Efficient Solid-Phase Synthesis of a Library of Imidazo[1,2-*a*]pyridine-8-carboxamides

Ahmed Kamal,* V. Devaiah, K. Laxma Reddy, Rajendar, Rajesh V. C. R. N. C. Shetti, and N. Shankaraiah

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received October 13, 2006

A versatile method for the solid-phase synthesis of imidazo[1,2-*a*]pyridine-based derivatives, imidazo[1,2-*a*]pyridine-8-carboxamides, has been developed. They were obtained by treatment of the amino group of the polymer-bound 2-aminonicotinate with different α-haloketones, followed by halogenation at the 3-position of the polymer-bound imidazo[1,2-*a*]pyridine. The derived polymer-bound imidazo[1,2-*a*]pyridines **5**, **6**, and **7** were finally cleaved from the solid-support with an excess of primary or secondary amines. The final crude products were purified from excess amines by solid-supported liquid−liquid extraction (SLE).

Introduction

Solid-phase methods have recently been used in a variety of applications, providing a new approach to the synthesis of combinatorial libraries of compounds. Libraries of small molecules are normally prepared either in solution or via solid-supported chemistry. The greater flexibility of solution chemistry is outweighed by the need for purification of the library.[1] As a consequence, a solid-phase organic synthesis (SPOS)[2] method has been developed that allows the synthesis of chemical libraries on a solid-phase support using an excess of reagents, which can be removed by simple filtration. Solid-phase synthesis along with high-throughput screening has emerged as a powerful tool for the discovery of novel drug candidates. The synthesis of combinatorial libraries based on so-called "privileged structures" is of particular interest because of the ability to provide high-affinity ligands for more than one type of receptor, depending on their substitution pattern.[3]

Nitrogen bridgehead-fused heterocycles containing an imidazole ring are common structural motifs in pharmacologically important molecules, with activities spanning a diverse range of targets. Probably the most widely used heterocyclic system from this group is imidazo[1,2-*a*]-pyridine, which is contained in marketed drugs such as the benzodiazepine agonist Zolpidem[4] and the PDE 3 inhibitor Olprinone,[5] as well as other experimental molecules.[6] However, alternative derivatives, such as the closely related imidazo[1,2-*a*]pyrimidine Divaplon,[7] are also prevalent. Bradykinin (BK) is an endogenous nonapeptide generated by tissue and plasma kallikreins. Because of its highly potent proinflammatory activities, BK has been implicated in a variety of pathophysiological responses, including pain, inflammation, asthma, rhinitis, and hypotension.[8] Two types of BK receptors, designated as B_1 and B_2, have been identified by molecular cloning and pharmacological means. B_2 receptors are expressed constitutively in many tissues and are thought to mediate most of the biological actions of BK. Published data[9] for structures **A**, **B**, and **C** (Figure 1) reveal that hydrophobic contacts via 2-methyl and 3-chloro or 3-bromo groups on the imidazo[1,2-*a*]pyridine ring, electrostatic interactions via linker oxygen, and hydrogen bonds via the terminal amide group significantly contributed to the binding affinity of B_2 receptors. Imidazo[1,2-*a*]pyridine moieties have also been shown to possess diverse therapeutic activities,[10] antiulcer,[11a] antibacterial,[11b,c] antifungal,[11d,e] herbicidal,[11f] calcium-channel blockers,[11g] cyclin-dependent kinases (CDK) inhibitors,[11h] $GABA_A$ receptor modulator,[11i] and more recently, 2-arylimidazo[1,2-*a*]pyridines have been explored[6a] as ligands for detecting β-amyloid (Aβ) plaques in the brain, the production of which is a pivotal event in the pathology of Alzheimer's disease. Indeed, the imidazo-[1,2-*a*]pyridine moiety may be regarded as a privileged class of structure. Both the solution and solid-phase synthesis of imidazo[1,2-*a*]pyridine libraries have been reported.[12] In this article, we report a facile and efficient method for the solid-phase synthesis of substituted imidazo[1,2-*a*]pyridine-8-carboxamide (three point diversity) compounds from 2-aminonicotinic acid, α-haloketones R, and amines R^1 and R^2 as versatile building blocks. Methods involving the cleavage of compounds from the solid support using diverse cleavage reagents (react and release) are attractive because of the conservation of synthetic operations and the diversity of product structures obtained.[13] However, there are numerous practical difficulties in the use of these react and release strategies for the generation of large compound libraries because of the linker activation steps, variable reactivity of cleavage reagents, and impure products resulting from incomplete consumption of cleavage reagents. Herein we have used a direct react and release cleavage strategy from a phenol-sulfide linker **1** (Marshall's linker)[14,15] for parallel solid-phase synthesis of imidazo[1,2-*a*]pyridine-8-carboxamides, followed by a solid-supported liquid−liquid extraction

* To whom correspondence should be addressed. Phone: +91-40-27193157. Fax.: +91-40-27193189. E-mail: ahmedkamal@iict.res.in; ahmedkamal@iictnet.org.

10.1021/cc060141i CCC: $37.00
Published on Web 02/24/2007

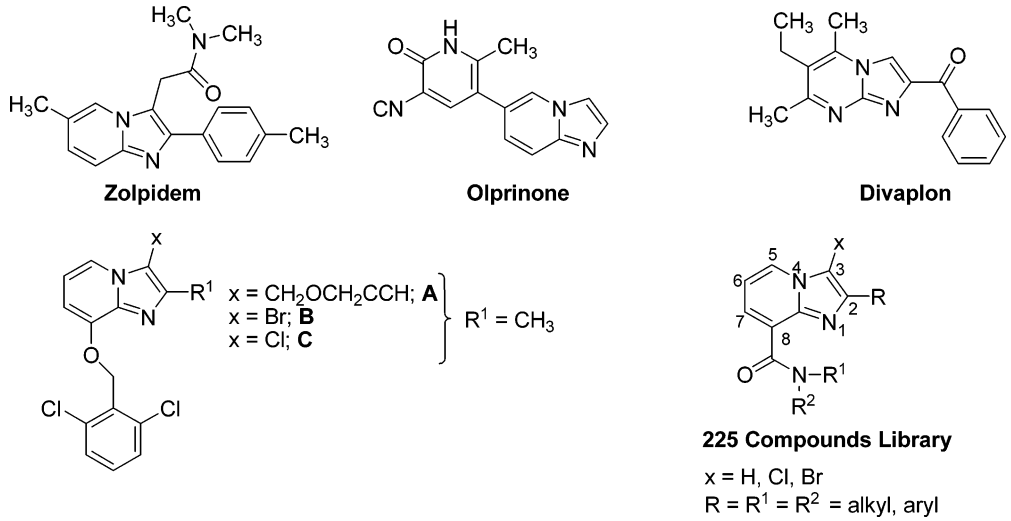


Figure 1. Biologically relevant imidazo[1,2-a]pyridine derivatives and present library.

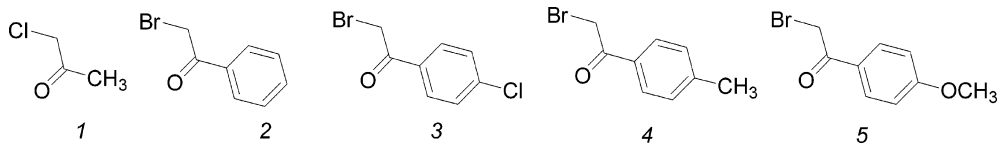
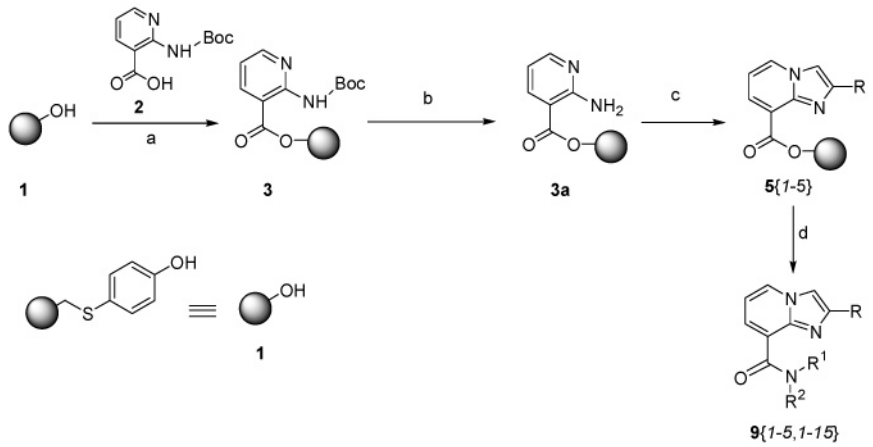


Figure 2. Set of α-haloketones R **4**{*1*−*5*} for the library.

Scheme 1[a]



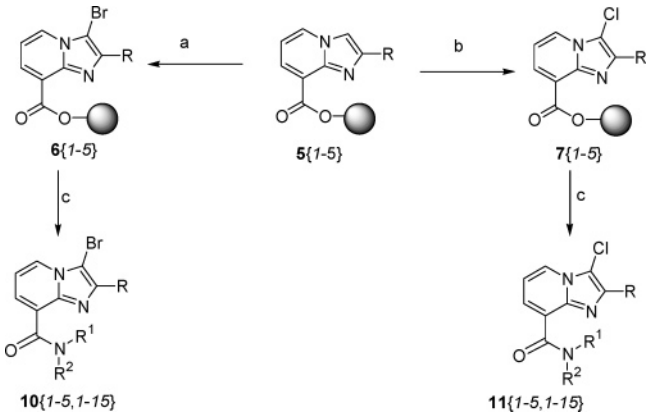
[a] Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2−DMF (1:1), 48 h; (b) 4 N HCl in 1,4-dioxane; (c) xCH_2COR **4**{*1*−*5*}, EtOH, reflux for 5 h; (d) (i) R^1R^2NH **8**{*1*−*15*}, py, 18−24 h; (ii) amine extraction (SLE method).

(SLE)[15a] process that is effective in the removal of excess amine from the cleaved final products in a high-throughput format.

Results and Discussion

The present strategy commenced with the synthesis of imidazo[1,2-*a*]pyridines by the direct attachment of the Boc-protected 2-aminonicotinic acid **2** to 4-hydroxyphenyl-sulfide resin **1**[14] via a carbodiimide-mediated esterification reaction using EDC and DMAP in a mixture of DCM and DMF to afford the polymer-bound Boc-protected 2-aminonicotinate **3** [confirmed by FT-IR, 1722 (COO-polymer-bound) and 1664 (NH-Boc) cm^{-1}]. Complete coupling to the solid-support was confirmed by a negative $FeCl_3$/pyridine test for phenol.[15c] Cleavage of the Boc-group in acidic media gave the polymer-bound 2-aminonicotinate **3a**. Condensation of this resin-bound intermediate with various α-haloketones **4**{*1*−*5*} (XCH_2COR) (Figure 2) results in the formation of resin-bound imidazo[1,2-*a*]pyridine-8-carboxylates **5**{*1*−*5*} (Scheme 1). Selective halogenation at the 3-position of **5**{*1*−*5*} was achieved by employing *N*-bromosuccinamide (NBS) or *N*-chlorosuccinamide (NCS) in ethanol to give **6**{*1*−*5*} and **7**{*1*−*5*} (Scheme 2), respectively. The desired amides **9**{*1*−*5*, *1*−*15*}, **10**{*1*−*5*, *1*−*15*}, and **11**{*1*−*5*, *1*−15} were liberated from the resins **5**{*1*−*5*}, **6**{*1*−*5*}, and **7**{*1*−*5*} using an excess of the amine **8**{*1-15*} (Figure 3) in pyridine (∼400 mol %). The use of pyridine provides more than 90% cleavage from the phenol-sulfide linker in 48 h. Pyridine

Scheme 2[a]



[a] Reagents and conditions: (a) NBS, EtOH, reflux for 3 h; (b) NCS, EtOH, reflux for 3 h; (c) (i) R^1R^2NH **8**{*1*−*15*}, py, 18−24 h; (ii) amine extraction (SLE method).

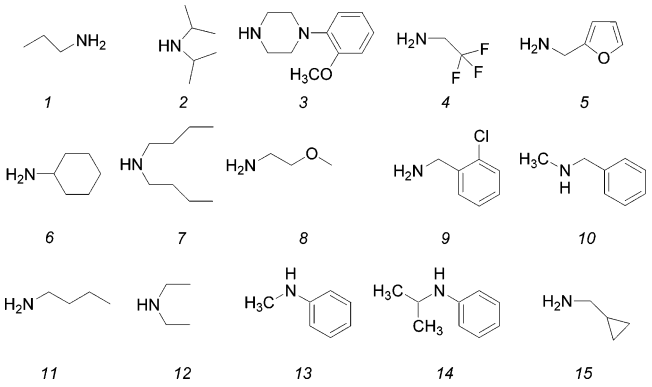


Figure 3. Set of amines R^1 and R^2 **8**{*1*−*15*} for the library.

also offers an additional advantage of excellent solubility and resin-swelling properties. Removal of the excess amine was accomplished using SLE with diatomaceous earth as the support. This extraction was found to be an effective method for the removal of water-soluble impurities in a high-throughput format. In this respect, we have utilized Varian's Hydromatrix (diatomaceous earth) for the amine extraction. The choice of aqueous buffer for extraction depended on the physical properties of the amine to be extracted. In general, 2 N aqueous hydrochloric acid was employed for hydrophobic amines, and water was the preferred buffer for removal of hydrophilic amines. The organic material passed through the Hydromatrix support into a collection plate below, while the amine salts were retained by the solid matrix, resulting in the effective removal of the amine impurities. The complete removal of the amine depends upon its *C* log *P* value.[15f] Further, it has been observed from the SLE method that the solubility of the target compound in organic solvent depends on its purity and its substitution pattern at the 3-position of the imidazo[1,2-*a*]pyridine. Crude yields and weight-percent purities for the product obtained in this manner are shown in Table 2 (Supporting Information). Analytical data for the purified compounds used in the quantitative purity analysis is provided in the Experimental Section and in Table 1.

Library Design and Synthesis. The building blocks for the library synthesis (Boc protected 2-aminonicotinic acid, α-haloketones, and primary and secondary amines) were selected and used for the generation of a 225 compound library with good yields of final products **9**, **10**, and **11**, comprising 3 sublibraries (75 + 75 + 75) as shown in Table 1. The coupling of Boc-protected 2-aminonicotinic acid to the Marshall's linker and cleavage of the Boc group was carried out manually in a single batch.[16a] The subsequent steps involving cyclized imidazo[1,2-*a*]pyridine, halogenations at the 3-position of polymer-bound imidazo[1,2-*a*]-pyridines, and cleavage with excess amines were performed in a semiautomated fashion using the MSW 500 synthesizer (Chemspeed). The removal of excess amine from the final cleaved crude product was achieved via the SLE extraction method. Selected compounds from each library were purified by flash chromatography and characterized by proton NMR and mass spectroscopy. The building blocks for the library construction, that is, Boc-protected 2-aminonicotinic acid were obtained from available literature sources.[16b] However, the α-haloketones **4**{*1*−*5*} and amines **8**{*1*−*15*} were obtained from commercial sources.

Table 1. Yields, Purity, and Molecular Weight (HRMS/ESI) of the Synthesized Imidazo[1,2-*a*]pyridine-8-carboxamides **9**, **10**, and **11**

compound	yield[a]	purity (%)[b]	HRMS/ESI
9{*1*, *1*}	50	80.4	218.1289
9{*2*, *2*}	65	88.3	322.1907
9{*3*, *3*}	60	54.8	447.1598
9{*4*, *4*}	62	77.1	334.1154
9{*5*, *5*}	68	82.5	348.1338
10{*1*, *6*}	52	86.2	336.0705
10{*2*, *7*}	66	93.3	428.1338
10{*3*, *8*}	58	97.8	408.0120
10{*4*, *9*}	64	93.7	454.0316
10{*5*, *10*}	70	67.4	450.0823
11{*1*, *11*}	55	94.2	266.1053
11{*2*, *12*}	63	93.0	328.1209
11{*3*, *13*}	62	98.1	396.0675
11{*4*, *14*}	66	97.1	404.1519
11{*5*, *15*}	69	96.4	356.1169

[a] Yields of cleaved products are based on the theoretical loading of commercial resin. [b] Determined by reversed-phase HPLC;[17] for details, see the Experimental Section.

Conclusion

In conclusion, a versatile approach employing a phenol-sulfide linker for the solid-phase synthesis of imidazo[1,2-*a*]pyridine-8-carboxamides has been demonstrated. The use of the phenol-sulfide linker with its chemical versatility in the cleavage step adds to the overall diversity of the library. The reaction conditions used in this protocol are mild, and the compounds are obtained in good yields and purity. Further, this procedure also demonstrated the application of high-throughput purification (SLE) methods which have been employed in conjunction with react and release solid-phase techniques to improve the purity of resulting libraries. This method has potential for use in the generation of a large number of imidazo[1,2-*a*]pyridine-based compounds using an automated synthesizer.

Experimental Section

General. Marshall's linker resin (3.3 mmol/g, 60−120 mesh, 1% DVB) was obtained from Advanced Chemtech

Ltd. All building blocks (except *N*-(*tert*-butoxycarbonyl)-2-aminonicotinic acid prepared by a literature method)[16a] and reagents were purchased from commercial sources and were used without further purification. Anhydrous solvents like CH_2Cl_2 dried over P_2O_5, DMF dried over CaH_2, and 1,4-dioxane dried over Na/molecular sieves were prepared by distillation under a nitrogen atmosphere. IR spectra were recorded on a NICOLER FT-IR spectrometer. All the polymer-bound intermediates were monitored by FT-IR spectroscopy. The final products were purified by solid-supported liquid−liquid extraction (SLE) with a fritted vessel previously packed with "Varian's Hydromatrix " (diatomaceous earth). Flash column chromatography was performed using silica gel 230−400 mesh (flash) from EM Science; analytical thin-layer chromatography was carried out on precoated plates (Merck silica gel 60, GF_{254}). ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200, Bruker WH Avance 300, and Varian Unity 400 MHz spectrometers using tetramethyl silane (TMS) as an internal standard. Chemical shifts were reported in parts per million (ppm) downfield from tetramethyl silane. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants are reported in hertz (Hz). High-resolution mass spectra were recorded on a QSTAR XL MS/MS system (Biosciences, USA) in the ESI mode. HPLC data of final crude samples were performed on a Shimadzu LC-10AT VP system controller instrument. The yield for purified products was determined on the basis of the loading of the polymeric-support starting from the Marshall's linker resin. The following abbreviations were used: EDC = *N*-[3-dimethylaminopropyl)-*N*-ethylcarbodiimide, DMAP = *N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, EtOH = ethanol, and Py = pyridine.

Preparation of Polymer-Bound *N*-(*tert*-Butoxycarbonyl)-2-aminonicotinate 3. 4-Hydroxyphenylsulfide resin **1** (20 g, 660 mmol, 100 mol %) was swollen with 40 mL of CH_2Cl_2. Scaffold **2** (47.12 g, 1.98 mol) and EDC (30.7 g, 1.98 mol) were dissolved in the minimum volume of CH_2Cl_2/DMF (1:1) required for complete dissolution. The activated scaffold solution was added to the resin, followed by the addition of a slurry of DMAP (40 mg, 10 mol %) in 2 mL of CH_2Cl_2. The reaction vessel was shaken for 48 h, and then the resin was washed with CH_2Cl_2 (2 × 15 mL), DMF (2 × 15 mL), MeOH (2 × 15 mL), DMF (2 × 15 mL), and CH_2Cl_2 (3 × 15 mL) to afford the polymer-bound *N*-(*tert*-butoxycarbonyl)-2-aminonicotinate **3**. The resin was dried in vacuo overnight and analyzed by FT-IR: 1722, 1664 cm^{-1}.

Preparation of Polymer-Bound 2-Aminonicotinate 3a. The resin-bound *N*-(*tert*-butoxycarbonyl)-2-aminonicotinate **3** (27.92 g) was washed with 1,4-dioxane (2 × 50 mL) and then treated with a solution of 4 N HCl in 1,4-dioxane (50 mL), and the resin was washed with CH_2Cl_2 (2 × 15 mL), DMF (2 × 15 mL), MeOH (2 × 15 mL) to give the polymer-bound 2-aminonicotinic acid **3a**, which was analyzed by FT-IR: 1722 cm^{-1}.

General Procedure for the Preparation of Polymer-Bound Substituted Imidazo[1,2-*a*]pyridine-8-carboxylates 5{*1*−*5*}. The polymer-bound 2-aminonicotinate **3a** (5.67 g, 1 equiv) was treated with various α-haloketones (XCH_2COR) **4**{*1-5*} (3 equiv) in EtOH (25 mL), and the solvent−resin suspension was refluxed for 24 h. After it was cooled, the support was washed with H_2O (3 × 15 mL) and CH_2Cl_2 (3 × 15 mL) to afford the polymer-bound substituted imidazo-[1,2-*a*]pyridine-8-carboxylates **5**{*1-5*} in a 50−65% yield.

General Procedure for the Preparation of Polymer-Bound 3-Bromo-Substituted Imidazo[1,2-*a*]pyridine-8-carboxylates 6{*1*−*5*}. The polymer-bound imidazo[1,2-*a*]pyridine-8-carboxylates **5**{*1*−*5*} (1 equiv) were swelled in EtOH (20 mL). To this resin, *N*-bromosuccinimide (1.3 equiv) was added at ambient temperature, and the suspension was stirred under reflux for 3 h. The solid-support was washed with H_2O (3 × 10 mL), CH_2Cl_2 (2 × 10 mL), and MeOH (3 × 10 mL) to afford the polymer-bound 3-bromo-substituted imidazo[1,2-*a*]pyridine-8-carboxylates **6**{*1*−*5*}.

General Procedure for the Preparation of Polymer-Bound 3-Chloro-Substituted Imidazo[1,2-*a*]pyridine-8-carboxylates 7{*1*−*5*}. The polymer-bound substituted imidazo[1,2-*a*]pyridine-8-carboxylates **5**{*1*−*5*} (1 equiv) were swelled in EtOH (20 mL). To this resin, *N*-chlorosuccinimide (1.3 equiv) was added at ambient temperature, and the suspension was stirred under reflux for 3 h. The solid-support was washed with H_2O (3 × 10 mL), CH_2Cl_2 (2 × 10 mL), and MeOH (3 × 10 mL) to afford the polymer-bound 3-chloro-substituted imidazo[1,2-*a*]pyridine-8-carboxylates **7**{*1*−*5*}.

General Procedure for the Cleavage of Imidazo[1,2-*a*]pyridines 5{*1*} and Preparation of *N*8-Propyl-2-methylimidazo[1,2-*a*]pyridine-8-carboxamide 9{*1, 1*}. Resin **5**{*1*} was divided into fifteen parts and each part (∼ 0.125 mmol) was suspended in pyridine to effect complete solvation. Each portion of the resin was then treated with an amine **8**{*1*−*15*} in pyridine (1.4 mL; 0.625 mmol, ∼500 mol %). The resin slurry was then shaken for 18−24 h on a platform shaker. The solution was collected, and the resin washed with MeOH (2 × 5 mL). The combined filtrate and washings were concentrated in vacuo. For example, to a suspension of polymer-bound 2-methylimidazo[1,2-*a*]pyridine-8-carboxylate **5**{*1*} (117 mg, 0.146 mmol) in pyridine (5 mL) was added propylamine **8**{*1*} (1.4 mL; 0.80 mmol, ∼ 400 mol %) in pyridine, and the mixture was agitated at room temperature for 18 h. The solvent was removed from the solid-support by filtration, and the resin was washed with CH_2Cl_2. The filtrate and washings were concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3 mL) and added to Varian Hydromatrix media (diatomaceous earth), previously treated with 1 mL of 2 M HCl or water, in a fritted reaction vessel. The CH_2Cl_2 filtrate was collected, and the source vessel was washed with further CH_2Cl_2 (2 × 1 mL). The combined organic solutions were concentrated in vacuo to give the crude imidazo[1,2-*a*]pyridine-8-carboxamide **9**{*1, 1*}. The final product **9**{*1, 1*} was purified by flash chromatography (elution solvent 20% EtOAc in hexane). Yield: 13 mg (50%). ^1H NMR (300 MHz, $CDCl_3$): δ 10.20 (bs, 1H), 8.10 (d, J = 6.79 Hz, 2H), 7.34 (s, 1H), 6.86 (t, J = 7.55 Hz, 1H), 3.50 (q, 2H), 2.46 (s, 3H), 1.68−1.80 (m, 2H), 1.06 (t, J = 7.55 Hz, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$): δ 163.0, 142.8, 127.0, 126.50, 120.0, 113.35, 111.0, 109.40, 68.5, 66.0, 40.80, 22.30, 13.50, 11.20. FT-IR: 3443.3, 2927.1, 1657.9, 1560.8 cm^{-1}. Purity: 80%. R_t: 7.11 min. HRMS (ESI) calcd for $C_{12}H_{16}N_3O$: $[M + H]^+$ 218.1293. Found: 218.1289.

***N*8,*N*8-Diisopropyl-2-phenylimidazo[1,2-*a*]pyridine-8-carboxamide 9{*2, 2*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 2-phenylimidazo[1,2-*a*]pyridine-8-carboxylate **5**{*2*} (129 mg, 0.183 mmol) and *N*,*N*-diisopropyl amine **8**{*2*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method, and the compound was further purified by flash chromatography (elution solvent 25% EtOAc in hexane) to afford the **9**{*2, 2*}. Yield: 38 mg (65%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 6.94 Hz, 1H), 7.96−7.78 (m, 4H), 7.40−7.20 (m, 3H), 6.72 (t, J = 6.94 Hz, 1H), 3.80−3.50 (m, 2H), 1.50 (d, J = 6.79 Hz, 6H), 1.20 (d, J = 6.79 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 148.57, 129.79, 128.20, 114.21, 112.49, 107.63, 99.08, 80.64, 34.99, 19.43, 11.20. FT-IR: 3399.9, 2961.6, 1623.0, 1304.1 cm^{-1}. Purity: >88%. R_t: 9.84 min. HRMS (ESI) calcd for $C_{20}H_{24}N_3O$: $[M + H]^+$ 322.1919. Found: 322.1907.

[2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-8-yl][4-(2-methoxyphenyl)piperazino]methanone 9{*3, 3*}. This compound was prepared as described earlier for compound **9**{*1, 1*} with 2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-8-carboxylate **5**{*3*} (132 mg, 0.165 mmol) and 1-(2-methoxyphenyl)-piperazine **8**{*3*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method, and the compound was further purified by flash chromatography (elution solvent 40% EtOAc in hexane) to afford the **9**{*3, 3*}. Yield: 44 mg (60%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 6.61 Hz, 1H), 7.90−7.75 (m, 3H), 7.41−7.25 (m, 3H), 7.00−6.75 (m, 5H), 4.13−4.05 (m, 2H), 3.85 (s, 3H), 3.70−3.45 (m, 2H), 3.26−3.00 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 152.2, 149.9, 134.1, 132.1, 131.4, 130.5, 129.0, 127.5, 126.8, 124.5, 123.6, 121.2, 118.6, 112.4, 111.4, 55.5, 53.2, 51.2, 47.8, 42.2. FT-IR: 2924.6, 1635.0, 1499.6, 1241.6 cm^{-1}. Purity: >54%. R_t: 7.47 min. HRMS (ESI) calcd for $C_{25}H_{14}N_3O_2Cl$: $[M + H]^+$ 447.1587. Found: 447.1598.

***N*8-(2,2,2-Trifluoroethyl)-2-(4-methylphenyl)imidazo-[1,2-*a*]pyridine-8-carboxamide 9{*4, 4*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-8-carboxylate **5**{*4*} (127 mg, 0.146 mmol) and 2,2,2-trifluoro-1-ethanamine **8**{*4*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method, and the compound was further purified by flash chromatography (elution solvent 22% EtOAc in hexane) to afford the **9**{*4, 4*}. Yield: 30 mg (62%). ^1H NMR (300 MHz, $CDCl_3$): δ 10.95 (bs, 1H), 8.23−8.15 (m, 2H), 7.84 (s, 1H), 7.74 (d, J = 7.55 Hz, 2H), 7.29−7.17 (m, 2H), 6.93 (t, J = 6.79 Hz, 1H), 4.20−4.31 (m, 2H), 3.10−3.15 (bs, 1H), 2.40 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.5, 151.5, 138.4, 137.2, 128.4, 124.1, 122.0, 113.3, 112.1, 110.2, 103.7, 36.1, 23.2. FT-IR: 3447.1, 2923.5, 1667.2, 1625.3, 1162.4 cm^{-1}. Purity: >77%. R_t: 5.58 min. HRMS (ESI) calcd for $C_{17}H_{15}F_3N_3O$: $[M + H]^+$ 334.1167. Found: 334.1154.

***N*8-(2-Furylmethyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-8-carboxamide 9{*5, 5*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-8-carboxylate **5**{*5*} (140 mg, 0.220 mmol) and 2-furylmethanamine **8**{*5*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method, and the compound was further purified by flash chromatography (elution solvent 18% EtOAc in hexane) to afford **9**{*5, 5*}. Yield: 77 mg (68%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (bs, 1H), 8.10−8.02 (m, 2H), 7.71−7.65 (m, 2H), 7.54−7.51 (m, 2H), 6.95−6.86 (m, 4H), 4.22 (d, J = 5.28 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 160, 151.8, 151.8, 145, 143.2, 130.9, 128.9, 128.1, 127.5, 127.3, 125.5, 114.2, 112.1, 110.5, 107.5, 107.1, 55.2, 37.1. FT-IR: 3233.9, 2923.9, 1660.8, 1299 cm^{-1}. Purity: >82%. R_t: 8.37 min. HRMS (ESI) calcd for $C_{20}H_{18}N_3O_3$: $[M + H]^+$ 348.1348. Found: 348.1338.

***N*8-Cyclohexyl-3-bromo-2-methylimidazo[1,2-*a*]pyridine-8-carboxamide 10{*1, 6*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-bromo-2-methylimidazo[1,2-*a*]pyridine-8-carboxylate **6**{*1*} (117 mg, 0.146 mmol) in pyridine (5 mL) and cyclohexylamine **8**{*6*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 15% EtOAc in hexane) to afford the **10**{*1, 6*}. Yield: 25 mg (52%). ^1H NMR (300 MHz, $CDCl_3$): δ 9.90−10.10 (bs, 1H), 8.23−8.10 (m, 2H), 7.03 (t, J = 6.78 Hz, 1H), 4.12−4.08 (m, 1H), 2.48 (s, 3H), 2.10−1.95 (m, 2H), 1.86−1.75 (m, 1H), 1.56−1.40 (m, 5H), 1.35−1.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6, 142.1, 141.0, 126.4, 124.6, 119.2, 92.8, 76.4, 75.4, 47.0, 31.6, 23.2, 12.4. FT-IR: 3446.9, 2924.6, 1636.5, 1467.6 cm^{-1}. Purity: >86%. R_t: 13.08 min. HRMS (ESI) calcd for $C_{15}H_{19}BrN_3O$: $[M + H]^+$ 336.0711. Found: 336.0705.

***N*8,*N*8-Dibutyl-3-bromo-2-phenylimidazo[1,2-*a*]pyridine-8-carboxamide 10{*2, 7*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-bromo-2-phenylimidazo[1,2-*a*]pyridine-8-carboxylate **6**{*2*} (129 mg, 0.183 mmol) and *N*,*N*-dibutylamine **8**{*7*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 35% EtOAc in hexane) to afford the **10**{*2, 7*}. Yield: 52 mg (66%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, J = 6.04 Hz, 1H), 8.17 (d, J = 9.08 Hz, 2H), 7.96 (t, J = 8.30 Hz, 1H), 7.45−7.32 (m, 3H), 6.97 (t, J = 6.79 Hz, 1H), 4.50 (q, J = 6.79 Hz, 2H), 4.45 (q, J = 6.79 Hz, 2H), 1.50 (t, J = 6.79 Hz, 4H), 1.40 (t, J = 6.79 Hz, 4H), 0.95−0.83 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166, 142.5, 141, 133.5, 132.3, 127.8, 127.4, 126.8, 123.8, 123.5, 122.8, 118.5, 112.2, 99.5, 48, 44, 36.5. FT-IR: 2924.8, 1635, 1603.3, 1459.8 cm^{-1}. Purity: >93%. R_t: 12.14 min. HRMS (ESI) calcd for $C_{22}H_{27}BrN_3O$: $[M + H]^+$ 428.1337. Found: 428.1338.

***N*8-(2-Methoxyethyl)-3-bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-8-carboxamide 10{*3, 8*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-8-carboxylate **6**{*3*} (132 mg, 0.158 mmol) and 2-methoxy-1-ethanamine **8**{*8*} (~500 mol %) in pyridine. The excess

amine was removed by the SLE method and further purified by flash chromatography (elution solvent 20% EtOAc in hexane) to afford the **10**{*3, 8*}. Yield: 37 mg (58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.33 (bs, 1H), 8.25−8.27 (m, 2H), 8.15 (d, J = 8.61 Hz, 2H), 7.43 (d, J = 8.61 Hz, 2H), 7.09 (t, J = 6.69 Hz, 1H), 3.76 (q, 2H), 3.65 (t, J = 4.78 Hz, 2H), 3.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 142.8, 140.1, 134.2, 128.4, 128.2, 125.8, 120.7, 112.6, 92, 70.6, 58.4, 39.2, 29.1. FT-IR: 2921.2, 1659.6, 1555.2, 1464 cm^{-1}. Purity: >97%. R_t: 7.45 min. HRMS (ESI) calcd for $C_{17}H_{16}BrClN_3O_2$: $[M + H]^+$ 408.0114. Found: 408.0120.

N*8-(2-Chlorobenzyl)-3-bromo-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-8-carboxamide 10**{4, 9***}**.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-bromo-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-8-carboxylate **6**{*4*} (127 mg, 0.141 mmol) and (2-chlorophenyl)methanamine **8**{*9*} (∼500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 33% EtOAc in hexane) to afford the **10**{*4, 9*}. Yield: 40 mg (64%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.7−10.6 (m, 1H), 8.29 (m, 2H), 7.95 (d, J = 8.68 Hz, 2H), 7.60−7.50 (m, 1H), 7.41−7.33 (m, 1H), 7.26−7.17 (m, 4H), 7.08 (t, J = 6.50 Hz, 1H), 4.83 (d, J = 5.78 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.5, 152.8, 145, 143.4, 142, 128.5, 127.6, 127.2, 125.5, 114.1, 112, 110.5, 107.4, 107.1, 55.4, 37. FT-IR: 3429.8, 2923.5, 1661.5, 1552.6, 1442.8 cm^{-1}. Purity: >93%. R_t: 10.5 min. HRMS (ESI) calcd for $C_{22}H_{18}BrClN_3O$: $[M + H]^+$ 454.0321. Found: 454.0316.

N*8-Benzyl-*N*8-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-8-carboxamide 10**{5, 10***}**.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]-pyridine-8-carboxylate **6**{*5*} (140 mg, 0.214 mmol) and *N*-benzyl-*N*-methylamine **8**{*10*} (∼500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 34% EtOAc in hexane) to afford the **10**{*5, 10*}. Yield: 67 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20−8.08 (m, 3H), 7.60 (d, J = 7.43 Hz, 1H), 7.42−7.23 (m, 5H), 7.02−6.92 (m, 3H), 4.70 (d, J = 8.49 Hz, 2H), 3.90 (s, 3H), 2.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 158.4, 142.0, 134.6, 128.2, 128.0, 127.60, 126.8, 126.0, 123.5, 122.6, 112.80, 115.5, 90.5, 54.4, 54.0, 35.4. FT-IR: 3421.9, 2926.1, 1638.4, 1608.7, 1536.3, 1478.9 cm^{-1}. Purity: >67%. R_t: 8.09 min. HRMS (ESI) calcd for $C_{23}H_{21}BrN_3O_2$: $[M + H]^+$ 450.0817. Found: 450.0823.

N*8-Butyl-3-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxamide 11**{1, 11***}**.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-chloro-2-methylimidazo[1,2-*a*]pyridine-8-carboxylate **7**{*1*} (117 mg, 0.143 mmol) and *N*-butylamine **8**{*11*} (∼500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 15% EtOAc in hexane) to afford **11**{*1, 11*}. Yield: 20 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (s, 1H), 8.11 (d, J = 6.73 Hz, 2H), 6.85 (t, J = 6.73 Hz, 1H), 3.52 (q, J = 6.73 Hz, 2H), 2.45 (s, 3H), 1.76−1.40 (m, 4H), 0.99 (t, J = 6.50 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 142.8, 128.8, 128.0, 126.3, 125.8, 120.4, 112.6, 111.1, 110.4, 108.6, 39.4, 31.5, 20.3, 15.0, 13.4. FT-IR: 3202.3, 2960.0, 2927.1, 1652.1, 1569.3 cm^{-1}. Purity: >94%. R_t: 10.09 min. HRMS (ESI) calcd for $C_{13}H_{17}ClN_3O$: $[M + H]^+$ 266.1060. Found: 266.1053.

N*8,*N*8-Diethyl-3-chloro-2-phenylimidazo[1,2-*a*]pyridine-8-carboxamide 11**{2, 12***}**.** This compound was prepared as described earlier for compound **9**{***1, 1***} with 3-chloro-2-phenylimidazo[1,2-*a*]pyridine-8-carboxylate **7**{*2*} (122 mg, 0.141 mmol) and *N*,*N*-diethylamine **8**{*12*} (∼500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 33% EtOAc in hexane) to afford **11**{*2, 12*}. Yield: 28 mg (63%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.14−8.12 (m, 3H), 7.44 (t, J = 6.79 Hz, 2H), 7.37−7.31 (m, 1H), 7.26−6.95 (t, J = 6.79 Hz, 2H), 3.70 (q, J = 6.79 Hz, 2H), 3.28 (q, J = 6.79 Hz, 2H), 1.36 (t, J = 7.54 Hz, 3H), 1.17 (t, J = 7.54 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166, 140.2, 132.5, 129.5, 128.6, 127.5, 126.6, 124, 121.8, 113.6, 111.5, 106.2, 100, 43.2, 39.5, 13.8, 13.6. FT-IR: 2973.9, 2930.8, 1635.4, 1353.2 cm^{-1}. Purity: >93%. R_t: 9.59 min. HRMS (ESI) calcd for $C_{18}H_{19}ClN_3O$: $[M + H]^+$ 328.1216. Found: 328.1209.

N*8-Methyl-*N*8-phenyl-3-chloro-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-8-carboxamide 11**{3, 13***}**.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-chloro-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-8-carboxylate **7**{*3*} (132 mg, 0.158 mmol) and *N*-methyl-*N*-phenylamine **8**{*13*} (∼500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 18% EtOAc in hexane) to afford **11**{*3, 13*}. Yield: 38 mg (62%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (d, J = 8.48 Hz, 2H), 7.59 (d, J = 6.78 Hz, 1H), 7.41 (d, J = 8.48 Hz, 2H), 7.33−7.05 (m, 6H), 6.84−6.77 (m, 1H), 3.70 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.7, 130.9, 129.8, 127.6, 125.9, 125.4, 124.4, 123.2, 121.7, 113.1, 110.9, 99.8, 51. FT-IR: 1651.7, 1493.8 cm^{-1}. Purity: >98%. R_t: 12.07 min. HRMS (ESI) calcd for $C_{21}H_{16}Cl_2N_3O$: $[M + H]^+$ 396.0670. Found: 396.0675.

N*8-Isopropyl-*N*8-phenyl-3-chloro-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-8-carboxamide 11**{4, 14***}**.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-chloro-2-(4-methylphenyl)imidazo[1,2-*a*]-pyridine-8-carboxylate **7**{*4*} (127 mg, 0.140 mmol) and *N*-isopropyl-*N*-phenylamine **8**{*14*} (∼500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 26% EtOAc in hexane) to afford **11**{*4, 14*}. Yield: 37 mg (66%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (d, J = 8.48 Hz, 2H), 7.82 (d, J = 6.78 Hz, 1H), 7.27−6.92 (m 8H), 6.66 (t, J = 6.78 Hz, 1H), 5.40−5.20 (m, 1H), 2.45 (s, 3H), 1.40−1.20 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.94, 143.1, 141.8, 138.7, 136.0, 133.82, 130, 129.5, 129.2, 128.7, 128.4, 127.6, 127.0, 126.3, 120.7, 112.7, 92.2, 41.8, 21.3. FT-IR: 3440.6, 2967, 2928.5, 1629.1, 1369.5 cm^{-1}. Purity: >97%. R_t: 9.67 min. HRMS (ESI) calcd for $C_{24}H_{23}ClN_3O$: $[M + H]^+$ 404.1529. Found: 404.1519.

***N*8-Cyclopropylmethyl-3-chloro-2-(4-methoxyphenyl)-imidazo[1,2-*a*]pyridine-8-carboxamide 11{*5, 15*}.** This compound was prepared as described earlier for compound **9**{*1, 1*} with 3-chloro-2-(4-methoxyphenyl)imidazo[1,2-*a*]-pyridine-8-carboxylate **7**{*5*} (140 mg, 0.215 mmol) and cyclopropylmethanamine **8**{*15*} (~500 mol %) in pyridine. The excess amine was removed by the SLE method and further purified by flash chromatography (elution solvent 23% EtOAc in hexane) to afford the **11**{5, *15*}. Yield: 52 mg (69%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.20 (bs, 1H), 8.19 (dd, $J^1 = 1.32$ Hz, $J^2 = 2.45$ Hz, 2H), 8.05 (d, $J = 9.06$ Hz, 2H), 7.06 (t, $J = 6.98$ Hz, 1H), 6.97 (d, $J = 8.87$ Hz, 2H), 3.87 (s, 3H), 3.46 (dd, $J^1 = 5.29$ Hz, $J^2 = 6.98$ Hz, 2H), 0.96−0.85 (m, 1H), 0.59−0.65 (m, 2H), 0.37−0.42 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.6, 160, 141.5, 138.9, 128.6, 127.9, 124.7, 124.3, 121, 114, 112.6, 55.6, 44.3, 29.5. FT-IR: 3448.3, 2922.8, 1663.37, 1614.54 cm^{-1}. Purity: >96%. R_t: 7.33 min. HRMS (ESI) calcd for $C_{19}H_{19}ClN_3O_2$: $[M + H]^+$ 356.1165. Found: 356.1169.

Acknowledgment. We are thankful to CSIR, New Delhi for the award of research fellowships to V.D., K.L.R., Rajendar, R.V.C.R.N.C.S. and N.S..

Supporting Information Available. FT-IR spectra for selected resin-bound intermediates, experimental procedures of intermediate compounds, FT-IR, ^{1}H NMR, HRMS, and HPLC spectral data for selected library members, and structural, mass, and purity data of libraries **9**, **10**, and **11** (Table 2). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For a review, see: Kaldor, S. W.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 54−59.

(2) For a comprehensive survey of combinatorial library synthesis, see: Dolle, R. E.; Bourdonnec, B. L.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597−635.

(3) (a) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, D. R. S. *Mini-Rev. Med. Chem.* **2006**, *6*, 53−68. (b) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Rao, M. V. *Mini-Rev. Med. Chem.* **2006**, *6*, 69−87. (c) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, G. S. K.; Ragavan, S. *J. Comb. Chem.* **2007**, *9*, 29−42.

(4) Harrison, T. S.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65−89.

(5) Ueda, T.; Mizusgige, K.; Yukiiri, K.; Takahashi, T.; Kohno, M. *Cerebrovasc. Dis.* **2003**, *16*, 396−401.

(6) (a) Zuang, Z.-P.; Kung, M.-P.; Wilson, A.; Lee, C.-W.; Plossl, K.; Hou, C.; Holzman, D. M.; Kung, H. F. *J. Med. Chem*. **2003**, *46*, 237−243. (b) Colletti, S. L.; Frie, J. L.; Dixon, E. C.; Singh, S. B.; Choi, B. K.; Scapin, G.; Fitzgerald, C. E.; Kumar, S.; Nichols, E. A.; O'Keefe, S. J.; Neill, E. A.; Porter, G.; Samual, K.; Schmatz, D. M.; Scwartz, C. D.; Shoop, W. L.; Thompson, C. M.; Thompson, J. E.; Wang, R.; Woods, A.; Zaller, D. M.; Doherty, J. B. *J. Med. Chem.* **2003**, *46*, 349−352.

(7) Clements-Jewery, S.; Danswan, G.; Gardner, C. R.; Matharu, S. S.; Murdoch, R.; Tully, W. R.; Westwood, W. *J. Med. Chem.* **1988**, *31*, 1220−1226.

(8) (a) Regoli, D.; Barabe, J. *Pharmacol. Rev.* **1980**, *32*, 1−46. (b) Marceau, F.; Lussier, A.; Regoli, D.; Giroud, J. P. *Gen. Pharmacol.* **1983**, *14*, 209−229. (c) Proud, D.; Kaplan, A. P. *Annu. Rev. Immunol.* **1988**, *6*, 49−83. (b) Dray, A.; Perkins, M. *Trends Neurosci.* **1993**, *16*, 99−104. (d) Greaves, M. W. *Br. J. Dermatol.* **1988**, *119*, 419−426. (e) Bhoola, K. D.; Figueroa, C. D.; Worthy, K. *Pharmacol. Rev.* **1992**, *44*, 1−80. (f) Farmer, S. G.; Burch, R. M. The Pharmacology of Bradykinin Receptors. In *Bradykinin Antagonists: Basic and Clinica Research*; Burch, R. M., Ed.; Marcel Dekker: New York, 1991; pp 1−31. (g) Burch, R. M.; Farmer, S. G.; Steranka, L. R. *Med. Res. Rev.* **1990**, *10*, 237−269.

(9) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K.; Inamura, N.; Asano, M.; Hatori, C.; Katayama, A.; Oku, T.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 564−578.

(10) (a) Amin, K.; Dahlstrom, M.; Nordberg, P.; Starke, I. International Patent WO 001000, 2000. (b) Farrerons Gallemi, C.; Miquel Bono, I. J.; Fernandez Serrat, A. M.; Monserrat Vidal, C.; Lagunas Arnal, C.; Gimenez Guasch, F.; Fenandez Garcia, A. International Patent WO 0008024, 2000. (c) Gueiffier, A.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J. C.; Kerbal, A.; Essassi, E. K.; Debouzy, J. C.; Witvrouw, M.; Blache, Y.; Balzarini, J.; De, Clercq, E.; Chapat, J. P. *J. Med. Chem.* **1996**, *39*, 2856−2859. (d) Silvestre, J.; Leeson, P. A.; Castaner, J. *Drugs Future* **1998**, *23*, 598−601. (e) Hamdouchi, C.; Blas, J.; Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50−59.

(11) (a) Kaminsky, J. J.; Doweyko, A. M. *J. Med. Chem.* **1997**, *40*, 427−436. (b) Rival, Y.; Grassy, G.; Michael, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170−1176. (c) Rewankar, G. R.; Matthews, J. R.; Robins, R. K. *J. Med. Chem.* **1975**, *18*, 1253−1255. (d) Beeswick, P. J.; Campbell, I. B.; Naylor, A. PCT Int. Patent Appl. WO 9 631 509, 1996; *Chem. Abstr.* **1997**, *126*, 8117j. (e) Abiegnente, E. *Actual. Chim. Ther.* **1991**, *18*, 1253−1255. (f) Franke, H.; Geisler, J.; Hartfiel, U.; Franke, W.; Dorfmeister, G.; Ganzer, M.; Johahann, G.; Rees, R. Ger. Offen. D., E. 4 120 108, 1991; *Chem. Abstr.* **1992**, *18*, 213075v. (g) Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Dubinsky, B.; Moore, J. B., Jr. *J. Med. Chem.* **1988**, *31*, 2221−2227. (h) Byth, K. F.; Culshaw, J. D.; Green, S.; Oakes, S.; Thomas, A. P. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 2245−2248. (i) Humphries, A. C.; Gancia, E.; Gilligan, M. T.; Goodacre, S.; Hallett, D.; Merchant, K. J.; Thomas, S. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1518−1522.

(12) (a) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269−2271. (b) Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495−1500. (c) Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469−5472. (d) Chen, Y.; Lam, Y.; Lai, Y. H. *Org. Lett.* **2002**, *4*, 3935−3937. (e) Kazzouli, S. El.; Berteina-Raboin, S.; Mouaddibb. A.; Guillaumet. G. *Tetrahedron Lett.* **2003**, *44*, 6265−6267. (f) Kazzouli, S. E.; Berthault, A.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Lett. Org. Chem.* **2005**, *2*, 184−187.

(13) (a) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055−3056. (b) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172. (c) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Comm.* **1971**, 636−637. (d) Osapay, G.; Taylor, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6046−6051. (e) Degrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295−1300.

(14) Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867−878.

(15) (a) Johnson, C. R.; Zang, B.; Fantauzzi, P.; Hockker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097−4106. (b) Breitenbucher, J. G.; Hui, H. C. *Tetrahedron Lett.* **1998**, *39*, 8207−8210. (c) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295−1298. (d) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−1294. (e) Boldi, A. M.; Dener, J. M.; Hopkins, T. P. *J. Comb. Chem.* **2001**, *3*, 367−373. (f) Breitenbucher, J. G.; Arienti, K. L.; McClure, K. J. *J. Comb. Chem.* **2001**, *3*,

528−533. (g) Bunin, B. A.; Dener, J. M.; Kelly, D. E.; Paras, N. A.; Tario, J. D.; Tushup, S. P. *J. Comb. Chem.* **2004**, *6*, 487−496. (h) Kane, T. R.; Ly, C. Q.; Kelly, D. E.; Dener, J. M. *J. Comb. Chem.* **2004**, *6*, 564−572.

(16) (a) Strazzolini, P.; Melloni, T.; Giumanini, A. *Tetrahedron* **2001**, *57*, 9033−9043. (b) Ponnusamy, E.; Fotadar, U.; Spisni, A.; Fiat, D. *Synthesis* **1986**, 48−49.

(17) Analytical HPLC of final crude samples was performed on a Shimadzu LC-10AT VP system controller instrument equipped with a Luna 5μ C18 (2), 250 × 4.6 mm column; linear gradient over 30 min using 0.01 M NH_4OAc−methanol (30:70 v/v), with a flow rate of 1.5 mL/min and UV absorbance at 220 and 254 nm.

CC060141I