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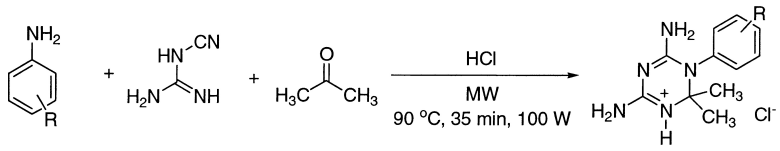

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Microwave-Assisted Parallel Synthesis of a 4,6-Diamino-2,2-dimethyl-1,2-dihydro-1-phenyl-*s*-triazine Library

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Microwave-assisted parallel synthesis of a library of 20 phenyl dihydrotriazines was successfully achieved and compared to an identical library generated by conventional parallel synthesis. Microwave synthesis dramatically decreased reaction times from an average of 22 h to 35 min, and compounds generated using microwave irradiation were purer. Isolated yields of all the compounds were comparable when the two methods were used.

Introduction

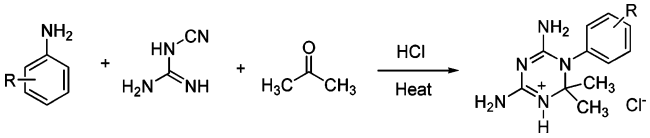
Combinatorial chemistry techniques have evolved very rapidly over the past 2 decades. Emphasis was initially placed on the development of solution-phase[1−3] and solid-phase[4−8] synthetic methods, as well as deconvolution methods for mixture synthesis.[9] In recent years, there has been a shift in emphasis toward the development of combinatorial synthetic techniques using microwave irradiation.[10] Microwave-assisted organic synthesis was first demonstrated independently by Gedye[11] and Giguere.[12] The use of microwave radiation for organic syntheses has improved the yields and purity of numerous classes of organic compounds.[13−16] This method has progressed so far that some reactions proceed even without the use of solvents[17] or catalysts.[18]

This paper aims to compare conventional and microwave-assisted organic syntheses of a library of phenyl dihydrotriazines. The 4,6-diamino-2,2-dimethyl-1,2-dihydro-1-phenyl-*s*-triazines are established inhibitors of dihydrofolate reductase (DHFR). Some of these phenyl dihydrotriazines have been used therapeutically as antimalarial,[19] anticancer,[20,21] and antiparasitic agents.[22,23]

Results and Discussion

The phenyl dihydrotriazines were first synthesized by E. J. Modest using the "one-pot−three-component" [24] and "two-component synthesis"[25] methods. The one-pot−three-component method (Scheme 1) was adopted herein as the conventional synthetic method for parallel synthesis of a library of phenyl dihydrotriazines because it produced very clean compounds in reasonable yields. In the conventional method, cyanoguanidine and acetone were kept constant while the substituted aniline was varied to produce a library of 20 phenyl dihydrotriazines in hydrochloride salt form. All reactions were carried out in individual reaction vessels under the same conditions. Although this one-pot−three-component synthesis has been well-established for synthesizing phenyl dihydrotriazines, the time to complete each reaction is very long. Most compounds in our library took approximately 22 h to be formed using this method. Microwave-assisted syntheses were attempted for the same library of phenyl dihydrotriazines with the aim of reducing the reaction time and producing purer compounds in higher yields.

Scheme 1. One-Pot−Three-Component Synthesis of Phenyl Dihydrotriazines



Optimization of Microwave-Assisted Synthesis. Microwave-assisted organic synthesis can be carried out with or without a solvent. Choosing an appropriate solvent is critical for successful synthesis because the solvent couples with the microwaves to cause a rapid rise in the temperature of the reaction mixture. In the synthesis of phenyl dihydrotriazines, acetone is a medium absorbing solvent that can couple well with microwave radiation during chemical reactions.[26]

In the optimization of these microwave-assisted syntheses, three parameters were monitored closely: temperature, reaction time, and microwave irradiation power. The temperature used for the conventional syntheses was approximately 56−60 °C, which is the boiling point of acetone. For the microwave-assisted syntheses, the temperature could be increased beyond the boiling point of acetone because the reactions were carried out in a sealed tube under a pressurized atmosphere. Reactions using 2-chloroaniline, cyanoguanidine, and acetone were carried out from 65 to 110 °C in increments of 5 °C (Scheme 2). All reactions were carried out at a maximum power of 300 W for 5 min, and the isolated yields were recorded (Table 1).

All compounds formed within 5 min, and the yields were similar when synthesized at temperatures between 65 and 85 °C. The yield was highest at 90 °C. Temperatures above 90 °C caused a reduction in yields. Above 100 °C, the

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Scheme 2. Synthesis of 4,6-Diamino-2,2-dimethyl-1,2-dihydro-1-2′-chlorophenyl-*s*-triazine Hydrochloride

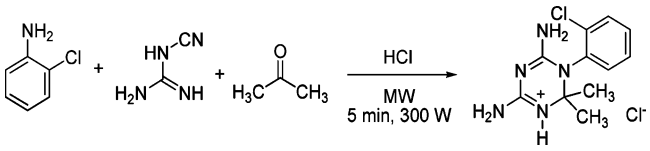


Table 1. Temperature Optimization of Microwave-Assisted Synthesis

temp (°C)	yield[a] (%)
65	52
70	49
75	59
80	52
85	54
90	66
95	64
100	45
105	40
110	35

[a] Isolated crude yield.

Table 2. Time Optimization of Microwave-Assisted Synthesis

time (min)	yield[a] (%)
5	66
10	54
15	49
20	50
25	52
30	61
35	69
40	56
45	52
50	49
55	49
60	59

[a] Isolated crude yield.

intermediate arylbiguanide was detected in the reaction mixture, suggesting that the thermal energy provided to the reaction mixture was too high, causing the triazine ring to break up to revert back to the intermediate arylbiguanide. Therefore, the reaction temperature should be kept below 100 °C. Keeping the temperature at 90 °C gave the highest yield with no detection of arylbiguanide, and this temperature was chosen for all further microwave-assisted reactions.

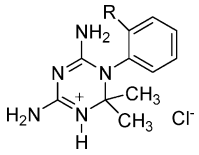
For optimization of the reaction time, all reactions were carried out as described above, but the temperature was kept at 90 °C, and a maximum power of 300 W was used. The reaction time was varied from 5 to 60 min in increments of 5 min (Table 2).

The isolated yields of the compounds varied between 49 and 66% when the reaction time was between 5 and 30 min. The highest yield was obtained when the reaction time was 35 min. Yields decreased when the reaction time was longer than 35 min. Reactions were completed at 35 min as judged by TLC, and this reaction time was chosen for all subsequent experiments.

The power of microwave irradiation was optimized by carrying out the same reaction at powers of 50, 100, 150, 200, 250, and 300 W. The reaction temperature was kept at 90 °C, and the reaction time was kept at 5 min. Microwave irradiation at 100 W gave the highest yield, and the maximum temperature reached during the whole reaction was 92 °C. When the power was 50 W, the time taken for the temperature to reach 90 °C was too long. For 150−300 W of microwave power, the maximum temperature reached during the reaction was above 100 °C. Temperatures above 100 °C are not favorable for the synthetic reaction because arylbiguanide formation could occur, as discussed above. Therefore, microwave power of 100 W was chosen as the optimum power.

The optimum conditions determined for the microwave-assisted syntheses were used in a separate experiment in which reactions were performed using two sets of conditions and two different anilines (Table 3). Results of these

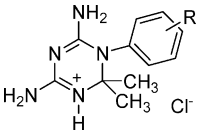
Table 3. Confirmation of Reaction Conditions for Microwave-Assisted Synthesis



compound	R	reaction time (min)	reaction temp (°C)	power (W)	yield[a] (%)
1	Cl	5	90	100	52
1	Cl	35	90	100	71
2	CH_3	5	90	100	28
2	CH_3	35	90	100	64

[a] Isolated crude yield.

Table 4. Comparison of Conventional and Microwave-Assisted Syntheses



		conventional			microwave-assisted	
compound	R	reaction time (h)	yield[a] (%)	purity[b] (%)	yield[a] (%)	purity[b] (%)
1	2-Cl	22	71	100	71	100
2	2-CH_3	22	47	100	64	100
3	2-OCH_3	22	62	99	69	100
4	3-Cl	22	43	82	36	100
5	3-CH_3	22	73	100	60	100
6	3-OCH_3	22	67	100	53	100
7	4-Cl	22	69	100	76	100
8	4-CH_3	22	79	100	84	100
9	4-OCH_3	22	74	100	62	100
10	3,4-diCl	8	74	74	47	99
11	3,4-diCH_3	22	34	100	48	100
12	3,4-diOCH_3	22	64	67	80	68
13	3-Cl-4-CH_3	8	68	80	63	99
14	3-Cl-4-OCH_3	22	72	97	72	100
15	4-Cl-3-NO_2	22	81	100	57	100
16	3-Br-4-CH_3	22	77	99	77	100
17	2-Cl-4-CH_3	22	68	99	75	100
18	4-Br-2-CH_3	30	45	100	45	100
19	5-Cl-2-OCH_3	24	61	58	72	100
20	2,6-diBr-4-CH_3	30	35	98	7	100

[a] Isolated crude yield. [b] Purity determined by HPLC peak area at 250 nm.

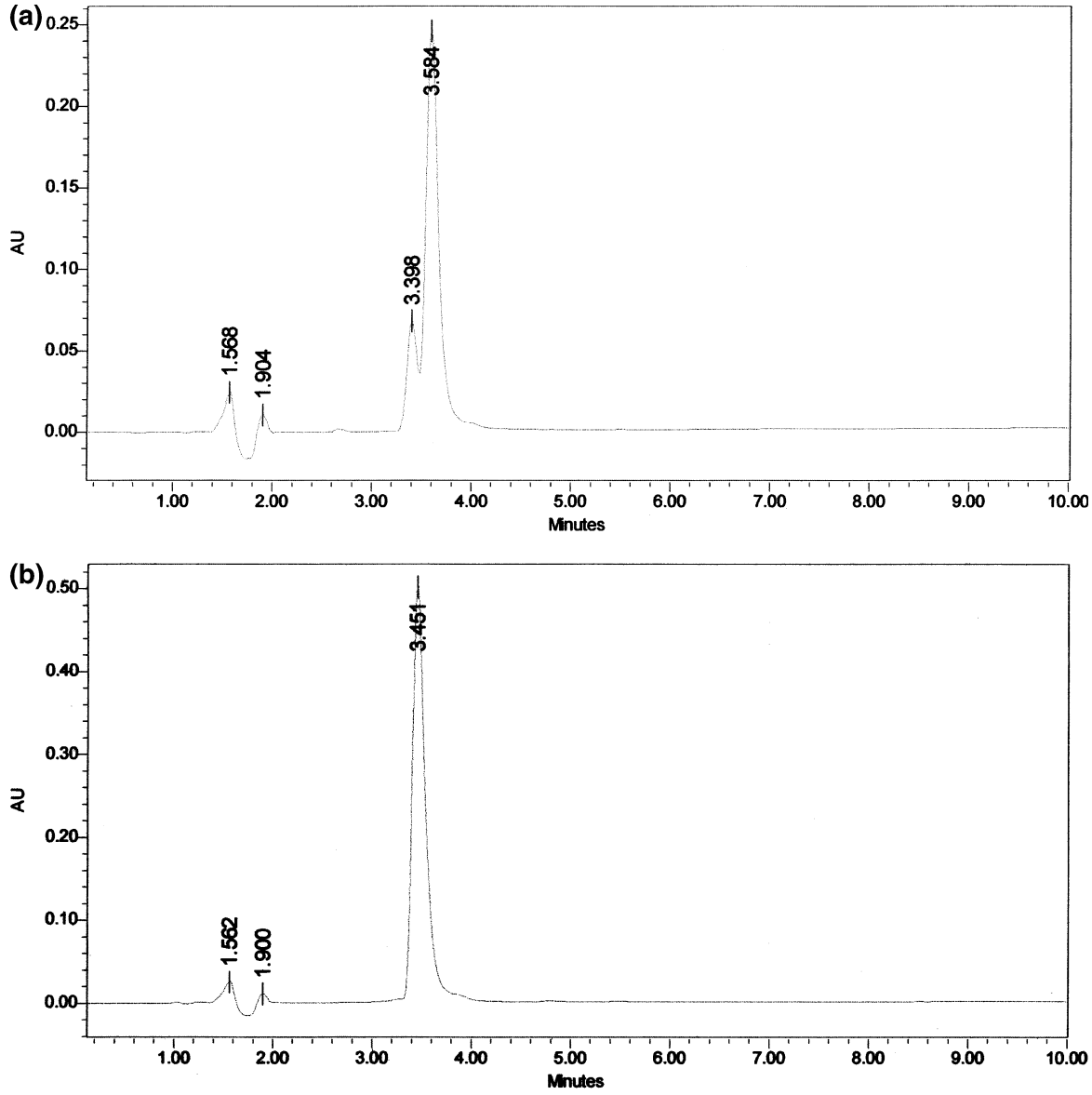


Figure 1. Chromatogram showing compound **4** when synthesized using (a) the conventional method and (b) the microwave-assisted method.

syntheses showed that microwave irradiation for 35 min produced a significantly higher yield than irradiation for 5 min.

The optimized conditions of microwave irradiation at 100 W and 90 °C for 35 min was applied to all compounds in the library, and a comparison of the yields and purities from the conventional and microwave-assisted syntheses was performed (Table 4).

A comparison of the 20 compounds indicated that eight showed improvement in isolated yield using the microwave-assisted synthesis. Four of the compounds showed similar yields regardless of the method used for synthesis. Another eight of the compounds showed a reduction in yield using microwave-assisted synthesis. Compound **4** showed a 16% reduction in yield, **10** showed a 36% reduction, and **13** showed a 7% reduction in yield. However, all three products demonstrated an increase in purity. Compounds **4**, **10**, and **13** showed improvements in purity of 22, 34, and 24%, respectively. For compounds **5**, **6**, **9**, and **15**, the yields were reduced by 16−30%, but the purities of these products were maintained.

Strikingly, the yield of compound **20** was reduced by 80%, but the purity was improved by 2% when the microwave-assisted synthesis was carried out. The reasons for this drop in yield are not clearly understood; however, this reduction in yield might be explained by the bulkiness of the substituents on the phenyl ring of the product. 2,6-Dibromo-4-methylaniline is a trisubstituted aniline, and the steric hindrance that was induced during the reaction was unfavorable. This could have resulted in a very low yield because microwave energy supplied to the reaction mixture might be too intense for the reaction to proceed favorably. In the conventional synthesis, the reaction was carried out over 30 h, and the temperature was kept at 60 °C, providing relatively milder conditions for the bulky reactants to react. Similarly, the reactions of other trisubstituted anilines such as 2,4-dibromo-6-methylaniline also resulted in poor yields (data not shown).

The microwave-assisted syntheses produced purer compounds of this phenyl dihydrotriazine library. Ten of the 20 compounds showed an improvement in purity as analyzed by HPLC. The other 10 compounds achieved 100% purity

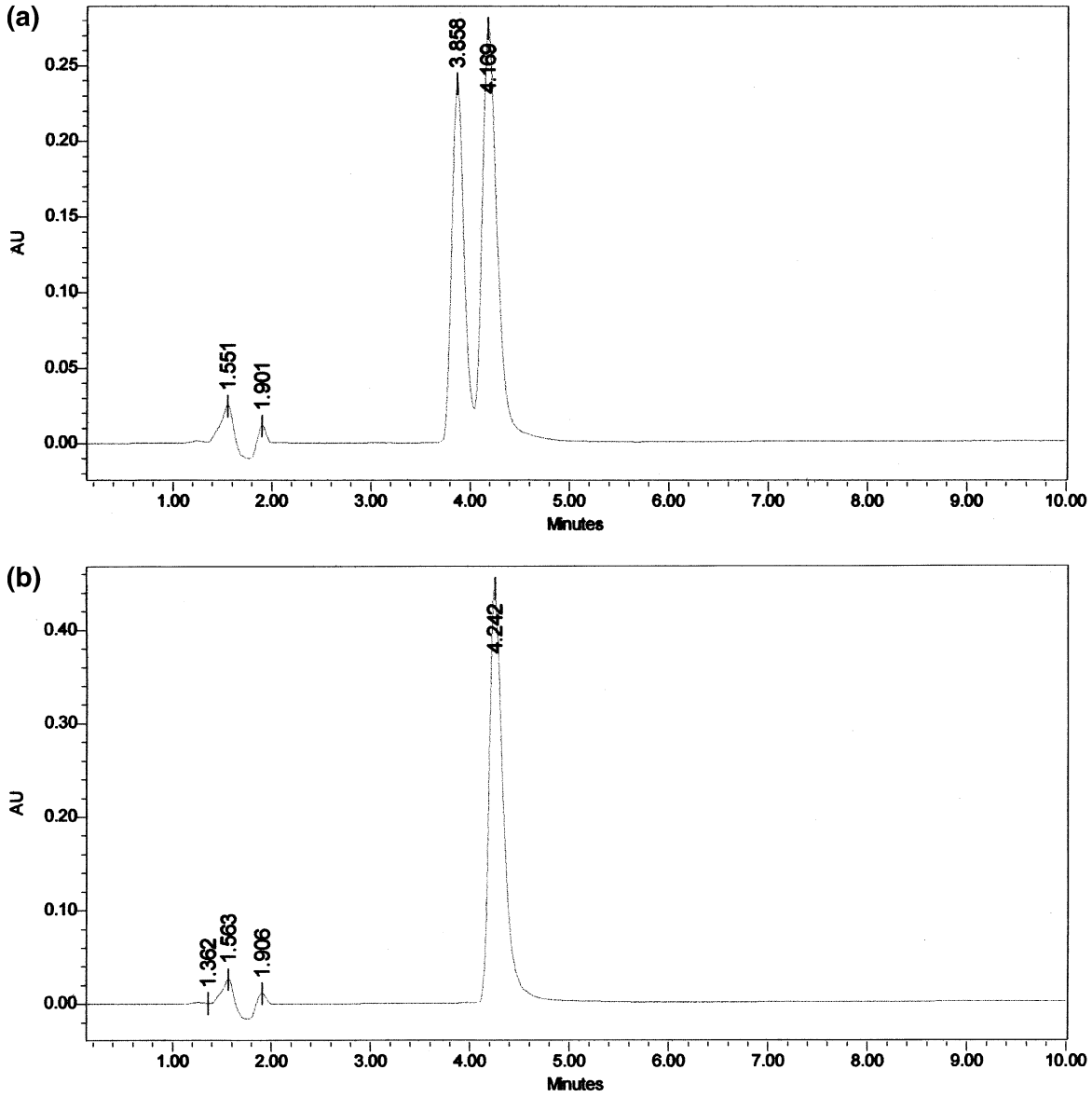


Figure 2. Chromatogram showing compound **19** when synthesized using (a) the conventional method and (b) the microwave-assisted method.

in both the conventional and microwave-assisted syntheses. Compounds **4**, **10**, **13**, and **19** showed significant improvements in purity. The chromatograms of compounds **4** and **19** are shown in Figures 1 and 2, respectively.

In general, the microwave-assisted synthetic method provided a very rapid means of synthesizing phenyl dihydrotriazines. In the conventional syntheses, most of the compounds required 22 h of reflux when they were synthesized in parallel. However, 35 min was sufficient to produce the same products when microwave irradiation was used, significantly saving time. Heating caused by microwave irradiation is a result of dipole rotation and ionic conductance.[27] In the case of the phenyl dihydrotriazine synthesis, acetone is a polar solvent with a dielectric constant of 20.7. When microwave irradiation is applied, acetone molecules will try to align themselves with the electric field. This rapid motion and the resulting intermolecular friction cause intense internal heat, increasing the temperature at rates up to 10 °C/s.[28] A combination of rapid microwave heating and sealed vessel technology further increases the reaction rate, which doubles as the temperature is increased in increments of 10 °C. Having the reaction sealed in a tube makes it possible for the temperature to be higher than the boiling point of acetone, and this also increases the reaction rate.

The improved purity of phenyl dihydrotriazines synthesized using microwave irradiation can be explained by the short reaction time. Because the reactions were allowed to proceed for only 35 min instead of 22 h, there was little time available for side products to form.

Conclusion

This report established the feasibility of synthesizing a library of phenyl dihydrotriazines using microwave technology. A comparison with conventional parallel syntheses of the same library revealed that microwave-assisted syntheses led to much shorter reaction times and purer products, indicating that less time would be needed for synthesis and purification using this method. Yields of the compounds from the two synthetic methods were comparable. The role of microwave technology in combinatorial chemistry, especially

with respect to the time saved during synthesis, is becoming more important, and soon, it might become a routine method for parallel library generation.

Experimental Section

Materials. All commercially available solvents and reagents were used as supplied by Aldrich Chemical Co., Acros Organics, and Alfa Aesar, unless otherwise stated.

Analysis. Mass spectral analyses were recorded on a Waters Alliance HT/Micromass ZQ system (ESI). ^{1}H NMR spectra were recorded on a Varian VNMR 400 MHz spectrometer and processed using the MestRe-C version 3.4.0 software (http://www.mestrec.com). All compounds were dissolved in DMSO-d_6 during NMR analysis. UV scans from 200 to 400 nm were recorded on a Shimadzu UV-1601 UV−visible spectrophotometer. Product purities were determined by HPLC analysis using a Waters 2690 separations module coupled to a Waters 996 photodiode array detector. A Waters Nova-Pak C18 (15 cm, 3.9 mm, 4 μm) column with a guard column was used for all HPLC experiments using a solvent system of ammonium acetate buffer (0.05 M), pH 4.0/acetonitrile. Gradient elution was performed from 80% ammonium acetate buffer to 60% buffer over 10 min.

Equipment. Conventional syntheses were carried out on Corning stirrer/hotplates with oil baths. Microwave syntheses were carried out on a CEM Corp. Discover laboratory microwave with Explorer unit.

General Procedure for Conventional Synthesis of the Library. A mixture of substituted aniline (2 mmol), cyanoguanidine (2.2 mmol), acetone (8 mL), and concentrated hydrochloric acid (2 mmol) was refluxed and stirred for 8−30 h. The progress of the reaction was followed by TLC, using a mixture of chloroform/methanol (9:1) as the mobile phase. Absence of the intermediate arylbiguanide was noted by an absence of a pink complex formation when an aqueous solution of the product was mixed with freshly prepared ammoniacal copper sulfate solution. The ammoniacal copper sulfate solution was prepared by dissolving 0.5 g of copper sulfate crystals in 100 mL of water and adding concentrated ammonia solution until a clear, deep blue solution was formed.[29] All products precipitated from the reaction mixture were washed with acetone and collected by suction filtration after being left at 4 °C overnight.

General Procedure for Microwave Synthesis of the Library. A mixture of substituted aniline (2 mmol), cyanoguanidine (2.2 mmol), acetone (7 mL), and concentrated hydrochloric acid (2 mmol) was added into a 10-mL glass tube with a magnetic stirring bar and covered with a plastic cap. The synthesis was carried out at 90 °C for 35 min under 100 W of microwave irradiation. Completion of the reaction was checked by TLC and the ammoniacal copper sulfate test as described above at the end of 35 min. All products were left at 4 °C overnight, collected by suction filtration and washed with acetone.

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Supporting Information Available. ^{1}H NMR, MS data, and HPLC chromatograms for the library. Table of λ_{max} values from UV spectrophotometry. This material is available free of charge via the Internet at http://pubs.acs.org.

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