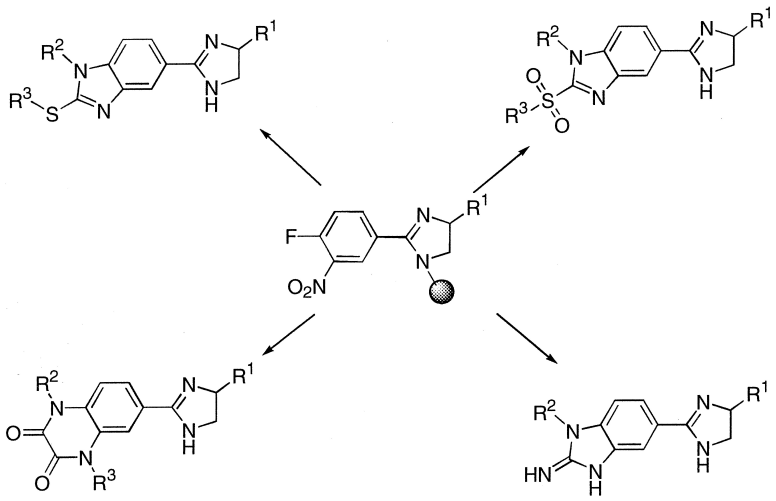
JOURNAL OF combinatorial CHEMISTRY

Article

Novel Approaches for the Solid-Phase Synthesis of Biheterocyclic Dihydroimidazole Analogues

Achyuta N. Acharya, John M. Ostresh, and Richard A. Houghten

J. Comb. Chem., **2002**, 4 (3), 214-222• DOI: 10.1021/cc010067y • Publication Date (Web): 16 February 2002



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Novel Approaches for the Solid-Phase Synthesis of Biheterocyclic Dihydroimidazole Analogues

Achyuta N. Acharya, John M. Ostresh, and Richard A. Houghten*

Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, California 92121

Received September 20, 2001

The solid-phase syntheses of dihydroimidazolyl 2-alkylthiobenzimidazoles, dihydroimidazolyl 2-alkylsulfonylbenzimidazoles, dihydroimidazolyl dihydroquinoxalin-2,3-diones, and dihydroimidazolyl dihydrobenzimidazol-2-imines are described. Following reduction of a resin-bound amino acid amide, the primary amine of the resulting resin-bound diamine was N-acylated with 4-fluoro-3-nitrobenzoic acid. Treatment with $POCl_3$ led to formation of a dihydroimidazole derivative via dehydrative cyclization. The resin-bound dihydroimidazole derivative was then used as the key starting material for the synthesis of the aforementioned biheterocycles. Following cleavage, the resulting compounds, obtained in moderate yield and good purity, were characterized by LC−MS and ^{1}H NMR and ^{13}C NMR spectroscopy.

Introduction

The design and synthesis of large numbers of small heterocyclic compounds of pharmacological significance by combinatorial methods[1] are receiving increased attention. Considerable effort has recently been directed toward the solid-phase synthesis of these compounds using peptides and amino acids as starting materials.[1] These approaches allow incorporation of diverse functional groups and specific positional arrangement of the functionalities around the heterocyclic moiety. Among heterocycles, benzimidazoles, sulfones, guanidines, and dihydroimidazoles exhibit promising biological and pharmacological activities. The benzimidazole moiety is a unique class of compounds and structurally resembles the widely used benzodiazepine nucleus. Examples of biologically active benzimidazoles include human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT) inhibitors,[2] potent topoisomerase I inhibitors,[3] human cytomegalovirus (HCMV) replication inhibitors,[4] selective neuropeptide Y Y1 receptor antagonists,[5] angiotensin II receptor antagonists,[6] and compounds exhibiting high binding affinity to DNA.[7] It has recently been revealed that the benzimidazole ring is an essential feature for binding to the cavity at the protein−protein interface of human growth hormone (hGH) and its receptor.[8] Examples of biologically active sulfones include inhibitors of HIV-1 RT,[9] selective COX-2 inhibitors,[10] and inhibitors of zinc proteases.[11] Celecoxib and refecoxib, both containing a sulfonyl moiety, have been approved for the treatment of certain inflammatory conditions.[10] Dihydroquinoxalin-2,3-diones are reported to be good NMDA (*N*-methyl-D-aspartate) antagonists.[12] Guanidino compounds exhibit diverse pharmacological properties including antiviral activity against *Herpes simplex* virus (type 1), antifungal activity against *Candida albicans*, and anti-HIV activity,[13−16] cytotoxicity against several human cancer cell lines,[13,16,17] as Na^+, K^+, Ca^{2+}-ATPase inhibitors,[18] as neuronal Na^+ and Ca^{2+} channel blockers,[19] and as antitumor drugs.[20] Examples of pharmacologically active dihydroimidazoles (imidazolines) include α-adrenergic inhibitors, vasodepressor agents, sympathomimetic agents, antihistaminic agents, antihypertensive agents,[21] anticancer agents,[22] and potent antihyperglycemic agents.[23] The biological and pharmacological activities of dihydroimidazoles and the other analogues described above prompted the development of solid-phase synthetic strategies for preparation of biheterocyclic dihydroimidazole analogues.

Results and Discussion

The synthetic strategy presented involves the synthesis of dihydroimidazoles from reduced resin-bound amino acid amides using 4-fluoro-3-nitrobenzoic acid and subsequent development of different building blocks from this common starting material using the bifunctional behavior of the fluoro- and nitrophenyl groups.[24−28]

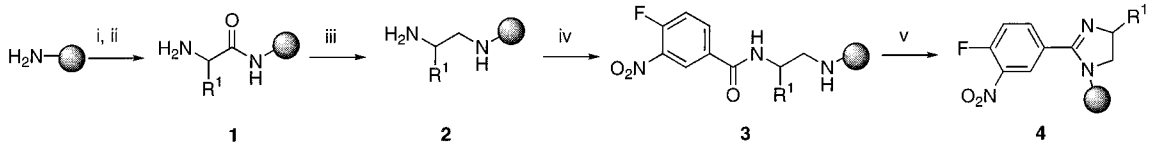
(i) Dihydroimidazole Synthesis. A Boc-protected amino acid was coupled to 4-methylbenzhydrylamine (MBHA) resin, followed by deprotection of the Boc group to generate compound **1** (Scheme 1). Reduction of the resin-bound amino acid amide **1** by treatment with BH_3−THF[29] generated diamine **2** having both a primary amine and a secondary amine.

To perform a selective N-acylation at the primary amine of resin-bound diamine **2** with 4-fluoro-3-nitrobenzoic acid (Scheme 1), a range of coupling conditions were tested. In this case, it was found that selective N-acylation at the primary amine of the diamine **2** could be achieved using either 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*-diisopropylethylamine (DIEA) or *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and DIEA at low concentrations (i.e., 3 equiv of 4-fluoro-3-nitrobenzoic acid, 0.06 M in DMF in the presence of 3 equiv of HBTU

* To whom correspondence should be addressed. Phone: 858-455-3803. Fax: 858-455-3804. E-mail: rhoughten@tpims.org.

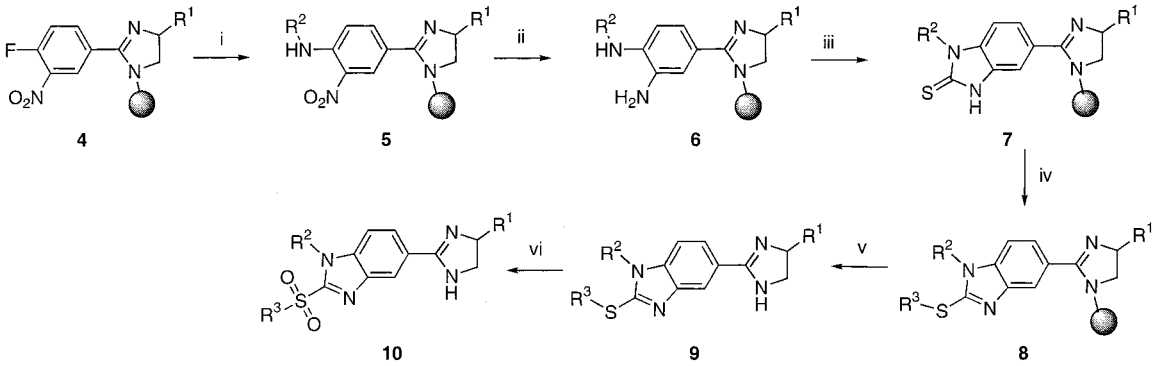
10.1021/cc010067y CCC: $22.00
Published on Web 02/16/2002

Scheme 1[a]



[a] (i) Boc-NHCH(R^1)CO_2H (6 equiv, 0.1 M, DMF), DIC (6 equiv), HOBt (6 equiv), 2 h, room temp; (ii) 55% TFA/45% DCM, 30 min, room temp; (iii) (a) BH_3−THF, 65 °C, 72 h, (b) piperidine, 65 °C, 20 h; (iv) 4-fluoro-3-nitrobenzoic acid (3 equiv, 0.06 M, DMF), HBTU (3 equiv), DIEA (6 equiv), 3 h, room temp; (v) $POCl_3$ (10 equiv, 0.09 M, anhydrous dioxane), 110 °C, 2.5 h.

Scheme 2[a]



[a] (i) R^2NH_2 (20 equiv, 0.2 M, DMF), DIEA (20 equiv), 20 h, room temp; (ii) $SnCl_2 \cdot 2H_2O$ (20 equiv, 0.5 M, DMF), 14 h, room temp; (iii) $CSIm_2$ (10 equiv, 0.1 M, DCM), overnight, room temp; (iv) R^3X (X = I, Br) (20 equiv, 0.2 M, DCM), 1-methylimidazole (10 equiv), room temp, 20 h; (v) HF, anisole, ~0 °C, 7 h; (vi) 10 mg of **9**, 8 mL of 1 M $(NH_4)_2CO_3$ in 50% acetonitrile in water, 100 μL of 30% (v/v) H_2O_2, 4 h, room temp.

and 6 equiv of DIEA, 3 h; or 2 equiv of 4-fluoro-3-nitrobenzoic acid, 0.04 M in DMF in the presence of 2 equiv of HATU and 4 equiv DIEA, 2.5 h).

The diamine **2** was selectively N-acylated using 4-fluoro-3-nitrobenzoic acid in the presence of HBTU and DIEA. The resulting resin-bound amide **3** was treated with $POCl_3$ to generate the dihydroimidazole **4** via cyclodehydration of the in situ formed imidoyl chloride intermediate.[30] Four different amino acids (Ala, Phe, *p*-fluoro-Phe, and cyclohexylglycine) were used to test the completeness of the cyclization. In all cases, complete cyclization was observed by LC−MS and reverse-phase high-pressure liquid chromatography (RP-HPLC), yielding negligible (<1%) amounts of starting material and/or undesirable byproducts. This resin-bound dihydroimidazole **4** was then used as the starting material to form the biheterocycles.

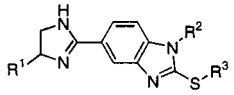
(ii) Trisubstituted Dihydroimidazolyl 2-Alkylthiobenzimidazole. The resin-bound dihydroimidazole derivative **4** was treated with a primary amine to generate the *o*-nitroaniline **5** via fluoro displacement (Scheme 2).

The resin-bound *o*-nitroaniline **5** was treated with a range of reducing agents to reduce the aromatic nitro group to generate the *o*-dianilino compound **6**. Several reports have appeared in the literature for reduction of aromatic nitro groups using different reducing agents (Na_2S, Na_2SO_4)[31] and also using varying conditions of tin(II) chloride dihydrate (i.e., 2 M for 24 h[25,27,28] or 2 M at 80 °C[26]). However, complete reduction of the aromatic nitro group, using 20 equiv of excess of tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) in 0.5 M DMF for 14 h at room temperature, was observed by LC−MS and RP-HPLC to yield a negligible amount (<1%) of undesirable impurities. It is worthwhile to mention that the purity of the *o*-dianilino compound **6** following cleavage was sensitive to the reaction conditions (i.e., concentration of tin(II) chloride dihydrate and duration of reaction time).

The resulting resin-bound *o*-dianilino compound **6** was then treated with thiocarbonyldiimidazole ($CSIm_2$) to yield dihydroimidazolyl dihydrobenzimidazol-2-thione **7**. Compound **7** was treated with an alkyl halide [R^3X, X = I, Br] in the presence of a weak base like 1-methylimidazole to yield the resin-bound dihydroimidazolyl 2-alkylthiobenzimidazole **8**. Complete alkylation was observed by LC−MS. Yeh et al. have reported a similar approach for the synthesis of benzimidazole libraries via a liquid-phase approach (i.e., soluble support PEG).[32] The compounds were cleaved using anhydrous HF and extracted with 95% acetic acid in water to give dihydroimidazolyl 2-alkylthiobenzimidazole **9**. Twelve individual control compounds were synthesized using four amino acids (Phe, Ile, 2-naphthylalanine, and Ala) for the first position of diversity (R^1), five primary amines (butylamine, cycloheptylamine, allylamine, 4-(2-aminoethyl)morpholine, and isoamylamine) for the second position of diversity (R^2), and five alkyl halides (benzyl bromide, iodomethane, 2-(bromomethyl)anthraquinone, 2-cyanobenzyl bromide, and 2,3,6-trifluorobenzyl bromide) for the third position of diversity (R^3). The final compounds were obtained in moderate yield and good purity (see Table 1). The compounds were purified by RP-HPLC and subsequently characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

Strong downfield signals at δ ~13.4 and ~10.5 ppm in the ^{1}H NMR spectra of compound **7** following cleavage (where R^1 and R^2 were $-CH(CH_3)_2$ and $(CH_2)_3CH_3$, respectively) were assigned to the thioamide proton and protonated dihydroimidazole,[33] respectively. Disappearance of the signal at δ ~13.4 ppm in the ^{1}H NMR spectra following alkylation with retention of proton signals at ~10.5 ppm indicated formation of dihydroimidazolyl 2-alkylthiobenzimidazole **9**.

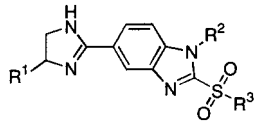
Table 1. MW and RP-HPLC Purity Found for Dihydroimidazolyl 2-Alkylthiobenzimidazoles **9**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
9a	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	454.6	455.2 ($M + H^+$)	80
9b	$-CH(CH_3)C_2H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	420.6	421.2 ($M + H^+$)	80
9c	$-CH_2C_{10}H_7$	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	504.7	505.2 ($M + H^+$)	81
9d	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	378.5	379.2 ($M + H^+$)	70
9e	$-CH_3$	$-C_7H_{13}$	$-CH_2C_6H_5$	418.6	419.2 ($M + H^+$)	78
9f	$-CH_3$	$-CH_2CHCH_2$	$-CH_2C_6H_5$	362.5	363.1 ($M + H^+$)	76
9g	$-CH_3$	-4-(2-ethyl)morpholine	$-CH_2C_6H_5$	435.6	436.3 ($M + H^+$)	71
9h	$-CH_3$	$-CH_2CH_2CH(CH_3)_2$	$-CH_2C_6H_5$	392.5	393.2 ($M + H^+$)	71
9i	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_3$	302.4	303.2 ($M + H^+$)	82
9j	$-CH_3$	$-(CH_2)_3CH_3$	2-methylanthraquinone-	508.6	509.2 ($M + H^+$)	75
9k	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(2-CN)	403.5	404.2 ($M + H^+$)	73
9l	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_2$(2,3,5-F_3)	432.5	433.1 ($M + H^+$)	72

[a] The yields obtained were 60−80% 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. MW and RP-HPLC Purity Found for Dihydroimidazolyl 2-Alkylsulfonylbenzimidazoles **10**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
10a	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(4-CH_3)	424.6	425.2 ($M + H^+$)	80
10b	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(2-Cl)	445.0	445.2 ($M + H^+$)	76
10c	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(4-F)	428.5	429.2 ($M + H^+$)	70
10d	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(2-$CH_2SO_2C_6H_5$)	564.7	565.3 ($M + H^+$)	62
10e	$-CH_3$	2−tetrahydrofulfuryl-	$-CH_2C_6H_5$	438.8	439.2 ($M + H^+$)	63
10f	$-CH_3$	1,2,3,4-tetrahydro-1-naphthyl-	$-CH_2C_6H_5$	484.6	485.2 ($M + H^+$)	61
10g	$-CH_3$	$-(CH_2)_2OCH_3$	$-CH_2C_6H_5$	412.5	413.1 ($M + H^+$)	61
10h	$-CH_3$	2,2−diphenylethyl-	$-CH_2C_6H_5$	534.7	535.3 ($M + H^+$)	63
10i	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	486.6	487.3 ($M + H^+$)	60
10j	$-CH_2C_6H_{11}$	$-(CH_2)_3CH_3$	$-CH_2C_6H_5$	492.7	493.3 ($M + H^+$)	62

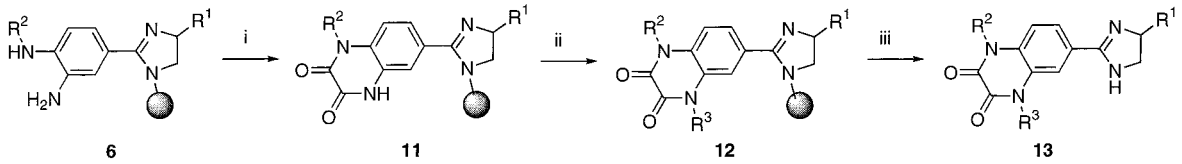
[a] The yields obtained were 60−80% in all cases with respect to the initial loading of the resin (1.15 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at $\lambda = 214$ nm.

(iii) Trisubstituted Dihydroimidazolyl 2-Alkylsulfonylbenzimidazole. The dihydroimidazolyl 2-alkylthiobenzimidazole **9** was treated with hydrogen peroxide[34] under weakly basic conditions (1 M $(NH_4)_2CO_3$ in 50% acetonitrile in water) to yield dihydroimidazolyl 2-alkylsulfonylbenzimidazole **10** (Scheme 2). It was found that after treatment with H_2O_2, a product was formed having a molecular weight 32 mass units higher than the mass of the dihydroimidazolyl 2-alkylthiobenzimidazole, corresponding to the dihydroimidazolyl 2-alkylsulfonylbenzimidazole **10** as expected. Negligible oxidation (<1%) of the dihydroimidazole ring to the imidazole was observed by LC−MS under these conditions. Ten individual control compounds were prepared using three amino acids (Ala, Phe, and cyclohexylalanine) for the first position of diversity (R^1), five primary amines (butylamine, tetrahydrofurfurylamine, 1,2,3,4-tetrahydro-1-naphthylamine, 2-methoxyethylamine, and 2,2-diphenylethylamine) for the second position of diversity (R^2), and five alkyl halides (α-bromo-*p*-xylene, 2-chlorobenzyl bromide, 4-fluorobenzyl bromide, 1-bromomethyl-2-[(phenylsulfonyl)methyl]benzene, and benzyl bromide) for the third position of diversity (R^3). The compounds were obtained in moderate yield and purity (Table 2). Syntheses of these compounds exemplify the use of both solid-phase and solution-phase approaches to obtain the desired final products. The final compounds were purified and analyzed as described above.

(iv) Trisubstituted Dihydroimidazolyl Dihydroquinoxalin-2,3-dione. Resin-bound *o*-dianilino compound **6** was treated with 1,1′-oxalyldiimidazole ($(COIm)_2$) to generate dihydroimidazolyl dihydroquinoxalin-2,3-dione **11** (Scheme 3). Complete cyclization was observed by LC−MS under these experimental conditions.

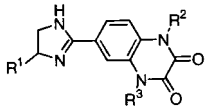
The resin-bound dihydroimidazolyl dihydroquinoxalin-2,3-dione **11** was tested for alkylation with an alkyl halide (R^3X, X = Br) in the presence of several bases in order to obtain the final compounds in good purity. Starting material was primarily obtained when alkylation was carried out in the presence of DIEA and triethylamine (TEA). Treatment with either NaH or lithium *tert*-butoxide led to formation of undesirable byproducts. The best results were obtained using

Scheme 3[a]



[a] (i) $(COIm)_2$ (10 equiv, 0.1 M, DMF), overnight, room temp; (ii) (a) DBU (2.5 equiv, 0.05 M, THF), 15 min, room temp, (b) R^3X (X = I, Br) (2.5 equiv, 0.05 M, THF), 2 h, room temp, "a" and "b" were repeated twice; (iii) HF, anisole, ~0 °C, 7 h.

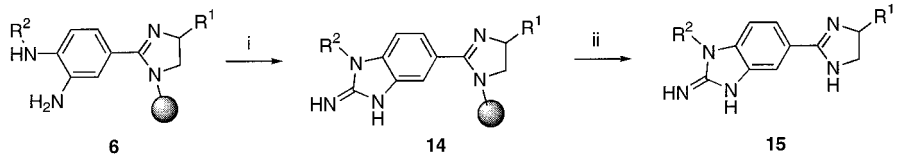
Table 3. MW and RP-HPLC Purity Found for Dihydroimidazolyl Dihydroquinoxalin-2,3-diones **13**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
13a	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_3(3,5\text{-}(OCH_3)_2)$	450.7	451.7 (M + H$^+$)	75
13b	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_3(3,5\text{-}F_2)$	426.5	427.5 (M + H$^+$)	74
13c	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2CHCHCO_2CH_3$	398.5	399.4 (M + H$^+$)	65
13d	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2CHCH_2$	340.4	341.5 (M + H$^+$)	68
13e	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4(3\text{-I})$	516.4	517.4 (M + H$^+$)	62
13f	$-CH_3$	$-CH_2C_6H_4(4\text{-}CF_3)$	$-CH_2C_6H_4(3\text{-F})$	510.5	511.3 (M + H$^+$)	70
13g	$-CH_3$	$-(CH_2)_2C_6H_5$	$-CH_2C_6H_4(3\text{-F})$	456.5	457.2 (M + H$^+$)	72
13h	$-CH_3$	$-CH_2CHCH_2$	$-CH_2C_6H_4(3\text{-F})$	392.4	393.2 (M + H$^+$)	63
13i	$-CH_3$	$-CH_2C_{10}H_7$	$-CH_2C_6H_4(3\text{-F})$	492.5	493.3 (M + H$^+$)	66
13j	$-CH_3$	$-CH_2C_6H_4(3\text{-Cl})$	$-CH_2C_6H_4(3\text{-F})$	476.9	477.4 (M + H$^+$)	67
13k	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4(3\text{-F})$	484.6	485.4 (M + H$^+$)	71
13l	$-CH(CH_3)C_2H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4(3\text{-F})$	450.6	451.4 (M + H$^+$)	73
13m	$-C_6H_{11}$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4(3\text{-F})$	476.6	477.4 (M + H$^+$)	71
13n	$-CH_2C_6H_4(2\text{-F})$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4(3\text{-F})$	502.6	503.4 (M + H$^+$)	75
13o	$-CH_2C_6H_4(2\text{-Cl})$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4(3\text{-F})$	519.0	519.4 (M + H$^+$)	71

[a] The yields obtained were 60−80% 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 λ = 214 nm.

Scheme 4[a]



[a] (i) CNBr (10 equiv, 0.1 M, DCM), overnight, room temp; (ii) HF, anisole, ~0 °C, 7 h.

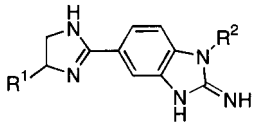
an alkyl halide [R^3X = 2.5 equiv (X = Br), 0.05 M in THF] in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.5 equiv, 0.05 M in THF).

The resin-bound dihydroimidazolyl dihydroquinoxalin-2,3-dione **11** was treated with an alkyl halide in the presence of DBU to generate alkylated dihydroimidazolyl dihydroquinoxalin-2,3-dione **12**. The final product was cleaved from the solid support using anhydrous HF and extracted with 95% acetic acid in water to give compound **13**. Fifteen individual control compounds were prepared using six amino acids (Ala, Phe, Ile, cyclohexylglycine, 2-fluorophenylalanine, and 2-chlorophenylalanine) for the first position of diversity (R^1), six primary amines (butylamine, 4-(trifluoromethyl)benzylamine, phenethylamine, allylamine, 1-naphthalenemethylamine, and 3-chlorobenzylamine) for the second position of diversity (R^2), and six alkyl halides (3,5-dimethoxybenzyl bromide, 3,5-difluorobenzyl bromide, methyl-4-bromocrotonate, allyl bromide, 3-iodobenzyl bromide, and 3-fluorobenzyl bromide) for the third position of diversity (R^3). The compounds were obtained in moderate yield and low purity (see Table 3). Purification and analysis of the final compounds were performed as described above.

Strong downfield signals at δ ~10.5 ppm (i.e., two singlets assigned with one proton each or broad singlet assigned with two protons) in the ^{1}H NMR spectra of compound **13** were assigned to the protonated dihydroimidazole,[33] confirming the structure of compound **13**.

(v) Disubstituted Dihydroimidazolyl Dihydrobenzimidazol-2-imine. The resin-bound *o*-dianilino compound **6** was treated with cyanogen bromide (CNBr) to generate the iminobenzimidazole derivative **14** (Scheme 4). Complete cyclization was observed by LC−MS and RP-HPLC under these experimental conditions. Our earlier studies have indicated complete cyclization when using CNBr for formation of disubstituted cyclic guanidines and bis-cyclic guanidines from reduced amino acid amides and dipeptides, respectively.[35] The final product was cleaved using anhydrous HF and extracted with 95% acetic acid in water to give **15**. The compounds were obtained in moderate yield and purity (Table 4). The compounds were purified and analyzed as

Table 4. MW and RP-HPLC Purity Found for the Dihydroimidazolyl Dihydrobenzimidazol-2-imine **15**[a]



product	R^1	R^2	MW (calcd)	MW (found)	purity[b] (%)
15a	$-CH_3$	$-(CH_2)_2OCH_3$	273.3	274.0 ($M + H^+$)	85
15b	$-CH_3$	$-C_6H_4$(4-F)	323.4	324.2 ($M + H^+$)	67
15c	$-CH(CH_3)_2$	$-(CH_2)_3CH_3$	299.4	300.2 ($M + H^+$)	75
15d	$-CH_3$	$-(CH_2)_3CH_3$	271.4	272.2 ($M + H^+$)	65
15e	$-C_6H_4$(4-F)	$-(CH_2)_3CH_3$	365.5	366.3 ($M + H^+$)	72
15f	$-CH_3$	$-C_5H_{11}$	283.4	284.2 ($M + H^+$)	65

[a] The yields obtained were 60−80% 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.

described above. Appearance of a peak at $\delta \sim 158$ ppm during ^{13}C NMR confirmed the presence of a guanidino moiety.[29,36,37]

Conclusion

Efficient approaches for the preparation of four different biheterocyclic dihydroimidazole analogues from a commonly prepared starting material have been described. Substituted dihydroimidazoles were prepared from resin-bound reduced amino acid amides via cyclization of the in situ formed imidoyl chloride intermediates. New conditions for reduction of the aromatic nitro group by tin(II) chloride dihydrate are described. These approaches can be extended to prepare combinatorial libraries using the "libraries from libraries" approach.[38]

Experimental Section

Boc-amino acids, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), and *N*-hydroxybenzotriazole (HOBt) 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). HF was purchased from Air Products (San Marcos, CA). Alkyl halides, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), and all other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). All amino acids used had the L configurations unless otherwise noted.

Analytical reverse-phase high-pressure chromatography (RP-HPLC) was carried out on a Beckman System Gold instrument (Fullerton, CA). Purification of the samples was made using a Vydac 218TP54 C18 column (0.46 cm × 25 cm). All HPLC experiments were performed using gradient elution: solvent A (H_2O with 0.05% TFA) and solvent B (CH_3CN with 0.05% TFA). Flow rates were 1.0 and 6.0 mL/min for analytical and preparative chromatograms, respectively, at $\lambda = 214$ nm.

LC−MS (ESI and APCI) was recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100 Å, 3 mm × 50 mm column.

NMR spectra were recorded on a Bruker AM 500 instrument at 500 and 125 MHz for ^1H NMR and ^{13}C NMR, respectively. NMR chemical shifts are expressed in ppm relative to internal solvent peaks, and coupling constants were calculated in hertz.

Typical Procedure for the Synthesis of Individual Control Compounds. A total of 100 mg of MBHA resin was sealed inside a polypropylene mesh packet.[39] Polypropylene bottles were used for all the reactions. The resin was washed with dichloromethane (DCM) followed by neutralization with 5% DIEA in DCM and washed with DCM.

(1) Dihydroimidazole Synthesis (See Scheme 1). (a) Coupling of Amino Acid to Resin. A Boc-amino acid (6 equiv, 0.1 M) in DMF was coupled to MBHA resin using DIC and HOBt (6 equiv each) for 2 h at room temperature, followed by washes with DMF (three times) and DCM (three times). The Boc group was deprotected using 55% trifluoroacetic acid (TFA) in DCM for 30 min followed by washes with DCM (two times), IPA (two times), and DCM (three times).

(b) Exhaustive Reduction of the Resin-Bound Amino Acid with BH_3−THF. Exhaustive reduction of the resin-bound amino acid was carried out in 50 mL glass conical tubes under nitrogen. To each tube was added boric acid (12 equiv), followed by trimethyl borate (12 equiv), and then borane−THF complex (1 M, 40 equiv) was added slowly. After cessation of hydrogen evolution, the resin packet (0.115 mequiv of resin, 100 mg of starting resin) was added and the capped tubes were heated at 65 °C for 72 h followed by decantation of the reaction solution and quenching with MeOH.[29] Following washes with MeOH (four times), the resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complexes.[29] Following decantation of the piperidine−borane solution, the resin was washed with DMF (four times), DCM (four times), and MeOH (two times) and dried.

(c) Selective N-Acylation at the Primary Amine Using 4-Fluoro-3-nitrobenzoic Acid. The resin-bound diamine was N-acylated with 4-fluoro-3-nitrobenzoic acid (3 equiv, 0.06 M) in DMF in the presence of HBTU (3 equiv) and DIEA (6 equiv) for 3 h at room temperature. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). Completeness of the coupling was performed by the ninhydrin test.[40]

(d) Cyclization Using $POCl_3$. The dehydrative cyclization of the resin-bound amino acid amide was carried out in 50 mL conical tubes under nitrogen. To each tube the resin packet (100 mg resin, 0.115 mequiv) and $POCl_3$ (10 equiv, 0.09 M) in anhydrous dioxane were added. The capped tubes were heated at 110 °C for 2.5 h. The resin was washed with dioxane, DMF, MeOH (five times), IPA (two times), and DCM (three times) and dried to generate the resin-bound dihydroimidazole **4**.

(2) Synthesis of Trisubstituted Dihydroimidazolyl 2-Alkylthiobenzimidazole (Scheme 2). The resin-bound dihydroimidazole **4** was treated with a primary amine (20 equiv, 0.2 M) in DMF in the presence of DIEA (20 equiv) for 18 h at room temperature, followed by washes with DMF (four times), DCM (two times), IPA (two times), and DCM (two times). Following treatment with tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) (20 equiv, 0.5 M) in DMF for 14 h at room temperature, the resin was washed with DMF (eight times), MeOH (two times), and DCM (three times) to generate the *o*-dianilino compound **6**. The resin-bound *o*-dianilino compound **6** was cyclized upon treatment with 1,1′-thiocarbonyldiimidazole ($CSIm_2$) (10 equiv, 0.1 M, overnight) in DCM followed by washes with DCM (four times), IPA (two times), and DCM (three times). Following treatment with an alkyl halide (20 equiv, 0.2 M) in DCM in the presence of 1-methylimidazole (10 equiv) for 20 h at room temperature, the resin was washed with DMF (three times), DCM (three times), IPA (three times), and DCM (three times) and dried.

(3) Synthesis of Trisubstituted Dihydroimidazolyl 2-Alkylsulfonylbenzimidazole (Scheme 2). Following cleavage of trisubstituted dihydroimidazolyl 2-alkylthiobenzimidazole **9** from the solid support using anhydrous HF, the compound was extracted with 95% acetic acid in water and lyophilized. In a typical experiment, ~10 mg of compound **9** was added to 8 mL of 1 M $(NH_4)_2CO_3$ in 50% (v/v) acetonitrile in water (pH ~9.0), followed by addition of hydrogen peroxide (100 μL, 30% (v/v)),[34] and left to react for 4 h at room temperature. After cessation of CO_2 formation following addition of 95% acetic acid in water, the solution was frozen and lyophilized to obtain the corresponding trisubstituted dihydroimidazolyl 2-alkylsulfonylbenzimidazole **10**. Relyophilization with 95% acetic acid in water was repeated twice to ensure complete removal of hydrogen peroxide.

(4) Synthesis of Trisubstituted Dihydroimidazolyl Dihydroquinoxalin-2,3-dione (Scheme 3). The resin-bound *o*-dianilino compound **6** (described in 2 above) was cyclized upon treatment with 1,1′-oxalyldiimidazole ($(COIm)_2$) (10 equiv, 0.1 M, overnight) in DMF, followed by washes with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). The resulting dihydroimidazolyl dihydroquinoxalin-2,3-dione analogue was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.5 equiv, 0.05 M) in THF for 15 min, followed by decantation of the base and treatment with an alkyl halide (2.5 equiv, 0.05 M) in THF for 2 h at room temperature. Following decantation, the base treatment and alkylation procedure were repeated to ensure complete alkylation. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times) and dried.

(5) Synthesis of Disubstituted Dihydroimidazolyl Dihydrobenzimidazol-2-imine (Scheme 4). The resin-bound *o*-dianilino compound **6** (described in 2 above) was cyclized by treatment with cyanogen bromide (CNBr) (10 equiv, 0.1 M) in DCM, followed by washes with DCM (four times), IPA (two times), and DCM (three times).

All washes of DCM, DMF, IPA, MeOH, THF, or 5% DIEA in DCM were made for ~2 min each. All the biheterocyclic dihydroimidazole analogues described above were cleaved using anhydrous HF in the presence of anisole for 7 h at 0 °C,[41] followed by extraction with 95% acetic acid in water and lyophilized. The compounds were purified using 0.05% TFA using a gradient of 5−95% acetonitrile−water, and the compounds were isolated as trifluoroacetate salts for their characterization.

1-Butyl-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-thione (7d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (m, 3H), 1.35−1.36 (m, 5H), 1.72 (m, 2H), 3.62 (m, 1H), 4.12 (m, 1H), 4.23 (m, 2H), 4.54 (m, 1H), 7.69−7.78 (m, 3H), 10.54 (m, 2H), 13.39 (s, 1H).

5-(4-Benzyl-4,5-dihydro-1*H*-imidazol-2-yl)-2-(benzylthio)-1-butyl-1*H*-benzimidazole (9a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (t, J = 7.4 Hz, 3H), 1.21−1.25 (m, 2H), 1.62−1.66 (m, 2H), 2.98−3.07 (m, 3H), 3.74−3.78 (dd, J = 6.8 Hz, J = 11.4 Hz, 1H), 4.05 (t, J = 11.4 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 4.65 (s, 1H), 4.73−4.74 (m, 1H), 7.24−7.28 (m, 2H), 7.30−7.35 (m, 6H), 7.47−7.48 (d, J = 7.3 Hz, 2H), 7.71−7.73 (d, J = 9.0 Hz, 1H), 7.79−7.81 (d, J = 8.7 Hz, 1H), 8.20 (s, 1H), 10.35 (s, 1H), 10.55 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.5, 19.3, 30.8, 35.6, 43.7, 48.5, 57.5, 110.6, 114.9, 118.4, 121.8, 126.8, 127.5, 128.5, 128.9, 129.6, 135.8, 137.1, 140.2, 142.4, 154.9, 164.5.

2-(Benzylthio)-1-butyl-5-(4-*sec*-butyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazole (9b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (t, J = 7.1 Hz, 3H), 0.90−0.94 (m, 4H), 1.20−1.23 (m, 3H), 1.52−1.55 (m, 2H), 1.63−1.66 (m, 1H), 1.71−1.73 (m, 1H), 3.76−3.78 (dd, J = 8.2 Hz, J = 14.1 Hz, 2H), 4.04 (t, J = 13.0 Hz, 1H), 4.16 (t, J = 7.0 Hz, 2H), 4.31−4.33 (m, 2H), 4.65 (s, 2H), 7.26−7.33 (m, 3H), 7.47−7.48 (d, J = 7.5 Hz, 2H), 7.77−7.82 (m, 2H), 8.28 (s, 1H), 10.35 (s, 1H), 10.55 (s, 1H).

2-(Benzylthio)-1-butyl-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazole (9d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (t, J = 7.1 Hz, 3H), 1.20−1.35 (m, 2H), 1.37−1.38 (d, J = 6.5 Hz, 3H), 1.63−1.66 (m, 2H), 3.58−3.62 (dd, J = 7.9 Hz, J = 11.3 Hz, 1H), 4.12−4.17 (m, 2H), 4.48−4.50 (m, 1H), 4.65 (s, 2H), 6.52 (s, 1H), 7.26−7.33 (m, 3H), 7.47−7.48 (d, J = 7.6 Hz, 2H), 7.75−7.77 (d, J = 9.4 Hz, 1H), 7.81−7.82 (d, J = 8.6 Hz, 1H), 8.25 (s, 1H), 10.33 (s, 1H), 10.46 (s, 1H).

1-Allyl-2-(benzylthio)-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazole (9f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.37−1.38 (d, J = 6.4 Hz, 3H), 3.59−3.62 (dd, J = 7.9 Hz, J = 10.9 Hz, 1H), 4.14 (t, J = 11.1 Hz, 1H), 4.47−4.50 (m, 1H), 4.65 (s, 2H), 4.82−4.83 (d, J = 4.8 Hz, 1H), 4.89−4.92 (d, J = 17.1 Hz, 1H), 5.15−5.17 (d, J = 10.5 Hz, 1H), 5.87−5.93 (m, 1H), 7.26−7.33 (m,

3H), 7.47−7.48 (d, J = 7.6 Hz, 2H), 7.75 (s, 2H), 8.26 (s, 2H), 10.33 (s, 1H), 10.46 (s, 1H).

2-(Benzylthio)-1-isopentyl-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazole (9h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89−0.90 (d, J = 6.0 Hz, 3H), 0.95−0.96 (d, J = 6.3 Hz, 3H), 1.37−1.39 (d, J = 6.2 Hz, 3H), 1.52−1.56 (m, 3H), 3.59−3.62 (dd, J = 7.9 Hz, J = 10.9 Hz, 1H), 4.12−4.17 (m, 3H), 4.47−4.50 (m, 1H), 4.66 (s, 2H), 7.25−7.33 (m, 3H), 7.46−7.48 (d, J = 7.3 Hz, 2H), 7.76−7.81 (m, 2H), 8.25 (s, 1H), 10.34 (s, 1H), 10.46 (s, 1H).

1-Butyl-2-[(4-methylbenzyl)sulfonyl]-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-benz imidazole (10a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.78 (t, J = 7.0 Hz, 3H), 1.12−1.15 (m, 2H), 1.39−1.40 (d, J = 5.4 Hz, 2H), 1.47−1.49 (m, 3H), 2.25 (s, 5H), 4.15−4.17 (m, 1H), 4.31−4.35 (m, 1H), 4.54−4.56 (m, 1H), 5.08 (s, 1H), 7.10 (m, 4H), 7.99 (m, 1H), 8.07−8.09 (m, 1H), 8.54 (s, 1H), 10.5 (br s, 2H).

2-(Benzylsulfonyl)-1-(2-methoxyethyl)-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-benzimidazole (10g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.39−1.40 (d, J = 5.9 Hz, 2H), 3.10 (m, 5H), 4.17−4.19 (m, 1H), 4.54−4.57 (m, 3H), 5.13 (m, 2H), 6.51 (s, 2H), 7.23−7.36 (m, 5H), 7.96−7.97 (d, J = 7.9 Hz, 1H), 8.03−8.05 (d, J = 8.5 Hz, 1H), 8.52 (s, 1H), 10.60 (br s, 2H).

1-Butyl-4-(3,5-dimethoxybenzyl)-6-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,4-dihydroquinoxaline-2,3-dione (13a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.94 (t, J = 7.1 Hz, 3H), 1.33−1.34 (d, J = 6.2 Hz, 3H), 1.39−1.44 (m, 1H), 1.61−1.65 (m, 2H), 3.55−3.58 (dd, J = 8.1 Hz, J = 10.9 Hz, 1H), 3.70 (s, 4H), 4.08−4.19 (m, 3H), 4.44−4.45 (m, 1H), 5.27−5.38 (m, 2H), 6.39 (s, 1H), 6.52 (s, 2H), 7.71−7.78 (m, 6H), 10.5 (s, 2H).

4-Allyl-1-butyl-6-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,4-dihydroquinoxaline-2,3-dione (13d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.93 (t, J = 7.1 Hz, 3H), 1.37−1.44 (m, 4H), 1.59−1.65 (m, 2H), 3.60−3.64 (dd, J = 8.0 Hz, J = 11.3 Hz, 1H), 4.13−4.18 (m, 2H), 4.49−4.52 (m, 1H), 4.80 (d, J = 2.8 Hz, 1H), 5.18 (t, J = 15.2 Hz, 1H), 5.92−5.97 (m, 1H), 6.53 (s, 1H), 7.02−7.04 (m, 1H), 7.12−7.14 (m, 1H), 7.21−7.23 (m, 1H), 7.71−7.81 (m, 3H), 10.54 (s, 1H), 10.65 (s, 1H).

1-Allyl-4-(3-fluorobenzyl)-6-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,4-dihydroquinoxaline-2,3-dione (13h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.32−1.33 (d, J = 6.2 Hz, 3H), 3.54−3.58 (dd, J = 8.1 Hz, J = 11.2 Hz, 1H), 4.09 (t, J = 11.4 Hz, 1H), 4.43−4.48 (m, 1H), 4.84−4.85 (m, 2H), 5.20−5.22 (d, J = 10.8 Hz, 2H), 5.29−5.33 (d, J = 17.8 Hz, 2H), 5.42 (m, 1H), 5.91−5.97 (m, 1H), 6.52 (s, 1H), 7.08−7.11 (m, 1H), 7.22−7.24 (m, 1H), 7.56−7.58 (d, J = 8.8 Hz, 1H), 7.65−7.66 (d, J = 1.4 Hz, 1H), 7.74−7.76 (dd, J = 1.4 Hz, J = 8.8 Hz, 1H), 10.43 (s, 1H), 10. 54 (s, 1H).

1-Butyl-6-(4-*sec*-butyl-4,5-dihydro-1*H*-imidazol-2-yl)-4-(3-fluorobenzyl)-1,4-dihydroquinoxaline-2,3-dione (13l). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83−0.85 (d, J = 6.8 Hz, 3H), 0.88−1.09 (m, 6H), 1.41−1.47 (m, 3H), 1.62−1.66 (m, 3H), 3.26−3.27 (m, 2H), 3.73−3.77 (dd, J = 7.8 Hz, J = 11.6 Hz, 1H), 4.00 (t, J = 11.7 Hz, 1H), 4.16−4.18 (m, 2H), 4.30−4.32 (m, 1H), 5.23−5.27 (d, J = 16.6 Hz, 1H), 5.56−5.59 (d, J = 16.7 Hz, 1H), 7.07−7.11 (m, 1H), 7.23 (t, J = 9.8 Hz, 1H), 7.34−7.39 (q, J = 7.8 Hz, J = 15.2 Hz, 1H), 7.63 (s, 1H), 7.71−7.73 (d, J = 8.8 Hz, 1H), 7.78−7.80 (d, J = 8.7 Hz, 1H), 10.42 (s, 2H).

1-(2-Methoxyethyl)-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-imine (15a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.35−1.37 (d, J = 6.3 Hz, 3H), 3.21−3.24 (m, 4H), 3.56−3.60 (dd, J = 8.1 Hz, J = 10.8 Hz, 2H), 3.62 (t, J = 4.9 Hz, 2H), 4.12 (t, J = 11.2 Hz, 1H), 4.29−4.31 (m, 2H), 4.44−4.48 (m, 1H), 7.63−7.66 (m, 2H), 7.81 (s, 1H), 10.29 (s, 1H), 10.42 (s, 1H).

1-Butyl-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-imine (15d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J = 7.5 Hz, 3H), 1.30−1.37 (m, 5H), 1.64−1.67 (m, 2H), 3.57−3.61 (dd, J = 8.0 Hz, J = 10.9 Hz, 2H), 4.11−4.16 (m, 3H), 4.45−4.50 (m, 1H), 7.60−7.80 (m, 2H), 7.91 (s, 2H), 10.48 (s, 1H), 10.61 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 19.2, 20.5, 29.74, 42.3, 51.0, 52.9, 110.3, 112.3, 116.3, 122.8, 135.8, 158.3, 163.6.

Acknowledgment. This work was funded by National Cancer Institute Grant 78040 (Houghten).

Supporting Information Available. LC−MS, ^{1}H NMR, and ^{13}C NMR of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.; Nefzi, A.; Ostresh, J. M. Mixture-Based Synthetic Combinatorial Libraries. *J. Med. Chem.* **1999**, *42*, 3743−3778. (b) Franzen, R. G. Recent Advances in the Preparation of Heterocycles on Solid Support: A Review of the Literature. *J. Comb. Chem.* **2000**, *2*, 195−214. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. The Current Status of Heterocyclic Combinatorial Libraries. *Chem. Rev.* **1997**, *97*, 449−472. (d) Thompson, L. A.; Ellman, J. A. Synthesis and Application of Small Molecule Libraries. *Chem. Rev.* **1996**, *96*, 555−600. (e) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. *J. Med. Chem.* **1994**, *37*, 1385−1401.

(2) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W., Jr.; Michejda, C. J. Synthesis and Biological Activity of Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase. 2-Aryl-Substituted Benzimidazoles. *J. Med. Chem.* **1997**, *40*, 4199−4207.

(3) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. Substituted 2,5′-Bi-1H-Benzimidazoles: Topoisomerase I Inhibition and Cytotoxicity. *J. Med. Chem.* **1996**, *39*, 992−995.

(4) Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. Design, Synthesis, and Antiviral Evaluations of 1-(Substituted benzyl)-2-substituted-5,6-dichlorobenzimidazoles as Nonnucleoside Analogues of 2,5,6-Trichloro-1-(β-ribofuranosyl)benzimidazole. *J. Med. Chem.* **1998**, *41*, 1252−1262.

(5) Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L. Z. D. M.; Arnold, M. B.; Schober, D. A.; Gackenheimer, S. L. B. R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, B. E.; Gehlert, D. R. Synthesis and Evaluation of a Series of Novel 2-[(4-Chlorophenoxy)methyl]-benzimidazoles as Selective Neuropeptide Y Y1 Receptor Antagonists. *J. Med. Chem.* **1998**, *41*, 2709−2719.

(6) Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres. *J. Med. Chem.* **1996**, *39*, 5228−5235.
(7) Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. Synthesis and DNA Interactions of Benzimidazole Dications Which Have Activity against Opportunistic Infections. *J. Med. Chem.* **1996**, *39*, 1452−1462.
(8) Gua, Z.; Zhou, D.; Schultz, P. G. Designing Small-Molecule Switches for Protein−Protein Interactions. *Science* **2000**, *288*, 2042−2045.
(9) Artico, M.; Silvestri, R.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, A. G.; Scintu, F.; Colla, P. L. Structre-Based Design, Synthesis, and Biological Evaluation of Novel Pyrrolyl Aryl Sulfones: HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors Active at Nanomolar Concentrations. *J. Med. Chem.* **2000**, *43*, 1886−1891.
(10) Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M.; M. J.; Kellog, M. S.; Koboldt, C. M.; Yuan, J.; Zhang, Y. Y.; Seibert, K. *N*-[[(5-Methyl-3-phenylisozol-4-yl)-phenyl]sulfonyl]propanamide: A Potent and Selective Inhibitor of COX-2 for Parenteral Administation. *J. Med. Chem.* **2000**, *43*, 1661−1663.
(11) Scozzafava, A.; Supuran, C. T. Protease Inhibitors: Synthesis of Potent Bacterial Collagenase and Matrix Metalloproteinase Inhibitors Incorporating *N*-4-Nitrobenzylsulfonylglycine Hydroxamate Moieties. *J. Med. Chem.* **2000**, *43*, 1858−1865.
(12) Schelkum, R. M.; Yuen, P.-W.; Serpa, K.; Meltzer, L. T.; Wise, L. D.; Whittemore, E. R.; Woodward, R. M. Subtype-Selective *N*-Methyl-D-aspartate Receptor Antagonists: Benzimidazolone and Hydantoin as Phenol Replacements. *J. Med. Chem.* **2000**, *43*, 1892−1897.
(13) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. A Practical Entry to the Crambescidin Family of Guanidine Alkaloids. Enantioselective Total Syntheses of Ptilomycalin A, Crambescidin 657 and Its Methyl Ester (Neofolitispates 2), and Crambescidin 800. *J. Am. Chem. Soc.* **2000**, *122*, 4893−4903.
(14) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. Structure and Chemical Properties of Ptilomycalin A. *J. Am. Chem. Soc.* **1992**, *114*, 8472−8479.
(15) Jares, E. A.-E.; Sakai, R.; Rinehart, K. L. Crambescidins: New Antiviral and Cytotoxic Compounds from the Sponge Crambe crambe. *J. Org. Chem.* **1991**, *56*, 5712−5715.
(16) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. Ptilomycalin A: A Novel Polycyclic Guanidine Alkaloid of Marine Origin. *J. Am. Chem. Soc.* **1989**, *111*, 8925−8926.
(17) Ohtani, I. I.; Kusumi, T.; Kakisawa, H. An Insight into the Conformation of Ptilomycalin A. The NMR Properties of Trifluoroacetylated Spermidine Analogues. *Tetrahedron Lett.* **1992**, *33*, 2525−2528.
(18) Ohizumi, Y.; Sasaki, S.; Kusumi, T.; Ohtani, I. I. Ptilomycalin A, a Novel Na^+, K^+- or Ca^{2+}-ATPase Inhibitor, Competitively Interacts with ATP at Its Binding Site. *Eur. J. Pharmacol.* **1996**, *310*, 95−98.
(19) Maillard, M. C.; Perlmn, M. E.; Amitay, O.; Baxter, D.; Berlove, D.; Connaghton, S.; Fischer, J. B.; Guo, J. Q.; Hu, L. Y.; McBurney, R. N.; Nagy, P. I.; Subbarao, K.; Yost, E. A.; Zhang, L.; Durant, G. J. Design, Synthesis, and Pharmacological Evaluation of Conformationally Constrained Analogues of *N*′,*N*′-Diaryl- and *N*-Aryl-*N*-aralkylguanidines as Potent Inhibitors of Neuronal Na^+ Channels. *J. Med. Chem.* **1998**, *41*, 3048−3061.
(20) Ganelin, C. R. In *Chronicles of Drug Discovery*; Bindra, J. S., Lednicer, D., Eds.; Wiley: New York, 1982; Vol. 1, pp 1−38.
(21) (a) Gilman, A. G.; Goodman, L. S. In *The Pharmacological Basis of Therapeutics*, 10th ed.; Macmillan Publishing Co.: New York, 2001; Chapter 10, pp 215−258. (b) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203.
(22) Matsumoto, H.; Ikeda, K.; Nagata, N.; Takayanagi, H.; Mizuno, Y.; Tanaka, M.; Sasaki, T. Synthesis of 2,8-Disubstituted Imidazo[1,5-*a*]pyrimidines with Potent Antitumor Activity. *J. Med. Chem.* **1999**, *42*, 1661−1666.
(23) Bihan, G. L.; Rondu, F.; Pele, A.-T.; Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola, B.-L.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. Design and Synthesis of Imidazoline Derivatives Active on Glucose Homeostasis in a Rat Model of Type II Diabetes. 2. Syntheses and Biological Activities of 1,4-Dialkyl-, 1,4-Dibenzyl, and 1-Benzyl-4-alkyl-2-(4′,5′-dihydro-1′*H*-imidazol-2′yl)piperazines and Isosteric Analogues of Imidazoline. *J. Med. Chem.* **1999**, *42*, 1587−1603.
(24) Kawamoto, H.; Ozaki, S.; Itoh, Y.; Miyaji, M.; Arai, S.; Nakashima, H.; Kato, T.; Ohta, H.; Iwasawa, Y. Discovery of the First Potent and Selective Small Molecule Opioid-Receptor-like (ORL1) Antagonist: 1-[(3*R*,4*R*-1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (J-113397). *J. Med. Chem.* **1999**, *42*, 5061−5063.
(25) Lee, J.; Murray, W. V.; Rivero, R. A. Solid Phase Synthesis of 3,4-Disubstituted-7-carbonyl-1,2,3,4-tetrahydroquinoxalin-2-ones. *J. Org. Chem.* **1997**, *62*, 3874−3879.
(26) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. Solid-Phase Synthesis of Benzopiperazinones. *J. Org. Chem.* **1998**, *63*, 1172−1177.
(27) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. Solid-Phase Synthesis of 1,5-Benzodiazepine-2-ones. *Tetrahedron Lett.* **1998**, *39*, 8397−8400.
(28) Schwarz, M. K.; Tumelty, D. G. M. A. Solid-Phase Synthesis of 3,5-Disubstituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones. *J. Org. Chem.* **1999**, *64*, 2219−2231.
(29) Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. Solid Phase Synthesis of Trisubstituted Bicyclic Guanidines via Cyclicization of Reduced N-Acylated Dipeptides. *J. Org. Chem.* **1998**, *63*, 8622−8623.
(30) (a) Fodor, G.; Nagubandi, S. Correlation of the Von Braun, Ritter, Bischler-Napieralski, Beckmann and Schmidt Reactions via Nitrilium Salt Intermediates. *Tetrahedron* **1980**, *36*, 1279−1300. (b) Gauthier, J. A.; Jirkovsky, I. U.S. Patent 4379926, 1983.
(31) Scheuerman, R. A.; Tumelty, D. The Reduction of Aromatic Nitro Groups on Solid Supports Using Sodium Hydrosulfite (Na_2SO_4). *Tetrahedron Lett.* **2000**, *41*, 6531−6535.
(32) Yeh, C. M.; Tung, C. L.; Sun, C.-M. Combinatorial Liquid-Phase Synthesis of Structurally Diverse Benzimidazole Libraries. *J. Comb. Chem.* **2000**, *2*, 341−348.
(33) (a) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. Solid-Phase Synthesis of Substituted Imidazoline-Tethered 2,3-Diketopiperazines, Cyclic Ureas, and Cyclic Thioureas. *J. Comb. Chem.* **2001**, *3*, 612−623. (b) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. A Novel Approach for Solid-Phase Synthesis of Substituted Imidazolines and Bis-Imidazolines. *J. Org. Chem.* **2001**, *66*, 8673−8676.
(34) Eichler, J.; Houghten, R. A. Synthesis of Cyclic Disulfide Peptides—Comparison of Oxidation Methods. *Protein Pept. Lett.* **1997**, *4*, 157−164.
(35) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. A Novel Approach for the Solid-Phase Synthesis of Substituted Cyclic Guanidines, Their Respective Bis Analogues, and N-Acylated Guanidines from N-Acylated Amino Acid Amides. *J. Comb. Chem.* **2001**, *3*, 578−589.

(36) Echavarren, A.; Gala, A.; Lehn, J.-M.; Mendoza, J. Chiral Recognition of Aromatic Carboxylate Anions by an Optically Active Abiotic Receptor Containing a Rigid Guanidinium Binding Subunit. *J. Am. Chem. Soc.* **1989**, *111*, 4994−4995.
(37) Acharya, A. N.; Nefzi, A.; Ostresh, J. M.; Houghten, R. A. Tethered Libraries: Solid-Phase Synthesis of Substituted Urea-Linked Bicyclic Guanidines. *J. Comb. Chem.* **2001**, *3*, 189−195.
(38) Ostresh, J. M.; Husar, G. M.; Blondelle, S. E.; Dörner, B.; Weber, P. A.; Houghten, R. A. "Libraries from libraries": Chemical Transformation of Combinatorial Libraries To Extend the Range and Repertoire of Chemical Diversity. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138−11142.
(39) Houghten, R. A. General Method for the Rapid Solid-Phase Synthesis of Large Numbers of Peptides: Specificity of Antigen−Antibody Interaction at the Level of Individual Amino Acids. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131−5135.
(40) Kaiser, E. T.; Colescott, R. L.; Blossinger, C. D.; Cook, P. I. Color Test for Detection of Free Terminal Amino Groups in the Solid-Phase Synthesis of Peptides. *Anal. Biochem.* **1970**, *34*, 595−598.
(41) Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. Simplified Procedure for Carrying Out Simultaneous Multiple Hydrogen Fluoride Cleavages of Protected Peptide Resins. *Int. J. Pept. Protein Res.* **1986**, *27*, 673−678.

CC010067Y