.51 (m, 1H), 3.73−3.74 (m, 1H), 3.90 (t, J = 11.2 Hz, 1H), 4.16 (m, 1H), 7.17−7.32 (m, 10H), 9.90 (s, 1H), 10.06 (s, 1H).

4-Benzyl-1-[4-(2-isopentyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-3-(2-phenylethyl)imidazolidin-2-one (11g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.88 (d, J = 6.15 Hz, 6H), 1.15−1 0.20 (m, 3H), 1.31−1.36 (m, 1H), 1.45−1.55 (m, 2H), 2.44 (t, J = 8.04 Hz, 1H), 2.54−2.59 (dd, J = 8.29 Hz, J = 13.2 Hz, 2H), 2.63−2.66 (m, 2H), 2.80 (m, 2H), 2.89 (t, J = 7.37 Hz, 1H), 2.96−3.04 (m, 2H), 3.09−3.19 (m, 2H), 3.42−3.46 (dd, J = 7.67 Hz, J = 11.1 Hz, 2H), 3.50−3.52 (m, 1H), 3.72−3.73 (m, 1H), 3.88 (t, J = 11.2 Hz, 1H), 4.14 (m, 1H), 6.52 (s, 1H), 7.17−7.32 (m, 10H), 9.87 (s, 1H), 10.02 (s, 1H).

4-Benzyl-1-[4-(2-methyl-4,5-dihydro-1*H*-imidazol-4-yl)-butyl]-3-(2-phenylethyl)imidazolidin-2-one (11h). ^{1}H NMR (500 MHz, DMSO-d_6): δ1.13−1.22 (m, 3H), 1.31−1.37 (m, 2H), 1.49−1.55 (m, 2H), 2.55 (dd, J = 8.57 Hz, J = 13.5 Hz, 2H), 2.65−2.66 (m, 3H), 2.80 (m, 1H), 2.87−2.90 (dd, J = 7.11 Hz, J = 8.6 Hz, 1H), 2.94−3.04 (m, 2H), 3.10 (t, J = 8.82 Hz, 1H), 3.16−3.19 (m, 1H), 3.40−3.53 (m, 2H), 3.73−3.74 (m, 1H), 3.88 (t, J = 11.1 Hz,1H), 4.12 (m, 1H), 7.17−7.32 (m, 10H), 9.86 (s, 1H), 10.04 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.12, 21.46, 26.39, 33.59, 34.03, 42.74, 42.81, 47.28, 49.40, 53.51, 56.89, 126.09, 126.41, 128.30, 128.38, 128.67, 129.21, 137.27, 139.36, 159.84, 166.98.

4-Benzyl-3-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidin-2-one (11i). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J = 7.0 Hz, 3H), 1.10−1.20 (m, 2H), 1.33−1.36 (m, 2H), 1.50−1.63 (m, 4H), 2.42 (t, J = 7.38 Hz, 2H), 2.54−2.59 (dd, J = 8.32 Hz, J = 13.2 Hz, 2H), 2.64−2.66 (m, 1H), 2.78−2.80 (m, 1H), 2.87−2.90 (dd, J = 7.03 Hz, J = 8.5 Hz, 1H), 2.94−3.04 (m, 1H), 3.10 (t, J = 8.62 Hz, 1H), 3.17−3.19 (m, 1H), 3.43−3.53 (m, 3H), 3.72−3.74 (m, 1H), 3.89 (t, J = 11.3 Hz, 1H),4.13−4.15 (m, 1H),7.17−7.32 (m, 10H), 9.92 (s, 1H), 10.06 (s, 1H). HRMS (DCI) *m/z* 447.3113 found ($[M + H]^+$), 447.3124 calculated for $C_{28}H_{39}N_4O$ ($[M + H]^+$).

4-Benzyl-3-(3-cyclopentylpropyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidin-2-one (11j). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J = 7.19 Hz, 3H), 1.02−1.03 (m, 2H), 1.17−1.21 (m, 4H), 1.33−1.35 (m, 3H), 1.45−1.63 (m, 9H), 1.71−1.72 (m, 3H), 2.42 (t, J = 7.33 Hz, 2H), 2.57−2.62 (dd, J = 8.45 Hz, J = 13.2 Hz, 1H), 2.88−3.06 (m, 5H), 3.14 (t, J = 8.42 Hz, 1H), 3.24−3.28 (m, 1H), 3.43−3.46 (dd, J = 7.64 Hz, J = 11.1 Hz, 1H), 3.76−3.78 (m, 1H), 3.88 (t, J = 11.1 Hz, 1H), 4.13−4.16 (m, 1H), 7.21−7.32 (m, 5H), 9.93 (s, 1H), 10.07 (s, 1H).

4-Benzyl-1-[4-(2-cyclobutyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-3-(2-phenylethyl)imidazolidin-2-one (11k). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14−1.15 (m, 2H), 1.21 (m, 2H), 1.31−1.36 (m, 1H), 1.49−1.56 (m, 1H), 1.80−1.84 (m, 1H), 1.97−2.03 (m, 1H), 2.20−2.25 (m, 4H), 2.54−2.59 (dd, J = 8.47 Hz, J = 13.2 Hz, 1H), 2.64−2.66 (m,

1H), 2.78−2.80 (m, 1H), 2.89 (t, J = 8.29 Hz, 1H), 2.94−3.04 (m, 3H), 3.10 (t, J = 8.45 Hz, 1H), 3.16−3.19 (m, 1H), 3.37−3.52 (m, 2H), 3.72−3.75 (m, 1H), 3.89 (t, J = 11.1 Hz, 1H), 4.13−4.16 (m, 2H), 7.17−7.32 (m, 10H), 9.91 (s, 1H), 10.01 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.92, 21.28, 25.50, 25.57, 26.44, 30.57, 33.61, 33.99, 38.11, 42.74, 42.84, 47.28, 49.15, 53.55, 56.77, 126.10, 126.43, 128.31, 128.40, 128.68, 129.22, 137.29, 139.38, 159.87, 171.76. HRMS (DCI): m/z 459.3113 found ($[M + H]^+$), 459.3124 calculated for $C_{29}H_{39}N_4O$ ($[M + H]^+$).

4-Butyl-3-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85−0.91 (m, 6H), 1.14−1.36 (m, 7H), 1.52−1.69 (m, 7H), 2.42 (t, J = 7.52 Hz, 2H), 2.72−2.74 (m, 1H), 2.89−2.91 (m, 1H), 3.16−3.19 (dd, J = 7.95 Hz, J = 9.6 Hz, 1H), 3.33−3.41 (m, 1H), 3.47−3.52 (m, 3H), 3.60 (t, J = 9.8 Hz, 1H), 3.70−3.72 (m, 1H), 3.88−3.98 (m, 2H), 4.18−4.21 (m, 1H), 7.19−7.31 (m, 5H), 9.92 (s, 1H), 10.07 (s, 1H).

4-Methyl-3-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (t, J = 7.13 Hz, 3H), 1.18−1.19 (d, J = 6.03 Hz, 3H), 1.22−1.33 (m, 2H), 1.50−1.64 (m, 6H), 2.42 (t, J = 7.50 Hz, 2H), 2.71−2.75 (m, 1H), 2.87−2.92 (m, 1H), 3.07 (t, J = 9.44 Hz, 1H), 3.32−3.44 (m, 4H), 3.47−3.53 (m, 1H), 3.64 (t, J = 9.7 Hz, 1H), 3.78−3.81 (m, 1H), 3.88−3.93 (m, 1H), 4.18−4.22 (m, 1H), 7.19−7.32 (m, 5H), 9.90 (s, 1H), 10.05 (s, 1H).

4-*sec*-Butyl-3-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.64−0.65 (d, J = 6.74 Hz, 3H), 0.85−0.92 (m, 6H), 1.12−1.30 (m, 4H), 1.52−1.64 (m, 6H), 1.87−1.88 (m, 1H), 2.42 (t, J = 7.38 Hz, 1H), 2.72−2.75 (m, 1H), 2.90−2.94 (m, 1H), 3.40−3.51 (m, 5H), 3.54−3.59 (m, 1H), 3.76−3.79 (m, 1H), 3.90 (t, J = 11.2 Hz, 1H), 4.07 (m, 1H), 4.17−4.20 (m, 1H), 6.52 (s, 1H), 7.19−7.31 (m, 5H), 9.89 (s, 1H), 10.04 (s, 1H).

4-Benzyl-3-(3-cyclohexylpropyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83−0.91 (m, 5H), 1.09−1.21 (m, 8H), 1.36−1.39 (m, 2H), 1.48−1.69 (m, 11H), 2.42 (t, J = 7.56 Hz, 2H), 2.65−2.69 (dd, J = 8.5 Hz, J = 13.5 Hz, 1H), 3.03−3.07 (dd, J = 4.32 Hz, J = 13.5 Hz, 1H), 3.19−3.24 (m, 2H), 3.33−3.48 (m, 4H), 3.85−3.90 (m, 2H), 4.10−4.17 (m, 2H), 7.22−7.32 (m, 5H), 9.93 (s, 1H), 10.06 (s, 1H). HRMS (DCI): m/z 483.3510 found ($[M + H]^+$), 483.3521 calculated for $C_{29}H_{47}N_4S$ ($[M + H]^+$).

4-Benzyl-3-ethyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J = 7.13 Hz, 3H), 1.10 (t, J = 6.95 Hz, 5H), 1.37−1.40 (m, 2H), 1.52−1.63 (m, 4H), 2.41 (t, J = 7.55 Hz, 1H), 2.64−2.68 (dd, J = 8.81 Hz, J = 13.5 Hz, 2H), 3.08−3.12 (dd, J = 4.05 Hz, J = 13.6 Hz, 2H), 3.19−3.22 (dd, J = 6.97 Hz, J = 9.8 Hz, 1H), 3.33−3.48 (m, 2H), 3.86−3.94 (m, 2H), 4.13−4.15 (m, 2H), 6.51 (s, 2H), 7.22−7.32 (m, 5H), 9.87 (s, 1H), 10.00 (s, 1H).

4-Benzyl-1-[4-(2-isopentyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-3-(2-phenylethyl)imidazolidine-2-thione (12f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.88 (d, J = 6.17 Hz, 6H), 1.16−1.22 (m, 2H), 1.38−1.57 (m, 7H), 2.44 (t, J = 7.91 Hz, 1H), 2.63−2.68 (dd, J = 8.55 Hz, J = 13.5 Hz, 1H), 2.77−2.80 (m, 2H), 2.91−2.95 (m, 2H), 3.06−3.09 (dd, J = 4.29 Hz, J = 13.4 Hz, 1H), 3.19−3.22 (dd, J = 6.89 Hz, J = 9.85 Hz, 1H), 3.38−3.51 (m, 3H), 3.88 (t, J = 11.1 Hz, 1H), 4.00 (m, 1H), 4.05−4.07 (m, 1H), 4.13−4.15 (m, 1H), 6.52 (s, 1H), 7.21−7.32 (m,10H), 9.87 (s, 1H), 10.01 (s, 1H).

1-[4-(2-Allyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]-4-benzyl-3-(2-phenylethyl)imidazolidine-2-thione (12g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.16 (m, 2H), 1.23 (m, 1H), 1.39−1.42 (m, 3H), 1.54−1.59 (m, 2H), 1.94−1.95 (dd, J = 1.18 Hz, J = 6.8 Hz, 2H), 2.63−2.68 (dd, J = 8.46 Hz, J = 13.4 Hz, 1H), 2.76−2.79 (m, 1H), 2.90−2.96 (m, 2H), 3.06−3.09 (dd, J = 4.34 Hz, J = 13.4 Hz, 2H), 3.19−3.22 (dd, J = 6.91 Hz, J = 9.8 Hz, 1H), 3.40−3.53 (m, 2H), 3.93 (t, J = 11.2 Hz, 1H), 3.98−4.02 9m, 1H), 4.05−4.09 (m, 1H), 4.17−4.20 (m, 1H), 6.06−6.09 (dd, J = 1.55 Hz, J = 15.9 Hz, 1H), 6.52 (s, 1H), 7.02−7.07 (m, 1H), 7.20−7.32 (m, 9H), 9.95 (s, 1H), 10.05 (s, 1H).

4-Benzyl-1-[4-(2-methyl-4,5-dihydro-1*H*-imidazol-4-yl)-butyl]-3-(2-phenylethyl)imidazolidine-2-thione (12h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.16−1.23 (m, 3H), 1.36−1.41 (m, 2H), 1.52−1.58 (m, 2H), 2.07−2.14 (m, 3H), 2.64−2.68 (dd, J = 8.53 Hz, J = 13.5 Hz, 1H), 2.76−2.80 (m, 1H), 2.91−2.95 (m, 1H), 3.05−3.09 (dd, J = 4.22 Hz, 13.4 Hz, 1H), 3.19−3.22 (dd, J = 6.9 Hz, J = 10.0 Hz, 1H), 3.40−3.53 (m, 3H), 3.88 (t, J = 11.1 Hz, 1H), 4.00 (m, 1H), 4.06−4.14 (m, 2H), 6.52 (s, 1H), 7.21−7.32 (m, 10H), 9.85 (s, 1H), 10.03 (s, 1H).

4-Benzyl-3-(2-phenylethyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12i). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10−1.19 (m, 2H), 1.36−1.40 (m, 2H), 1.51−1.57 (m, 2H), 2.63−2.68 (dd, J = 8.52 Hz, J = 13.5 Hz, 1H), 2.77−2.78 (m, 1H), 2.92−2.94 (m, 1H), 3.05−3.09 (dd, J = 4.28 Hz, J = 12.6 Hz, 1H), 3.18−3.21 (dd, J = 6.9 Hz, J = 9.9 Hz, 1H), 3.33−3.51 (m, 5H), 3.83 (s, 2H), 3.90 (t, J = 11.3 Hz, 1H), 3.99−4.00 (m, 1H), 4.04−4.08 (m, 1H), 4.16−4.20 (m, 1H), 7.20−7.40 (m, 15H), 10.05 (s, 1H), 10.24 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.16, 25.79, 31.94, 33.09, 34.00, 37.47, 45.92, 46.12, 49.33, 50.38, 56.95, 57.51, 126.23, 126.57, 127.77, 128.38, 128.44, 128.71, 128.89, 128.93, 129.31, 132.87, 136.72, 139.09, 168.26, 181.07. HRMS (DCI): m/z 511.2905 found ($[M + H]^+$), 511.2895 calculated for $C_{32}H_{39}N_4S$ ($[M + H]^+$).

4-Benzyl-3-(2-methylbutyl)-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12j). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.77−0.78 (d, J = 6.69 Hz, 2H), 0.84−0.91 (m, 7H), 1.05−1.09 (m, 2H), 1.11−1.20 (m, 1H), 1.33−1.40 (m, 3H), 1.51−1.61 (m, 4H), 1.84−1.88 (m, 1H), 2.41 (t, J = 7.56 Hz, 2H), 2.63−2.68 (m, 1H), 3.00−3.08 (m, 2H), 3.12−3.15 (m, 2H), 3.22−3.25 (dd, J = 4.91 Hz, J = 9.87 Hz, 1H), 3.43−3.50 (m, 2H), 3.86−3.91 (m, 2H), 4.07−4.08 (m, 1H), 4.13−4.17 (m, 1H), 7.22−7.32 (m, 5H), 9.90 (s, 1H), 10.04 (s, 1H).

4-Benzyl-3-pentyl-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12k). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.91 (m, 9H), 1.11−1.21 (m, 2H),

1.35−1.63 (m, 9H), 2.42 (t, J = 7.49 Hz, 2H), 2.66−2.70 (dd, J = 8.26 Hz, J = 13.4 Hz, 1H), 3.03−3.06 (dd, J = 4.43 Hz, J = 13.6 Hz, 1H), 3.19−3.27 (m, 3H), 3.39−3.48 (m, 3H), 3.88 (t, J = 11.1 Hz, 1H), 3.95−3.98 (m, 1H), 4.11−4.17 (m, 2H), 7.24−7.32 (m, 5H), 9.91 (s, 1H), 10.04 (m, 1H).

4-Benzyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-1-[4-(2-propyl-4,5-dihydro-1*H*-imidazol-4-yl)butyl]imidazolidine-2-thione (12l). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88−0.91 (t, J = 7.44 Hz, 3H), 1.14−1.22 (m, 3H), 1.36−1.41 (m, 2H), 1.52−1.65 (m, 4H), 2.42 (t, J = 7.53 Hz, 1H), 2.64−2.72 (m, 2H), 2.84−2.86 (m, 1H), 3.05−3.08 (dd, J = 4.49 Hz, J = 13.5 Hz, 1H), 3.18−3.21 (dd, J = 6.62 Hz, J = 10.0 Hz, 1H), 3.36−3.41 (m, 5H), 3.71−3.74 (m, 6H), 3.89 (t, J = 11.1 Hz, 1H), 3.97 (m, 1H), 4.06−4.08 (m, 1H), 4.14−4.17 (m, 1H), 6.73−6.75 (m, 1H), 6.81 (d, J = 1.65 Hz, 1H), 6.86−6.87 (d, J = 8.0 Hz, 1H), 7.20−7.32 (m, 5H), 9.91 (s, 1H), 10.05 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.06, 18.83, 21.22, 24.05, 25.81, 27.63, 32.65, 34.11, 37.47, 45.90, 46.08, 49.15, 50.39, 55.48, 55.54, 56.72, 57.45, 111.97, 112.53, 126.56, 128.41, 129.28, 131.51, 136.75, 147.34, 148.66, 169.88, 181.05.

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Supporting Information Available. LC−MS of individual imidazoline-tethered DKPs, cyclic ureas, and cyclic thioureas and HRMS and NMR spectra (both ^{1}H and ^{13}C) of some selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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