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Fast and Facile Synthesis of 4-Nitrophenyl 2-Azidoethylcarbamate Derivatives from *N*-Fmoc-Protected α-Amino Acids as Activated Building Blocks for Urea Moiety-Containing Compound Library

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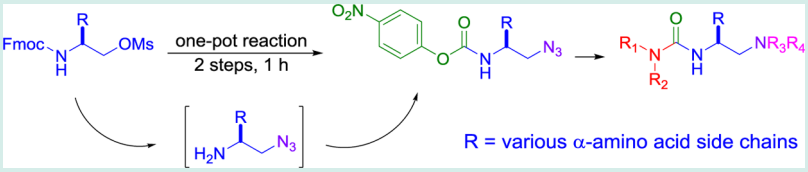
Supporting Information



ABSTRACT: A fast and facile synthesis of a series of 4-nitrophenyl 2-azidoethylcarbamate derivatives as activated urea building blocks was developed. The *N*-Fmoc-protected 2-aminoethyl mesylates derived from various commercially available *N*-Fmoc-protected α-amino acids, including those having functionalized side chains with acid-labile protective groups, were directly transformed into 4-nitrophenyl 2-azidoethylcarbamate derivatives in 1 h via a one-pot two-step reaction. These urea building blocks were utilized for the preparation of a series of urea moiety-containing mitoxantrone-amino acid conjugates in 75−92% yields and parallel solution-phase synthesis of a urea compound library consisted of 30 members in 38−70% total yields.

KEYWORDS: *urea building block, one-pot synthesis, parallel synthesis, amino acid, microwave-assisted*

The urea functionality exists in a variety of biologically active compounds, and is an essential component in many clinically useful drugs with various indications, such as anticancer,[1] antiviral,[2] antibacterial,[3] antiepileptic,[4] neuroleptic,[5] antiarrhythmic,[6] etc., approved by U.S. FDA in last two decades. Incorporation of the urea group into peptides as a bioisosteric replacement for the amide group provided oligoureas as unnatural biopolymers with different physicochemical and biological activity from the natural peptides. For example, an oligourea derived from HIV-1 Tat protein was resistant to proteinase K degradation and retained the high affinity and selectivity to the trans-activation responsive region (TAR) RNA.[7]

Several synthetic approaches provide activated urea building blocks derived from α-amino acids for the preparation of *N,N′*-linked oligoureas. Burgess and co-workers first demonstrated the synthesis of *N*-phthalimide-protected isocyanates in situ with phosgene as urea monomers for the solid-phase synthesis of oligoureas.[8,9] Later, Schultz et al. described a series of 4-nitrophenyl 2-azidoethylcarbamates prepared from either *N*-Boc- or *N*-2-(trimethylsilyl)ethoxycarbonyl (Teoc)-protected α-amino acids as urea monomers.[10] Liskamp and co-workers developed methods for the preparation of *N*-Boc- and *N*-Fmoc-protected 4-nitrophenyl carbamates as urea monomers from the corresponding *N*-Boc- and *N*-Fmoc-protected α-amino acids.[11,12] Guichard et al. described the synthesis of *N*-Boc- and *N*-Fmoc-protected *O*-succinimidyl-carbamates as activated urea building blocks from the corresponding *N*-Boc- and *N*-Fmoc-protected α- and β-amino acids.[13−17] In the Schultz's methodology,[10] the handling of highly toxic chemicals, such as azidic acid and triphosgene, and the harsh reaction conditions, such as 60% $N_2H_4{\cdot}H_2O$ in DMF to remove the phthaloyl group, were avoided. In addition, those azido-substituted urea monomers are versatile, which can serve as precursors to amines and participate in the click reaction, Staudinger ligation, and Curtius rearrangement, lending themselves to various combinatorial libraries.

A series of mitoxantrone-amino acid conjugates (MAC) demonstrated more potent anticancer activity and lower drug resistance than mitoxantrone, which has been used in clinic for many years (Figure 1).[18−20] As a continued effort to develop novel anticancer agents with higher metabolic stability, a focused urea moiety-containing library, urea-MAC was designed (Figure 1). To increase the diversity, the Schultz's urea monomers derived from various α-amino acids including those with functional side chains protected by acid-labile protective groups were chosen as the building blocks for the construction of urea-MAC library.

Based on previous structure−activity relationships of MAC, the urea building blocks derived from the arginine, lysine, and tyrosine are the most promising members in the focused library. Therefore, *N*-Teoc-protected α-amino acid derivatives are needed for the synthesis of these urea monomers with acid-labile side-chain protective groups in Schultz's methodology.

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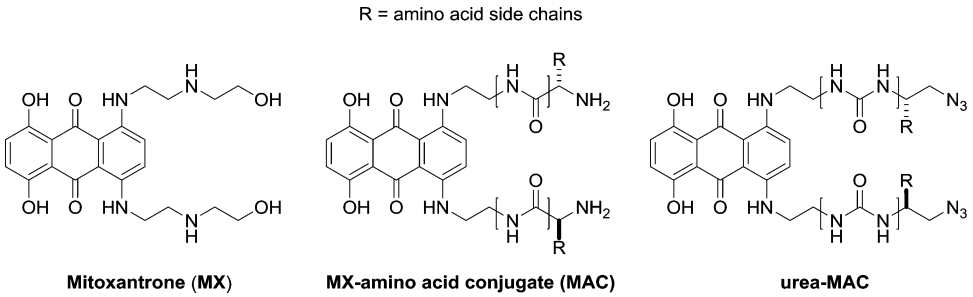
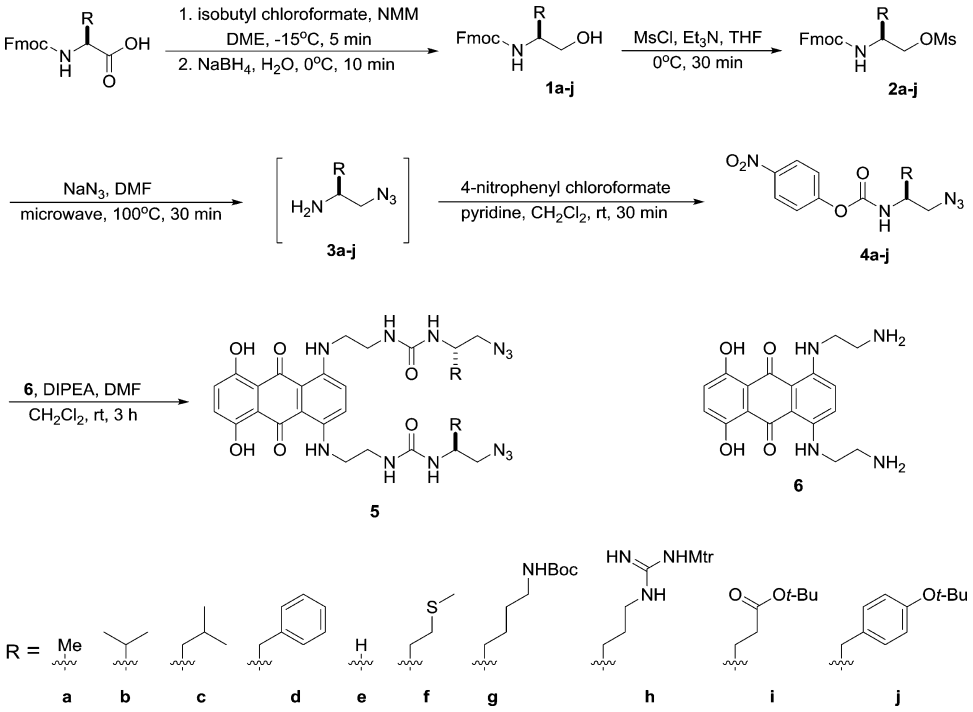


Figure 1. Structures of mitoxantrone-amino acid conjugate (MAC).

Scheme 1. Synthesis of 4-Nitrophenyl 2-Azidoethylcarbamates 4 and Urea-MAC 5



The necessity of additional protection and deprotection steps for the *N*-Teoc protective group resulted in tedious purification processes and difficulties to prepare the activated urea building blocks in parallel way. In addition, the isolation and purification of highly polar, water-soluble, and volatile low-molecular weight azido amine intermediates (i.e., **3a**−**c** and **3e**) were troublesome. Thus, here we report a concise, fast, and feasible methodology for parallel synthesis of various 4-nitrophenyl 2-azidoethylcarbamate derivatives **4** as activated urea building blocks via a one-pot, two-step synthesis from the *N*-Fmoc-protected amino mesylates **2**. Utilization of these activated urea building blocks **4** for the preparation of urea-MAC **5** and a urea-moiety containing compound library **7**-**9** by parallel solution-phase synthesis was demonstrated.

The *N*-Fmoc-protected amino alcohols **1a**−**j** were prepared using the corresponding *N*-Fmoc-protected α-amino acids by a method described by Rodriguez et al.[21] Alcohols **1a**−**j** were obtained as solids in high yields and directly used without further purification for the following steps. Treatment of the crude alcohols **1a**−**j** with methanesulfonyl chloride provided the *N*-Fmoc-protected amino mesylates **2a**−**j** in high yields and purity as shown in Scheme 1.[22]

In original Schultz's methodology, the (2-azidoethyl)amines **3** were prepared via nucleophilic substitution of *N*-Boc- or *N*-Teoc-protected amino mesylates using NaN_3 followed by deprotection reactions. We envisioned that if the *N*-Fmoc-protected amino mesylates **2a**−**j** were used in the same reaction condition, the Fmoc-protective group could be removed simultaneously by the excess amount of NaN_3 in the nucleophilic reaction condition, and therefore the instability of the Fmoc group can be utilized to shorten the route for the preparation of urea building blocks. The model study was conducted by treatment of compound **2d** with 5 eq of NaN_3 in DMF at 60−70 °C for 8 h. The reaction provided a complicate mixture containing the desired product **3d**, but the yield was low and time-consuming column chromatography was necessary to obtain **3d** in high purity. In addition, the high polarity and water solubility of azido amines **3** and the high volatility of low-molecular weight azido amines (i.e., **3a**−**c**, and **3e**) significantly increased the difficulty in purification and resulted in lower yields.

The large excess amount of NaN_3 and the long reaction time were responsible for the undesired intramolecular cyclization, decomposition, and rearrangement. In Govindaraju's study, *N*-Boc- and *N*-Cbz-protected amino azides were synthesized from corresponding mesylates in the presence of 1.5−2.0 equiv of NaN_3 in 2−12 min using microwave-assisted heating, in which both the reaction time and the amount of NaN_3 used were

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substantially reduced in comparison with conventional heating.[23] Moreover, if only a stoichiometric amount of NaN_3 is used, then the potential interaction between the excess NaN_3 and 4-nitrophenyl chloroformate, which is the reagent used in the following reaction step, would be prevented. Therefore, the tedious and time-consuming isolation and purification steps for azido amines **3** may be eliminated and the 4-nitrophenyl 2-azidoethylcarbamate derivatives **4** can be obtained directly from the *N*-Fmoc-protected mesylates **2** by this one-pot two-step synthesis strategy.

Amino mesylate **2d** was used to explore the reaction parameters for the microwave-assisted nucleophilic substitution (Table 1). Initially, a mixture of NaN_3 (1.5 equiv) and **2d** (0.1 M) in DMF (3 mL) was heated in a sealed heavy-duty glass tube using microwave synthesizer at 80 °C for 20 min (entry 1). The reaction was complete and only the azido amine **3d** and the dibenzofulvene derivatives were observed by TLC monitoring. When the reaction temperature increased to 100 °C, the reaction was finished in 10 min (entry 2). When the amount of NaN_3 was reduced, the rate of reaction was significantly decreased. Using 1.3 equiv and 1.2 equiv of NaN_3 at 100 °C, the reaction was complete in 20 and 30 min, respectively (entries 3 and 4). Attempt to further accelerate the reaction by increasing the reaction temperature to 120 °C resulted in unknown products (entry 5). When the amount of NaN_3 was reduced to 1.1 equiv, 40 min at 100 °C was needed for complete reaction (entry 6).

Table 1. Microwave-Assisted Heating Reaction Conditions[a]

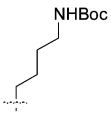
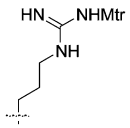
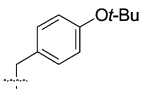
entry	NaN_3 (equiv)	temp (°C)	time (min)	results
1	1.5	80	20	complete reaction
2	1.5	100	10	complete reaction
3	1.3	100	20	complete reaction
4	1.2	100	30	complete reaction
5	1.2	120	10	bad mixture
6	1.1	100	40	complete reaction

[a]A solution of **2d** (0.1 M, 3 mL) in anhydrous DMF in a sealed tube was used.

Therefore, the *N*-Fmoc-protected amino mesylates **2a−j** and 1.3 equiv of NaN_3 were heated at 100 °C using microwave for 30 min and then cooled in an ice bath. A solution of 4-nitrophenyl chloroformate (1.6 equiv) in CH_2Cl_2 and pyridine (1.8 equiv) were added to the cooled reaction mixture containing the azido amine intermediates **3a−j** and then the solution was stirred at room temperature for 30 min to obtain 4-nitrophenyl 2-azidoethylcarbamates **4a−j** (Scheme 1). The yields were acceptable for our need, and therefore no attempt was made to optimize the chemical yields for individual product. Carbamates **4a−j** were afforded as white to pale-yellow solids which are stable for months when stored in the refrigerator. Treatment of anthraquinone **6** with the activated urea building blocks **4** at room temperature in the presence of *N*,*N*-diisopropylethylamine yielded the urea-MAC **5** in the yields of 75−92% (Table 2). The cytotoxicity of urea-MAC **5** against different human cancer cell lines is currently under investigation and will be published in due course.

In comparison to the *N*-Boc- and *N*-Teoc-protected strategies, in which five and seven reaction steps, respectively were needed to prepare 4-nitrophenyl 2-azidoethylcarbamates **4** from commercially available protected α-amino acids, this *N*-Fmoc-protected one-pot strategy enabled the parallel synthesis of a variety of 4-nitrophenyl 2-azidoethylcarbamates by only three reaction steps from *N*-Fmoc-protected α-amino acids. Furthermore, this methodology is efficient and economic, since it significantly diminished the tedious purification processes, which were necessary in the previous methods.

Table 2. Structures, Melting Points, and Yields of Urea-MAC 5

Compd	amino acid derived from	R	mp (°C)	Yield (%)[a]
5d	Phe		212-215	76
5f	Met		214-216	75
5g	Lys		169-172	80
5h	Arg		131-135	92
5j	Tyr		190-192	80

[a]Isolated yields.

Previously, carbamates **4** have been used for the preparation of oligoureas by solid-phase synthesis.[7,10] In this study, the parallel synthesis of a urea-moiety containing compound library using activated monomers **4** via solution-phase strategy was investigated as shown in Scheme 2. Treatment of carbamates **4** with linear or cyclic amines at room temperature obtained azido ureas **7** in quantitative yields. In previous solid-phase synthesis of oligoureas, $SnCl_2$ was used for reduction of azido groups. However, it is not convenient to remove the Sn-related substances after reduction reaction in parallel solution-phase synthesis as in the solid-phase synthesis. Therefore, catalytic hydrogenation of compounds **7** using Pd/C under atmospheric hydrogen provided amino ureas **8**, which were then coupled with acyl chlorides at 0 °C to afford amido ureas **9** in 38−70% total yields. The crude products **7** and **8** were used directly for the following reactions without purification. Only compounds **9** were isolated to determine the total yields of these reactions. Most reactions produced the expected compounds as the major products except the benzoylation reaction of compound **8a**, which gave dibenzoyl-substituted imide **9b** as the major product.

In summary, a fast and facile synthesis of various 4-nitrophenyl 2-azidoethylcarbamate derivatives **4** as activated urea building blocks from the commercially available *N*-Fmoc-protected α-amino acids including those having functionalized side chains was demonstrated. The key reaction was a one-pot two-step reaction which provided the desired urea building blocks **4** starting from the *N*-Fmoc-protected amino mesylates **2** in 1 h with acceptable yields. The utility of these urea building

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Scheme 2. Solution-Phase Parallel Synthesis of Ureas 7−9

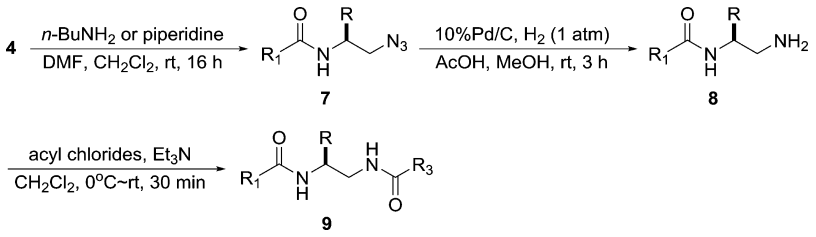
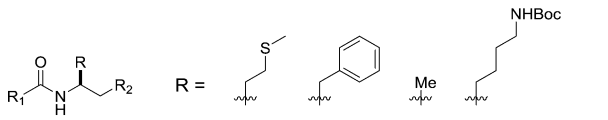


Table 3. Structures and Yields of Urea Compound Library



compd	R_1	R	R_2	total yield (%)[a,b]
7a	BuNH	M	N_3	>99[c]
7b	piperidinyl	M	N_3	ND
7c	BuNH	P	N_3	ND
7d	piperidinyl	P	N_3	ND
7e	BuNH	A	N_3	ND
7f	piperidinyl	A	N_3	ND
7g	BuNH	L	N_3	ND
7h	piperidinyl	L	N_3	ND
8a	BuNH	M	NH_2	ND
8b	piperidinyl	M	NH_2	ND
8c	BuNH	P	NH_2	ND
8d	piperidinyl	P	NH_2	ND
8e	BuNH	A	NH_2	ND
8f	piperidinyl	A	NH_2	ND
8g	BuNH	L	NH_2	ND
8h	piperidinyl	L	NH_2	ND
9a	BuNH	M	AcNH	66
9b	BuNH	M	Bz_2N	38
9c	piperidinyl	M	BzNH	66
9d	piperidinyl	M	BsNH	>99[c]
9e	BuNH	P	BzNH	70
9f	BuNH	P	BsNH	70
9g	piperidinyl	P	BzNH	44
9h	BuNH	A	AcNH	56
9i	BuNH	A	BzNH	>99[c]
9j	piperidinyl	A	BzNH	78
9k	BuNH	L	BzNH	58
9l	BuNH	L	BsNH	63
9m	piperidinyl	L	BzNH	64
9n	piperidinyl	L	BsNH	46

[a]ND: Not determined. Bz: Benzoyl. Bs: Benzenesulfonyl. [b]Isolated yield. [c]Crude yield.

blocks was demonstrated by the efficient preparation of a series of urea-MAC **5** under mild reaction conditions, and the parallel synthesis of a urea-moiety containing library consisted of 30 compounds in solution-phase. Thus, these methods are practical and could be suitable for the construction of various compound libraries for medicinal and combinatorial chemistry purposes.

EXPERIMENTAL PROCEDURES

Microwave Experimental Procedure. The reactions under microwave irradiation were conducted in sealed heavy-walled Pyrex tubes. Microwave heating was carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, P.O. Box 200, Matthews, NC 28106, USA), producing continuous irradiation at 2.45 GHz. The reaction temperature was measured and feedback controlled with an Infrared device under the reaction vessel.

General Procedure for the Preparation of *N*-Fmoc-Protected Amino Mesylates 2. To a stirred solution of *N*-Fmoc-protected amino alcohol (2.0 mmol) and Et_3N (0.36 mL, 2.6 mmol) in THF (10 mL) was added methanesulfonyl chloride (MsCl, 0.20 mL, 2.6 mmol) dropwise at 0 °C. After it was stirred for 30 min at room temperature, the reaction mixture was filtered, and then the filtrate was evaporated. The residue was purified by flash column chromatography to afford *N*-Fmoc-protected amino mesylate. Mesylates **2a−2d** are known compounds and were prepared according to the literature procedures.[22]

General Procedure for the Microwave-Assisted One-Pot Synthesis of 1-Azidoalkyl 4-Nitrophenyl Carbamates 4. A mixture of *N*-Fmoc-protected amino mesylate (0.50 mmol) and sodium azide (42.3 mg, 0.65 mmol) in DMF (5 mL) was heated by microwave (ramp time = 1 min, hold time = 30 min, temperature = 100 °C). The reaction mixture was cooled in an ice bath and then was added a solution of 4-nitrophenyl chloroformate (161 mg, 0.80 mmol) in CH_2Cl_2 (5 mL) followed by pyridine (70 μL, 0.90 mmol). The mixture was stirred at rt for 30 min and then diluted with diethyl ether (50 mL). The solution was washed with 1 N $KHSO_4$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography to afford 4-nitrophenyl (2-azidoethyl)-carbamate **4**.

General Procedure for the Preparation of 1,4-Bis-[(azidoalkyl)ureido]anthracene-9,10-diones 5. To a solution of diamine **6** (24.9 mg, 0.070 mmol) in 10% DMF/CH_2Cl_2 (4 mL) was added a solution of urea monomer **4f** (60 mg, 0.18 mmol) in 10% DMF/CH_2Cl_2 (1 mL) at room temperature. DIPEA (60 μL, 0.34 mmol) was added dropwise to the mixture, and stirred for 3 h. The resulting solution was diluted with CH_2Cl_2 (30 mL) and then washed with 10% $NH_4OH_{(aq)}$ (6 × 30 mL). The organic fraction was evaporated, and then treated with diethyl ether. The precipitate was collected by filtration to afford **5f** (38.3 mg, 75%) as a blue solid.

General Procedure for the Parallel Synthesis of Azido Urea 7. To a solution of urea monomer **4** (1.00 mmol) in 10% DMF/CH_2Cl_2 (4 mL) was added *n*-butylamine or piperidine (5.00 mmol) at room temperature and stirred for 16 h. After evaporation, the residue was dissolved in 2-propanol/$CHCl_3$ (1/9; 30 mL), washed with a mixture of water (20 mL) and 10 N NaOH (0.3 mL), followed by brine (20 mL), and evaporated to afford the crude azido urea **7** in quantitative yield, which was used in the following reaction without further purification. The

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^{1}H NMR spectrum of crude **7a** is shown in Figure 43 (Supporting Information), as a representative.

General Procedure for the Parallel Synthesis of Amino Urea 8. A mixture of azido urea **7** (1.00 mmol) and 10% Pd/C (50 mg) in 20% HOAc/MeOH (3 mL) was stirred at room temperature under H_2 (1 atm) for 3 h. The reaction mixture was filtered and evaporated. The residue was dissolved in CH_2Cl_2 (25 mL), and then anhydrous K_2CO_3 was added and stirred for 10 min to remove the trace of HOAc. The mixture was filtered and evaporated to obtain the crude amino urea **8**, which was used in the following reaction without further purification. Analytical samples of amino urea **8** were obtained by column chromatography using a solution of NH_4OH/MeOH/CH_2Cl_2 (1/9/90).

General Procedure for the Parallel Synthesis of Amido Urea 9. A mixture of amino urea **8** (0.50 mmol) and Et_3N (0.75 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C under N_2. Acyl chloride (0.55 mmol) in CH_2Cl_2 (0.5 mL) was added and stirred at 0 °C for 30 min. The resulting mixture was diluted with CH_2Cl_2 (25 mL), washed with 1 N HCl (20 mL × 2), 1 N NaOH (20 mL), and brine (20 mL), dried with $MgSO_4$, filtered, and evaporated to yield the crude amido urea **9**. Pure amido urea **9** was afforded by flash column chromatography using EtOAc and *n*-hexane (1:1).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00160.

Detailed experimental procedures, the ^{1}H and ^{13}C NMR spectra, and HRMS data for compounds **2e−j**, **4a−j**, **5**, and **7−9** (PDF)

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Author Contributions

L.-W.H. conceived and designed the experiments and wrote the manuscript and Supporting Information. Y.-Y.C., L.-T.C., H.-W.C., and C.-Y.Y. performed the experiments.

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Notes

The authors declare no competing financial interest.

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