A Novel Approach for Solid-Phase Synthesis of Substituted Imidazolines and Bis-Imidazolines

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

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

rhoughten@tpims.org

Received August 10, 2001

Introduction

The practical syntheses of structurally diverse peptidic and nonpeptidic compounds by solid-phase approaches are finding widespread practical utility. In particular, the synthesis of low-molecular-weight heterocyclic compounds with potential pharmacological properties has garnered considerable attention owing to the need to identify active compounds by high-throughput screening of large combinatorial libraries of such compounds.[1] Solid-phase synthetic approaches[2] are an extremely efficient means for the rapid synthesis of combinatorial libraries.[3] This is primarily due to the ability to vary a large number of building blocks available for a wide variety of pharmacophore ensembles, thus permitting the generation of multifunctional structural motifs. The effectiveness of solid-phase approaches is primarily due to the facile removal by washing of excess reagents and solvents from the solid support. This allows the use of large reagent excesses to drive reactions to completion, thus enabling the efficient synthesis of resin-bound products. In most cases, acidolytic cleavage of the final products from the solid support, accomplished by hydrogen fluoride or trifluoroacetic acid,[4,5] followed by extraction with acetic acid−H_2O, has made it straightforward to obtain the desired final compounds in excellent yield and purity. These approaches have been adopted by many pharmaceutical companies to prepare large arrays of individual compounds as well as mixture-based combinatorial libraries for high-throughput screening to identify individual active compounds in a variety of biological assays. These approaches have also been reported as one of the major scientific breakthroughs of 1998.[6]

Imidazolines are known to exhibit a wide range of pharmacological activities, including α-receptor stimulation; vasodepressor activity; α-adrenergic inhibition; and sympathomimetic, antihistaminic, histamine-like, and cholinomimetic activity.[7] Imidazoline derivatives such as midaglizole, deriglidole, and efaroxan are highly active antihyperglycemic agents.[8] Imidazoline derivatives have also been found to exhibit antiinflammatory, antinociceptive, immunomodulating, antioxidant, antitumor, and anticancer activities.[7]

As part of our ongoing efforts directed toward the solid-phase synthesis of low-molecular-weight heterocycles and their subsequent mixture-based combinatorial libraries from amino acids and peptides, we report here an efficient and novel approach for the synthesis of imidazolines and bis-imidazolines via cyclization using $POCl_3$[9] using resin-bound amino acids as the starting materials. In the synthesis of these compounds, one nitrogen of the imidazoline ring was used as the attachment point to the resin. The compounds herein were obtained in moderate yield and high purity. Because of the large number of commercially available amino acids and carboxylic acids, these approaches make it possible to readily prepare combinatorial libraries made up of thousands of these compounds.

Results and Discussion

(i) Disubstituted Imidazolines. A variety of Boc-L-amino acids were coupled to *p*-methylbenzhydrylamine (MBHA) resin (Scheme 1), and then the Boc groups were deprotected to generate primary amines **1**. The reduction of the amide bond of the resin-bound amino acids using BH_3−THF[10] generated diamines **2** having both a secondary amine and a primary amine. The resin-bound diamines **2** were selectively *N*-acylated at the primary amine using a moderate excess of incoming carboxylic acids (3 equiv, 0.06 M in DMF) in the presence of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*-diisopropylethylamine (DIEA) resulting in amides **3**. The treatment of amides with phosphorus oxychloride ($POCl_3$) in dioxane led to cyclodehydration[9] of the resulting in-situ-formed imidoyl chloride intermediates to generate the resin-bound imidazolines **4**. The final compounds were cleaved from the solid support using anhydrous HF and were then extracted with 95% acetic acid in H_2O to give compounds **5**. Initially, we prepared eight individual imidazolines derived from four amino acids (L-Ala, L-Phe, L-Val, and L-Ile) and four different carboxylic acids (isovaleric acid, phenylacetic acid, 1-adamantaneacetic acid, and cyclopentylacetic acid) (see Table 1). In all cases, complete cyclization was observed by LC-MS and reverse-phase high-pressure liquid chromatography (RP-HPLC). The products were obtained in moderate yield (>60%) based on the theoretical loading of the resin (1.10 mequiv/g) and in high purity (see Table 1). The reaction stoichi-

* Author to whom correspondence should be addressed. Tel.: 858-455-3803. Fax: 858-455-3804.

(1) (a) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.; Nefzi, A.; Ostresh, J. M. *J. Med. Chem.* **1999**, *42*, 3743−3778. (b) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (d) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (e) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med Chem.* **1994**, *37*, 1385.

(2) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

(3) Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. *Biotechniques* **1992**, *13*, 901.

(4) Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. *Int. J. Pept. Protein Res.* **1986**, *27*, 673.

(5) Lebl, M.; Pires, J.; Poncar, P.; Pokorny, V. *J. Comb. Chem.* **1999**, *1*, 474.

(6) *Science* **1998**, *282*, 2156.

(7) (a) Gilman, A. G.; Goodman, L. S. In *The Pharmacological Basis of Therapeutics*, 10th ed.; Macmillan & Co.: New York, 2001; Chapter 10, p 215−268. (b) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203.

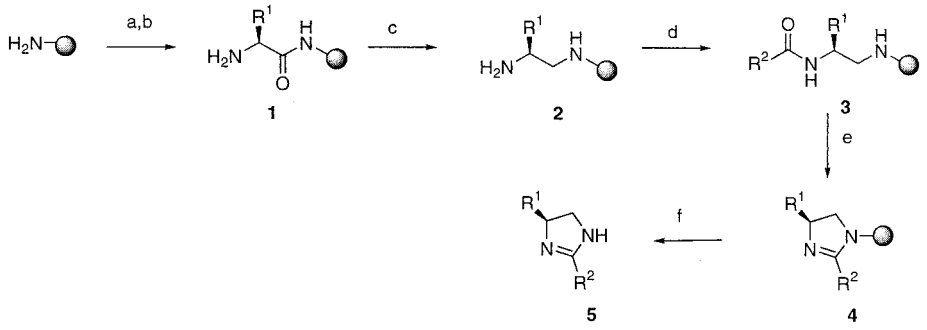
(8) Bihan, G. L.; Rondu, F.; Tounian, A. P.; Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1999**, *42*, 1587.

(9) (a) Fodor, G.; Nagubandi, S. *Tetrahedron.* **1980**, *36*, 1279. (b) Bohle, E.; Egg, H.; Gollner, B.; Jussel, C. *Sci. Pharm.* **1989**, *57*, 333. (c) Gauthier, J. A.; Jirkovsky, I. U.S. Patent 4,379,926, 1983.

(10) Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622.

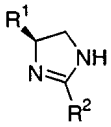
10.1021/jo010814d CCC: $20.00
Published on Web 11/15/2001

Scheme 1[a]



[a] (a) Boc-L-NHCH(R^1)CO_2H (6 equiv, 0.1 M in DMF), DIC (6 equiv), HOBt (6 equiv), 2 h, room temperature (rt); (b) 55% TFA/45% DCM, 30 min, rt; (c) (i)BH_3−THF, 65 °C, 72 h; (ii) piperidine, 65 °C, 20 h; (d) R^2CO_2H (3 equiv, 0.06 M in DMF), HBTU (3 equiv), DIEA (6 equiv), 3 h, rt; (e) $POCl_3$ (10 equiv, 0.09 M in anhydrous dioxane), 110 °C, 2.5 h; (f) HF, anisole, 0 °C, 7 h.

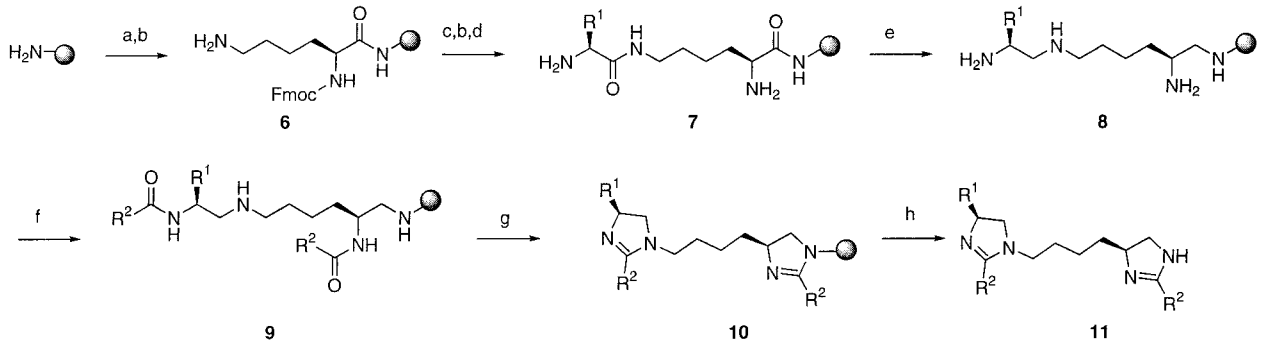
Table 1. HPLC Purity and MW for Substituted Imidazolines 5[a]



entry	R^1	R^2	purity (%)[b]	MW (expected)	MW (found)
5a	$-CH_3$	$-CH_2CH(CH_3)_2$	89	140.2	141.1 ($M + H^+$)
5b	$-CH_3$	$-CH_2C_6H_5$	89	174.2	175.1 ($M + H^+$)
5c	$-CH_2C_6H_5$	−1-adamantanemethyl	81	308.5	309.5 ($M + H^+$)
5d	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	91	216.3	217.3 ($M + H^+$)
5e	$-CH_2C_6H_5$	$-CH_2C_5H_9$	92	242.4	243.3 ($M + H^+$)
5f	$-CH(CH_3)C_2H_5$	$-CH_2C_5H_9$	81	208.3	209.3 ($M + H^+$)
5g	$-CH_2C_6H_5$	$-CH_2C_6H_5$	82	250.3	251.3 ($M + H^+$)
5h	$-CH(CH_3)_2$	$-CH_2C_5H_9$	84	194.3	195.2 ($M + H^+$)

[a] Yields ranged from 60 to 80% based on theoretical loading of the resin (1.10 mequiv/g). [b] Purity was determined from the relative peak areas of the HPLC chromatograms at $\lambda = 214$ nm. The samples were run using a gradient of 5−95% acetonitrile in water (0.05% TFA) over 30 min.

Scheme 2[a]



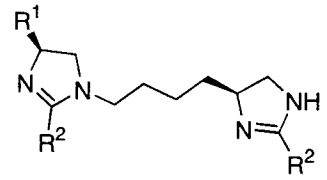
[a] (a) N^{α}-Fmoc-N^{ϵ}-Boc-L-lysine (2.5 equiv, 0.05 M in DMF), DIC (2.5 equiv), HOBt (2.5 equiv), room temperature (rt), overnight; (b) 55% TFA/45% DCM, rt, 30 min, (c) Boc-L-NHCH(R^1)CO_2H (6 equiv, 0.1 M in DMF), DIC (6 equiv), HOBt (6 equiv), 2 h, rt; (d) 20% piperidine/80% DMF, rt, 30 min; (e) (i) BH_3−THF, 65 °C, 72 h; (ii) Piperidine, 65 °C, 20 h; (f) R^2CO_2H (5 equiv, 0.1 M in DMF), HBTU (5 equiv), DIEA (10 equiv), rt, 3 h; (g) $POCl_3$ (10 equiv, 0.09 M in anhydrous dioxane), 110 °C, 2.5 h; (h) HF, anisole, 0 °C, 7 h.

ometry of a 10-equiv excess of $POCl_3$ in anhydrous dioxane (110 °C for 2.5 h) was found to yield the cyclized products in high purity. The compounds were purified for characterization by high-resolution mass spectroscopy (HRMS) and ^1H and ^{13}C NMR spectroscopy.

It is expected that the imidazoline ring would be protonated ($pK_a \approx 9.5$)[8] during purification (0.05% trifluoroacetic acid). The appearance of two strong individual downfield proton signals at $\delta \approx 9.9-10.3$ ppm in the ^1H NMR spectra corresponded to the protonated imidazoline.[8]

(ii) Trisubstituted Bis-imidazolines. N^{α}-Fmoc-N^{ϵ}-Boc-L-lysine was coupled to MBHA resin (Scheme 2), and then the N^{ϵ}-Boc group from the side chain of the lysine was deprotected to generate primary amine **6**. Boc-protected L-amino acids were coupled to the primary amine of **6**. Removal of the Boc and Fmoc groups generated the dipeptides **7** having two primary amines. Exhaustive reduction of the two amides in these dipeptides upon treatment with BH_3−THF[10] generated tetramines **8** having two secondary amines and two primary amines. Selective *N*-acylation was performed successfully at the two primary amines of the tetra-amines **8** using a moderate excess of a wide range of carboxylic acids (5 equiv, 0.1 M in DMF) in the presence of HBTU and DIEA, generating diamides **9**. Treatment of **9** with $POCl_3$ in

Table 2. HPLC Purity and MW for Trisubstituted Bis-imidazolines 11[a]



entry	R^1	R^2	purity[b] (%)	MW (expected)	MW (found)
11a	$-CH_3$	$-CH_2CH_2CH_3$	80	292.5	293.5 ($M + H^+$)
11b	$-CH_2C_6H_5$	$-CH_2CH_2CH_3$	83	368.6	369.7 ($M + H^+$)
11c	$-CH_2C_{10}H_7$	$-CH_2CH_2CH_3$	74	418.6	419.5 ($M + H^+$)
11d	$-CH_2C_6H_4$(4-Cl)	$-CH_2CH_2CH_3$	76	403.0	403.6 ($M + H^+$)
11e	$-C_6H_{11}$	$-CH_2CH_2CH_3$	74	360.6	361.5 ($M + H^+$)
11f	$-CH_3$	$-CH_2C_6H_5$	71	388.6	389.4 ($M + H^+$)
11g	$-CH_3$	$-CH_2C_6H_4$(3-CH_3)	63	416.6	417.3 ($M + H^+$)
11h	$-CH_3$	$-CH_2C_6H_4$(4-C_6H_5)	83	540.6	541.4 ($M + H^+$)
11i	$-CH_3$	$-C_4H_7$	84	316.5	317.5 ($M + H^+$)
11j	$-CH_3$	$-C_5H_9$	70	344.5	345.6 ($M + H^+$)
11k	$-CH_3$	$-CH_2CH(CH_3)_2$	69	320.5	321.5 ($M + H^+$)
11l	$-CH_3$	−(2-norbornanemethyl)	65	424.7	425.6 ($M + H^+$)

[a] Yields ranged from 60 to 80% based on theoretical loading of the resin (1.10 mequiv/g). [b] Determined from the relative peak areas of the HPLC chromatograms at $\lambda = 214$ nm. The samples were run using a gradient of 5−95% acetonitrile in water (0.05% TFA) over 30 min.

dioxane resulted in resin-bound bis-imidazolines **10** via cyclization of the imidoyl chloride intermediates.[9] The selectivity in generating the bis-imidazolines **10** was due to the formation of energetically favored five-membered rings.[11] The resin-bound bis-imidazolines were cleaved by anhydrous HF and extracted with 95% acetic acid in water to give the desired products **11**. Twelve individual control bis-imidazolines were synthesized from five different amino acids (L-Ala, L-Phe, L-cyclohexylglycine, *p*-chloro-L-phenylalanine, and 2-naphthyl-L-alanine) and eight different carboxylic acids (butyric acid, isovaleric acid, phenylacetic acid, *m*-tolylacetic acid, 4,4′-biphenylacetic acid, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, and 2-norbornaneacetic acid) (see Table 2). In all cases, complete cyclization was observed by LC-MS and HPLC (see Table 2). The products were obtained in moderate yield (>60%) and high purity (see Table 2). The possibility of racemization was determined as described earlier.[10,12] Negligible amounts of racemization (<1%) were observed either during exhaustive reduction of amide bonds[10] or during $POCl_3$ treatment. The purified compounds were analyzed by HRMS and ^1H and ^{13}C NMR spectroscopy to confirm their identities and structures.

Three strong downfield proton signals observed at $\delta \approx 9.9-10.2$ ppm in the ^1H NMR spectra in d_6-DMSO corresponded to the protonated bis-imidazolines.

Conclusion

We have developed an efficient strategy for the solid-phase synthesis of imidazolines and their respective bis analogues via direct linkage of the resin of the resulting imidazoline moiety. This approach utilizes cyclization of the in-situ-generated imidoyl chloride intermediates in the key step and allows variation of the substituents on the imidazoline core. This approach can be employed to prepare a large number of individual substituted imidazolines and bis-imidazolines, as well as mixture-based synthetic combinatorial libraries.[3]

Experimental Section

p-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100−200 mesh, 1.1 mequiv/g substitution) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex Intl. (Wood Dale, IL). Boc-amino acid derivatives, *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). HF was purchased from Air Products (San Marcos, CA). All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Analytical RP-HPLC was performed on a Beckman System Gold instrument (Fullerton, CA). Samples were analyzed using a Vydac 218TP54 C18 column (0.46 × 25 cm). LC-MS (ESI and APCI) were recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, San Jose, CA) at 214 nm using a Betasil C18, 3 μm, 100 Å, 3 × 50 mm column. Preparative RP-HPLC was performed on a Waters DeltaPrep preparative HPLC (Millipore) using a Vydac 218TP1022 C18 column (2.2 × 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 Syntheses of Disubstituted Imidazolines and Their Bis Analogues. MBHA resin (100 mg) was sealed inside a polypropylene mesh packet.[13] Polypropylene bottles were used for all reactions. The resin was washed with dichloromethane (DCM) and then neutralized with 5% diisopropylethylamine (DIEA) in DCM and washed with DCM.

(1) Coupling of an Amino Acid to the Resin. *(a) Disubstituted Imidazoline.* Boc-L-amino acid (6 equiv, 0.1 M in DMF) was coupled to MBHA resin using the classical coupling reagents DIC and HOBt (6 equiv each) for 2 h at room temperature and then washed with DMF (three times) and DCM (three times). The Boc group was deprotected using 55% TFA in DCM for 30 min. *(b) Trisubstituted Bis-imidazoline.* Orthogonally protected amino acid, N^{α}-Fmoc-N^{ϵ}-Boc-L-lysine (2.5 equiv, 0.05 M in DMF), was coupled to MBHA resin using DIC and HOBt (2.5 equiv each) overnight at room temperature. Following washes with DMF (four times) and removal of the N^{ϵ}-Boc group, coupling of the Boc-L-amino acid followed by removal of the Boc group was performed in the same manner as described in 1a. The N^{α}-Fmoc group was removed using 20% piperidine in DMF for 30 min, followed by washing with DMF (four times), 2-propanol (IPA) (two times), and DCM (two times). Completeness of the coupling was verified by the ninhydrin test.[14]

(11) Nefzi, A.; Giulianotti, M. A.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 68.

(12) Acharya, A. N.; Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 189.

(13) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131.

(2) Exhaustive Reduction of Amide Groups by BH_3−THF. Exhaustive reduction of the resin-bound amino acids or dipeptides was carried out in 50-mL glass conical tubes under nitrogen. To each tube were added the resin packet (0.11 mequiv of resin, 100 mg of starting resin) and boric acid (12 equiv), followed by trimethyl borate (12 equiv). Borane−THF complex (1 M, 40 equiv) was added slowly. After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 72 h; then the solution was decanted, and the reaction quenched with methanol (MeOH). Following washes with DMF and MeOH (four times) the resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complexes.[10] Following decantation of the piperidine−borane solution, the resin packet was washed with DMF (four times), DCM (four times), and MeOH (two times) and dried.

(3) Selective *N*-Acylation at the Primary Amine(s). *(a) Disubstituted Imidazoline (See Scheme 1).* The resin-bound diamine was neutralized with 5% DIEA in DCM. *N*-acylation was performed with a carboxylic acid (3 equiv, 0.06 M in DMF) in the presence of HBTU (3 equiv) and DIEA (6 equiv) for 3 h. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). *(b) Trisubstituted Bisimidazoline (See Scheme 2).* The resin-bound tetra-amine was neutralized with 5% DIEA in DCM and then *N*-acylated with a carboxylic acid (5 equiv, 0.1 M in DMF) in the presence of HBTU (5 equiv) and DIEA (10 equiv) for 3 h. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times).

(4) Cyclization with $POCl_3$. Cyclization of the amide of the *N*-acylated reduced amino acids or amides of the reduced dipeptides was carried out in 50-mL conical tubes under nitrogen. To each tube were added the resin packet (0.11 mequiv of resin, 100 mg of starting resin) and $POCl_3$ (10 equiv, 0.09 M in anhydrous dioxane). The capped tubes were heated at 110 °C for 2.5 h, and then the reaction solution was decanted. The resin was washed with dioxane (two times), DMF (four times), MeOH (four times), DCM (two times), IPA (two times), and DCM (four times). The resin-bound compound was cleaved by anhydrous HF in the presence of anisole at 0 °C for 7 h,[4] and the cleaved product was extracted with 95% acetic acid in H_2O 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.

(4*S*)-2-Isobutyl-4-methyl-4,5-dihydro-1*H*-imidazole (5a). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.91−0.93 (d, J = 6.7 Hz, 6H), 1.23−1.24 (d, J = 6.38 Hz, 3H), 1.98−2.01 (m, 1H), 2.31−2.32 (d, J = 7.48 Hz, 1H), 3.38−3.42 (dd, J = 7.16 Hz, J = 10.9 Hz, 2H), 3.93 (t, J = 11.0, 1H), 4.26−4.30 (m, 1H), 9.85−9.95 (s, 2H).

(4*S*)-2-Benzyl-4-methyl-4,5-dihydro-1*H*-imidazole (5b). HRMS (DEI) *m/z*: 173.1079 found ([M−H]$^+$), 173.1079 calculated for $C_{11}H_{15}N_2$ ([M−H]$^+$).

(4*S*)-2-(1-Adamantylmethyl)-4-benzyl-4,5-dihydro-1*H*-imidazole (5c). HRMS (DEI) *m/z*: 308.2248 found ([M]$^+$), 308.2253 calculated for $C_{21}H_{29}N_2$ ([M]$^+$).

(4*S*)-4-Benzyl-2-isobutyl-4,5-dihydro-1*H*-imidazole (5d). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.84−0.88 (dd, J = 6.7 Hz, J = 13.4 Hz, 6H), 1.90−1.98 (m, 1H), 2.26−2.28 (d, J = 7.31 Hz, 2H), 2.88−2.89 (d, J = 6.26 Hz, 2H), 3.55−3.59 (dd, J = 7.19 Hz, J = 11.5 Hz, 1H), 3.88 (t, J = 11.2 Hz, 1H), 4.53−4.57 (m, 1H), 7.25−7.35 (m, 5H), 9.90−9.98 (s, 2H).

(4*S*)-4-Benyl-2-(cyclopentylmethyl)-4,5-dihydro-1*H*-imidazole (5e). HRMS (DEI) *m/z*: 243.1865 found ([M + H]$^+$), 243.1861 calculated for $C_{16}H_{23}N_2$ ([M + H]$^+$).

(4*S*)-4-*sec*-Butyl-2-(cyclopentylmethyl)-4,5-dihydro-1*H*-imidazole (5f). HRMS (DCI) *m/z*: 209.2011 found ([M + H]$^+$), 209.2018 calculated for $C_{13}H_{25}N_2$ ([M + H]$^+$).

(4*S*)-2,4-Dibenzyl-4,5-dihydro-1*H*-imidazole (5g). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.86−2.88 (d, J = 6.16 Hz, 2H), 3.54−3.58 (dd, J = 6.99 Hz, J = 11.6 Hz, 1H), 3.78 (s, 2H), 3.87 (t, J = 11.5 Hz, 1H), 4.54−4.58 (m, 1H), 7.22−7.40 (m, 10H), 9.98 (s, 1H), 10.23 (s, 1H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 31.8, 48.7, 57.6, 126.8, 127.8, 128.5, 128.9, 129.0, 129.5, 132.8, 135.8, 168.5. HRMS (DCI) *m/z*: 251.1552 found ([M + H]$^+$), 251.1548 calculated for $C_{17}H_{19}N_2$ ([M + H]$^+$).

(4*S*)-2-(Cyclopentylmethyl)-4-isopropyl-4,5-dihydro-1*H*-imidazole (5h). HRMS (DEI) *m/z*: 195.1858 found ([M + H]$^+$), 195.1861 calculated for $C_{12}H_{23}N_2$ ([M + H]$^+$).

(4*S*)-4-Methyl-2-propyl-1-{4-[(4*S*)-2-propyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11a). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.89−0.95 (m, 5H), 1.23−1.24 (d, J = 6.56 Hz, 4H), 1.55−1.64 (m, 7H), 2.43 (t, J = 7.58 Hz, 2H), 2.49−2.53 (m, 4H), 3.35−3.48 (m, 4H), 3.92−3.98 (m, 2H), 4.19−4.21 (m, 2H), 9.96 (s, 1H), 9.99 (s, 1H), 10.14 (s, 1H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 13.1, 13.2, 18.8, 18.9, 20.6, 21.2, 26.3, 26.3, 27.4, 34.1, 40.9, 45.2, 49.2, 50.5, 55.2, 56.7, 168.0, 170.0. HRMS (DCI) *m/z*: 293.2698 found ([M + H]$^+$), 293.2705 calculated for $C_{17}H_{33}N_4$ ([M + H]$^+$).

(4*S*)-4-Benzyl-2-propyl-1-{4-[(4*S*)-2-propyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11b). HRMS (DEI) *m/z*: 367.2862 found ([M−H]$^+$), 367.2849 calculated for $C_{23}H_{37}N_4$ ([M−H]$^+$).

(4*S*)-4-(1-Naphthylmethyl)-2-propyl-1-{4-[(4*S*)-2-propyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11c). HRMS (DEI) *m/z*: 417.3017 found ([M−H]$^+$), 417.3019 calculated for $C_{27}H_{39}N_4$ ([M−H]$^+$).

(4*S*)-4-(4-Chlorobenzyl)-2-propyl-1-{4-[(4*S*)-2-propyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11d). HRMS (DCI) *m/z*: 401.2465 found ([M−H]$^+$), 401.2472 calculated for $C_{23}H_{36}N_4$ ([M−H]$^+$).

(4*S*)-4-Cyclohexyl-2-propyl-1-{4-[(4*S*)-2-propyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11e). HRMS (DEI) *m/z*: 359.3184 found ([M−H]$^+$), 359.3175 calculated for $C_{22}H_{41}N_4$ ([M−H]$^+$).

(4*S*)-2-Benzyl-1-{4-[(4*S*)-2-benzyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4-methyl-4,5-dihydro-1*H*-imidazole (11f). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.91−0.95 (m, 12H), 1.23−1.32 (m, 5H), 1.55−1.58 (m, 4H), 1.96−2.02 (2H), 2.33−2.35 (d, J = 7.32 Hz, 1H), 2.42−2.44 (d, J = 7.44 Hz, 1H), 3.38−3.51 (m, 4H), 3.91−4.01 (m, 2H), 4.19−4.22 (m, 2H), 6.54 (s, 1H), 10.02 (s, 1H), 10.08 (s, 1H), 10.23 (s, 1H).

(4*S*)-4-Methyl-2-(3-methylbenzyl)-1-{4-[(4*S*)-2-(3-methylbenzyl)-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11g). HRMS (DEI) *m/z*: 415.2875 found ([M−H]$^+$), 415.2862 calculated for $C_{27}H_{37}N_4$ ([M−H]$^+$).

(4*S*)-2-(1,1′-Biphenyl-4-ylmethyl)-1-{4-[(4*S*)-2-(1,1′-biphenyl-4-ylmethyl)-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4-methyl-4,5-dihydro-1*H*-imidazole (11h). HRMS (DEI) *m/z*: 539.3163 found ([M−H]$^+$), 539.3175 calculated for $C_{37}H_{41}N_4$ ([M−H]$^+$).

(4*S*)-2-Cyclobutyl-1-{4-[(4*S*)-2-cyclobutyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4-methyl-4,5-dihydro-1*H*-imidazole (11i). HRMS (DEI) *m/z*: 315.2545 found ([M−H]$^+$), 315.2549 calculated for $C_{19}H_{33}N_4$ ([M−H]$^+$).

(4*S*)-2-Cyclopentyl-1-{4-[(4*S*)-2-cyclopentyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4-methyl-4,5-dihydro-1*H*-imidazole (11j). HRMS (DEI) *m/z*: 343.2869 found ([M−H]$^+$), 343.2862 calculated for $C_{21}H_{37}N_4$ ([M−H]$^+$).

(4*S*)-2-Isobutyl-1-{4-[(4*S*)-2-isobutyl-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4-methyl-4,5-dihydro-1*H*-imidazole (11k). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.09−1.10 (m, 2H), 1.25−1.26 (d, J = 6.13 Hz, 2H), 1.32−1.47 (m, 4H), 3.36−3.47 (m, 3H), 3.84 (s, 3H), 3.89 (t, J = 11.2 Hz, 1H), 3.97−4.02 (m, 1H), 4.11−4.14 (m, 1H), 4.26−4.28 (m, 1H), 6.52 (s, 1H), 7.32−7.41 (m, 10H), 10.10 (s, 1H), 10.20 (s, 1H), 10.28 (s, 1H).

(4*S*)-4-Methyl-2-(2-norbornylmethyl)-1-{4-[(4*S*)-2-(2-norbornylmethyl)-4,5-dihydro-1*H*-imidazol-4-yl]butyl}-4,5-dihydro-1*H*-imidazole (11l). HRMS (DEI) *m/z*: 423.3478 found ([M−H]$^+$), 423.3488 calculated for $C_{27}H_{45}N_4$ ([M−H]$^+$).

Acknowledgment. A.N.A. thanks Department of Industries, Govt. of Orissa, India, for sanction of study leave. This work was funded by National Cancer Institute Grant 78040 (Houghten).

Supporting Information Available: LC-MS and ^{1}H and ^{13}C NMR spectra of selected imidazolines and their bis analogues are enclosed. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010814D

(14) Kaiser, E. T.; Colescott, R. L.; Blossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.