

Multidisciplinary Synthetic Approach for Rapid Combinatorial Library Synthesis of Triaza-Fluorenes

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A new multidisciplinary synthetic approach comprising polymer-support synthesis, microwave-assisted synthesis, and multicomponent condensation facilitates synthesis of triaza-fluorenes library with a set of advantages such as rapid process, simple purification, and structural diversity in one shot. Microwave-assisted multistep synthetic protocol was used to construct the benzimidazole ring on soluble polymer support using activated aryl-fluorides. The PEG anchored aryl fluoride was condensed with selective primary amines via an *ipso*-fluoro displacement reaction followed by reduction of nitro group. The subsequent cyclization with cyanogen bromide is used as a key step to furnish immobilized benzimidazoles. Finally multicomponent condensation of resulted polymer bound benzimidazoles with various aldehydes and 1,3-diones under microwave irradiations provides rapid access for triaza-fluorenes with high purity and excellent yields. Microwave irradiation greatly accelerates the rate of all reactions while polymer support facilitates purifications by simple precipitation technique. This strategy dramatically increases efficiency of overall multistep synthesis.

Introduction

The role played by an organic chemist is one of the main drivers in drug discovery process.¹ Along with the development of new synthetic methods and technologies, the precise nature of this role is particularly the fast access toward the novel compounds. Rapid synthesis, construction of diverse library in automated format, short step processes, easy workup procedure, and simple isolation and purification methods along with environmental friendly chemistry, are the main objectives to speed up the current organic synthesis. Several advanced techniques like microwave synthesis,² ionic liquid synthesis,³ sonication,⁴ polymer-support synthesis,⁵ multicomponent condensation,⁶ and combinatorial synthesis⁷ are established to accelerate the synthetic organic chemistry. However, success in this arena still requires more embellishments that will meet the plethora of hurdles that initial drug discovery process must surmount. The separated efforts through each technique are insufficient to execute this obligation.⁸ Driving through this modern organic synthesis, integrating a variety of advanced technologies for the rapid generation of numerous multifunctionalized molecule libraries can provide the high speed path for modern drug discovery (Figure 1). Multidisciplinary synthetic approach is an integrated concept which supports the coagulation of different disciplines of synthetic organic chemistry along with their advantages to facilitate the drug discovery.⁹ Hence in addition to the advent of combinatorial synthesis, we are now focused on application of advanced techniques in synthetic methodologies.¹⁰

Over the last number of years, scientists have been exploring the microwave heating for enhancing the combi-

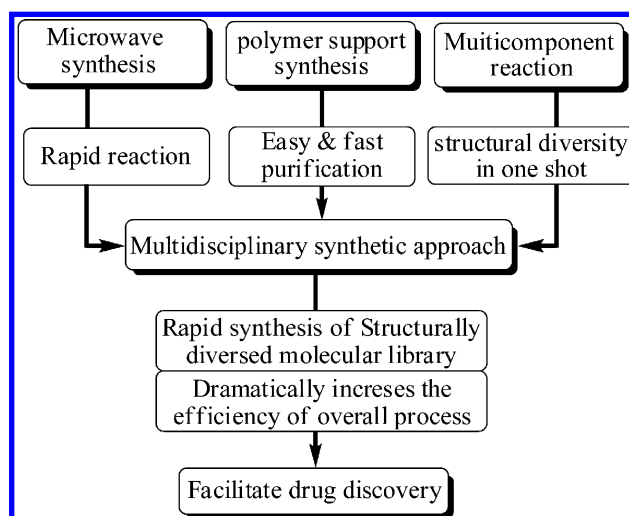


Figure 1. Multidisciplinary synthetic approach.

natorial synthesis. Controlled microwave irradiation has proven to be a powerful tool both for speeding up reaction optimizations and for the efficient preparation of new target compounds related to drug discovery projects.^{2,11} One of the many advantages of microwave heating in chemical synthesis is the dramatic reduction in reaction time, intended its use in multicomponent condensations for the construction of heterocycles.¹² Multicomponent synthesis is an evolutionary approach of introducing structural diversity in a single step synthetic operation. Over the years, combinatorial synthesis research interest turned to multicomponent condensation reaction because it provides the fast diversified access for multifunctionalized ring systems.¹³ Hence, multicomponent reactions are well-suited for both combinatorial chemistry and high-speed parallel synthesis, and therefore, they possess high exploratory power.

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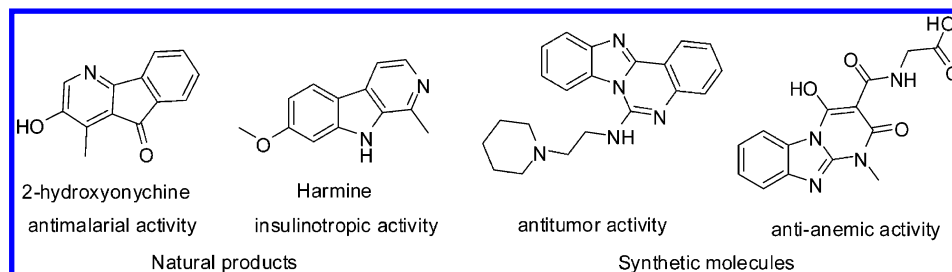
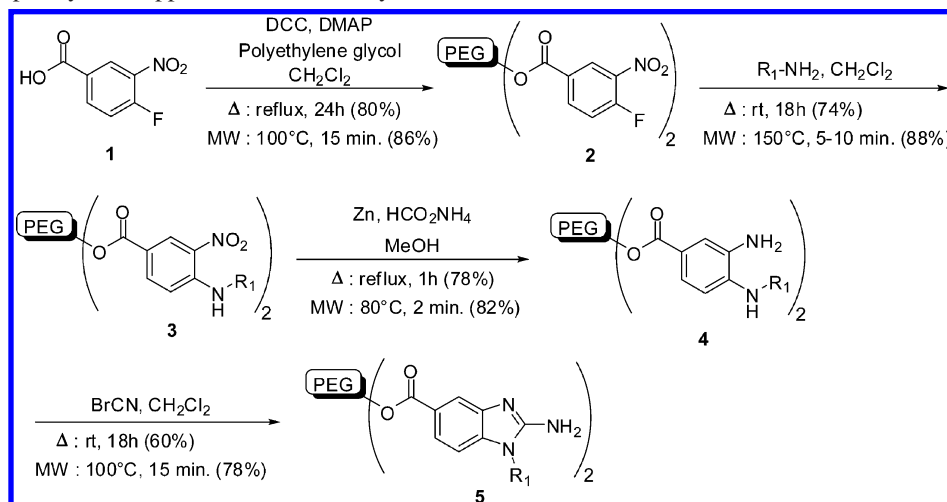


Figure 2. Azafluorene ring containing bioactive natural products and synthetic molecules.

In the recent past, polymer supported organic synthesis has been extensively used as a platform for the rapid generation of molecular libraries.¹⁴ Molecules attached with a polymer can be easily isolated from the reaction mixture by precipitation or phase extraction techniques. Although solid polymer supported organic synthesis has demonstrated its utility, it still exhibits several limitations like solvation problem, nonlinear kinetic behavior and irregular distribution in the chemical reaction due to the heterogeneous nature of reactions. Soluble polymer supports provides alternative strategies in essence avoids the difficulties of solid-phase synthesis while preserving its positive aspects like easy workup, effortless product purification in addition to enabling homogeneous reaction conditions.¹⁵ Among the various soluble polymers, polyethylene glycol (PEG) has proven to be the most versatile and successful support to simplify and speed up the synthesis.¹⁶ Research in soluble polymer support synthesis has led to the development of newer methodologies in combinatorial synthesis to screen small molecule libraries for drug lead discovery.

In an effort to investigate multidisciplinary synthetic approach for drug-like molecules, we targeted tricyclic triazafluorene ring construction with various substitutions. Fluorene and aza-fluorene derivatives possesses a broad spectrum of biological properties. These compounds have been described as propyl hydroxylase inhibitor,¹⁷ antidiabetics,¹⁸ anti-inflammatory,¹⁹ antiviral,²⁰ antimicrobial,²¹ antineoplastic,²² and potent immunosuppressive agents.²³ Aza-fluorenes also emerged as an integral backbones of calcium channel blockers.²⁴ Some of the analogs of aza-fluorene compound show potent antitumor activity.²⁵ Aza-fluorene heterocycles are the subunit of several natural alkaloids and active pharmaceuticals (Figure 2).^{17,26}

Scheme 1. Multistep Polymer Supported Microwave Synthesis of Amino-benzimidazoles



Results and Discussions

Taking into consideration the advantages of multicomponent reaction, microwave synthesis, and soluble polymer-support synthesis, along with biological importance of azafluorene ring system, the ultimate goal of our research is to develop rapid, efficient, and simple multidisciplinary approach to construct the structurally diverse library of molecules containing aza-fluorene skeleton. Our current work was divided into two major parts. The first part is to synthesize the polymer supported benzimidazole skeleton from 4-fluoro-3-nitro-benzoic acid by microwave accelerated linear four steps sequence. The second part involves the microwave enhanced multicomponent condensation of resulted polymer supported benzimidazoles with aldehydes and 1,3-diketones for the high speed library synthesis of triazafluorenes.

In previous synthesis, Kurth et al. reported the fluorene synthesis in linear fashion from isothiocyanate ester using barium hydroxide.²⁷ The strategy to assemble fluorene framework by Martin group was the reaction of aniline with chloro-benzimidazole.²⁸ However Lunn achieved the azafluorene ring construction by pyrolytic rearrangement.²³ Almost all the synthetic routes to these medicinally pertinent heterocycles suffer from one of the limitations, such as (i) prolonged reaction time, (ii) low yields, (iii) thermal decomposition of substrates, reagents, or products, (iv) narrow scope for substrates, and (iv) tedious work up procedures.²⁹ In our earlier work, we have reported³⁰ the microwave assisted PEG-supported synthesis of 2-(aryl amino)benzimidazoles, bis-benzimidazole and benzimidazolyl quinoxalinones. Herein we disclose a soluble polymer supported microwave synthesis of triaza-fluorenes in excel-

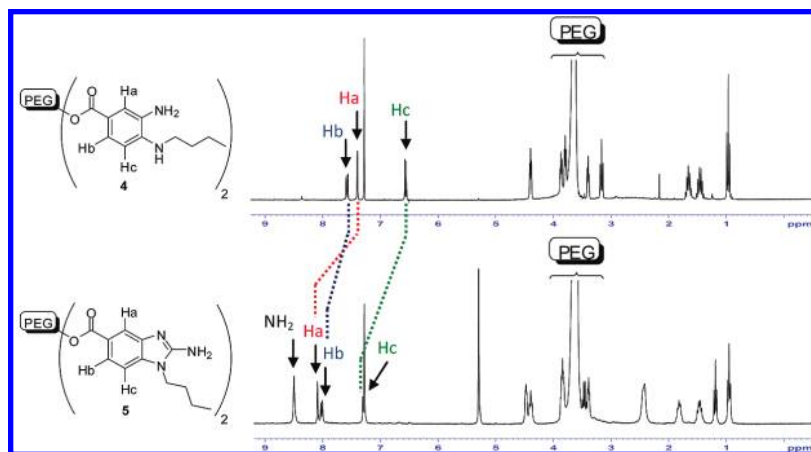
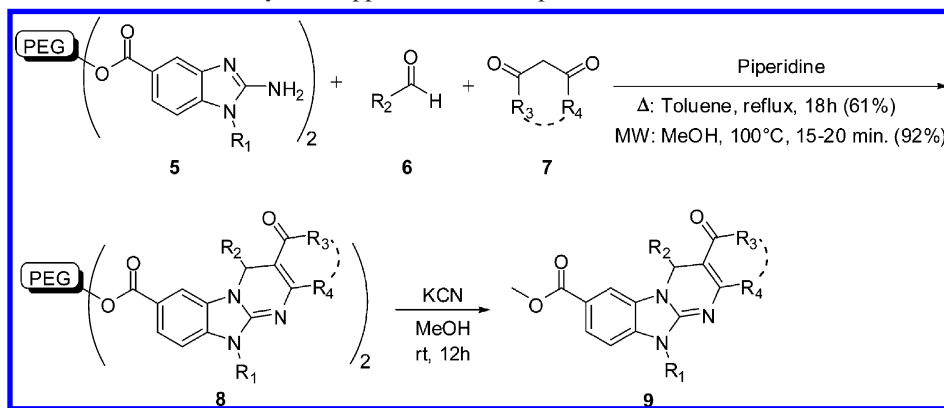
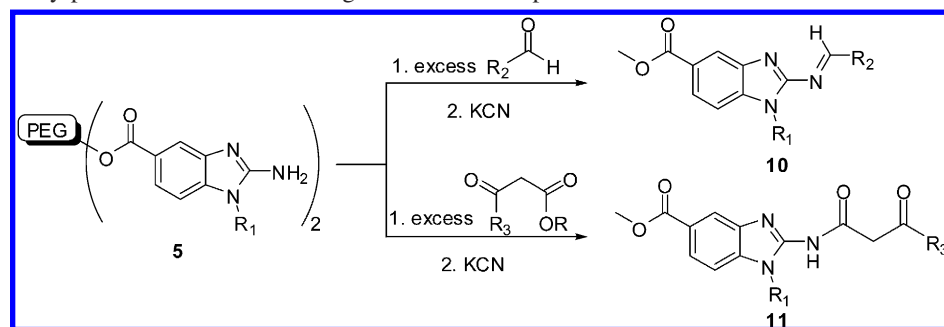


Figure 3. Comparison of ^1H NMR spectra of polymer bound compound **4** and **5**.

Scheme 2. Microwave-Assisted Soluble Polymer Supported Multicomponent Reaction



Scheme 3. Observed By-products in Excess of Reagents in Multicomponent Reaction



lent yields and high purity. Since PEG has received attention as soluble polymer support in a wide variety of reactions, we have decided to investigate the possibility of using PEG, which has an average molecular weight of 2000 and can functionalize at both ends, as a soluble polymeric support in microwave heating.

Initially, 4-fluoro-3-nitrobenzoic acid **1** was anchored on polymer by standard esterification conditions. 4-fluoro-3-nitrobenzoic acid **1** treated with PEG in the presence of DCC and DMAP in dichloromethane at reflux for 18 h to afford PEG-bound 4-fluoro-3-nitrobenzoate **2** with 86% yield. Nevertheless, to speed up the process, we attempted the reaction of PEG and 4-fluoro-3-nitrobenzoic acid **1** under microwave irradiation at 150 °C for 15 min to prepare PEG-bound 4-fluoro-3-nitrobenzoate **2** through ester linkage (Scheme 1). The reaction proceeded to completion as evidenced by the disappearance of the absorption of the acid hydroxyl group and the appearance of the absorption of the

ester group at 1729 cm^{-1} in the IR spectrum. To introduce the additional diversity in the skeleton, variety of primary amines were coupled to PEG linked 4-fluoro-3-nitrobenzoate **2** by nucleophilic aromatic substitution. The reactions were completed within 18 h in dichloromethane at room temperature to afford PEG supported nitroarenes **3**. Microwave heating used in the same reaction greatly reduced the reaction time to 5–10 min. The time required for the completion of reaction under microwave heating depends upon the type of primary amines used. Common linear-chain aliphatic amines and aromatic amines with strong electron donating groups gave good yield in short reaction time (5 min) while aromatic amines with strong electron withdrawing groups requires 10 min to furnish the targeted compounds. All supported amines **3** were purified by precipitation using cold ether. Subsequently, reduction of nitro group was achieved in microwave by using zinc and ammonium formate in methanol. The reduction was completed within 2 min to furnish the aniline

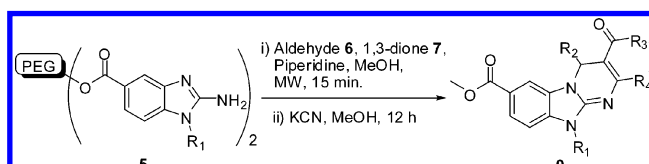
derivative **4**. The reduction in a thermal heating was carried out with the same stoichiometric amounts of reagents in refluxing methanol and took 30 min for completion. After the reaction was completed, the heterogeneous material was removed by filtration and the PEG-bound amines were again purified by precipitation.

The next task of this endeavor was the construction of benzimidazole ring through cyclization of soluble supported anilines **4** using cyanogen bromide. Initially, the compound **4** was refluxed in dichloromethane with cyanogen bromide furnished the desired cyclization product PEG linked aminobenzimidazole **5** after 18 h with 60% yield. The same reaction when carried out under microwave heating at 100 °C was completed in only 15 min to furnish PEG linked amino-benzimidazole **5** in 78% yield. Mechanistically, the bromo substitution from cyanogen bromide by the less hindered more reactive primary aniline affords cyanoaniline. Subsequent cyclization through secondary aniline followed by aromatization furnishes the 2-amino-benzimidazoles. Progress of one-pot cyclization was easily monitored by regular proton NMR spectroscopy as shown in Figure 3. The peaks corresponding to aromatic protons at 7.40 (Ha), 7.58 (Hb), and 6.66 (Hc) ppm of compound **4** are shifted to downfield region and appeared at 8.12 (Ha), 8.00 (Hb), and 7.30 (Hc) ppm, respectively, in benzimidazole **5**. Additionally, the appearance of the peak from amine protons at 8.48 ppm was the evidence for the cyclization of the imidazolene ring. When both microwave results and conventional pre-heated oil bath results were compared, we observed a clear improvement in yields and reaction time with microwave heating. Moreover the products were purified simply by precipitation in cold ether.

The main objective of our studies is the investigation of multidisciplinary approach comprising the soluble polymer supported multicomponent reaction under microwave irradiation. For comparison point of view, we performed the multicomponent condensation under both microwave irradiation and classical heating conditions. The mixture of PEG-supported amino-benzimidazoles **5**, aldehydes **6**, and 1,3-diones/3-oxoesters **7** was subjected to condensation in refluxing toluene (Scheme 2). The reaction was completed after 18 h to furnish triaza-fluorenes **9** in 61% yield. Moreover, the reagent equivalents also play an important role in this condensation reaction. If excess aldehyde was used, imine **10** was isolated as the byproduct while in case of excess 1,3-dione or 3-oxoesters, amide **11** was the byproduct which diminish the yield of the condensed products **8** (Scheme 3). However, to investigate the multidisciplinary effect, the equimolar amounts of PEG-supported amino-benzimidazole **5**, aldehyde **6**, 1,3-dione **7** and 10 mol % piperidine in toluene was subjected to microwave irradiation at 100 °C (4 bar). The time required for the completion of reaction was more than 30 min because microwave absorption coefficient of toluene is very small. Hence, to optimize the appropriate reaction medium, various solvents were screened and based on the outcome, methanol was selected as the optimum solvent for multicomponent reaction.

Consequently, the equimolar amount of PEG-linked benzimidazole **5**, aldehyde **6**, 1,3-dione **7**, and piperidine in

Table 1. Reaction Substrate Scope



Entry	Amines NH ₂ -R ₁	Aldehydes (6) R ₂ -CHO	1,3-diones (7) R ₃ -R ₄	LRMS ^a	Yield ^b (%)	HPLC (%) ^b
9a				448	85	81
9b				458	73	99
9c				475	77	99
9d				464	80	80
9e				482	78	95
9f				472	81	62
9g				498	78	97
9h				496	75	92
9i				412	69	85
9j				514	82	99
9k				534	69	99
9l				444	80	94
9m				502	78	98
9n				561	75	96
9o				436	80	99
9p				554	80	99

^a ESI mass, molecular peak obtained as [M + 1]. ^b Total isolated yield after both steps. ^c Crude HPLC purity after PEG cleavage.

methanol was treated under microwave irradiation at 100 °C (4 bar). The reaction was efficiently promoted by microwave irradiation to furnish polymer supported triaza-fluorenes **8**. The reaction time was strikingly shortened to 15–20 min from 18 h required under traditional heating condition and the yield was increased to 92% from 61% (Scheme 2). Moreover, no byproduct (**10** and **11**) were observed and no decomposition of polymer bound intermediates were detected during this one pot coupling reaction.

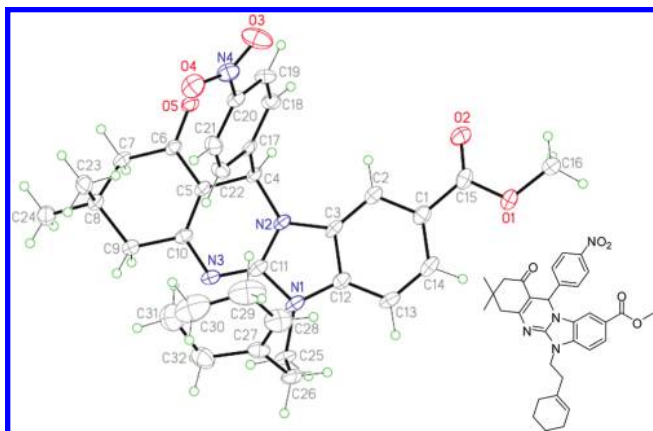


Figure 4. ORTEP diagram of compound **9p**.

Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield. Gratifyingly, the procedure is easy to operate and the workup procedure is simple precipitation in ether. Regular proton NMR spectroscopy was used to monitor multicomponent coupling reaction. In ^1H NMR spectrum of condensed compounds **8**, the peaks due to benzimidazoles aromatic protons at 8.12 (Ha), 8.00 (Hb) and 7.30 (Hc) ppm shifted to the upfield region and appeared at δ 7.65 (Ha), 7.83 (Hb), and 7.32 (Hc), respectively. Moreover the absence of peak of amine protons and the appearance of characteristic signal at 6.45 ppm because of a proton on newly created pyrimidine ring were the clear indications for the formation of polymer supported triaza-fluorenes **8**.

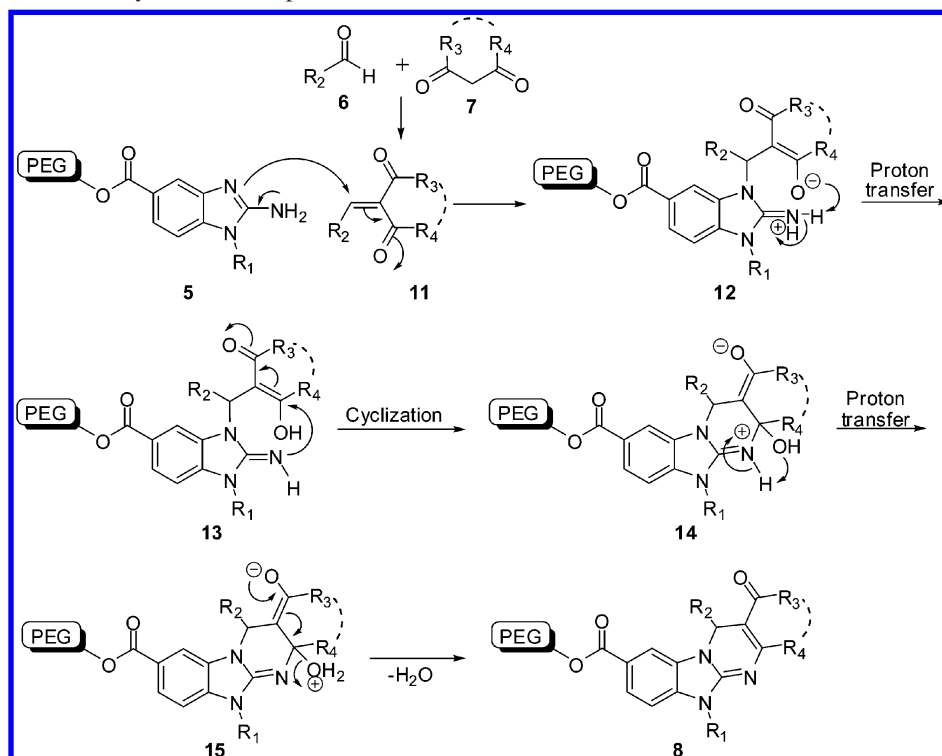
Finally, polymer support was cleaved in a potassium cyanide solution in methanol to deliver methyl ester of penta-substituted triaza-fluorenes **9** in good yields (Table 1). In most of the cases, a cleavage reaction was completed at room

temperature within 12 h. The crude mixture was concentrated; the polymer was precipitated out with excess of cold ether and removed by filtration. The filtrate was dried and subjected to HPLC analysis (Table 1), which depicted high purity and excellent yield of all the compounds without further purification. The completion of cleavage from the polymer support was verified by observing an upfield shift of *N*-methylene protons at para-position of the polymer disconnected site from 4.4 to 3.6 ppm in addition to the disappearance of characteristic set of peaks corresponding to polymer protons.

The structure of the final compounds was also unambiguously confirmed on the basis of X-ray crystallographic study. The X-ray crystallographic data of **9p** are in full agreement with its structure (see Supporting Information). The 4-nitrophenyl ring attached to main core was situated at C4 and bears antiparallel orientation. The carbonyl group is at C6 position and alkyl substitution on N1, all clearly confirmed the expected structure of **9p** (Figure 4).

To examine the efficiency and the generality of this novel three component condensation reaction, 10 amino-benzimidazole derivatives, 10 aldehydes, and 7 1,3-diones were investigated. Based on the optimized reaction conditions, a series of penta-substituted-dihydrofluorene derivatives were synthesized by equimolar amounts of aldehydes, 1,3-diones or 3-oxoesters and PEG supported 2-aminobenzimidazoles in methanol at 100 °C at 4 bar pressure under microwave irradiation. After irradiation for 15–20 min, the immobilized triaza-fluorene derivatives **8** were obtained in quantitative yields. Subsequent removal of polymer support furnished triaza-fluorenes **9** in good to excellent yields (Scheme 2). The results were summarized in Table 1. The protocol was applied to the aryl aldehydes with either electron-withdrawing groups or electron-donating groups and

Scheme 4. Mechanistic Pathway of Multicomponent Reaction



aliphatic aldehydes. As can be seen from Table 1, the electronic effect of the substituted benzaldehydes has an insignificant impact on the conversion. The feasibility of employing aliphatic aldehydes instead of aryl aldehydes in the reaction was also investigated. Providentially, aliphatic aldehydes also condensed providing products in good yield. Additionally, different types of 1,3-diones and 3-oxoesters were used to examine this protocol and to increase the diversity in the scaffold. It was observed that when 1,3-diones were used the multicomponent reaction proceeded little faster than 3-oxoesters were employed. Also the yields were superior when 1,3-diones were used. These results were correlated to the higher reactivity of 1,3-diones than 3-oxoesters.

The observed outcome of the multicomponent condensation reaction can be explained on the basis of the plausible mechanism depicted in Scheme 4. The first generally proposed step is the formation of the unsaturated diones **11** through Knoevenagel condensation of aldehyde and 1,3-dione. The unsaturated diones **11** were detected and identified in the reaction mixture by mass spectroscopy and TLC analysis. Michael addition type reaction of benzimidazole **5** with unsaturated diones **11** could afford **12** which on further proton transfer rearrange to adduct **13**. Intermolecular cyclization to **14** and subsequent proton transfer provide **15** which upon dehydration could furnish triaza-fluorenes **8**.

We have successfully integrated three disciplines of the synthetic organic chemistry along with their advantages for the high speed library synthesis of triaza-fluorenes. Rate of each step is accelerated by microwave irradiation. Soluble polymer support enables the homogeneous reaction conditions and also speeds up the separation and purification simply by precipitation technique. Hence this method dramatically shortens the time required for overall reaction sequence and increases efficiency of the total process.

Conclusion

Multicomponent condensation of polymer-bound benzimidazole, aldehydes, and 1,3-diones under microwave irradiation afforded the novel library of triaza-fluorene molecules. It has been demonstrated that the microwave heating is very effective in speeding up both the soluble supported multistep synthesis, as well as in accelerating the rate of subsequent multicomponent reaction. Noteworthy, soluble supported intermediates and soluble support itself are stable during microwave harsh irradiation. Monitoring reaction progress in each step by regular proton NMR is feasible by using PEG as a soluble polymer support. Great substrate scope, high yields, short reaction time, pure products and easy work up are advantages of this procedure in comparison to other methods. In multidisciplinary synthetic approach, we have successfully used multicomponent reaction to introduce the structural diversity in one pot, applied the microwave irradiation to accelerate the rate of reactions and soluble polymer support for the speedy and simple purifications of products. This approach provides a high speed path for the rapid synthesis of molecular libraries with high degree of structural diversity. The powerful potential of multidisciplinary synthetic approach, bringing

together multiple facets of synthetic chemistry has great expectations in terms of the potential to transform the future of drug discovery.

Experimental Section

General Methods. Dichloromethane and toluene were distilled from calcium hydride before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel coated Kiselgel 60 F₂₅₄ plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (230–400 mesh). All the microwave experiments were performed in a Biotage initiator under optimized reaction conditions of power and equipped with an infrared pyrometer for the control of temperature and compressed air system for cooling was used. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard.

Synthesis of Dimethyl 9-Butyl-7-ethyl-5-phenyl-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9a). Activated ester was prepared by dissolving 4-fluoro-3-nitrobenzoic acid **1** (0.185 g, 1.0 mmol) in dry dichloromethane and DCC (0.206 g, 1.0 mmol) as well as 4-dimethylaminopyridine (DMAP) (0.033 g) were added to the solution. After 10 min, the solution of PEG (2000) (1.2 g, 0.6 mmol) in dry dichloromethane (10 mL) was added. The reaction mixtures were subjected to microwave irradiation at 100 °C for 15 min. The precipitating reaction mixture and washing with excess cold ether (50 mL × 3) afford PEG bounded 4-fluoro-3-nitrobenzoate **2** in 86% (2.0 g) yield. 1-aminobutane (0.09 g, 1.2 mmol) was added to a solution of PEG bounded 4-fluoro-3-nitrobenzoate **2** in dichloromethane. After irradiation in a microwave reactor at 150 °C for 10 min, the PEG bound 4-(butylamino)-3-nitrobenzoate **3** was purified as the same procedure described previously with 88% yield. Zinc (1.0 g, 15.0 mmol) and ammonium formate (0.63 g, 10.0 mmol) were added to a solution of **3** (1.84 g, 0.76 mmol) in methanol, and the reaction mixture was subjected to microwave irradiation at 80 °C for 2 min. The mixture was filtered with Celite to remove zinc and the filtrate was collected and concentrated under reduced pressure. Then dichloromethane (25 mL) was added to precipitate ammonium formate, and the mixture was again passed through a thin layer of Celite to remove ammonium formate. To a solution of PEG-bound 3-amino-4-(butylamino)benzoate **4** (0.80 g, 0.35 mmol) in dichloromethane, cyanogen bromide (BrCN) (0.075 g, 0.7 mmol) was added. The reaction mixture was irradiated by microwave at 100 °C for 15 min. The solvent was removed under reduced pressure and washed with ether to deliver PEG bound amino-benzimidazole **5** with 78% (0.64 g) yield. Benzaldehyde **6a** (0.028 g, 0.26 mmol), methyl 3-oxopentanoate **7a** (0.034 g, 0.26 mmol) and piperidine (0.005 g, 0.03 mmol) were added to a solution of PEG bound amino-benzimidazole **5** (0.64 g, 0.26 mmol) in methanol. The reaction mixture was irradiated under microwave at 100 °C for 15 min using 180 W power (4 bar). The reaction is monitored by thin layer chromatography and ¹H NMR spectroscopy. After completion, the reaction mixture was washed with cold ether. The precipitate was filtered and dried

well to furnish the PEG bound triaza-fluorene **8a** in 92% yield. The 1 M solution of potassium cyanide (0.325 g, 0.5 mmol in 5 mL) in methanol was added to a solution of PEG-bound triaza-fluorene **8a** (0.70 g, 0.25 mmol) in methanol (5 mL). The mixture was stirred at ambient temperature for 12 h. After completion of reaction, the inorganic material was removed by filtration and then filtrate was concentrated under reduced pressure. The polymer was precipitated out with excess of cold ether and removed by filtration. The filtrate was dried and subjected to HPLC analysis which depicts high purity. The title compound **9a** was obtained in 85% (0.123 g) overall yield of two steps after column chromatography purification.

¹H NMR (300 MHz, CDCl₃): δ 7.85 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.69 (d, *J* = 1.2 Hz, 1H), 7.43 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.40 (s, 1H), 7.29–7.20 (m, 3H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.42 (s, 1H), 4.14 (dt, *J* = 14.1, 7.0 Hz, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 3.03 (dd, *J* = 19.5, 7.3 Hz, 1H), 2.83 (dd, *J* = 19.5, 7.3 Hz, 1H), 1.82 (q, *J* = 7.4 Hz, 2H), 1.48–1.35 (m, 2H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.1, 167.0, 150.3, 142.4, 135.2, 129.0, 128.9(2C), 128.4, 127.5(2C), 125.3, 110.8, 108.0, 99.2, 57.6, 52.6, 51.1, 42.1, 35.0, 30.6, 30.4, 25.6, 20.2, 14.1, 13.4. MS (ESI): *m/z* 448 (M + H)⁺. HRMS (ESI) Calcd for C₂₆H₃₀N₃O₄: *m/z* 448.2236. Found: 448.2234 (M + 1)⁺. IR (neat): 2954, 1716, 1602, 1521, 1241 cm⁻¹. HPLC: 81%.

Methyl 6-Oxo-8,8-dimethyl-11-butyl-5-phenyl-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[*b*]fluorene-3-carboxylate (9b). ¹H NMR (300 MHz, CDCl₃): δ 7.89 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.70 (d, *J* = 1.4 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.18 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.51 (s, 1H), 4.17 (t, *J* = 7.6 Hz, 2H), 3.88 (s, 3H), 2.57 (d, *J* = 17.5 Hz, 1H), 2.50 (d, *J* = 17.5 Hz, 1H), 2.28 (d, *J* = 16.2 Hz, 1H), 2.17 (d, *J* = 16.2 Hz, 1H), 1.85 (quint, *J* = 7.3 Hz, 2H), 1.44 (sextet, *J* = 7.3 Hz, 2H), 1.09 (s, 3H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.98 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 194.7, 166.8, 162.8, 150.9, 141.6, 134.7, 129.6, 128.9(2C), 128.3, 127.4(2C), 125.5, 124.8, 111.4, 109.0, 108.4, 55.8, 52.6, 51.1, 46.7, 42.4, 32.8, 30.7, 29.8, 27.7, 20.3, 14.1. MS (ESI): *m/z* 458 (M + H)⁺. HRMS (ESI) Calcd for C₂₈H₃₂N₃O₃: *m/z* 458.2444. Found: 458.2443 (M + 1)⁺. IR (neat): 2954, 2865, 1712, 1612, 1589 cm⁻¹; HPLC: 99%.

Methyl 6-Oxo-11-butyl-5-(3-nitrophenyl)-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[*b*]fluorene-3-carboxylate (9c). ¹H NMR (300 MHz, CDCl₃): δ 8.10 (t, *J* = 1.8 Hz, 1H), 8.06 (ddd, *J* = 8.2, 1.8, 1.0 Hz, 1H), 7.94 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.90 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.59 (d, *J* = 1.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 5.65 (s, 1H), 4.25 (dt, *J* = 11.3, 7.0 Hz, 2H), 3.88 (s, 3H), 2.74 (dt, *J* = 17.6, 5.2 Hz, 1H), 2.60 (ddd, *J* = 17.6, 9.1, 5.2 Hz, 1H), 2.38 (d, *J* = 7.4 Hz, 2H), 2.06–1.96 (m, 2H), 1.89 (quint, *J* = 7.4 Hz, 2H), 1.45 (sextet, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 195.0, 166.6, 165.4, 150.6, 149.0, 143.7, 134.7, 133.8, 129.8, 129.1, 126.0, 125.1, 123.4, 121.9, 111.0, 109.2, 108.8, 55.4, 52.7, 42.6, 37.4, 33.0, 30.7, 21.9, 20.3, 14.1. MS (ESI): *m/z* 475 (M + H)⁺. HRMS (ESI) Calcd for C₂₆H₂₇N₄O₅: *m/z* 475.1981. Found: 475.1984 (M + 1)⁺. IR (neat): 2937, 1720, 1608, 1508, 1386, 767 cm⁻¹. HPLC: 99%.

Dimethyl 9-(3-Methoxypropyl)-7-ethyl-5-phenyl-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9d). ¹H NMR (300 MHz, CDCl₃): δ 7.86 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.68 (d, *J* = 1.4 Hz, 1H), 7.41 (dd, *J* = 6.9, 1.5 Hz, 2H), 7.29–7.18 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.42 (s, 1H), 4.22 (dt, *J* = 6.7, 2.9 Hz, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 3.39 (dt, *J* = 6.2, 2.3 Hz, 2H), 3.31 (s, 3H), 3.00 (m, 1H), 2.84 (m, 1H), 2.22–2.06 (m, 2H), 1.25 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 166.7, 166.6, 164.2, 149.8, 142.0, 135.1, 128.8, 128.4(2C), 127.9, 127.0(2C), 124.8, 123.7, 110.2, 107.5, 98.8, 68.9, 58.5, 57.1, 52.0, 50.6, 39.0, 29.9, 28.3, 12.9. MS (ESI): *m/z* 464 (M + H)⁺. HRMS (ESI) Calcd for C₂₆H₃₀N₃O₅: *m/z* 464.2185. Found: 464.2182 (M + 1)⁺. IR (neat): 2952, 2879, 1710, 1600, 1525 cm⁻¹. HPLC: 80%.

Dimethyl 9-(3-Methoxypropyl)-7-ethyl-5-(2-fluorophenyl)-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9e). ¹H NMR (300 MHz, CDCl₃): δ 7.88 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.80 (d, *J* = 1.3 Hz, 1H), 7.43 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.17 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.07–6.97 (m, 2H), 6.75 (s, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 3.91 (s, 3H), 3.64 (s, 3H), 3.37 (t, *J* = 5.8 Hz, 2H), 3.31 (s, 3H), 3.07–2.88 (m, 2H), 2.10 (quint, *J* = 6.2 Hz, 3H), 1.27 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.0, 165.7, 161.3, 158.0, 150.1, 135.4, 130.1, 129.9, 129.3, 129.1, 125.5, 125.1, 124.4, 115.8, 110.3, 107.9, 97.7, 69.3, 58.9, 52.5, 51.1, 50.8, 39.5, 30.3, 28.8, 13.4. MS (ESI): *m/z* 482 (M + H)⁺. HRMS (ESI) Calcd for C₂₆H₂₉FN₃O₅: *m/z* 482.2091. Found: 482.2089 (M + 1)⁺. IR (neat): 2948, 2873, 1716, 1604, 1243, 763 cm⁻¹. HPLC: 95%.

3-Methyl 6-tert-Butyl 9-(3-methoxypropyl)-7-methyl-5-butyl-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9f). ¹H NMR (300 MHz, CDCl₃): δ 7.90 (dd, *J* = 8.4 Hz, 1.4 Hz, 1H), 7.80 (d, *J* = 1.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.57 (t, *J* = 4.0 Hz, 1H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.94 (s, 3H), 3.33 (dt, *J* = 6.5 Hz, 3.5 Hz, 2H), 3.29 (s, 3H), 2.40 (s, 3H), 2.04 (quint, *J* = 6.5 Hz, 2H), 1.87 (m, 1H), 1.66 (m, 1H), 1.53 (s, 9H), 1.32 (m, 1H), 1.13 (sextet, *J* = 7.2 Hz, 2H), 0.89 (m, 1H), 0.75 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.3, 166.9, 159.4, 150.7, 135.6, 129.4, 125.1, 124.1, 110.1, 108.0, 99.2, 79.8, 69.3, 59.0, 53.2, 52.6, 39.3, 34.2, 28.9(3C), 28.7, 26.1, 24.9, 23.0, 14.3. MS (ESI): *m/z* 472 (M + H)⁺. HRMS (ESI) Calcd for C₂₆H₃₈N₃O₅: *m/z* 472.2811. Found: 472.2814 (M + 1)⁺. IR (neat): 2956, 2929, 1720, 1604, 1376 cm⁻¹. HPLC: 62%.

Dimethyl 9-Isobutyl-7-(methoxymethyl)-5-(2-chlorophenyl)-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9g). ¹H NMR (300 MHz, CDCl₃): δ 7.98 (d, *J* = 1.2 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.50 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.31 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.22–7.11 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 4.75 (d, *J* = 16.2 Hz, 1H), 4.69 (d, *J* = 16.2 Hz, 1H), 3.98 (dd, *J* = 7.4, 17.2 Hz, 1H), 3.96 (dd, *J* = 7.4, 17.2 Hz, 1H), 3.89 (s, 3H), 3.63 (s, 3H), 3.52 (s, 3H), 2.33 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 166.9, 166.5, 159.3, 150.7, 139.8, 135.2, 132.3, 130.5, 129.9, 129.8, 129.0, 128.2, 125.6, 124.6, 111.3, 108.4, 99.9, 73.6, 59.5, 54.3, 52.6, 51.2, 49.8, 28.2, 20.5, 20.4. MS (ESI): *m/z* 498 (M + H)⁺. HRMS (ESI) Calcd for C₂₆H₂₉ClN₃O₅: *m/z* 498.1796. Found:

498.1800 (M + 1)⁺. IR(neat): 2954, 1720, 1602, 1525, 1095, 765 cm⁻¹. HPLC: 97%.

3-Methyl 6-tert-Butyl 9-Isopropyl-7-methyl-5-(2-chlorophenyl)-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9h). ¹H NMR (300 MHz, CDCl₃): δ 8.08 (d, *J* = 1.4 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.21–7.11 (m, 2H), 6.79 (s, 1H), 5.15 (quint, *J* = 7.0 Hz, 1H), 3.9 (s, 3H), 2.51 (s, 3H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.41 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 166.7, 166.1, 148.6, 138.9, 133.2, 131.9, 130.9, 129.6, 129.4, 129.3, 129.2, 127.4, 124.6, 123.4, 111.0, 109.0, 100.4, 79.9, 54.7, 52.1, 46.0, 28.4(3C), 24.6, 20.3, 20.1. MS (ESI): *m/z* 496 (M + H)⁺. HRMS (ESI) Calcd for C₂₇H₃₁ClN₃O₄: *m/z* 496.2003. Found: 496.2006 (M + 1)⁺. IR(neat): 2971, 2927, 1720, 1662, 1590, 1089, 763 cm⁻¹. HPLC: 92%.

Dimethyl 9-Cyclopentyl-5-ethyl-7-ethyl-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9i). ¹H NMR (300 MHz, CDCl₃): δ 7.86 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.81 (d, *J* = 1.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.64 (t, *J* = 3.8 Hz, 1H), 5.09 (quint, *J* = 8.7 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 2.93 (dq, *J* = 12.3, 7.4 Hz, 1H), 2.75 (dq, *J* = 12.3, 7.4 Hz, 1H), 2.14–1.94 (m, 8H), 1.76–1.66 (m, 2H), 1.18 (t, *J* = 7.4, 3H), 0.70 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.4, 167.2, 167.0, 151.4, 134.0, 129.7, 124.7, 123.8, 110.2, 109.3, 95.4, 54.6, 53.7, 52.6, 51.1, 30.5, 29.4, 29.3, 27.2, 25.6, 25.5, 13.5, 8.1. MS (ESI): *m/z* 412 (M + H)⁺. HRMS (ESI) Calcd for C₂₃H₃₀N₃O₄: *m/z* 412.2236. Found: 412.2234 (M + 1)⁺. IR(neat): 2960, 2873, 1720, 1673, 1467 cm⁻¹. HPLC: 85%.

Methyl 6-Oxo-8,8-dimethyl-11-cyclohexyl-5-(4-methoxyphenyl)-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[b]fluorene-3-carboxylate (9j). ¹H NMR (300 MHz, CDCl₃): δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.72 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.46 (s, 1H), 4.75 (t, *J* = 12.2 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 2.54 (s, 2H), 2.28 (d, *J* = 16.3 Hz, 1H), 2.18 (d, *J* = 16.3 Hz, 1H), 2.17 (m, 2H), 2.06–1.81 (m, 4H), 1.62–1.54 (m, 2H), 1.39–1.25 (m, 2H), 1.10 (s, 3H), 1.00 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 194.7, 166.8, 162.5, 159.4, 150.5, 134.0, 133.8, 129.9, 128.6(2C), 125.0, 124.3, 114.2(2C), 111.4, 110.5, 109.0, 55.8, 55.7, 55.5, 52.6, 51.2, 46.6, 32.9, 30.8, 30.5, 30.0, 27.6, 26.2, 26.1, 25.6. MS (ESI): *m/z* 514 (MH⁺). HRMS (ESI) Calcd for C₃₁H₃₆N₃O₄: *m/z* 514.2706. Found: 514.2708 (M + 1)⁺. IR(neat): 2931, 2861, 1716, 1614, 1589, 850 cm⁻¹. HPLC: 99%.

Dimethyl 9-Cyclohexyl-7-(methoxymethyl)-5-(1,3-benzodioxol-4-yl)-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9k). ¹H NMR (300 MHz, CDCl₃): δ 7.83 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.70 (d, *J* = 1.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.84 (d, *J* = 1.7 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.38 (s, 1H), 5.86 (dd, *J* = 4.9, 1.2 Hz, 2H), 4.75 (m, 1H), 4.68 (s, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.52 (s, 3H), 2.21–2.12 (m, 2H), 2.01–1.78 (m, 6H), 1.55–1.46 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 166.9, 166.7, 158.2, 150.1, 148.4, 147.8, 136.0, 134.3, 129.4, 125.1, 124.0, 121.1, 111.0, 110.2, 108.3, 107.8,

101.4, 100.3, 73.9, 59.5, 57.3, 54.5, 52.6, 51.3, 30.7, 30.5, 30.2, 26.1, 25.6. MS (ESI): *m/z* 534 (M + H)⁺. HRMS (ESI) Calcd for C₂₉H₃₂N₃O₇: *m/z* 534.2240. Found: 534.2243 (M + 1)⁺. IR(neat): 2933, 2857, 1718, 1596, 1521, 1243, 763 cm⁻¹. HPLC: 99%.

Methyl 6-Oxo-8,8-dimethyl-11-benzyl-5-ethyl-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[b]fluorene-3-carboxylate (9l). ¹H NMR (300 MHz, CDCl₃): δ 7.91 (d, *J* = 1.2 Hz, 1H), 7.86 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.27–7.28 (m, 5H), 7.01 (d, *J* = 8.3 Hz, 1H), 5.84 (t, *J* = 3.0 Hz, 1H), 5.37 (d, *J* = 15.6 Hz, 1H), 5.25 (d, *J* = 15.6 Hz, 1H), 3.92 (s, 3H), 2.54 (d, *J* = 17.4 Hz, 1H), 2.46 (d, *J* = 17.4 Hz, 1H), 2.33 (s, 2H), 2.10 (m, 1H), 1.92 (m, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.72 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 195.4, 166.8, 165.4, 152.3, 135.4, 134.5, 129.6, 129.3(2C), 128.5, 127.7(2C), 125.5, 125.1, 110.9, 109.2, 106.2, 52.7, 52.6, 51.4, 46.6, 45.9, 32.7, 30.0, 27.9, 25.5, 7.8. MS (ESI): *m/z* 491 (M⁺). HRMS (ESI) Calcd for C₃₁H₂₉N₃O₃: *m/z* 492.2209. Found: 492.2207 (M + 1)⁺. IR(neat): 2962, 2923, 1712, 1612, 1396 cm⁻¹. HPLC: 94%.

Methyl 6-Oxo-11-(4-methoxybenzyl)-8,8-dimethyl-5-butyl-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[b]fluorene-3-carboxylate (9m). ¹H NMR (300 MHz, CDCl₃): δ 7.87 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.80 (t, *J* = 3.2 Hz, 1H), 5.30 (d, *J* = 15.4 Hz, 1H), 5.20 (d, *J* = 15.4 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 2.53 (d, *J* = 17.3 Hz, 1H), 2.45 (d, *J* = 17.3 Hz, 1H), 2.31 (s, 2H), 2.06–1.80 (m, 2H), 1.34–1.20 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H), 0.90–0.80 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 195.0, 166.9, 165.2, 159.8, 152.2, 134.5, 129.5, 129.3(2C), 127.5, 125.5, 125.0, 114.7(2C), 110.9, 109.2, 106.8, 55.7, 52.6, 51.9, 51.4, 46.6, 45.5, 32.8, 32.6, 30.0, 27.8, 25.8, 22.9, 14.5. MS (ESI): *m/z* 502 (MH⁺). HRMS (ESI) Calcd for C₃₀H₃₆N₃O₄: *m/z* 502.2706. Found: 502.2704 (M + 1)⁺. IR(neat): 2954, 1718, 1616, 1594, 823 cm⁻¹. HPLC: 98%.

3-Methyl 6-tert-Butyl 9-(2-thienylmethyl)-7-methyl-5-(4-nitrophenyl)-5-hydro-5a,8,9-triaza-fluorene-3,6-dicarboxylate (9n). ¹H NMR (300 MHz, CDCl₃): δ 8.13 (d, *J* = 8.7 Hz, 2H), 7.84 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 (dd, *J* = 3.4, 1.2 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.47 (s, 1H), 5.53 (d, *J* = 14.8 Hz, 1H), 5.42 (d, *J* = 14.8 Hz, 1H), 3.89 (s, 3H), 2.54 (s, 3H), 1.44 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 166.7, 166.1, 158.7, 149.4, 148.8, 147.9, 137.4, 134.4, 129.1, 128.6(2C), 127.7, 127.4, 126.6, 125.8, 124.8, 124.3(2C), 110.5, 108.8, 101.1, 80.7, 57.7, 52.7, 40.8, 30.1, 28.8(2C), 25.1. MS (ESI): *m/z* 561 (M + H)⁺. HRMS (ESI) Calcd for C₂₉H₂₉N₄O₆S: *m/z* 561.1808. Found: 561.1804 (M + 1)⁺. IR(neat): 2923, 2852, 1714, 1608, 1521, 1346, 819 cm⁻¹. HPLC: 96%.

Methyl 6-Oxo-11-(2-thienylmethyl)-5-propyl-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[b]fluorene-3-carboxylate (9o). ¹H NMR (300 MHz, CDCl₃): 7.90 (d, *J* = 8.3 Hz, 1H), 7.88 (s, 1H), 7.22 (d, *J* = 4.9 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.94 (dd, *J* =

4.9, 3.2 Hz, 1H), 5.77 (t, $J = 3.4$ Hz, 1H), 5.47 (d, $J = 15.8$ Hz, 1H), 5.41 (d, $J = 15.8$ Hz, 1H), 3.92 (s, 3H), 2.74 (dt, $J = 17.6, 4.7$ Hz, 1H), 2.60–2.46 (m, 2H), 2.60 (dd, $J = 17.6, 9.1, 5.2$ Hz, 1H), 2.07–2.02 (m, 2H), 1.40–1.28 (m, 2H), 0.97–0.82 (m, 2H), 0.75 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 195.8, 166.9, 166.8, 151.3, 137.4, 134.0, 127.6, 127.3, 126.6, 125.5, 125.1, 110.9, 108.9, 108.0, 52.7, 51.7, 40.8, 37.7, 35.1, 32.8, 30.1, 22.2, 16.9, 14.3. MS (ESI): m/z 436 (M + H) $^+$. HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_3\text{S}$: m/z 436.1695. Found: 436.1692 (M + 1) $^+$. IR(neat): 3060, 3008, 2950, 1697, 1614 cm^{-1} . HPLC: 99%.

Methyl 6-Oxo-11-(2-thienylmethyl)-5-propyl-5,6,7,8,9,11-hexahydro-7H-4b,10,11-triaza-benzo[*b*]fluorene-3-carboxylate (9p). ^1H NMR (300 MHz, CDCl_3): δ 8.10 (d, $J = 8.6$ Hz, 2H), 7.92 (dd, $J = 8.4, 1.3$ Hz, 1H), 7.55 (d, $J = 1.3$ Hz, 1H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 1H), 6.60 (s, 1H), 5.26 (s, 1H), 4.28 (m, 2H), 3.87 (s, 3H), 2.52 (s, 2H), 2.47 (t, $J = 6.9$ Hz, 2H), 2.27 (d, $J = 16.4$ Hz, 1H), 2.12 (m, 2H), 2.10 (d, $J = 16.4$ Hz, 1H), 1.85 (m, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.08 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 194.6, 166.6, 163.6, 150.8, 148.2, 147.7, 134.5, 133.9, 129.0, 128.2(2C), 125.9, 125.1(2C), 124.3(2C), 111.0, 108.9, 107.6, 55.5, 52.7, 51.1, 46.8, 41.2, 36.8, 32.9, 29.6, 28.4, 27.7, 25.6, 23.1, 22.4. MS (ESI): m/z 555 (M + H) $^+$. HRMS (ESI) Calcd for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_5$: m/z 555.0916. Found: 436.0961 (M + 1) $^+$. IR(neat): 3060, 3008, 2950, 1697, 1614 cm^{-1} . HPLC: 97%.

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Supporting Information Available. ^1H and ^{13}C NMR, IR, and mass spectra of compounds **9a–9p**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) (a) Malcolm, M.; Thomas, A. B. *Science* **2004**, *303*, 1810–1813.
- (2) (a) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 51–63. (b) Kappe, C. O.; Dallinger, D.; Murphree, S. *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols*; Wiley-VCH: Weinheim, Germany, 2009. (c) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.
- (3) (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2084. (b) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789. (c) Morris, R. E. *Chem. Commun.* **2009**, *21*, 2990–2998. (d) Sheldon, R. J. *Chem. Soc., Chem. Commun.* **2001**, 2399–2407. (e) Dupont, J.; Souza, R. F. D.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
- (4) (a) Smith, M. B. *Compendium of Organic Synthetic Methods*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; Vol. 12. (b) Polackova, V.; Hutka, M.; Toma, S. *Ultrason. Sonochem.* **2005**, *12*, 99–102. (c) Luche, J. L.; Cintas, P. In *Advances in Sonochemistry*; Mason, T. J., Ed; JAI Press: Greenwich, CT, 1998; Vol. 5, pp 147–174.
- (5) (a) Lu, J.; Toy, P. H. *Chem. Rev.* **2009**, *109*, 815–838. (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509. (c) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632–7633. (d) Merrifield, B. *Science* **1986**, *232*, 341–347.
- (6) (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: New York, 2005. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (c) Jiang, B.; Tu, S. J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660–11661. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (e) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (f) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (g) Eilbracht, P.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329–3366. (h) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 137–166.
- (7) (a) Boldi, A. M. *Combinatorial Synthesis of Natural Product-Based Libraries*; CRC Press LLC: Boca Raton, FL, 2006. (b) Van der Eycken, E.; Van der Eycken, J. *Microwaves in Combinatorial and High-Throughput Synthesis*; Wiley-VCH: Weinheim, Germany, 2004. (c) Tomoda, H.; Doi, T. *Acc. Chem. Res.* **2008**, *41*, 32–39. (d) Zhang, S.; Chen, L.; Luo, Y.; Gunawan, A.; Lawrence, D. S.; Zhang, Z. Y. *J. Am. Chem. Soc.* **2009**, *131*, 13072–13079. (e) Kim, Y.; Koh, M.; Kim, D. K.; Choi, H. S.; Park, S. B. *J. Comb. Chem.* **2009**, *11*, 928–937. (f) Spatz, J. H.; Bach, T.; Umkehrer, M.; Bardin, J.; Ross, G.; Burdack, C.; Kolb, J. *Tetrahedron Lett.* **2007**, *48*, 9030–9034. (g) Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 633–636.
- (8) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
- (9) Our recent work focused on the bringing the different disciplines of organic synthesis on one platform with their advances and apply their integrated effect to speed up library synthesis of drug-like compounds. This concept is termed as “multidisciplinary synthetic approach” by its profound nature in organic synthesis which could bring the two or more disciplines of organic synthesis on one path to facilitate initial drug discovery process. Some of the reports already available which supports the multidisciplinary synthetic approach. See: (a) Zhang, W.; Chen, C. H.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473–1476. (b) Bai, L.; Wang, J. X. *Adv. Synth. Cat.* **2008**, *350*, 315–320. (c) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205–1208. (d) Bai, L.; Wang, J. X. *Curr. Org. Chem.* **2005**, *9*, 535–553. (e) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Mol. Diversity* **2003**, *7*, 135–144.
- (10) (a) Maiti, B.; Chanda, K.; Sun, C. M. *Org. Lett.* **2009**, *11*, 4826–4829. (b) Lin, M. J.; Zhang, W.; Sun, C. M. *J. Comb. Chem.* **2007**, *9*, 951–958. (c) Wu, C. Y.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 959–962.
- (11) (a) Yanez, C. O.; Andrade, C. D.; Belfield, K. D. *Chem. Commun.* **2009**, *7*, 827–829. (b) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715–5724. (c) Selvi, S. T.; Nadaraj, V.; Mohan, S.; Sasi, R.; Hema, M. *Bioorg. Med. Chem.* **2006**, *14*, 3896–3903. (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
- (12) (a) Besson, T.; Brain, C. T. In *Microwave-Assisted Organic Synthesis*; Lidsrom, P., Tieney, J. P., Eds.; Blackwell Publishing: Oxford, U.K., 2005. (b) Hamelin, J.; Bazureau, J. P.; Texier-Boullet, F. In *Microwaves in Organic Synthesis*; Loupy, A., Ed., Wiley-VCH: Weinheim, Germany, 2002; pp 253–294. (c) Kappe, C. O.; Stadler, A. *Combinatorial Chemistry, Part B*; Bunin, B. B., Morales, G., Eds.; Elsevier Science: New York, 2003; pp 197–223. (d) Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625–8627. (e) Mont, N.; Teixido, J.; Borell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385–5387.
- (13) (a) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546–5549. (b) Tour, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (c) Ma, Y.; Wang, M.; Li, D.; Bekturhyn, B.; Liu, J.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 3116–3121. (d) Fontaine, P.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 1555–1558. (e) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472. (f) Piersanti, G.; Remi, F.; Fusi, V.; Formica, M.; Giorgi, L.; Zappia, G. *Org. Lett.* **2009**, *11*, 417–420. (g) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156–8162. (h) Chen, Y. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 3702–3703.

- (14) (a) Meredith, J. C.; Smith, A. P.; Karim, A.; Amis, E. J. In *Combinatorial Materials Development*; Malhotra, R., Ed.; ACS Symposium Series 814; American Chemical Society: Washington, DC, 2002; pp 23–47. (b) Bergbreiter, D. E.; Kobayashi, S. *Chem. Rev.* **2009**, *109*, 257–258. (c) Wang, Z.; Chen, G.; Ding, K. *Chem. Rev.* **2009**, *10*, 322–359. (d) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472. (e) Zhou, F.; Zheng, Z.; Yu, B.; Liu, W.; Huck, W. T. S. *J. Am. Chem. Soc.* **2006**, *128*, 16253–16258. (f) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866–2869. (g) Yin, Y.; Zhao, G.; Li, G. L. *Tetrahedron* **2005**, *61*, 12042–12052. (h) Arai, T.; Sekiguti, T.; Otsuki, K.; Takizawa, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2144–2147.
- (15) (a) Demaude, T.; Knerr, L.; Pasau, P. *J. Comb. Chem.* **2004**, *6*, 768–775. (b) Wiles, C.; Watts, P. *Org. Process Res. Dev.* **2008**, *12*, 1001–1006. (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2002**, *7*, 1184–1190. (d) Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959–4962.
- (16) (a) Yue, G.; Wan, Y.; Song, S.; Yang, G.; Chen, Z. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 453–458. (b) Jiang, L. L.; Li, B. L.; Lv, F. T.; Dou, L. F.; Wang, L. C. *Tetrahedron* **2009**, *65*, 5257–5264. (c) Fishman, A.; Farrah, M. E.; Zhong, J. H.; Paramanatham, S.; Carrera, C.; Lee-Ruff, E. *J. Org. Chem.* **2003**, *68*, 9843–9846. (d) Gravert, D. J.; Datta, A.; Wentworth, P., Jr.; Janda, K. D. *J. Am. Chem. Soc.* **1998**, *120*, 9481–9495. (e) Ando, H.; Manabe, S.; Nakahara, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 4725–4728.
- (17) Chai, D.; Fitch, D. M. Propyl hydroxylase inhibitors. WO Patent 09039322 A1, March 26, 2009.
- (18) Kato, F.; Kimura, H.; Omatsu, M.; Yamamoto, K.; Miyamoto, R. Preventive or therapeutic medicines for diabetes containing fused-heterocycle compounds or their salts. WO Patent 02040485, May 23, 2002.
- (19) McMaster, B. Anti-Inflammatory compositions and methods of use. WO Patent 03105857, December 24, 2003.
- (20) Shigeta, S.; Mori, S.; Baba, M.; Hosoya, M.; Mochizuki, N.; Chiba, T.; De Clercq, E. *Antiviral Chem. Chemother.* **1992**, *3*, 171–177.
- (21) Nofal, Z. M.; Fahmy, H. H.; Mohamed, H. S. *Arch. Pharm. Res.* **2002**, *25*, 28–38.
- (22) Hafez, A.; Monem, A. A. *Arch. Pharm. Res.* **2007**, *30*, 678–684.
- (23) Lunn, W. H. W.; Harper, R. W.; Stone, R. L. *J. Med. Chem.* **1971**, *14*, 1069–1071.
- (24) Alajarin, R.; Vaquero, J. J.; Alvarez-Builla, J.; Faude Casa-Juana, M.; Sunkel, C.; Priego, J. G.; Gomez-Sal, P.; Torres, R. *Bioorg. Med. Chem.* **1994**, *2*, 323–329.
- (25) (a) Ishida, J.; Wang, H. K.; Bastow, K. F.; Hu, C. Q.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3319–3324. (b) Da Settimo, A.; Da Settimo, F.; Marini, A. M.; Primofiore, G.; Salerno, S.; Viola, G.; Dalla Via, L.; Magno, S. M. *Eur. J. Med. Chem.* **1998**, *33*, 685–696. (c) Dalla Via, L.; Gia, O.; Magno, S. M.; Da Settimo, A.; Marini, A. M.; Primofiore, G.; Da Settimo, F.; Salerno, S. *Farmaco* **2001**, *56*, 159–167.
- (26) (a) Wu, Y. C.; Duh, C. Y. *J. Nat. Prod.* **1990**, *53*, 1327–1331. (b) He, X. F.; Wang, X. N.; Fan, C. Q.; Gan, L. S.; Yin, S.; Yue, J. M. *Helv. Chim. Acta* **2007**, *90*, 783–791.
- (27) Carpenter, R. D.; Lam, K. S.; Kurth, M. J. *J. Org. Chem.* **2007**, *72*, 284–287.
- (28) Martin, M. W.; Newcomb, J.; Nunes, J. J.; Boucher, C.; Chai, L.; Epstein, L. F.; Faust, T.; Flores, S.; Gallant, P.; Gore, A.; Gu, Y.; Hsieh, F.; Huang, X.; Kim, J. L.; Middleton, S.; Morgenstern, K.; Oliveira-dos-Santos, A.; Patel, V.; Powers, D.; Rose, O. P.; Tudor, Y.; Turci, S. M.; Welcher, A. A.; Zack, D.; Zhao, H.; Zhu, L.; Zhu, X.; Ghiron, C.; Ermann, M.; Johnston, D.; Saluste, C. G. P. *J. Med. Chem.* **2008**, *51*, 1637–1648.
- (29) (a) Bauvois, B.; Puiffe, M. L.; Bongui, J. B.; Paillat, S.; Monneret, C.; Dauzonne, D. *J. Med. Chem.* **2003**, *46*, 3900–3913. (b) Sharma, S.; Saha, B.; Sawant, D.; Kundu, B. *J. Comb. Chem.* **2007**, *9*, 783–792. (c) Shaabani, A.; Rahmati, A.; Naderi, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5553–5557. (d) Rong, L.; Han, H.; Jiang, H.; Tu, S. *Synth. Commun.* **2009**, *39*, 3493–3499.
- (30) (a) Bendale, P. M.; Sun, C. M. *J. Comb. Chem.* **2002**, *4*, 359–361. (b) Yeh, W. B.; Sun, C. M. *J. Comb. Chem.* **2004**, *6*, 279–282. (c) Chen, C. H.; Chien, M. H.; Kuo, M. L.; Chou, C. T.; Lai, J. J.; Lin, S. F.; Thummanagoti, S.; Sun, C. M. *J. Comb. Chem.* **2009**, *11*, 1038–1046. (d) Chanda, K.; Kuo, J.; Chen, C. H.; Sun, C. M. *J. Comb. Chem.* **2009**, *11*, 252–260.

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