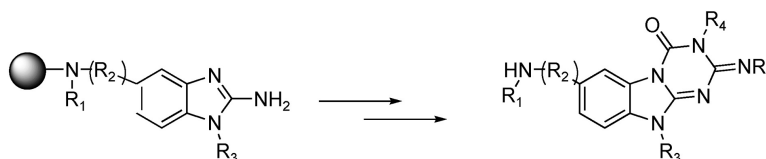


Parallel Solid-Phase Synthesis of 2-Imino-4-oxo-1,3,5-triazino[1,2-a]benzimidazoles via Tandem Aza-Wittig/Heterocumulene-Mediated Annulation Reaction

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Parallel Solid-Phase Synthesis of 2-Imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazoles via Tandem Aza-Wittig/Heterocumulene-Mediated Annulation Reaction

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The parallel synthesis of a large number of 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazole derivatives via a solid-phase 1,3,5-triazino-annulation reaction is described. The solid-phase approach involves the in situ generation of iminophosphorane derivatives derived from resin-bound 2-aminobenzimidazoles employing Mitsunobu conditions. The subsequent Aza-Wittig reaction of the iminophosphoranes with isocyanates leads to highly reactive carbodiimides, which undergo an intramolecular heterocyclization reaction to form tetrasubstituted 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazoles in high yields (74–94%) and good purity (>80%).

Introduction

The use of combinatorial chemistry has radically changed the theory and practice of designing and preparing new substances for pharmaceutical research. Initially almost exclusively explored with peptide, peptidomimetic, and oligonucleotide libraries, subsequent efforts have been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents. Among the heterocyclic templates, 1,3,5-triazines and 1,3,5-triazinones are present in various biologically active compounds, including HIV-replication inhibitors, corticotropin-releasing factor antagonists, angiogenesis inhibitors, and antiprotozoal drugs.¹ However, so far, there is no report on the pharmacological properties of 2-imino-4-oxo-1,3,5-triazine derivatives. As part of our continuing efforts toward the identification and synthesis of heterocycles endowed with pharmacological activities, we decided to design a combinatorial approach to 2-imino-4-oxo-1,3,5-triazines condensed to a benzimidazole moiety. Benzimidazole derivatives have been extensively described in the literature as an important class of compounds with a wide variety of known biological properties, including anthelmintic, antiviral, antiallergic, and antineoplastic activity.² The benzimidazole ring, furthermore, represents a key structural element in angiotensin-II-antagonists, NMDA-antagonists, anticoagulants, and gastric proton-pump inhibitors.³

Our solid-phase approach to the desired 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazole derivatives is based on the generation of an iminophosphorane as a key intermediate. First prepared at the beginning of the century by Staudinger,⁴ iminophosphoranes have become a powerful tool for the construction of nitrogen-containing heterocycles, and their general use as reagents and intermediates in organic synthesis

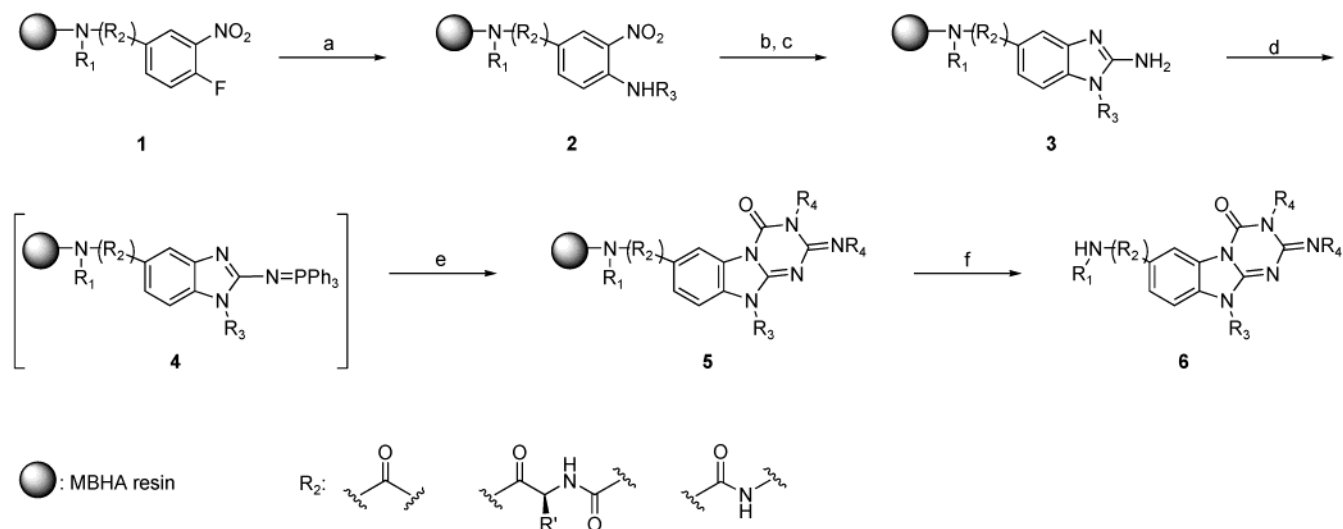
has been described in several review articles.⁵ In particular, the Aza-Wittig reaction of iminophosphoranes has attracted considerable attention, because it provides access to functionalized heterocumulenes that are able to undergo heterocyclization reactions. Employing this methodology in solution phase, the synthesis of fused heterocycles, including 7*H*-pyrido[4,3-*c*]carbazoles, pyrido[3,4-*b*]indoles, pyrazolo[3,4-*d*]pyrimidines, and 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazoles were reported during the past decade.⁶ Recently, studies on the solid-phase application of iminophosphoranes have emerged as a result of their high potential for the synthesis of nitrogen-containing heterocycles under mild and neutral conditions.⁷

We describe herein the first parallel solid-phase 1,3,5-triazino-annulation synthesis. Aza-Wittig reaction of an iminophosphorane derived from a resin-bound 2-aminobenzimidazole results in the formation of a highly reactive carbodiimide intermediate, which subsequently undergoes an intramolecular cyclization to afford the corresponding triazino-benzimidazole. Following HF cleavage, the desired compounds were obtained in high yield and good purity.

Results and Discussion

The synthesis of all compounds described were carried out utilizing Houghten's tea-bag method, in which the resin is contained within sealed polypropylene mesh packets.⁸ To obtain a large number of different resin-bound 2-aminobenzimidazoles **3** (Scheme 1), we coupled 4-fluoro-3-nitrobenzoic acid either to an amino acid linked to MBHA resin or directly to MBHA resin. The second position of diversity was introduced by nucleophilic displacement of the fluoro atom with a variety of different amines. Quantitative reduction of the nitro group was achieved using sodium hydrogensulfite (Na₂S₂O₄) in combination with 1,1'-diocetadecyl-4,4'-bipyridinium dibromide.⁹ This reduction reagent is preferable to tin(II) chloride dihydrate, which is widely used for the reduction of solid-phase bound nitro groups¹⁰ and which is

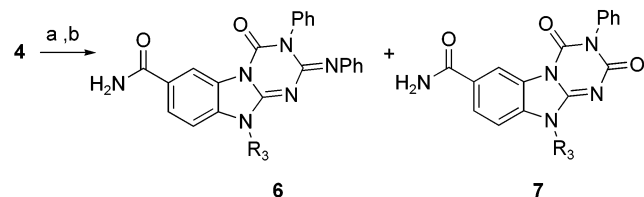
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Scheme 1^a

^a (a) R₃NH₂, DIPEA, DMF, 12 h, RT; (b) Na₂S₂O₄, K₂CO₃, 1,1'-dioctadecyl-4,4'-bipyridinium dibromide, DCM/H₂O, 22 h, RT; (c) CNBr, DCM, 12 h, RT; (d) PPh₃, DEAD, THF, 36 h, RT; (e) R₄NCO, toluene, 24–72 h, 100 °C; and (f) HF/anisole, 1.5 h, 0 °C.

reported to be problematic because of toxic tin species remaining within the resin.^{9a} Cyclization with cyanogen bromide yielded a wide range of 2-aminobenzimidazoles **3** bound to the MBHA resin either by an amide or amino acid linkage in purities greater than 95%. To generate the iminophosphorane intermediate **4** from the resin-bound 2-aminobenzimidazole **3**, we first tried to perform the Kirsanov reaction (Ph₃PBr₂/Et₃N)¹¹ on the solid phase. In the solution phase, this reaction is widely used for the formation of iminophosphoranes derived from aromatic and heterocyclic amines¹² and affords the iminophosphorane from 2-aminobenzimidazole in 95% yield.⁶ However, we found that the use of Ph₃PBr₂ on the solid phase provided the desired products **6** only in very low yields (<5%). By treating the resin-bound 2-aminobenzimidazoles **3** with an excess of Ph₃P and diethyl azodicarboxylate (DEAD) in THF at room temperature following typical Mitsunobu reaction conditions, we were able to form the corresponding iminophosphoranes **4** quantitatively. The tandem Aza-Wittig/heterocyclization reaction of iminophosphorane **4** was carried out using an excess of alkyl isocyanate (15 equiv) in anhydrous toluene at 100 °C for 1 day and yielded after HF cleavage the 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazole **6**. Triphenylphosphine oxide, formed during the reaction as a byproduct, tended to stick to the resin and was still present in the cleaved product as contamination following a standard washing cycle. However, this impurity could be removed by an exhaustive washing procedure with toluene, and the desired products were obtained in high purities (>80%) and very good yields (74–94%). Figure 1 illustrates a typical LC/MS spectrum of the triazino-benzimidazole obtained from 3-methoxypropylamine and ethyl isocyanate. A selection of 20 triazino-benzimidazoles **6** have been purified by reverse-phase HPLC and fully characterized by LC/MS (ESI) and NMR (¹H and ¹³C) (Table 1).

As we expanded this synthetic approach using a wide range of different isocyanates, we observed that we recovered starting material **3** when bulky isocyanates were employed. However, by increasing the amount of isocyanate to 90 equiv

Scheme 2^a

^a (a) PhNCO, toluene, 24 h, 100 °C; (b) HF/anisole, 1.5 h, 0 °C.

and the reaction time to 3 days, we were able to alleviate this problem and to drive the reaction to completion even with bulky isocyanates.

It is noteworthy that the annulation reaction with aryl isocyanates under our standard reaction conditions (100 °C for 1 day) leads to the desired compounds **6** and to a byproduct **7** (ratio of **6m**/**7m** = 49:51 as determined by HPLC at 214 nm, Table 1). Characterization of the byproduct by LC/MS (ESI) and ¹³C NMR showed that 2,4-dioxo-1,3,5-triazines **7** are formed in a side reaction (Scheme 2). This observation is in accordance with results of Bruché et al.,¹³ who obtained by an Aza-Wittig/heterocyclization reaction in solution phase a mixture of 3-imino-1,2,4-triazoles and 3-oxo-1,2,4-triazoles, probably as a result of an abnormal Aza-Wittig reaction involving loss of triphenylphosphine phenylimide. By lowering the reaction temperature to 40 °C, we could significantly increase the amount of **6m** (ratio **6m**/**7m** = 90:10). However, we observed that the ratio (**6**/**7**) was strongly influenced by the type of amine (R₃) employed. Therefore, aryl isocyanates will not be included at the fourth position (R₄) of diversity in the synthesis of libraries.

The described synthetic route to the 1,3,5-triazino-benzimidazoles **6** has been expanded to a wide range of amino acids (R₁ = H, R₂ = COCH(R')NHCO), amines (R₃), and alkyl isocyanates (R₄). For each potential building block tested, only those yielding individual control-1,3,5-triazinones **6** having crude purities >80% were considered for inclusion in the preparation of a combinatorial library. We are in the course of synthesizing a mixture-based triazino-benzimida-

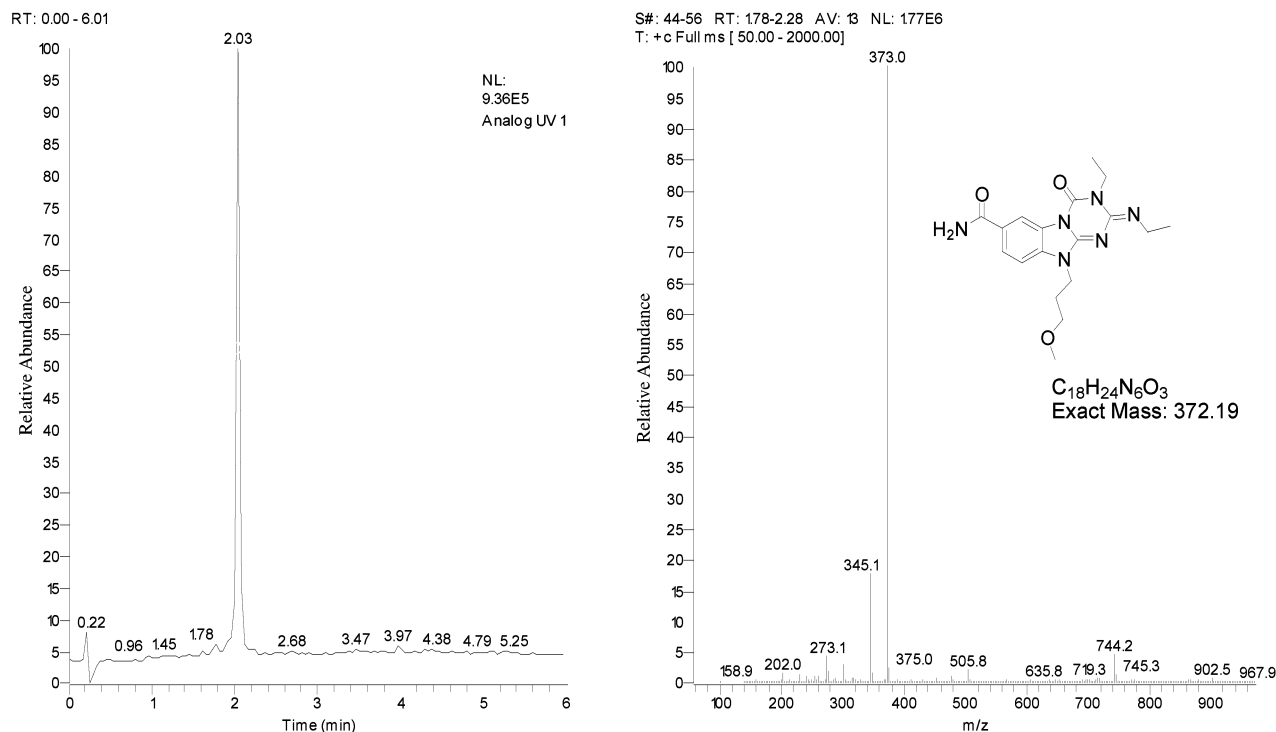


Figure 1. LC/MS spectra of the 1,3,5-triazino[1,2-*a*]benzimidazole **6h** obtained from 3-methoxypropylamine and ethyl isocyanate.

zole library employing the presented solid-phase Tandem Aza-Wittig/heterocumulene-mediated annulation reaction.

To further increase the number of diversities, we attached 4-fluoro-3-nitrophenylisocyanate to MBHA resin or N-alkylated MBHA resin. The N-alkylated resin was obtained by acylation of the amino group with a wide variety of carboxylic acids and subsequent reduction of the amide bond with borane in THF.¹⁴ At room temperature, the nucleophilic substitution of the fluoro group by an amine (R₃) was complete only for nonalkylated 4-fluoro-3-nitrophenyl ureas **1** (R₁ = H). By increasing the reaction temperature (50 °C) and the amine concentration (0.5 M in DMSO), complete displacement of the fluoro group was achieved, even when alkylated 4-fluoro-3-nitrophenyl ureas **1** (R₁ = ethyl, 2-phenylethyl) and bulky amines were employed. The generated resin-bound 4-amino-3-nitrophenyl ureas **2** were treated under the same conditions as described above to afford the corresponding urea-linked 2-aminobenzimidazoles **3** in high purity (>90%). The tandem Aza-Wittig-annulation reaction provided the corresponding urea-linked 2-imino-4-oxo-1,3,5-triazines **6** in purities ranging from 45 to 60% (Table 1, Scheme 1). Because of the low purity, the urea-linked compounds **6** will not be considered for library synthesis. Nevertheless, the herein presented reaction sequence provided access to a range of individual compounds **6** bearing a urea moiety, which will be tested after purification in various assays for their pharmacological properties. The solid-phase Aza-Wittig/heterocyclization reaction of several other resin-bound heterocyclic amines via iminophosphoranes is under investigation.

Conclusion

In summary, an efficient solid-phase synthesis of pharmacologically promising, fused 2-imino-4-oxo-1,3,5-triazines

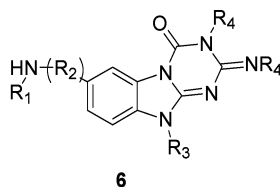
is presented. The synthetic design includes the synthesis of a large array of resin-bound 2-aminobenzimidazoles, the generation of iminophosphoranes from the corresponding resin-bound 2-aminobenzimidazoles, and the solid-phase Aza-Wittig-reaction of the iminophosphorane intermediates to highly reactive carbodiimides, which undergo an intramolecular cyclization reaction. The described transformations are applicable to the preparation of a large number of individual compounds as well as mixture-based combinatorial libraries.

Experimental Section

Commercially available reagents were used without further purification unless otherwise stated. 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 × 25 cm). LC/MS (ESI) results were recorded on a Finnigan Mat LCQ (ThermoQuest Corporation, CA) using a Betasil C18 column (3 μm, 100 Å, 3 × 50 mm) at 214 nm. The ¹H and ¹³C NMR spectra were recorded in DMSO-*d*₆ solutions at 500 MHz (¹H) and 125 MHz (¹³C), respectively. The yield for purified products was determined on the basis of the loading of the polymeric support starting from 50 mg of the resin.

Typical Procedure for the Synthesis of Resin-Bound Compounds 2. *p*-Methylbenzhydramine (MBHA) resin (50 mg, 1.10 meq/g, 100–200 mesh) was sealed inside a polypropylene mesh packet. Polypropylene bottles were used for all of the reactions. The resin was washed with dichloromethane (DCM), followed by neutralization with 5% diisopropylethylamine (DIEA) in DCM and washed with DCM prior to any coupling reaction.

(1) Preparation of Compounds 2 (R₂ = CO, COCH₂, R'NHCO). (a) **Coupling of an Amino Acid to the Resin.**

Table 1. Formation of 1,3,5-Triazino[1,2-*a*]benzimidazoles from Resin-Bound Benzimidazoles

	R ₁	R ₂	R ₃	R ₄	mass (M+H ⁺) (found/calc.)	yield ^a (%)	purity ^b (%)
6a	H	CO	butyl	hexyl	469.3/469.3	74	86
6b	H	CO	hexyl	hexyl	497.4/497.4	70	85
6c	H	CO	cyclohexyl	hexyl	495.3/495.3	73	83
6d	H	CO	1-ethylpropyl	hexyl	483.3/483.3	83	85
6e	H	CO	3-methoxypropyl	hexyl	485.3/485.3	75	86
6f	H	CO	butyl	ethyl	357.2/357.1	83	90
6g	H	CO	cyclohexyl	ethyl	383.2/383.0	76	90
6h	H	CO	3-methoxypropyl	ethyl	373.4/373.1	80	84
6i	H	CO	butyl	butyl	413.3/413.1	85	88
6j	H	CO	cyclohexyl	butyl	439.3/439.1	76	85
6k	H	CO	3-methoxypropyl	butyl	429.3/429.1	82	87
6l	H	CO	3-methoxypropyl	cyclohexyl	481.2/481.0	82	83 ^c
6m	H	CO	butyl	phenyl	453.2/453.2	80	46
6n	H	CO	butyl	phenyl	453.4/453.2	85	81 ^d
6n	H		butyl	hexyl	540.4/540.5	82	84
6o	H		3-methoxypropyl	hexyl	556.5/556.4	94	86
6p	H		butyl	ethyl	428.1/428.2	74	92
6q	H		3-methoxypropyl	ethyl	444.1/444.2	91	89
6r	H		butyl	butyl	484.3/484.3	88	89
6s	H		butyl	ethyl	504.4/504.3	83	90
6t	H	CONH	cyclohexyl	hexyl	510.5/510.4	98	45
6u	ethyl	CONH	cyclohexyl	hexyl	538.6/538.4	75	52
6v	PhCH ₂ CH ₂	CONH	butyl	hexyl	588.7/588.4	84	60

^a Crude yields were calculated on the basis of the initial loading of the resin (1.10 meq/g). ^b Purities were determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5–95% acetonitrile in water (0.05% TFA) over 10 min at 214 nm. ^c 90 equiv of cyclohexylisocyanate, 100 °C, 3 days. ^d 30 equiv of phenylisocyanate, 40 °C, 3 days.

Boc-amino acid (6 equiv, 0.1 M in anhydrous DCM) was coupled to MBHA resin for 2 h at room temperature using the coupling reagent DIC (6 equiv, 0.1 M), followed by washes with DMF (3×) and DCM (3×). The Boc group was deprotected using 55% TFA in DCM for 30 min, followed by neutralization with 5% DIEA in DCM. Completeness of the coupling was verified by the ninhydrin test.¹⁵

(b) N-Acylation with 4-Fluoro-3-nitrobenzoic acid. 4-Fluoro-3-nitrobenzoic acid (7 equiv, 0.1 M in anhydrous DMF) was coupled overnight at room temperature to MBHA resin (R₂ = CO) or resin-bound amino acids (R₂ = COCHR'NHCO) using DIC (7 equiv, 0.1 M), followed by

washes with DMF (4×) and DCM (3×). Completeness of the coupling was verified by the ninhydrin test.¹⁵

(c) Nucleophilic Substitution of the Fluoro Group. The resulting *o*-fluoro-nitro derivative was treated with a primary amine (12 equiv, 0.1 M in anhydrous DMF) in the presence of DIEA (12 equiv, 0.1 M) overnight at room temperature, followed by washes with DMF (4×), DCM (2×), IPA (2×), and DCM (3×).

(2) Preparation of Compounds 2 (R₂ = CONH). **(a) Synthesis of Resin-Bound Secondary Amines.** MBHA resin was acylated with 10 equiv of a carboxylic acid (0.1 M in anhydrous DMF) in the presence of DIC (10 equiv,

0.1 M) and HOBt (10 equiv, 0.1 M) overnight at room temperature, followed by washes with DMF (4 \times) and DCM (3 \times). Completeness of the coupling was verified by the ninhydrin test.¹⁵ Reduction of the amide bond¹⁴ was performed in 50-mL Kimax tubes under nitrogen using 1 M BH₃-THF (40 equiv). The tubes were heated at 65 °C for 72 h. The solution was decanted and quenched with MeOH. Following washing (3 \times MeOH, 1 \times THF, 1 \times MeOH), the resin was treated overnight with piperidine at 65 °C. The resin was washed with DMF (3 \times), DCM (3 \times) and MeOH (1 \times) to yield the corresponding resin-bound secondary amines.

(b) Preparation of Resin-Bound Ureas Using 4-Fluoro-3-nitrophenyl Isocyanate. MBHA resin (R₁ = H) or resin-bound secondary amines (R₁ = PhCH₂CH₂, CH₃CH₂) were treated with 4-fluoro-3-nitrophenyl isocyanate (7 equiv, 0.1 M in anhydrous DMF) overnight at room temperature, followed by washes with DMF (5 \times) and DCM (3 \times).

(c) Nucleophilic Substitution of the Fluoro Group. The resulting *o*-fluoro-nitro derivative was treated with a primary amine (80 equiv, 0.5 M in DMSO) in the presence of pyridine (20 equiv) overnight at 50 °C, followed by washes with DMF (4 \times) and DCM (3 \times).

Typical Procedure for the Synthesis of Resin-Bound 2-Amino-benzimidazoles 3. (1) Reduction of the Aromatic Nitro Group. A 2.030-g (14.70 mmol, 26 equiv) portion of K₂CO₃, 2.300 g (13.20 mmol, 24 equiv) of Na₂S₂O₄, and 0.293 g (0.36 mmol, 0.65 equiv) of 1,1'-dioctadecyl-4,4'-bipyridinium dibromide in 29 mL of DCM and 1.2 mL of H₂O were added to 550 mg of resin-bound compound **2**. The reaction mixture was vigorously shaken overnight at room temperature. Following extensive washes with a 50/50 solution of DCM/1% AcOH in H₂O (5 \times), ethyl acetate/H₂O (1/1, 4 \times), acetone (4 \times), IPA (3 \times), DCM (2 \times), DIPEA (5% in DCM, 3 \times), and DCM (2 \times), the resin was dried in vacuo.

(2) 2-Amino-benzimidazole Formation. A 550-mg portion of the resin-bound *o*-dianiline derivative was treated with 583 mg (5.50 mmol, 10 equiv, 0.1 M in DCM) of cyanogen bromide under nitrogen overnight at room temperature, followed by washes with DCM (4 \times), IPA (2 \times), and DCM (3 \times). The resin was dried in vacuo.

Typical Procedure for the Preparation of Compounds 6 by Tandem Aza-Wittig/Heterocyclization-Reaction. The reaction was performed in 50 mL Kimax tubes under argon. A 1.080-g portion of PPh₃ (4.11 mmol, 25 equiv) and 638 μ L (4.05 mmol, 25 equiv) of DEAD were added to 150 mg of the resin-bound benzimidazole derivative **3** in 15 mL of anhydrous THF. The reaction mixture was shaken for 48 h at room temperature. The solution was removed via cannula. The resulting resin-bound iminophosphorane intermediate **4** was washed with anhydrous toluene (1 \times) under argon. The resin was treated under argon with the respective isocyanate (15 equiv, 0.2 M) in 11 mL anhydrous toluene for 24 h at 100 °C. The resin was vigorously washed with toluene (11 \times , 15 min each) and DCM (3 \times). The final compound **6** was obtained after cleavage from the resin by anhydrous HF in the presence of anisole for 1.5 h at 0 °C, extracted with 95% acetic acid in H₂O, and lyophilized.

1-Butyl-2-imino-2,3-dihydro-1H-benzimidazol-5-carboxamide (3a). ¹H NMR (DMSO-*d*₆): δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.30–1.37 (m, 2H), 1.63–1.69 (m, 2H), 4.14 (t, *J* = 7.3 Hz, 2H), 7.39 (br, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.88 (s, 1H), 8.05 (br, 1H), 8.86 (s, 2H). ¹³C NMR (DMSO-*d*₆): δ 13.6, 19.2, 22.6, 42.2, 109.8, 110.9, 122.6, 128.8, 129.9, 132.6, 151.0, 167.2. MS (ESI): calcd [MH⁺], 233.1; found, 233.1.

***N*-(*S*)-Alanyl-1-butyl-2-imino-2,3-dihydro-1H-benzimidazole-5-carboxamide (3p).** ¹H NMR (DMSO-*d*₆): δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.33 (m, 5H), 1.67 (m, 2H), 4.15 (t, *J* = 7.2 Hz, 2H), 4.43 (m, 1H), 6.99 (br, 1H), 7.40 (br, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.91 (s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 8.84 (s, 2H). ¹³C NMR (DMSO-*d*₆): δ 13.6, 18.0, 19.2, 29.6, 42.2, 48.9, 109.7, 111.0, 122.8, 128.7, 129.8, 132.6, 150.9, 165.3, 174.4. MS (ESI): calcd [MH⁺], 304.2; found, 304.0.

***N*-(1-Butyl-2-imino-2,3-dihydro-1H-benzimidazol-5-yl)-urea (3t).** ¹H NMR (DMSO-*d*₆): δ 0.89 (t, *J* = 7.5 Hz, 3H), 1.28–1.33 (m, 2H), 1.62–1.65 (m, 2H), 4.05 (t, *J* = 7.3 Hz, 2H), 5.95 (br, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.78 (s, 1H), 8.57 (s, 2H), 8.84 (s, 1H), 12.7 (s, 1H). ¹³C NMR (DMSO-*d*₆): δ 13.6, 19.2, 29.6, 41.9, 100.9, 110.2, 113.1, 124.6, 129.1, 137.3, 149.6, 156.1. MS (ESI): calcd [MH⁺], 248.2; found, 248.3.

***N*-(1-Butyl-2-imino-2,3-dihydro-1H-benzimidazol-5-yl)-*N'*-(2-phenylethyl)urea (3v).** ¹H NMR (DMSO-*d*₆): δ 0.89 (t, *J* = 7.6 Hz, 3H), 1.29–1.34 (m, 2H), 1.62–1.65 (m, 2H), 2.72–2.77 (m, 2H), 4.05 (t, *J* = 7.3 Hz, 2H), 6.21 (t, *J* = 5.7 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 7.19–7.25 (m, 6H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 8.50 (s, 2H), 8.72 (s, 1H), 12.6 (br, 1H). ¹³C NMR (DMSO-*d*₆): δ 13.6, 19.2, 29.6, 35.8, 39.8, 41.9, 100.9, 110.2, 113.0, 124.6, 126.1, 128.3, 126.8, 129.1, 137.1, 139.5, 149.5, 155.2. MS (ESI): calcd [MH⁺], 352.2; found, 352.4.

10-Butyl-3-hexyl-2-hexylimino-4-oxo-2,3,4,10-tetrahydro-[1,3,5]triazino[1,2-*a*]benzimidazole-7-carboxamide (6a). ¹H NMR (DMSO-*d*₆): δ 0.87–0.89 (m, 9H), 0.93 (t, *J* = 7.3 Hz, 3H), 1.30–1.34 (m, 8H), 1.35–1.40 (m, 6H), 1.61–1.69 (m, 4H), 1.78–1.84 (m, 2H), 3.58 (dt, *J* = 5.5, 6.6 Hz, 2H), 4.07 (t, *J* = 7.5 Hz, 2H), 4.32 (t, *J* = 6.8 Hz, 2H), 7.55 (br, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.27 (br, 1H), 8.65 (s, 1H), 9.30 (t, *J* = 5.5 Hz, 1H). ¹³C NMR (DMSO-*d*₆): δ 13.4, 13.8, 19.1, 21.9, 22.0, 25.4, 25.8, 26.3, 28.3, 29.5, 30.9, 42.4, 42.5, 111.1, 113.8, 124.6, 126.2, 131.0, 132.6, 144.7, 149.8, 154.2, 165.6. MS (ESI): calcd [MH⁺], 469.3; found, 469.3.

10-Butyl-3-phenyl-2-phenylimino-4-oxo-2,3,4,10-tetrahydro-[1,3,5]triazino[1,2-*a*]benzimidazole-7-carboxamide (6m). ¹H NMR (DMSO-*d*₆): δ 0.85 (t, *J* = 7.3 Hz, 3H), 1.27–1.34 (m, 2H), 1.74–1.79 (m, 2H), 4.21 (t, *J* = 6.8 Hz, 2H), 7.33–7.37 (m, 3H), 7.44–7.47 (m, 2H), 7.58 (br, 1H), 7.64–7.66 (m, 2H), 7.68–7.75 (m, 3H), 8.01 (d, *J* = 8.7 Hz, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 8.28 (br, 1H), 8.62 (s, 1H), 10.17 (br, 1H). ¹³C NMR (DMSO-*d*₆): δ 13.3, 19.0, 29.4, 42.6, 111.6, 113.8, 124.5, 126.0, 126.5, 127.1, 128.6, 129.0, 130.7, 131.0, 131.4, 132.0, 132.5, 144.6, 150.0, 166.5. MS (ESI): calcd [MH⁺], 453.4; found, 453.2.

10-Butyl-3-phenyl-2,4-dioxo-2,3,4,10-tetrahydro[1,3,5]-triazino[1,2-*a*]benzimidazole-7-carboxamide (7m). ¹H NMR (DMSO-*d*₆): δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.37–1.42 (m, 2H), 1.75–1.82 (m, 2H), 4.17 (t, *J* = 7.2 Hz, 2H), 7.34–7.36 (m, 2H), 7.42 (br, 1H), 7.44–7.46 (m, 1H), 7.49–7.53 (m, 2H), 7.74 (d, *J* = 8.7 Hz, 1H), 8.00–8.02 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.13 (br, 1H), 8.51 (d, *J* = 1.6 Hz, 1H). ¹³C NMR (DMSO-*d*₆): δ 13.6, 19.3, 29.5, 41.8, 109.8, 113.2, 125.2, 128.2, 128.8, 128.9, 129.6, 133.3, 135.7, 147.0, 151.7, 154.2, 167.0. MS (ESI): calcd [MH⁺], 378.2; found, 378.1.

***N*-(*S*-Alanyl-10-butyl-3-ethyl-2-ethylimino-4-oxo-2,3,4,10-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole-7-carboxamide (6p).** ¹H NMR (DMSO-*d*₆): δ 0.92 (t, *J* = 7.6 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.33–1.40 (m, 5H), 1.78–1.85 (m, 2H), 3.60–3.65 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.34 (t, *J* = 6.6 Hz, 2H), 4.42–4.49 (m, 1H), 7.01 (br, 1H), 7.44 (br, 1H), 7.95 (d, *J* = 8.7 Hz, 1H), 8.17–8.19 (d, *J* = 8.7 Hz, 1H), 8.66 (s, 1H), 8.78 (d, *J* = 7.3 Hz, 1H), 9.34 (t, *J* = 5.2 Hz, 1H). ¹³C NMR (DMSO-*d*₆): δ 11.8, 13.4, 14.0, 18.0, 19.1, 29.5, 37.7, 38.1, 42.3, 49.0, 111.1, 113.8, 124.5, 126.4, 130.9, 132.5, 144.6, 149.9, 154.0, 164.7, 174.3. MS (ESI): calcd [MH⁺], 428.2; found, 428.1.

***N*-(*S*-Phenylalanyl-10-butyl-3-ethyl-2-ethylimino-4-oxo-2,3,4,10-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole-7-carboxamide (6s).** ¹H NMR (DMSO-*d*₆): δ 0.92 (t, *J* = 7.5 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.32–1.39 (m, 2H), 1.78–1.83 (m, 2H), 3.02 (dd, *J* = 13.5, 11.0 Hz, 1H), 3.14 (dd, *J* = 13.5, 3.9 Hz, 1H), 3.61 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 4.67–4.71 (m, 1H), 7.13–7.16 (m, 2H), 7.22–7.25 (m, 2H), 7.34–7.36 (m, 2H), 7.63 (br, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 8.59 (s, 1H), 8.87 (d, *J* = 8.5 Hz, 1H), 9.33 (t, *J* = 5.3 Hz, 1H). MS (ESI): calcd [MH⁺], 504.3; found, 504.4.

***N*-(10-Cyclohexyl-3-hexyl-2-hexylimino-4-oxo-2,3,4,10-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazol-7-yl)-urea (6t).** ¹H NMR (DMSO-*d*₆): δ 0.88 (m, 6H), 1.23–1.38 (m, 15H), 1.59–1.73 (m, 5H), 1.87–1.90 (m, 4H), 2.27–2.30 (m, 2H), 3.50–3.54 (m, 2H), 4.00 (t, *J* = 7.3 Hz, 2H), 4.54–4.58 (m, 1H), 5.97 (br, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 8.56 (s, 1H), 8.96 (s, 1H), 8.98–8.99 (m, 1H). ¹³C NMR (DMSO-*d*₆): δ 13.9, 21.9, 22.0, 24.7, 25.1, 25.4, 25.9, 26.3, 28.3, 29.2, 30.9, 42.3, 42.5, 55.1, 103.6, 112.2, 116.4, 123.9, 125.1, 138.2, 144.9, 147.9, 153.3, 155.8. MS (ESI): calcd [MH⁺], 510.4; found, 510.5.

***N*-(10-Butyl-3-hexyl-2-hexylimino-4-oxo-2,3,4,10-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazol-7-yl)-*N'*-(2-phenylethyl)urea (6v).** ¹H NMR (DMSO-*d*₆): δ 0.86–0.93 (m, 9H), 1.23–1.38 (m, 14H), 1.60–1.66 (m, 4H), 1.76–1.79 (m, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 3.35–3.38 (m, 2H), 3.50–3.56 (m, 2H), 4.01 (t, *J* = 7.2 Hz, 2H), 4.23 (t, *J* = 6.6 Hz, 1H), 6.23 (t, *J* = 5.6 Hz, 1H), 7.20–7.26 (m, 3H), 7.30–7.33 (m, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 8.55 (s, 1H), 8.95 (s, 1H), 8.98–8.99 (m, 1H). MS (ESI): calcd [MH⁺], 588.4; found, 588.7.

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Supporting Information Available. Copies of LC/MS, ¹H, and ¹³C NMR spectra of **3a**, **3p**, **3t**, **3v**, **6a**, **6m**, **7m**, **6p**, **6s**, **6t** and **6v**. Description of compounds **6b–6u**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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