Pergamon

Tetrahedron 58 (2002) 2095–2100

TETRAHEDRON

Solid-phase parallel synthesis of substituted dihydroimidazolyl dihydrobenzimidazol-2-ones

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

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

Received 5 December 2001; accepted 22 January 2002

Abstract—The solid-phase synthesis of substituted (4,5-dihydro-1*H*-imidazole-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-ones is described. Following the amide reduction of a resin-bound (MBHA resin) amino acid, the primary amine was selectively acylated with 4-fluoro-3-nitrobenzoic acid. Treatment with $POCl_3$, displacement of the fluoro group, and reduction of the nitro group generated an *o*-dianiline. Cyclization with 1,1-carbonyldiimidazole resulted in a benzimidazolone analogue, which was subsequently *N*-alkylated with an alkyl halide. The compounds were cleaved from the solid-support using anhydrous HF and characterized by LC–MS and ^1H and ^{13}C NMR spectroscopy.

1. Introduction

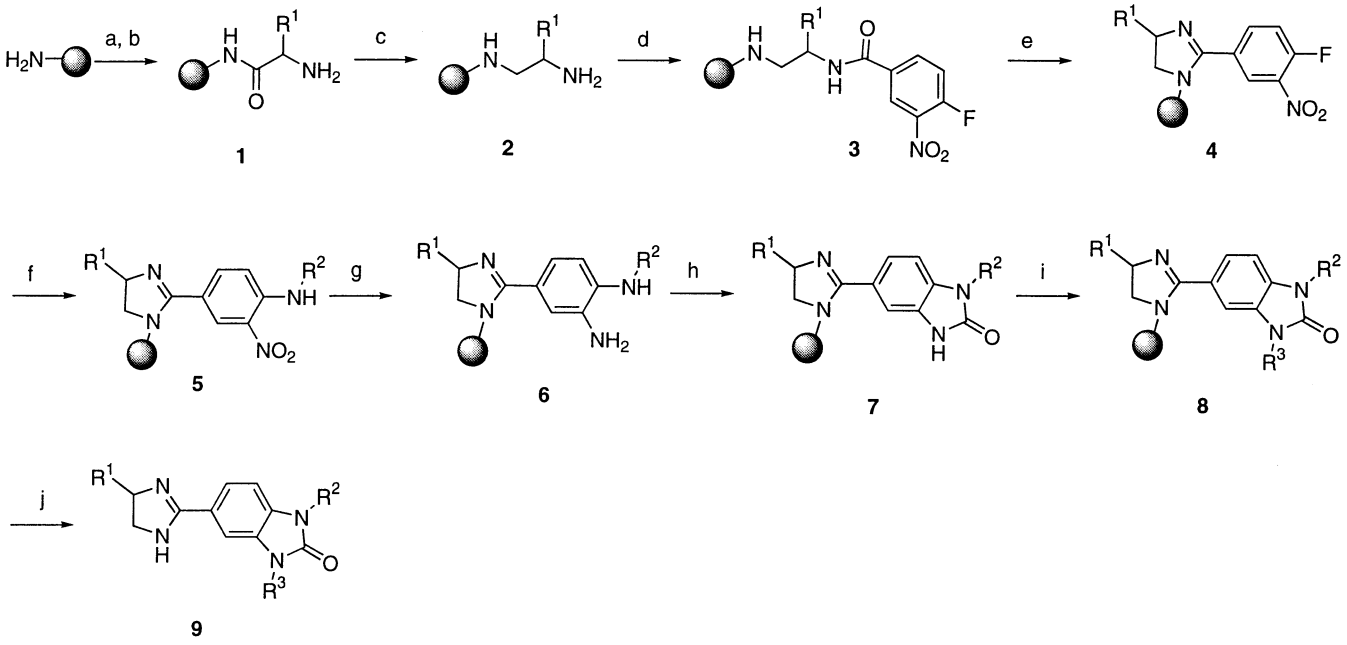
The effectiveness of some well known drugs (for example, the antimalarial drug chloroquine) has been undermined due to drug-resistant bacterial strains[1] that necessitate the discovery of newer therapeutic compounds. Development of solid-phase synthetic techniques for the synthesis of compounds ranging from peptides[2] to heterocycles[3] has expedited the process of drug discovery. Benzimidazolones are a unique class of building blocks exhibiting potent biological properties. Benzimidazolones are reported to be the first potent opioid receptor-like (ORL-1) antagonists active at nanomolar concentration[4] and also act as good NMDA (*N*-methyl-D-aspartate) antagonists.[5] Examples of additional properties include activation of cystic fibrosis transmembrane regulator (CFTR) and as potent Ca^{2+} activated potassium channel openers.[1] Examples of pharmacologically active dihydroimidazoles (imidazolines) include α-receptor agonists/antagonists, α-adrenergic inhibitors, vasodepressor agents, sympathomimetic agents, antihistaminic agents, antihypertensive agents,[6] anticancer agents,[7] and potent antihyperglycemic agents.[8] Considering the diverse biological and pharmacological activities of both benzimidazolones and dihydroimidazoles described above, development of solid-phase synthetic strategies of substituted (4,5-dihydro-1*H*-imidazole-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-ones were explored.

2. Results and discussion

A Boc-L-amino acid was coupled to *p*-methylbenzhydrylamine (MBHA) resin sealed inside a polypropylene mesh packet,[9] followed by deprotection of the Boc group to generate the compound **1** (Scheme 1). Exhaustive reduction of the resin-bound amino acid **1** by treatment with BH_3–THF[10] generated diamine **2** having both a primary amine and a secondary amine. The primary amine of the resin-bound diamine **2** was selectively *N*-acylated with 4-fluoro-3-nitrobenzoic acid in the presence of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*′-diisopropylethylamine (DIEA).[11] The resulting N-terminal acylated diamine **3** was treated with phosphorous oxychloride ($POCl_3$) to generate the dihydroimidazole analogue **4** via cyclodehydration of the in situ formed imidoyl chloride intermediate.[12,13] A negligible amount of racemization as detected by ^1H NMR was observed for compound **4** following cleavage and purification (i.e. at the carbon bearing R^1) in conformity with our earlier observations.[11,14] The resin-bound dihydroimidazole analogue was treated with a primary amine in the presence of DIEA to generate an *o*-nitroaniline **5** by displacement of the fluoro group.[11] Reduction of the nitro group with tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$) in DMF[11] generated *o*-dianiline **6**, which was treated with 1,1′-carbonyldiimidazole ($COIm_2$) to obtain benzimidazolone derivative **7**. Complete cyclization was observed by LC–MS under these experimental conditions. In order to introduce a third position of diversity into the resin-bound benzimidazolone derivative **7**, *N*-alkylation at the anilide nitrogen was desired. Alkylation was carried out with an alkyl halide (R^3X, X=Br, I) in the presence of base. Several different bases were tested. Primarily starting material was obtained when alkylation was carried out in the presence of DIEA

Keywords: solid-phase synthesis; dihydroimidazole; imidazoline; benzimidazolone.
* Corresponding author. Tel.: +1-858-455-3803; fax: +1-858-455-3804; e-mail: rhoughten@tpims.org

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00104-7



Scheme 1. Boc-NHCH(R^1)CO_2H (6 equiv., 0.1 M, DMF), DIC (6 equiv.), HOBt (6 equiv.), 2 h, 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) 4-fluoro-3-nitrobenzoic acid (3 equiv., 0.06 M, DMF), HBTU (3 equiv.), DIEA (6 equiv.), 3 h, rt; (e) $POCl_3$ (10 equiv., 0.09 M, anhydrous dioxane), 110°C, 2.5 h; (f) R^2NH_2 (20 equiv., 0.2 M, DMF), DIEA (20 equiv.), 20 h, rt; (g) $SnCl_2{\cdot}2H_2O$ (20 equiv., 0.5 M, DMF), 14 h, rt; (h) $COIm_2$ (10 equiv., 0.1 M, DCM), overnight, rt; (i) DBU (10 equiv., 0.06 M, THF), 15 min, rt; R^3X (X=I, Br) (10 equiv., 0.06 M, THF), 2 h, rt, (a) and (b) were repeated twice; (j) HF, anisole, 0°C, 7 h.

and triethylamine (TEA). Alkylation using either NaH or lithium *tert*-butoxide as the base yielded undesirable by-products. Treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the alkyl halide was found to yield final products with improved purity. Thus, the resin-bound benzimidazolone derivative **7** was treated with DBU, followed by treatment with an alkyl halide to generate alkylated benzimidazolone **8**. The alkylation was repeated twice to ensure complete reaction. The final product was cleaved from the solid-support using anhydrous HF and extracted with 95% acetic acid in water to give compound **9**.

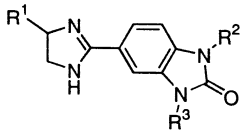
Thirty individual control compounds were prepared using 10 amino acids at the first (R^1) position of diversity, 15 amines at the second (R^2) position of diversity, and 8 alkyl halides at the third (R^3) position of diversity. Amino acids having either an extra amine functionality (e.g. ornithine, lysine) or generating an extra amine functionality after BH_3–THF reduction (e.g. glutamine) were not included due to undesirable *N*-acylation at the primary amine during acylation with 4-fluoro-3-nitrobenzoic acid (Scheme 1, step d).[11,13,14] Also, serine, threonine, aspartic acid, and glutamic acid analogues at the first (R^1) position of diversity yielded undesirable impurities during $POCl_3$ treatment (Scheme 1, step e).[11,13,14] Thus, these amino acid analogues were not included at the first (R^1) position of diversity. Twenty-two selected compounds are presented in Table 1. The compounds were obtained in moderate yield and purity (Table 1). The steric and electronic nature of alkyl halides (R^3X) at the third position of diversity influenced the purity of final products and also the type of final products (i.e. yielding either a monoalkylated product or a dialkylated product). The low purity of the final compounds is due to formation of undesirable dialkylated products. One representative LC–MS for compound **9h** is presented as Fig. 1. The compounds were purified by preparative HPLC and characterized by ^1H and ^{13}C NMR spectroscopy. Negligible amounts (<1%) of racemization as detected by ^1H NMR were observed for the final products.

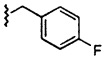
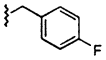
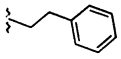
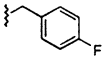
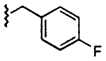
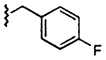
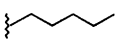
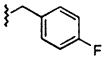
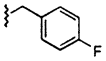
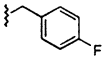
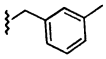
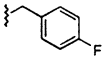
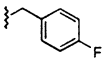
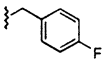
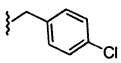
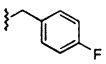
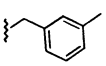
Appearance of two proton signals δ at 10.28 and 10.32 ppm (assigned with one proton each) in the ^1H NMR spectra of **7a** (R^1=–$CH(CH_3)_2$, R^2=–$(CH_2)_3CH_3$) following cleavage corresponded to the two (–NH) protons of the protonated dihydroimidazole.[13] In addition, appearance of a signal at 11.51 ppm in the ^1H NMR spectra of **7a** corresponded to the anilide proton. Disappearance of the proton signal δ at 11.51 ppm with retention of signals δ at 10.2–10.4 ppm in the ^1H NMR spectra for compound **9** indicated that alkylation occurred at the anilide nitrogen. Alkyl halides such as (*o*, *m*, and *p*)-cyanobenzyl bromide, 4-nitrobenzyl bromide, 3-chlorobenzyl bromide, 2,6-dichlorobenzyl bromide, and methyl iodide yielded dialkylated products (Fig. 2) as detected by LC–MS that corresponded to alkylation both at the anilide nitrogen and the dihydroimidazole moiety.[14] Appearance of a proton signal assigned to one proton δ at 10.23 ppm in the ^1H NMR spectra of dialkylated analogue derived from 4-nitrobenzyl bromide (**10**, Fig. 2, where R^1=–CH_3, R^2=–$(CH_2)_3CH_3$) supported the alkylation of the dihydroimidazole moiety[14] under these experimental conditions.

3. Conclusion

The solid-phase synthesis of substituted (4,5-dihydro-1*H*-imidazole-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-ones have been presented. Substituted dihydroimidazoles are prepared from the resin-bound reduced amino acids via cyclization of the in situ formed imidoyl chloride intermediates. These

Table 1. MW and RP-HPLC purity found for substituted (4,5-dihydro-1*H*-imidazole-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-ones **9**



Product	R^1	R^2	R^3	Yield[a]	MW (calcd)	MW (found)	Purity (%)[b]
9a				65	380.5	381.3 ($M+H^+$)	76
9b				68	408.5	409.3 ($M+H^+$)	78
9c				64	470.6	471.3 ($M+H^+$)	70
9d				66	474.5	475.3 ($M+H^+$)	65
9e				67	422.5	423.2 ($M+H^+$)	72
9f				68	394.5	395.2 ($M+H^+$)	76
9g				70	366.4	367.2 ($M+H^+$)	76
9h				72	382.4	383.3 ($M+H^+$)	80
9i				68	428.5	429.2 ($M+H^+$)	69
9j				65	444.5	445.2 ($M+H^+$)	78
9k				66	408.5	409.3 ($M+H^+$)	72
9l				68	448.9	449.2 ($M+H^+$)	63
9m				68	376.5	377.3 ($M+H^+$)	64
9n				68	376.5	377.3 ($M+H^+$)	60
9o				60	491.0	493.2 ($M+H^+$)	60
9p				62	462.6	463.2 ($M+H^+$)	52
9q				60	506.6	507.3 ($M+H^+$)	53
9r				62	422.5	423.3 ($M+H^+$)	55
9s				61	392.5	393.2 ($M+H^+$)	54
9t				65	312.4	313.2 ($M+H^+$)	52
9u				68	398.5	399.2 ($M+H^+$)	52
9v				64	418.6	419.3 ($M+H^+$)	55

[a] The yields (by weight) obtained were greater than 60–72% 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.

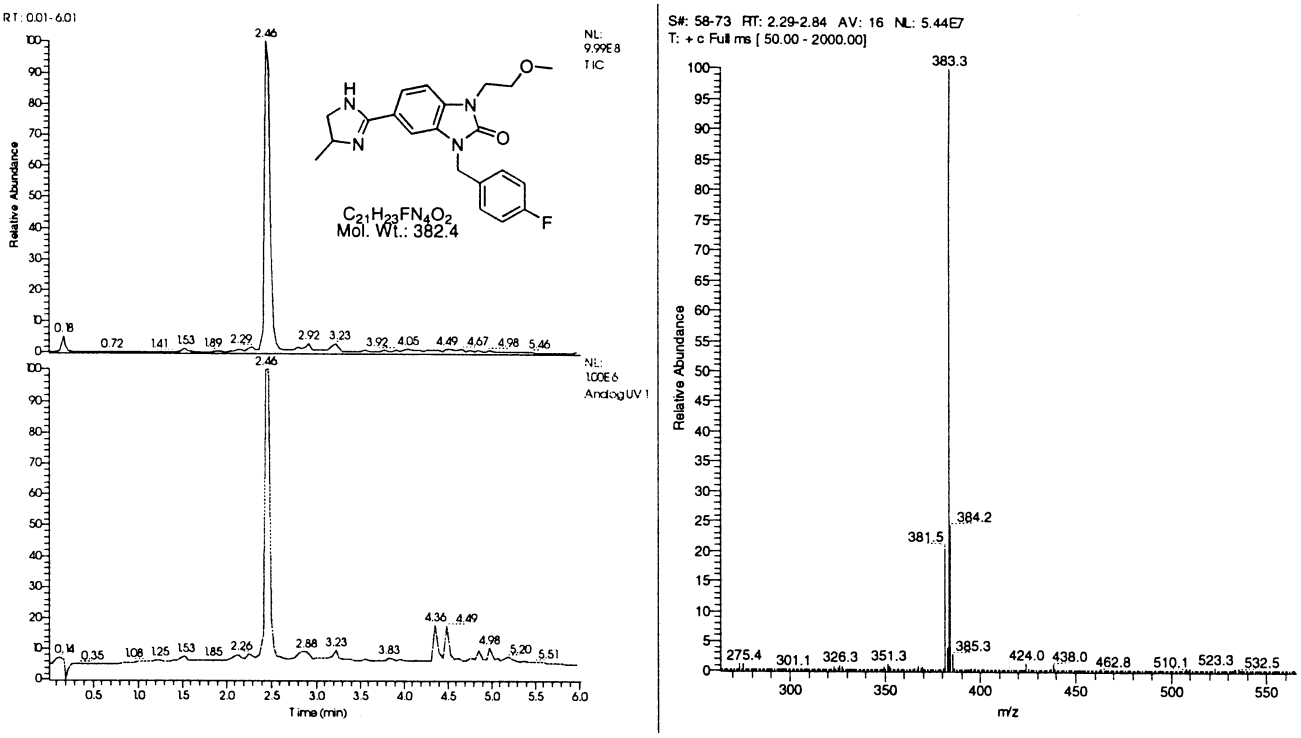


Figure 1. LC–MS of compound **9h** derived from L-Ala, 2-methoxyethylamine, 4-fluorobenzylamine for R^1, R^2, and R^3, respectively.

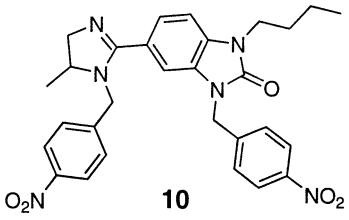


Figure 2. Structure of the dialkylated product (**10**), 1-butyl-5-[5-methyl-1-(4-nitrobenzyl)-4,5-dihydro-1*H*-imidazol-2-yl]-3-(4-nitrobenzyl)-1,3-dihydro-2*H*-benzimidazol-2-one.

approaches could be extended to prepare combinatorial libraries using the 'libraries from libraries' approach.[15]

4. Experimental

Boc-L-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). *p*-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100–200 mesh, 1.15 mequiv./g substitution) and *N,N'*-diisopropylcarbodiimide (DIC) were purchased from Chem Impex, Int. (Wood Dale, IL). HF was purchased from Air Products (San Marcos, CA). Alkyl halides 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 carried out using a Vydac 218TP54 C18 column of 0.46×25 cm^2. All HPLC experiments were performed using gradient conditions of two eluents: solvent A (H_2O with 0.05 % TFA) and solvent B (CH_3CN with 0.05% TFA). Flow rates were maintained at 1.0 and 6.0 mL/min for analytical and preparative chromatograms, respectively, at λ=214 nm. LC–MS (APCI) was recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100 A, 3×50 mm^2 column.

4.1. Typical procedure for the individual synthesis of substituted (4,5-dihydro-1*H*-imidazole-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-ones

100 mg of MBHA resin was sealed inside a polypropylene mesh packet.[9] 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.

(a) *Coupling of Boc-L-amino acid to MBHA resin*. Boc-L-amino acid (6 equiv., 0.1 M, DMF) was coupled to MBHA resin using DIC and HOBt (6 equiv. each) for 2 h at room temperature, followed by washes with DMF (3 times) and DCM (3 times). The Boc group was deprotected using 55% trifluoroacetic acid (TFA) in DCM for 30 min, followed by washes with DCM (2 times), IPA (2 times), and DCM (3 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.). Borane–THF complex (1 M, 40 equiv.) was added slowly. After cessation of hydrogen evolution, the resin packet 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.[10] Following washes with MeOH (4 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 was washed with DMF (4 times), DCM (4 times) and MeOH (2 times) and dried. (c) *Selective N-acylation at the primary amine with 4-fluoro-3-nitrobenzoic acid*. The resin-bound diamine was treated with 4-fluoro-3-nitrobenzoic acid (3 equiv., 0.06 M, DMF) in the presence of HBTU (3 equiv.) and DIEA (6 equiv.) for 3 h at room temperature. The resin was washed with DMF (4 times), DCM (2 times), IPA (2 times), and DCM (3 times). Completeness of the coupling was verified by the ninhydrin test.[16] (d) *Cyclization using $POCl_3$*. The dehydrative cyclization of the resin-bound amide was carried out in 50 mL conical tubes under nitrogen. To each tube the resin packet and $POCl_3$ (10 equiv., 0.09 M, anhydrous dioxane) was added. The capped tubes were heated at 110°C for 2.5 h. The resin was washed with dioxane, DMF and MeOH (5 times each), IPA (2 times), and DCM (3 times) and dried. (e) *Displacement of the fluoro group*. The resin-bound dihydroimidazole analogue **4** was treated with a primary amine (20 equiv., 0.2 M, DMF) in the presence of DIEA (20 equiv.) for 18 h at room temperature, followed by washes with DMF (4 times), DCM (2 times), IPA (2 times), and DCM (2 times). (f) *Reduction of the nitro group*. The resin-bound *o*-nitroaniline **5** was treated with tin(II) chloride dihydrate (20 equiv., 0.5 M in DMF) for 14 h at room temperature, followed by washes with DMF (8 times), MeOH (2 times), and DCM (3 times) to generate the *o*-dianiline analogue **6**. (g) *Formation of benzimidazolone*. The *o*-dianiline analogue **6** was cyclized by treatment with $COIm_2$ (10 equiv., 0.1 M, DCM, overnight), followed by washes with DCM (4 times), IPA (2 times), and DCM (3 times). (h) *Alkylation with an alkyl halide*. The resulting resin-bound benzimidazolone analogue **7** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10 equiv., 0.06 M, THF) for 15 min, followed by decantation of the base solution and treatment with an alkyl halide (R^3X, X=Br, I) (10 equiv., 0.06 M, THF) for 2 h at room temperature. Following decantation, the base and alkylation treatments were repeated twice and the resin was washed with DMF (4 times), DCM (2 times), IPA (2 times), and DCM (3 times).

All the resin-bound compounds were cleaved using anhydrous HF in the presence of anisole for 7 h at 0°C,[17] followed by extraction with 95% acetic acid in water and lyophilized.

4.1.1. 1-Butyl-5-(4-isopropyl-4,5-dihydro-1*H*-imidazol-2-yl]-1,3-dihydro-2*H*-benzimidazol-2-one (7a). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87–0.95 (m, 6H), 1.27–1.43 (m, 4H), 1.58–1.66 (m, 4H), 3.62–3.65 (m, 1H), 3.82–3.85 (m, 2H), 4.05–4.09 (m, 1H), 4.32–4.37 (m, 1H), 7.42–7.43 (d, *J*=7.9 Hz, 1H), 7.58 (s, 1H), 7.65–7.67 (d, *J*=7.8 Hz, 1H), 10.28 (s, 1H), 10.32 (s, 1H), 11.51 (s, 1H).

4.1.2. 1-Butyl-3-(4-fluorobenzyl)-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (9a). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, *J*=7.6 Hz, 3H), 1.26–1.31 (m, 2H), 1.34–1.36 (d, *J*=6.5 Hz, 3H), 1.64–1.67 (m, 2H), 3.55–3.59 (dd, *J*=8.0, 11.1 Hz, 1H), 3.93 (t, *J*=7.1 Hz, 2H), 4.10 (t, *J*=11.0 Hz, 1H), 4.45–4.47 (m, 1H), 5.04 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 7.35–7.38 (dd, *J*=5.6, 8.6 Hz, 2H), 7.53–7.55 (d, *J*=8.4 Hz, 1H), 7.71–7.75 (m, 2H), 10.27 (s, 1H), 10.38 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 0.9, 13.1, 13.5, 19.3, 20.5, 29.8, 40.6, 43.4, 50.9, 52.8, 107.4, 108.5, 115.5, 115.6, 122.8, 128.9, 129.3, 153.6, 163.6.

4.1.3. 1-Butyl-5-(4-*sec*-butyl-4,5-dihydro-1*H*-imidazol-2-yl)-3-(4-fluorobenzyl)-1,3-dihydro-2*H*-benzimidazol-2-one (9e). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87–0.93 (m, 6H), 1.15–1.19 (m, 2H), 1.26–1.31 (m, 3H), 1.48–1.52 (m, 2H), 1.63–1.70 (m, 3H), 3.73–3.77 (dd, *J*=8.3, 11.5 Hz, 1H), 3.93 (t, *J*=7.0 Hz, 1H), 4.00 (t, *J*=11.6 Hz, 2H), 4.29–4.33 (m, 1H), 5.01–5.09 (m, 2H), 7.18 (t, *J*=8.8 Hz, 2H), 7.35–7.38 (dd, *J*=5.8, 8.5 Hz, 2H), 7.53–7.54 (d, *J*=8.3 Hz, 1H), 7.74–7.76 (dd, *J*=3.4, 11.6 Hz, 2H), 10.27–10.32 (s, 2H).

4.1.4. 3-(4-Fluorobenzyl)-1-(2-methoxybenzyl)-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (9j). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33–1.34 (d, *J*=6.1 Hz, 3H), 3.54–3.57 (dd, *J*=7.9 Hz, 1H), 3.79 (m, 3H), 4.09 (t, *J*=11.0 Hz, 1H), 4.44–4.46 (m, 2H), 5.07–5.10 (d, *J*=11.6 Hz, 3H), 6.87 (t, *J*=7.3 Hz, 1H), 6.98–6.99 (d, *J*=7.6 Hz, 1H), 7.02–7.03 (d, *J*=8.3 Hz, 1H), 7.18–7.21 (dd, *J*=8.8, 15.9 Hz, 2H), 7.26–7.32 (m, 2H), 7.38–7.41 (dd, *J*=5.7, 8.6 Hz, 2H), 7.64–7.66 (m, 1H), 7.77–7.78 (d, *J*=1.4 Hz, 1H), 10.27 (s, 1H), 10.39 (s, 1H).

4.1.5. 1-(4-Chlorobenzyl)-3-(4-fluorobenzyl)-5-(4-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (9l). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33–1.34 (d, *J*=6.1 Hz, 3H), 3.54–3.58 (dd, *J*=7.9, 10.9 Hz, 1H), 4.09 (t, *J*=10.9 Hz, 2H), 4.45–4.48 (m, 2H), 5.08 (s, 1H), 5.16 (s, 1H), 7.20 (t, *J*=8.8 Hz, 2H), 7.35–7.42 (m, 4H), 7.46–7.48 (d, *J*=8.3 Hz, 1H), 7.66–7.68 (m, 2H), 7.77 (s, 2H), 10.28 (s, 1H), 10.41 (s, 1H).

4.1.6. 1-Butyl-5-[5-methyl-1-(4-nitrobenzyl)-4,5-dihydro-1*H*-imidazol-2-yl]-3-(4-nitrobenzyl)-1,3-dihydro-2*H*-benzimidazol-2-one (10). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.27–1.34 (m, 4H), 1.63–1.66 (m, 2H), 3.56–3.60 (m, 2H), 3.92 (t, *J*=6.9 Hz, 1H), 4.11–4.15 (m, 2H), 4.28–4.31 (m, 1H), 4.77 (s, 2H), 5.19 (s, 2H), 6.52 (m, 2H), 7.38–7.42 (m, 3H), 7.51–7.53 (m, 3H), 8.11–8.14 (dd, *J*=2.8 Hz, *J*=8.8 Hz, 3H), 10.61 (s, 1H).

5. Supporting information

LC–MS and ^{1}H and ^{13}C NMR of selected compounds are available.

Acknowledgements

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

References

1. Doherty, A. M. *Annual Reports in Medicinal Chemistry*, Vol. 36; Academic: San Diego, USA, 2001 p 38, 100.
2. (a) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84. (b) Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. *Biotechniques* **1992**, *13*, 901. (c) Dooley, C. T.; Chung, N. N.; Schiller, P. W.; Houghten, R. A. *Proc. Natl Acad. Sci. USA* **1993**, *90*, 10811. (d) Dooley, C. T.; Chung, N. N.; Wilkes, B. C.; Schiller, P. W.; Bidlack, J. M.; Pasternak, G. W.; Houghten, R. A. *Science* **1994**, *266*, 2019. (e) Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Dorner, B.; Eichler, J.; Ostresh, J. M.; Houghten, R. A. *Biopolymers* **1995**, *37*, 221. (f) Dooley, C. T.; Houghten, R. A. *Biopolymers* **2000**, *51*, 379.
3. (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. (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*, 138.
4. Kawamoto, H.; Ozaki, S.; Itoh, Y.; Miyaji, M.; Arai, S.; Nakashima, H.; Kato, T.; Ohta, H.; Iwasawa, Y. *J. Med. Chem.* **1999**, *42*, 5061.
5. Schelkum, R. M.; Yuen, P.-W.; Serpa, K.; Meltzer, L. T.; Wise, L. D.; Whittemore, E. R.; Woodward, R. M. *J. Med. Chem.* **2000**, *43*, 1892.
6. (a) Gilman, A. G.; Goodman, L. S. *The Pharmacological Basis of Therapeutics*; 10th ed; Macmillan: New York, 2001 Chapter 10, pp 215–268. (b) Greenhill, J. V.; Lue, P. *Progress in Medicinal Chemistry*, 30; 1993 p 203.
7. Matsumoto, H.; Ikeda, K.; Nagata, N.; Takayanagi, H.; Mizuno, Y.; Tanaka, M.; Sasaki, T. *J. Med. Chem.* **2001**, *42*, 1661.
8. 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. *J. Med. Chem.* **1999**, *42*, 1587.
9. Houghten, R. A. *Proc. Natl Acad. Sci. USA* **1985**, *82*, 5131.
10. Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622.
11. Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2002** in press.
12. (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. US Patent No. 4,379,926, 1983.
13. (a) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8673. (b) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 612.
14. Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **2002**, *58*, 221.
15. Ostresh, J. M.; Husar, G. M.; Blondelle, S. E.; Dörner, B.; Weber, P. A.; Houghten, R. A. *Proc. Natl Acad. Sci. USA* **1994**, *91*, 11138.
16. Kaiser, E. T.; Colescott, R. L.; Blossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.
17. Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. *Int. J. Pept. Protein Res.* **1986**, *27*, 673.