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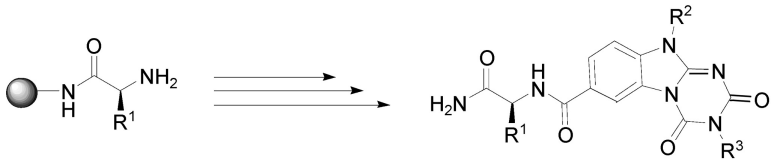

Parallel Solid-Phase Synthesis of Trisubstituted Triazinobenzimidazolediones

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

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

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An efficient method for the solid-phase synthesis of trisubstituted [1,3,5]triazino[1,2-*a*]benzimidazole-2,4-(3*H*,10*H*)-diones from resin-bound amino acids is described. N-acylation of the primary amine of a resin-bound amino acid with 4-fluoro-3-nitrobenzoic acid, followed by displacement of the fluoro group and reduction of the nitro group, generated a resin-bound *o*-dianilino derivative. The dianilino compound was treated with cyanogen bromide to generate the corresponding iminobenzimidazole, which, following treatment with *N*-(chlorocarbonyl)isocyanate, afforded the resin-bound triazinodione derivative. Alkylation of the triazinodione compound with an alkyl halide yielded, following cleavage of the solid-support, the trisubstituted [1,3,5]triazino[1,2-*a*]benzimidazole-2,4(3*H*,10*H*)-dione.

Introduction

The application of solid-phase synthetic techniques in recent years has largely focused on advancing medicinal chemistry.[1] Successful syntheses of mixture-based combinatorial libraries, starting from peptides[1,2] and proceeding to heterocycles,[1,3−5] have augmented new directions for pragmatic high-throughput screening (HTS) utilizing a wide range of biological assays. Many pharmaceutical companies have adapted these techniques to synthesize large individual arrays of compounds, as well as mixture-based libraries,[2] in order to rapidly identify lead compounds. Triazinodiones are structurally novel molecules reported to exhibit interesting biological,[6] herbicidal,[7] and analgesic[8] properties. The related triazinobenzimidazolones are reported to act as selective A_1 adenosine receptor antagonists[9] and as benzodiazepine receptor inverse agonists.[10]

In a continuation of our efforts to synthesize small-molecule heterocycles and their synthetic combinatorial libraries (SCLs),[2] we describe herein an efficient strategy for the solid-phase synthesis of substituted [1,3,5]triazino-[1,2-*a*]benzimidazole-2,4(3*H*,10*H*)-diones. The final products were obtained in high purity (>80%), and the general nature of these synthetic approaches will enable the synthesis of a mixture-based combinatorial library of these compounds.

Results and Discussion

A Boc-protected amino acid was coupled to 4-methylbenzhydrylamine (MBHA) resin, followed by deprotection of the Boc group to generate compound **1** having a primary amine (Scheme 1). The primary amine was N-acylated with 4-fluoro-3-nitrobenzoic acid using *N*,*N*′-diisopropylcarbodiimide (DIC)[11] to generate compound **2**. Following treatment with a primary amine, *o*-nitroaniline derivative **3** was formed via arylfluoro displacement. Reduction of the aromatic nitro group of the resin-bound *o*-nitroaniline **3** with tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$)[11] generated *o*-dianilino compound **4**, which was cyclized using cyanogen bromide (CNBr) to form iminobenzimidazole **5**. Recently, we have reported complete cyclization of *o*-dianilino derivatives using cyanogen bromide to form iminobenzimidazole derivatives.[11] The resin-bound iminobenzimidazole **5** was cyclized with *N*-(chlorocarbonyl)isocyanate[12] to form triazinobenzimidazoledione compound **6**. In all cases, LC−MS showed complete triazinobenzimidazoledione formation.

On the basis of our ongoing efforts toward the preparation of mixture-based combinatorial libraries, the scope of diversity of compound **6** was found to be limited because of its having only two positions of variability. To increase the number of diversities around the triazinobenzimidazoledione scaffold, necessary for the potential synthesis of a large mixture-based combinatorial library, alkylation at the amide of the triazinobenzimidazoledione moiety was carried out with different commercially available alkyl halides (R^3X; X = I, Br). The best results were obtained using an alkyl halide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base to generate compound **7**. The final product was cleaved from the solid support using anhydrous HF and extracted with 95% acetic acid in water to yield compound **8**.

Seventeen individual control compounds (Table 1) were prepared using five amino acids (L-alanine, L-phenylalanine, L-leucine, L-serine, and *p*-fluoro-L-phenylalanine) to incorporate the first (R^1) position of diversity, nine amines (butylamine, cylopentylamine, 4-methylbenzylamine, hexylamine, 2-methoxyethylamine, cyclohexylethylamine (*R* and *S*), and *sec*-butylamine (*R* and *S*)) to incorporate the second (R^2) position of diversity, and five alkyl halides (iodomethane, 3-trifluoromethoxybenzyl bromide, 4-fluorobenzyl bromide, 2,3-difluorobenzyl bromide, and 3-methylbenzyl bromide) to incorporate the third (R^3) position of diversity.

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

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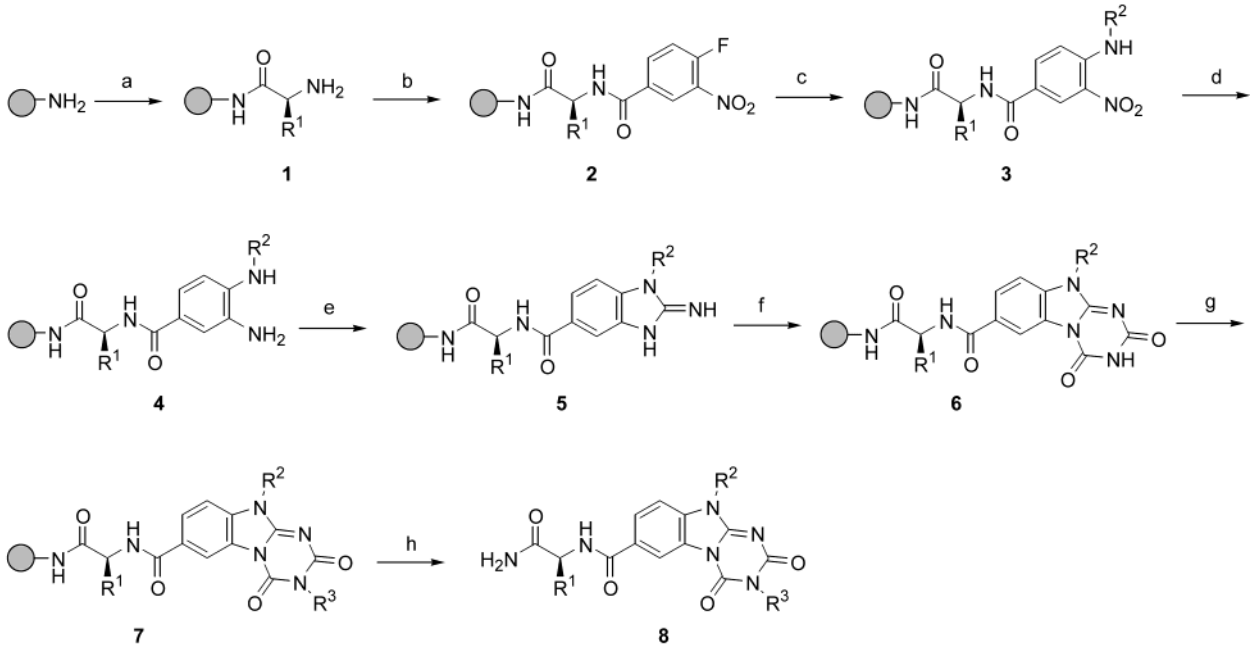
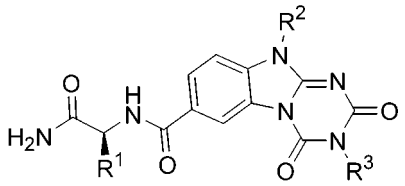
Scheme 1[a]



[a] (a) (i) Boc-NHCH(R^1)CO_2H (6 equiv, 0.1 M, DMF), DIC (6 equiv), HOBt (6 equiv), 2 h, room temp, (ii) 55% TFA/45% DCM, 30 min, room temp; (b) 4-fluoro-3-nitrobenzoic acid (10 equiv, 0.1 M, DMF), DIC (10 equiv), room temp, overnight; (c) R^2NH_2 (20 equiv, 0.2 M, DMF), DIEA (20 equiv), room temp, overnight; (d) $SnCl_2 \cdot 2H_2O$ (20 equiv, 0.5 M, DMF), 14 h, room temp; (e) CNBr (10 equiv, 0.1 M, DCM), room temp, overnight; (f) *N*-(chlorocarbonyl)isocyanate (10 equiv, 0.1 M, THF), room temp, overnight; (g) (i) DBU (10 equiv, 0.1 M, THF), 15 min, room temp, (ii) R^3X (X = I, Br) (10 equiv, 0.1 M, DMSO), 2 h, room temp, (i) and (ii) were repeated twice; (h) HF, anisole, ~0 °C, 1.5 h.

Table 1. MW and RP-HPLC Purity Found for the Trisubstituted [1,3,5]Triazino[1,2-*a*]benzimidazole-2,4(3*H*,10*H*)-diones[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
8a	$-CH_3$	$-(CH_2)_3CH_3$	$-CH_3$	386.2	387.2 ($M + H^+$)	85
8b	$-CH_2CH(CH_3)_2$	$-(CH_2)_3CH_3$	$-CH_3$	428.2	429.2 ($M + H^+$)	81
8c	$-CH_2OH$	$-(CH_2)_3CH_3$	$-CH_3$	402.2	403.4 ($M + H^+$)	83
8d	$-CH_2C_6H_4$(4-F)	$-(CH_2)_3CH_3$	$-CH_3$	480.2	481.3 ($M + H^+$)	81
8e	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_3$	462.2	463.2 ($M + H^+$)	82
8f	$-CH_2C_6H_5$	$-C_5H_9$	$-CH_3$	474.2	475.2 ($M + H^+$)	82
8g	$-CH_2C_6H_5$	$-CH_2C_6H_4$(4-CH_3)	$-CH_3$	510.2	511.3 ($M + H^+$)	81
8h	$-CH_2C_6H_5$	$-(CH_2)_5CH_3$	$-CH_3$	490.2	491.4 ($M + H^+$)	81
8i	$-CH_2C_6H_5$	$-(CH_2)_2OCH_3$	$-CH_3$	464.2	465.3 ($M + H^+$)	80
8j	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(3-OCF_3)	622.2	623.4 ($M + H^+$)	80
8k	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(4-F)	556.2	557.3 ($M + H^+$)	84
8l	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(2,3-F_2)	574.2	575.4 ($M + H^+$)	80
8m	$-CH_2C_6H_5$	$-(CH_2)_3CH_3$	$-CH_2C_6H_4$(3-CH_3)	552.2	553.4 ($M + H^+$)	80
8n	$-CH_3$	$-CH(C_6H_{11})CH_3$[c]	$-CH_3$	440.2	441.3 ($M + H^+$)	72
8o	$-CH_3$	$-CH(C_6H_{11})CH_3$[d]	$-CH_3$	440.2	441.3 ($M + H^+$)	73
8p	$-CH_2C_6H_5$	$-CH(CH_3)C_2H_5$[c]	$-CH_3$	462.2	463.3 ($M + H^+$)	80
8q	$-CH_2C_6H_5$	$-CH(CH_3)C_2H_5$[d]	$-CH_3$	462.2	463.2 ($M + H^+$)	80

[a] The yields obtained were greater than 80% in all cases with respect to the initial loading of the resin (1.10 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at $\lambda = 214$ nm. [c] (*R*) configuration. [d] (*S*) configuration.

The compounds were purified by RP-HPLC and were characterized by HRMS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

The ^{1}H NMR spectra of intermediate compounds **5** and **6** [**a**, $R^1 = -CH_3$, $R^2 = -(CH_2)_3CH_3$; **b**, $R^1 = -CH_2CH(CH_3)_2$, $R^2 = -(CH_2)_3CH_3$] after cleavage and purification indicated negligible racemization (<1%) during either the CNBr or *N*-(chlorocarbonyl)isocyanate cyclization reactions.[2a] Appearance of a strong proton signal at δ ~11.4 ppm in the ^{1}H NMR spectra of **6** corresponded to the −CO−NH−CO− of the triazinodione moiety. Disappearance of this signal in the ^{1}H NMR spectra of compounds **8** indicated that N-alkylation occurred at the amide of the triazinodione moiety (step g, Scheme 1). However, the ^{1}H NMR spectra for a

few compounds of **8** (examples **a**, **b**, **c**, and **d**) indicated that while N-alkylated compound **8** was the major product (~90%), approximately 10% of side product was obtained, most likely due to O-alkylation. It has been reported that *N*-alkyl and *O*-alkyl barbiturates were formed during alkylation of barbituric acid.[13] Similar O-alkylation was observed for compounds **8n**−**q** derived from chiral primary amines [(*R*)- and (*S*)-cyclohexylethylamine and (*R*)- and (*S*)-*sec*-butylamine] at the second (R^2) position of diversity. These results also indicated that negligible racemization (<1%) occurred during fluoro displacement by amine or DBU-mediated alkylation. Five signals at δ 146−178 ppm in the ^{13}C NMR spectra for all of the compounds **8** were assignable to the two amide carbons, the two amide carbons of the triazinodione moiety, and the guanidine carbon.[5b,c,14]

Following optimization of the different reaction steps, 120 additional control compounds based on product **8a**, in which each position of diversity was varied, were synthesized. A total of 57 different amino acids were used at the first (R^1) position of diversity, 32 primary amines at the second (R^2) position of diversity, and 31 alkyl halides at the third (R^3) position of diversity to determine their potential suitability for inclusion in the synthesis of a mixture-based combinatorial library.[2] Amino acids having an extra amine functionality (i.e., lysine and ornithine) at the first position (R^1) of diversity were found to lead to the formation of undesirable byproducts. Similarly, products derived from glutamine, asparagine, tryptophan, histidine, and methionine analogues at the first (R^1) position of diversity were found to have low purity (<40%). The use of bulky amines, such as 1-aminoindan and 1,2,3,4-tetrahydro-1-naphthylamine, at the second (R^2) position of diversity led to low-purity (30%) products. Approximately one-third of the alkyl halides, such as 2-phenylbenzyl bromide, geranyl bromide, and crotonyl bromide, used at the third (R^3) position of diversity also gave low-purity (<40%) products.

The percent yield of the crude compounds was calculated with respect to the theoretical loading of the resin (1.10 mequiv/g). The percent purity of the final compounds was calculated from the relative percentage areas of HPLC chromatograms run at $\lambda = 214$ nm. From the building blocks tested, those having crude purity greater than 80% were selected for potential use in the synthesis of a mixture-based combinatorial library.[1a,2] Thus, 40 amino acids for the first (R^1) position of diversity, 20 primary amines for the second (R^2) position of diversity, and 20 alkyl halides for the third (R^3) position of diversity (included in the Supporting Information) were found to be suitable for use in the synthesis of a mixture-based combinatorial library. Predetermined isokinetic ratios for Boc-amino acids will be used for coupling of mixtures[15] for the first (R^1) position of diversity. Because of the current lack of availability of isokinetic ratios for the reaction steps involving the primary amines and alkyl halides for second (R^2) and third (R^3) positions of diversity, respectively, 400 mixtures made up of 40 compounds each will be used for the synthesis of a combinatorial library. These results will be reported elsewhere.

Conclusion

A novel approach for the solid-phase synthesis of trisubstituted [1,3,5]triazino[1,2-*a*]benzimidazole-2,4(3*H*,10*H*)-diones has been presented. *N*-(Chlorocarbonyl)isocyanate was used as an efficient cyclization reagent for cyclization of iminobenzimidazoles to form [1,3,5]triazino[1,2-*a*]benzimidazole-2,4-(3*H*,10*H*)-diones.

Experimental Section

4-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100−200 mesh, 1.1 mequiv/g substitution) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex, International (Wood Dale, IL). Boc-amino acids and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA) and Bachem Bioscience, Inc. (Philadelphia, PA). 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). Purification of the samples was made using a Vydac 218TP54 C18 column (0.46 cm × 25 cm). LC−MS (ESI) data were recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) using a Betasil C18, 3 μm, 100 Å, 3 mm × 50 mm column. High-resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Facility of the University of California at Riverside, California.

Typical Procedure for the Individual Synthesis of Trisubstituted [1,3,5]Triazino[1,2-*a*]benzimidazole-2,4-(3*H*,10*H*)-diones. MBHA resin (100 mg, 0.11 mequiv) was sealed inside a polypropylene mesh packet.[16] 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. A Boc-amino acid (6 equiv, 0.1 M) in DMF was coupled to MBHA resin using DIC and HOBt (6 equiv each) for 2 h at room temperature followed by washes with DMF (three times) and DCM (three times). The Boc group was deprotected using 55% TFA in DCM for 30 min, followed by neutralization with 5% DIEA in DCM.

(b) N-Acylation of the Primary Amine Using 4-Fluoro-3-nitrobenzoic Acid. The primary amine of the resin-bound amino acid was N-acylated with 4-fluoro-3-nitrobenzoic acid (10 equiv, 0.1 M, overnight) in DMF using DIC (10 equiv), followed by washes with DMF (three times) and DCM (three times). A negative ninhydrin test confirmed the completeness of the coupling reactions.[17]

(c) Displacement of the Fluoro Group. The resulting resin-bound *o*-fluoronitro derivative was treated with a primary amine (20 equiv, 0.2 M, overnight) in DMF in the presence of DIEA (20 equiv), followed by washes with DMF (four times), DCM (two times), IPA (two times), and DCM (three times).

(d) Reduction of the Aromatic Nitro Group. The resulting resin-bound *o*-nitroaniline 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 (eight

times), MeOH (two times), and DCM (three times) to generate the *o*-dianilino analogue.

(e) Cyclization Using Cyanogen Bromide. The resin-bound *o*-dianilino compound was cyclized by treatment with cyanogen bromide (CNBr) (10 equiv, 0.1 M, overnight) in DCM followed by washes with DCM (four times), IPA (two times), and DCM (three times).

(f) Cyclization Using *N*-(Chlorocarbonyl)isocyanate. The resulting resin-bound iminobenzimidazole derivative was treated with *N*-(chlorocarbonyl)isocyanate (10 equiv, 0.1 M, overnight) in THF followed by washes with DCM (two times), DMF (two times), DCM (two times), IPA (two times), and DCM (three times).

(g) Alkylation with an Alkyl Halide. The resulting triazinobenzimidazoledione analogue was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10 equiv, 0.1 M, 15 min) in THF, followed by decantation of the base solution and treatment with an alkyl halide (10 equiv, 0.1 M, 2 h) in DMSO at room temperature. Following decantation, the base treatment and alkylation procedure were repeated once to ensure complete alkylation. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times) and was dried.

All washes with DCM, DMF, IPA, THF, or 5% DIEA in DCM were made for ~2 min each. The final compounds were cleaved using anhydrous HF in the presence of anisole for 1.5 h at 0 °C,[18] followed by extraction with 95% acetic acid in water and lyophilized.

1-Butyl-2-imino-2,3-dihydro-1*H*-benzoimidazole-5-(carboxylic acid)[(1*R*)-1-carbamoylethyl]amide (5a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J = 7.4 Hz, 3H), 1.30−1.34 (m, 5H), 1.64−1.67 (m, 2H), 4.14 (t, J = 7.1 Hz, 2H), 4.40−4.43 (m, 1H), 6.99 (s, 1H), 7.39 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.91 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 8.79 (s, 2H).

1-Butyl-2-imino-2,3-dihydro-1*H*-benzoimidazole-5-(carboxylic acid)[(1*R*)-1-carbamoyl-3-methylbutyl]amide (5b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.91 (m, 9H), 1.30−1.35 (m, 2H), 1.52−1.56 (m, 1H), 1.63−1.72 (m, 4H), 4.14 (t, J = 7.1 Hz, 2H), 4.43−4.47 (m, 1H), 6.97 (s, 1H), 7.41 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.91 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 8.79 (s, 2H).

10-Butyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo-[1,2-*a*][1,3,5]triazene-7-(carboxylic acid)[(1*R*)-1-carbamoylethyl]amide (6a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, J = 7.4 Hz, 3H), 1.33−1.35 (m, 5H), 1.71−1.74 (m, 2H), 4.14 (t, J = 7.1 Hz, 2H), 4.43−4.46 (m, 1H), 6.99 (s, 1H), 7.39 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 8.01−8.03 (m, 1H), 8.49 (s, 1H), 8.59 (d, J = 7.4 Hz, 1H), 11.41 (s, 1H).

10-Butyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo-[1,2-*a*][1,3,5]triazene-7-(carboxylic acid)[(1*R*)-1-carbamoyl-3-methylbutyl]amide (6b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87−0.92 (m, 9H), 1.32−1.37 (m, 2H), 1.52−1.56 (m, 1H), 1.68−1.74 (m, 4H), 4.14 (t, J = 7.1 Hz, 2H), 4.43−4.47 (m, 1H), 6.98 (s, 1H), 7.41 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 8.01−8.03 (m, 1H), 8.49 (s, 1H), 8.55 (d, J = 8.1 Hz, 1H), 11.41 (s, 1H).

10-Butyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo-[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoylethyl]amide (8a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, J = 7.4 Hz, 3H), 1.33−1.37 (m, 5H), 1.72−1.75 (m, 2H), 3.27 (s, 3H), 4.13 (t, J = 7.1 Hz, 2H), 4.43−4.46 (m, 1H), 6.99 (s, 1H), 7.39 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 7.2 Hz, 1H), 8.56 (s, 1H), 8.61 (d, J = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 18.0, 19.2, 28.1, 29.4, 42.5, 48.9, 109.6, 113.1, 124.9, 125.2, 129.3, 133.2, 147.2, 151.3, 154.5, 165.1, 174.3. HRMS (EI) *m*/*z*: 386.1694 found ([M$^+$]), 386.1703 calculated for $C_{18}H_{22}N_6O_4$ ([M$^+$]).

10-Butyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo-[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-3-methylbutyl]amide (8b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87−0.92 (m, 9H), 1.33−1.37 (m, 4H), 1.52−1.57 (m, 1H), 1.65−1.75 (m, 2H), 3.27 (s, 3H), 4.13 (t, J = 7.1 Hz, 2H), 4.48 (m, 1H), 6.98 (s, 1H), 7.41 (s, 1H), 7.70 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 8.56−8.57 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 19.2, 21.4, 23.1, 24.5, 28.1, 29.4, 40.4, 41.6, 51.8, 109.6, 113.1, 124.9, 125.3, 129.3, 133.2, 147.2, 151.3, 154.6, 165.4, 174.3. HRMS (EI) *m*/*z*: 428.2155 found ([M$^+$]), 428.2172 calculated for $C_{21}H_{28}N_6O_4$ ([M$^+$]).

10-Butyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo-[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-hydroxyethyl]amide (8c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, J = 7.4 Hz, 3H), 1.33−1.37 (m, 2H), 1.74 (m, 2H), 3.28 (s, 3H), 3.73 (t, J = 5.9 Hz, 2H), 4.13 (t, J = 7.3 Hz, 2H), 4.46 (m, 1H), 4.94 (m, 1H), 6.51 (s, 1H), 7.11 (s, 1H), 7.42 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 9.4 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.56 (s, 1H).

10-Butyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo-[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-(4-fluorophenyl)ethyl]amide (8d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, J = 7.4 Hz, 3H), 1.33 (m, 2H), 1.72 (m, 2H), 2.98−3.13 (m, 2H), 3.27 (s, 3H), 4.11 (t, J = 7.1 Hz, 2H), 4.66 (m, 1H), 7.04−7.09 (m, 3H), 7.35−7.38 (m, 2H), 7.57 (s, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 8.48 (s, 1H), 8.70 (d, J = 8.6 Hz, 1H).

10-Butyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo-[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (t, J = 7.4 Hz, 3H), 1.31−1.36 (m, 2H), 1.69−1.73 (m, 2H), 2.99−3.04 (m, 1H), 3.11−3.14 (m, 1H), 3.27 (s, 3H), 4.11 (t, J = 7.1 Hz, 2H), 4.67 (m, 1H), 7.13−7.16 (m, 2H), 7.22−7.25 (m, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.58 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 8.48 (s, 1H), 8.71 (d, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 19.2, 28.1, 29.4, 37.2, 41.6, 54.9, 109.6, 112.9, 124.9, 125.1, 126.1, 128.1, 129.1, 129.2, 133.2, 138.5, 147.2, 151.3, 154.5, 165.3, 173.3.

10-Cyclopentyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)-[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.70 (m, 2H), 2.01 (m, 4H), 2.17 (m, 2H), 3.01−3.13 (m, 2H), 3.26 (s, 3H), 4.66−4.69 (m,

1H), 5.06 (t, J = 8.7 Hz, 1H), 7.12−7.32 (m, 5H), 7.57 (s, 2H), 7.64 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 8.52 (s, 1H), 8.70 (d, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.4, 28.1, 28.2, 37.2, 54.5, 54.8, 110.3, 113.1, 124.9, 125.1, 126.1, 128.0, 129.0, 129.1, 132.2, 138.5, 147.2, 151.0, 154.2, 165.2, 173.3. HRMS (EI) *m/z*: 474.2022 found ([M$^+$]), 474.2016 calculated for $C_{25}H_{26}N_6O_4$ ([M$^+$]).

3-Methyl-10-(4-methylbenzyl)-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8g). ^{1}H NMR (500 MHz, DMSO-d_6): $\boldsymbol{\delta}$ 2.26 (s, 3H), 2.96−3.12 (m, 2H), 3.29 (s, 3H), 4.65 (m, 1H), 5.30 (s, 2H), 7.15−7.22 (m, 5H), 7.28−7.32 (m, 4H), 7.48 (d, J = 8.2 Hz, 1H), 7.55 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 8.48 (s, 1H), 8.66 (d, J = 8.6 Hz, 1H).

10-Hexyl-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo-[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84 (t, J = 7.4 Hz, 3H), 1.21−1.30 (m, 6H), 1.73 (m, 2H), 2.99−3.14 (m, 2H), 3.26 (s, 3H), 4.10 (t, J = 7.1 Hz, 2H), 4.66−4.68 (m, 1H), 7.11−7.33 (m, 5H), 7.58 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 8.33 (s, 1H), 8.48 (s, 1H), 8.70 (d, J = 8.5 Hz, 1H).

10-(2-Methoxyethyl)-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8i). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.94−3.03 (m, 2H), 3.18 (s, 3H), 3.45 (s, 3H), 3.69 (t, J = 5.3 Hz, 2H), 4.29 (t, J = 5.1 Hz, 2H), 4.65−4.69 (m, 1H), 7.11−7.34 (m, 5H), 7.57 (m, 1H), 7.91−7.93 (m, 2H), 8.35 (s, 1H), 8.47 (s, 1H), 8.69 (d, J = 8.5 Hz, 1H).

10-Butyl-2,4-dioxo-3-(3-trifluoromethoxybenzyl)-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8j). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (t, J = 7.4 Hz, 3H), 1.34−1.38 (m, 2H), 1.70−1.76 (m, 2H), 2.99−3.13 (m, 2H), 4.12 (t, J = 7.1 Hz, 2H), 4.67 (m, 1H), 5.10 (s, 2H), 7.09−7.15 (m, 2H), 7.21−7.33 (m, 6H), 7.40−7.45 (m, 2H), 7.56 (s, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 8.49 (s, 1H), 8.71 (d, J = 8.5 Hz, 1H).

10-Butyl-3-(4-fluorobenzyl)-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)-[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8k). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, J = 7.4 Hz, 3H), 1.33−1.38 (m, 2H), 1.69−1.75 (m, 2H), 2.98−3.14 (m, 2H), 4.10 (t, J = 7.3 Hz, 2H), 4.66−4.70 (m, 1H), 5.04 (s, 2H), 7.11−7.24 (m, 6H), 7.31−7.34 (m, 2H), 7.44−7.47 (m, 2H), 7.56 (s, 1H), 7.66−7.68 (m, 1H), 7.91−7.93 (m, 1H), 8.49 (s, 1H), 8.70 (d, J = 8.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 19.3, 29.4, 37.2, 43.5, 43.7, 54.8, 109.7, 112.9, 114.8, 115.0, 124.9, 125.2, 126.1, 127.9, 129.1, 129.2, 129.8, 129.9, 133.2, 133.3, 138.5, 147.2, 151.4, 154.1, 165.2, 173.2. HRMS (EI) *m/z*: 556.2227 found ([M$^+$]), 556.2234 calculated for $C_{30}H_{29}FN_6O_4$ ([M$^+$]).

10-Butyl-3-(2,3-difluorobenzyl)-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8l). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (t, J = 7.4 Hz, 3H), 1.34−1.39 (m, 2H), 1.72−1.76 (m, 2H), 2.99−3.13 (m, 2H), 4.12 (t, J = 7.1 Hz, 2H), 4.68 (m, 2H), 5.15 (s, 1H), 6.52 (s, 2H), 7.10−7.15 (m, 2H), 7.19−7.34 (m, 5H), 7.55 (m, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 8.49 (s, 1H), 8.71 (d, J = 8.6 Hz, 1H).

10-Butyl-3-(3-methylbenzyl)-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)-[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8m). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.91 (t, J = 7.4 Hz, 3H), 1.35−1.37 (m, 2H), 1.71−1.74 (m, 2H), 2.27 (s, 3H), 2.98−3.14 (m, 2H), 4.10−4.13 (m, 2H), 4.68 (m, 1H), 5.02 (s, 2H), 6.52 (s, 2H), 7.06−7.24 (m, 7H), 7.32 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 8.49 (s, 1H), 8.58 (d, J = 8.6 Hz, 1H).

10-[(1*S*)-1-Cyclohexylethyl]-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoylethyl]amide (8n). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83−0.86 (m, 1H), 1.01−1.12 (m, 3H), 1.27−1.30 (m, 2H), 1.35 (d, J = 7.3 Hz, 3H), 1.54−1.60 (m, 5H), 1.75−1.78 (m, 1H), 1.93−1.96 (m, 1H), 2.17−2.18 (m, 1H), 3.27 (s, 3H), 4.41−4.47 (m, 2H), 6.99 (s, 1H), 7.39 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.98−8.01 (m, 1H), 8.58−8.62 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.5, 17.9, 25.1, 25.2, 25.6, 28.1, 29.2, 29.6, 40.1, 48.9, 55.7, 110.7, 113.1, 125.1, 129.1, 147.2, 151.1, 154.4, 165.1, 174.3.

10-[(1*R*)-1-Cyclohexylethyl]-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine-7-(carboxylic acid)[(1*R*)-1-carbamoylethyl]amide (8o). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83−0.88 (m, 1H), 1.01−1.12 (m, 3H), 1.27−1.30 (m, 2H), 1.35 (d, J = 7.3 Hz, 3H), 1.54−1.60 (m, 5H), 1.75−1.78 (m, 1H), 1.93−1.96 (m, 1H), 2.17−2.18 (m, 1H), 3.27 (s, 3H), 4.41−4.47 (m, 2H), 6.99 (s, 1H), 7.39 (s, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.98−8.01 (m, 1H), 8.59−8.62 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.5, 17.9, 25.1, 25.2, 25.6, 28.1, 29.2, 29.6, 40.1, 40.9, 48.9, 55.7, 110.7, 113.2, 125.1, 129.1, 147.2, 151.1, 154.4, 165.1, 174.3.

10-[(1*S*)-*sec*-Butyl]-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo1,2-*a*][1,3,5]triazine-7-(carboxylic acid)-[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8p). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (t, J = 7.4 Hz, 3H), 1.53 (d, J = 6.9 Hz, 3H), 1.87−1.90 (m, 1H), 2.08−2.14 (m, 1H), 2.99−3.04 (m, 1H), 3.11−3.14 (m, 1H), 3.26 (s, 3H), 4.66−4.70 (m, 3H), 7.14−7.16 (m, 2H), 7.22−7.25 (m, 2H), 7.34 (d, J = 7.4 Hz, 1H), 7.59 (m, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.89−7.91 (m, 1H), 8.51 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.8, 17.5, 25.9, 28.1, 37.2, 52.6, 54.8, 110.5, 113.1, 124.9, 125.1, 126.1, 128.1, 128.9, 129.1, 132.3, 138.5, 147.2, 151.1, 154.3, 165.2, 173.3.

10-[(1*R*)-*sec*-Butyl]-3-methyl-2,4-dioxo-2,3,4,10-tetrahydrobenzo[4,5]imidazo1,2-*a*][1,3,5]triazine-7-(carboxylic acid)-[(1*R*)-1-carbamoyl-2-phenylethyl]amide (8q). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.79 (t, J = 7.4 Hz, 3H), 1.53 (d, J = 6.9 Hz, 3H), 1.87−1.90 (m, 1H), 2.08−2.14 (m, 1H), 2.99−3.04 (m, 1H), 3.11−3.14 (m, 1H), 3.26 (s, 3H), 4.66−4.70 (m, 3H), 7.14−7.16 (m, 2H), 7.22−7.25 (m, 2H), 7.34 (d, J = 7.4 Hz, 1H), 7.59 (m, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.89−7.91 (m, 1H), 8.51 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.8, 17.5, 25.9, 28.1,

37.2, 52.6, 54.8, 110.5, 113.1, 124.9, 125.1, 126.1, 128.1, 128.9, 129.1, 132.3, 138.5, 147.2, 151.1, 154.3, 165.2, 173.3.

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

References and Notes

(1) (a) Dolle, R. E. Comprehensive Survey of Combinatorial Libraries: 2000. *J. Comb. Chem*. **2001**, *3*, 477−517. (b) Franzen, R. G. Recent Advances in the Preparation of Heterocycles on Solid Support: A Review of the Literature. *J. Comb. Chem*. **2000**, *2*, 195−214. (c) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.; Nefzi, A.; Ostresh, J. M. Mixture-Based Synthetic Combinatorial Libraries. *J. Med. Chem.* **1999**, *42*, 3743−3778. (d) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. The Current Status of Heterocyclic Combinatorial Libraries. *Chem. Rev.* **1997**, *97*, 449−472. (e) Thompson, L. A.; Ellman, J. A. Synthesis and Application of Small Molecule Libraries. *Chem. Rev*. **1996**, *96*, 555−600. (f) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. *J. Med. Chem*. **1994**, *37*, 1385−1401.

(2) (a) Ostresh, J. M.; Husar, G. M.; Blondelle, S. E.; Dörner, B.; Weber, P. A.; Houghten, R. A. "Libraries from Libraries": Chemical Transformation of Combinatorial Libraries To Extend the Range and Repertoire of Chemical Diversity. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138−11142. (b) Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. Rapid Identification of High Affinity Peptide Ligands Using Positional Scanning Synthetic Peptide Combinatorial Libraries. *Biotechniques* **1992**, *13*, 901−905.

(3) Houghten, R. A.; Dooley, C. T.; Giulianotti, M. A.; Hamashin, V. T.; Schoner, C.; Ostresh, J. M.; Nefzi, A. Solid Phase Synthesis of Heterocyclic Positional Scanning Combinatorial Libraries. In *Innovation and Perspectives in Solid Phase Synthesis and Combinatorial Libraries*, Proceedings of the 5th International Symposium; Epton, R., Ed.; Mayflower Scientific Limited: London, 1998; pp 11−14.

(4) Nefzi, A.; Dooley, C. T.; Ostresh, J. M.; Houghten, R. A. Combinatorial Chemistry: From Peptides and Peptidomimetics to Small Organic and Heterocyclic Compounds. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2273−2278.

(5) (a) Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. Solid Phase Synthesis of Trisubstituted Bicyclic Guanidines via Cyclicization of Reduced N-Acylated Dipeptides. *J. Org. Chem.* **1998**, *63*, 8622−8623. (b) Acharya, A. N.; Nefzi, A.; Ostresh, J. M.; Houghten, R. A. Tethered Libraries: Solid-Phase Synthesis of Substituted Urea-Linked Bicyclic Guanidines. *J. Comb. Chem* **2001**, *3*, 189−195. (c) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. A Novel Approach for the Solid-Phase Synthesis of Substituted Cyclic Guanidines, Their Respective Bis Analogues, and N-Acylated Guanidines from N-Acylated Amino Acid Amides. *J. Comb. Chem* **2001**, *3*, 578−589. (d) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. Solid-Phase Synthesis of Substituted Imidazoline-Tethered 2,3-Diketopiperazines, Cyclic Ureas, and Cyclic Thioureas. *J. Comb. Chem.* **2001**, *3*, 612−623.

(6) (a) Pawlak, D.; Adamkiewicz, M.; Malyszko, J.; Takada, A. Vascular and Cardiac Effect of DV-7028, A Selective, 5-HT2-Receptor Antagonist in Rats. *J. Cardiovasc. Pharmacol*. **1998**, *32*, 266−273. (b) Hall, I. H.; Taylor, K.; Izydore, R. A.; Coleman, D. E.; Mitchell, J. A.; Cummings, R. The Cytotoxic Action of 1,3,5-Triazabicyclo-[3.1.0]-hexane-2,4-diones and 1,3,5-Triazine-4,6-(1H, 5H)-diones in Murine and Human Tumor Cells. *Pharmazie* **1998**, *53*, 398−405.

(7) (a) Kay, I. T. Substituted Triazinediones, Their Preparation and Use as Herbicides. British Patent GB1464248, 1974. (b) Sato, J.; Fukuda, K.; Ito, K.; Suzuki, K.; Nawamaki, T.; Watanabe, S. Preparation of 3-Phenyl-1,3,5-triazine-2,4-(1H,-3H)-dione Derivatives as Selective Herbicides. Japanese Patent JP03077874, 1991.

(8) Brown, E. D. Analgesic 6-Acylaminotetrahydro-1,3,5-triazine-2,4-dione Derivatives, Pharmaceutical Compositions Thereof, and Process for Their Manufacture. European Patent EP 5911, 1979.

(9) Da Settimo, F.; Primofiore, G.; Taliani, S.; Marini, A. M.; La Motta, C.; Novellino, E.; Greco, G.; Lavecchia, A.; Trincavelli, L.; Martini, C. 3-Aryl[1,2,4]triazino[4,3-a]benzimidazol-4(10H)-ones: A New Class of Selective A_1 Adenosine Receptor Antagonists. *J. Med. Chem*. **2001**, *44*, 316−327.

(10) Primofiore, G.; Da Settimo, F.; Taliani, S.; Marini, A. M.; La Motta, C.; Novellino, E.; Greco, G.; Gesi, M.; Trincavelli, L.; Martini, C. 3-Aryl-[1,2,4]triazino[4,3-a]benzimidazol-4(10H)-ones: Tricyclic Heteroaromatic Derivatives as a New Class of Benzodiazepine Receptor Ligands. *J. Med. Chem.* **2000**, *43*, 96−102.

(11) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. Novel Approaches for the Solid-Phase Synthesis of Biheterocyclic Dihydroimidazole Analogues. *J. Comb. Chem*. **2002**, *4*, 214−222.

(12) (a) Gopalsamy, A.; Yang, H. Combinatorial Synthesis of Heterocycles: Solid-Phase Synthesis of 6-Amino-2,4-dioxo-3,4-dihydro-1,3,5-triazine derivatives. *J. Comb. Chem*. **2001**, *3*, 278−283. (b) Hagemann, H. Synthesis and Reactions of N-Chlorocarbonyl isocyanate. *Angew. Chem., Int. Ed. Engl*. **1997**, *16*, 743−750. (c) Gorbatenko, V. I. Chemistry of Chlorocarbonylisocyanate. V. *Tetrahedron* **1993**, *49*, 3227−3257.

(13) (a) Neville, G. A.; Avdovich, H. W. Isomeric Pyrimidone and Uracil Derivatives Obtained by Reaction of Barbiturates with Diazomethane. *Can. J. Chem*. **1972**, *50*, 880−886. (b) Dilli, S.; Pillai, D. N. The Synthesis of Volatile Barbituric Acid Derivatives. *Aust. J. Chem*. **1975**, *28*, 2265−2274.

(14) (a) Isobe, T.; Fukuda, K.; Ishikawa, T. Modified Guanidines as Potential Chiral Superbases. 1. Preparation of 1,3-Disubstituted 2-Iminoimidazolidines and the Related Guanidines through Chloroamidine Derivatives. *J. Org. Chem.* **2000**, *65*, 7770−7773. (b) Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. Modified Guanidines as Potential Chiral Superbases. 2. Preparation of 1,3-Unsubstituted and 1-Substituted 2-Iminoimidazolidine Derivatives and a Related Guanidine by the 2-Chloro-1,3-dimethylimidazolinium Chloride-Induced Cyclization of Thioureas. *J. Org. Chem.* **2000**, *65*, 7774−7778.

(15) Ostresh, J. M.; Winkle, J. H.; Hamashin, V. T.; Houghten, R. A. Peptide Libraries: Determination of Relative Reaction Rates of Protected Amino Acids in Competitive Couplings. *Biopolymers* **1994**, *34*, 1681−1689.

(16) Houghten, R. A. General Method for the Rapid Solid-Phase Synthesis of Large Numbers of Peptides: Specificity of Antigen−Antibody Interaction at the Level of IndividualAmino Acids. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131−5135.
(17) Kaiser, E. T.; Colescott, R. L.; Blossinger, C. D.; Cook, P. I. Color Test for Detection of Free Terminal Amino Groups in the Solid-Phase Synthesis of Peptides. *Anal. Biochem.* **1970**, *34*, 595−598.
(18) Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. Simplified Procedure for Carrying Out Simultaneous Multiple Hydrogen Fluoride Cleavages of Protected Peptide Resins. *Int. J. Pept. Protein Res.* **1986**, *27*, 673−678.

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