Synthesis of Novel N-Rich Polycyclic Skeletons Based on Azoles and Pyridines

Sunil Sharma, Biswajit Saha, Devesh Sawant, and Bijoy Kundu*

Combichem Unit, Medicinal Chemistry & Process Division, Central Drug Research Institute, Lucknow 226001, India

Received March 9, 2007

An efficient method for the synthesis of new polycyclic skeletons: triaza-benzofluorenes and triaza-pentalenonaphthalene from bicyclic privileged structures imidazopyridine and imidazothiazole, respectively, has been described using the Pictet−Spengler cyclization.

Introduction

Heterocyclic chemistry has always been one of the most-valuable sources of novel compounds with diverse biological activity, mainly, because of the unique ability of the compounds to mimic the structure of peptides and to bind reversibly to proteins.[1] To medicinal chemists, the true utility of heterocyclic structures is the ability to synthesize one library based on one core scaffold and screen it against a variety of different receptors, yielding several active compounds. Almost unlimited combinations of fused heterocyclic structures can be designed, resulting in novel polycyclic frameworks with the most diverse physical, chemical, and biological properties. The fusion of several rings leads to geometrically well-defined rigid polycyclic structures and, thus, holds the promise of a high functional specialization resulting from the ability to orient substituents in three-dimensional space. Therefore, efficient methodologies resulting in polycyclic structures from biologically active heterocyclic templates are always of interest to both organic and medicinal chemists. Since the advent of small-molecule combinatorial synthesis, countless libraries of biologically interesting molecules have been synthesized using both solid- and solution-phase strategies.[2] A subset of these has been synthesized using biologically validated heterocyclic structures (privileged structures) as starting points for the library design.[3] The resulting libraries are then used to address a variety of protein targets to identify new leads with high affinity.[4]

Recently, we demonstrated application of the Pictet−Spengler reaction on a variety of "second-generation" substrates, having an aryl amine linked to the activated heteroaromatic ring, resulting in the synthesis of both 6- and 7-member benzoannealated heterosystem libraries.[5] Following our report, two groups demonstrated the application of the Pictet−Spengler reaction on substrates with heteroarylamines linked to the activated heteroaromatic rings, thereby resulting in the libraries of fused heterocyclic systems.[6] However, while the reaction has been successfully demonstrated on monocyclic activated rings linked to either aliphatic or aryl amines, it has not, to the best of our knowledge, been applied to bicyclic privileged structures.[3] Such a strategy would furnish novel libraries of polycyclic frameworks derived from privileged structures that, in turn, could be used as a source for new chemical entities in medical and biological research.

In the first case, we selected imidazole-based bicyclic systems, imidazopyridine and imidazothiazole, as privileged structures (Figure 1) for our study because of their association with a variety of biological activities.[7] To convert these bicyclic structures into Pictet−Spengler substrates, we proposed the introduction of an arylamine at one of the carbons in the imidazole moiety of the bicyclic ring to facilitate the Pictet−Spengler cyclization. To select the appropriate carbon in the ring for linkage with an aryl amine, we analyzed the electrophilic substitution patterns both in the imidazole, as well as in bicyclic structures (Figure 1). The multiply bonded nitrogen atom present in azoles is generally known to have differential deactivating affects on the carbon atoms in the ring.[8] The positions α and γ to the multiply bonded N atom (N-1) are deactivated toward electrophilic attack, whereas the β-carbon is the least deactivated and is therefore prone toward electrophilic substitution. Comparison of the resonance-contributing structures for imidazole, imidazopyridine, and imidazothiazole show that positions C-5 in imidazole, C-3 in imidazopyridine, and C-5 in imidazothiazole are most susceptible toward electrophilic substitutions (Figure 1).

Armed with these observations, we envisioned that an aryl amine originating from the carbon atom adjacent to the β-positions of the imidazo rings in both imidazo-pyridine and -thiazole may furnish bicyclic substrates for the Pictet−Spengler cyclization. In this paper, we report application of privileged structure-based bicyclic derivatives as novel substrates for the Pictet−Spengler reaction (6 *endo trig*) leading to the synthesis of novel N-rich polycyclic heterosystems. Among the various heterocyclic frameworks, N-rich polycyclic skeletons are known to be associated with a wide range of biologically activities.[9]

* To whom correspondence should be addressed. E-mail: bijoy_kundu@yahoo.com. Phone: +91 522 2612411-18x4383. Fax: +91 522 2623405.

10.1021/cc0700445 CCC: $37.00
Published on Web 06/15/2007

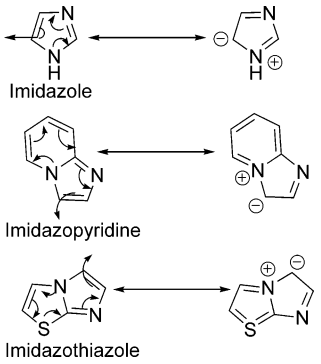
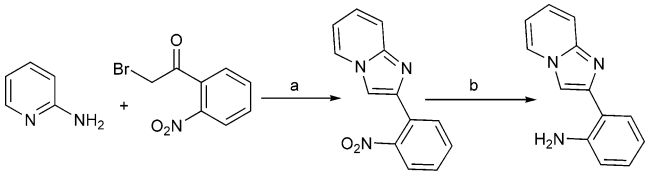


Figure 1. Pattern of electrophilic substitution in the imidazole and its bicyclic derivatives.

Scheme 1[a]



[a] Reagents and conditions: (a) C_2H_5OH, reflux, 4 h; (b) $SnCl_2 \cdot 2H_2O$ (5 equiv), C_2H_5OH, under N_2 atmosphere, reflux, 1.5 h.

Results and Discussion

Initially, we directed our efforts to the bicyclic imidazopyridine nucleus. The bicyclic substrate 2-imidazo[1,2-a]-pyridin-2-yl-phenylamine **4**, required as key intermediate for the Pictet−Spengler reaction, was synthesized in two steps as depicted in Scheme 1 The treatment of commercially available 2-aminopyridine **1** with 2-nitrophenacyl bromide **2**, according to the literature procedure, furnished imidazopyridine[10] **3** in a quantitative yield. Subsequent reduction of the nitro functionality to its corresponding aryl amine was achieved with $SnCl_2 \cdot 2H_2O$ in C_2H_5OH to yield the key intermediate **4**. The latter was then subjected to the Pictet−Spengler reaction with salicylaldehyde by refluxing in toluene in the presence of *p*-TsOH.

As expected, the cyclization occurred at the electron-rich imidazole moiety of the imidazopyridine ring to obtain an oxidized product triazabenzofluorenes **6a** as a novel N-rich polycyclic system hitherto not reported (Scheme 2). However, we were unable to isolate intermediate **5**, and this may be the result of spontaneous aerial oxidation of intermediate **5** in situ to generate more stable aromatic system **6** devoid of any stereochemical center.

This is in contrast to the traditional Pictet−Spengler reaction involving substrates based on aliphatic amines linked to an activated heterocyclic ring, which invariably furnishes tetrahydro derivatives with a new stereochemical center. The scope of this reaction was further studied with various aliphatic and aromatic aldehydes, and the results are summarized in Table 1. The crude product obtained after workup was purified by silica gel column chromatography using EtOAc/hexane as an eluant and was characterized by LC-MS and NMR. The results suggest that substrate **4** reacted with a wide range of aldehydes to give *endo*-cyclized products **6** in good isolated yields. Indeed, substrate **4** demonstrated differential reactivity toward aldehydes. The cyclization with aromatic aldehydes having electron-withdrawing group proceeded quite fast (1.5−2.5 h, Table 1, compounds **6f**−**h**.). However, the reactions with aromatic aldehydes having an electron-donating substituent and aliphatic aldehyde went at a slower pace (3−8 h, Table 1, compounds **6a**−**e** and **j**). The reaction with salicylaldehyde was sluggish in comparison to that with 3-OH-benzaldehyde because of the steric hindrance. This trend in the reactivity also suggests that 6-*endo*-cyclization is the slowest step, even slower than imine formation; hence, it can be considered to be a rate-determining step. The *endo*-cyclization of **4** with aldehydes could be envisioned to proceed through an iminium intermediate analogous to the traditional Pictet−Spengler reactions, as depicted in Scheme 2. Compound **4** reacts with an aldehyde in the presence of *p*-TsOH to give an imine which could be protonated under acidic conditions to yield an iminium ion, followed by electrophilic substitution at the electron-rich C-3 of the imidazole ring and subsequent aerial oxidation to furnish the final product **6**.

Interestingly, since the traditional Pictet−Spengler reaction involves aliphatic amines (tryptamine/Trp-OMe), aldehydes with an electron-donating group generally result in the imines and do not undergo *endo*-cyclization. Cook et al. attributed the electrophilicity of the imine double bond resulting from the condensation of amines with aldehydes as the limiting factor for the Pictet−Spengler cyclization and applied pK_a values of amines to compare the electrophillicities of imines.[11]

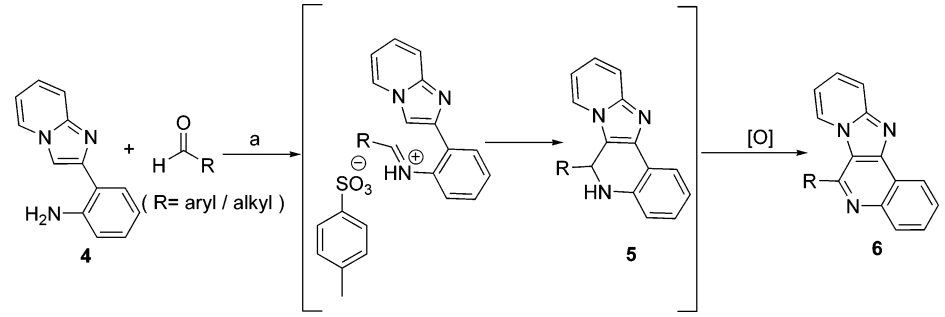
Accordingly, we believe that in the substrate **4**, the imine intermediate derived from the aldehydes with electron donating group is relatively more electrophilic than the imine derived from the Trp-OMe using the same aldehyde because the p*K*a value of aryl amine (4.2 for aniline) is significantly less than that of Trp-OMe (7.29). The reaction rate followed the order of reactivity of the aldehyde with the amino group: aromatic aldehydes with electron with drawing group > aromatic aldehydes with electron donating group ≥ aliphatic aldehyde.

The scope of the substrate **4** was further studied with ketones (Scheme 3), and the results are summarized in Table 2. Surprisingly, our initial attempts with *p*-TsOH in toluene failed to yield the desired product **7**.

The application of other traditionally used Pictet−Spengler protocols, AcOH in ethanol, toluene at reflux, 5% TFA in DCM at 0 °C, and $Yb(OTf)_3$, also failed to yield the *endo*-cyclized product. However, when substrate **4** was treated with acetophenone in CH_3CN in the presence of TFA at reflux, we obtained the desired compound **7**. Next, we applied the same protocol for the condensation of compound **4** with other aliphatic and aromatic ketones to give Pictet−Spengler products **7**, in moderate to excellent isolated yields.

Encouraged by our results with substrate **4**, we extended our studies to the other fused bicyclic imidazole derivative imidazothiazole, a class of compounds known to be associated with antitumor, anti-inflammatory, anthelmintic, and MDR-reversal activities.[12] The synthesis of the imidazothiazole-based substrate **11** was carried out by condensation of 2-aminothiazole[13] with *o*-nitrophenacyl bromide[14] by a

Scheme 2[a]

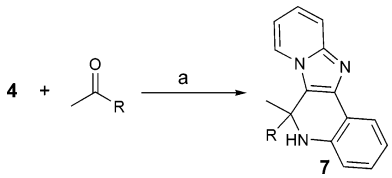


[a] Reagents and conditions: (a) *p*-TsOH, toluene, 120 °C, 1−8 h.

Table 1. Synthesis of 5,6b,11-triazbenzo[a]fluorenes **6a**−**j**

	R	isolated yield (%)	time (h)
6a	2-OHC_6H_4	65	8
6b	3-OHC_6H_4	72	5
6c	4-$CH_3C_6H_4$	67	3
6d	2-$OCH_3C_6H_4$	70	4.
6e	4-$N(CH_3)_2C_6H_4$	63	7
6f	2-ClC_6H_4	72	1.5
6g	4-BrC_6H_4	70	2.5
6h	4-$NO_2C_6H_4$	74	1
6i	2-furyl	77	5
6j	C_2H_5	70	8

Scheme 3[a]



[a] Reagent and conditions: (a) TFA, CH_3CN, reflux, 2−4 h.

Table 2. Synthesis of Dihydro-5,6b,11-triazbenzo[a]fluorenes **7a**−**e**

	R	isolated yield (%)	time (h)
7a	C_6H_5	77	3
7b	*p*-MeO-C_6H_4	66	3.5
7c	*p*-NO_2-C_6H_4	77	2
7d	CH_3	55	4
7e	CH_3CH_2	57	4

literature procedure, followed by reduction of the nitro group (Scheme 4).

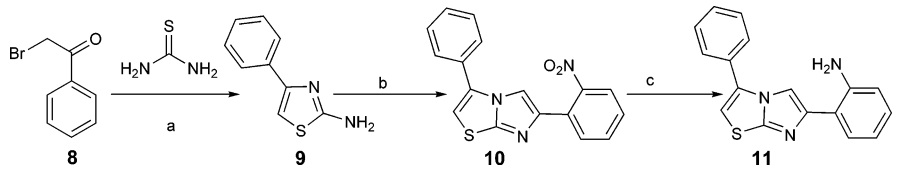
Substrate **11** was then subjected to the Pictet−Spengler reaction by being refluxed with various aldehydes in toluene in the presence of *p*-TsOH (Scheme 5, Table 3). As expected, the cyclization occurred at the imidazo moiety of the bicyclic imidazothiazole ring to give an oxidized product triazapentalenonaphthalene **12** as polycyclic systems. A careful literature survey for **12** revealed a single reference for the synthesis of thiazolo[2′,3′:2,3]imidazo[4,5-*c*]quinoline obtained by reductive cyclization of corresponding 6-(2-nitrophenyl)-imidazo[2,1-b]thiazole-5-carbaldehyde, and were found to be associated with antitumor activity.[15] In contrast, our strategy was based on 6-*endo trig*-cyclization of the iminium ion formed between an aldehyde and imidazothiazole-based aryl-amine substrate 2-imidazo[2,1-b]thiazol-6-yl-phenylamine **11** in the presence of an acid.

Reactivity of Monocyclic versus Bicyclic Substrates toward *endo*-Cyclization. Although the bicyclic substrates successfully underwent Pictet−Spengler cyclization, we decided to compare the reactivity of bicyclic substrates toward 6-*endo*-cyclization with that of monocyclic substrates with the view to establish the generality of our modified strategy for the Pictet−Spengler reaction. Accordingly, we compared the reactivity of imidazole (monocyclic) with imidazopyridines (bicyclic) toward the Pictet−Spengler reaction. Comparison of the canonical forms of imidazole and imidazopyridine (Figure 2) suggests that A-II is more stabilized than B-II. This may be attributed to the introduction of a positive charge in electron-deficient pyridine ring systems in the imidazolpyridine, which in turn diminishes the stability of the corresponding cannonical form, B-II. Hence, delocalization of π-electrons at the C-5 of the imidazole is more stabilized than at the C-3 of the imidazopyridine, thereby suggesting that C-5 in imidazole is more prone to electrophilic substitution than C-3 of the imidazopyridine. Thus, the imidazopyridine appears to be relatively deactivated than the imidazole toward an electrophile.

For experimental evidence, we compared the reactivities of the imidazole (monocyclic) substrate 2-(1*H*-Imidazol-4-yl)-phenylamine **15** (analogous to histamine) with the other two bicyclic substrates **4** and **19** (derived from imidazopyridine) toward *endo*-cyclization. In substrate **19**, an amide group was additionally introduced on the pyridine ring of the imidazopyridine because its electron-withdrawing nature would further decrease the reactivity of the imidazopyridine ring toward electrophilic substitution. The substrates (**4**, **15**, and **19**) were next subjected to Pictet−Spengler cyclization by treatment with *p*-tolualdehyde in the presence of *p*-TsOH, and the results have been summarized in Table 4. We were pleased to see that both monocyclic (**15**) and bicyclic (**4** and **19**) substrates successfully underwent *endo*-cyclization and that the difference in the activation of monocyclic and bicyclic heterosystems had no effect on the yield of the corresponding cyclized products except that the rate of reaction varied from 1 to 7 h and followed the order of reactivity **15** > **4** > **19**.

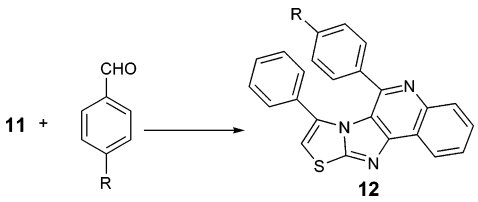
Thus, it is the enhanced electrophilic nature of the iminium ion derived from the aryl amine in comparison to that of the iminium ion derived from the aliphatic amine that acted as a driving force for *endo*-cyclization in both monocyclic and bicyclic substrates. It is worth mentioning that occurrence of *6-endo*-cyclization in substrate **19** with a relatively

Scheme 4[a]



[a] Reagents and conditions: (a) C_2H_5OH reflux, 1 h, 1 N HCl, reflux, 1 h; (b) *o*-nitrophenacyl bromide, acetone, reflux, 24 h, 2 N HCl, reflux, 1 h; (c) $SnCl_2 \cdot 2H_2O$ (5 equiv), C_2H_5OH, under N_2 atmosphere, reflux, 1 h.

Scheme 5[a]



[a] Reagents and conditions: *p*-TsOH, toluene, reflux.

Table 3. Synthesis of Thia-5,6b,10-triaza-pentaleno[2,1-a]-naphthalenes **12a**−**d**

	R	isolated yield (%)	time (h)
12a	*p*-CH_3	65	3
12b	*p*-NO_2	71	1
12c	*p*-$N(CH_3)_2$	60	9
12d	*p*-Br	63	1.5

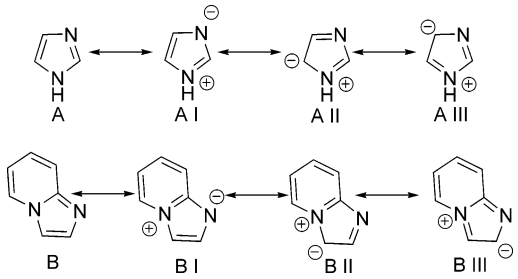


Figure 2. Pattern of resonance in imidazole and imidazopyridine nucleus.

deactivated imidazo ring suggests that the Pictet−Spengler cyclization may occur even when an aryl amine is linked to a deactivated heterosystem. Indeed, a systematic study is required to establish this fact by selecting monocyclic deactivated rings (triazoles/tetrazoles) attached to the aryl-amine as substrates for 6-*endo*-*trig*-cyclization.

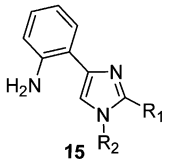
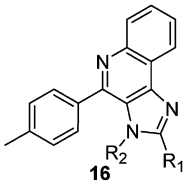
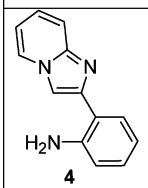
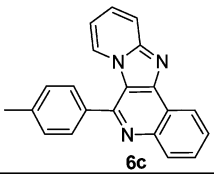
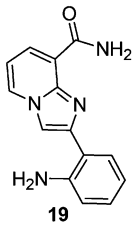
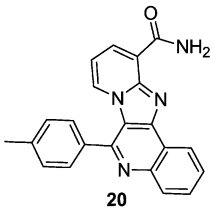
Conclusion

In conclusion, our present methodology allows efficient preparation of a polycyclic heterosystem from bicyclic substrates using the Pictet−Spengler reaction. This in turn will set the stage for a wide application of this powerful reaction for the synthesis of structurally diverse and novel polyheterocyclic skeletons based on privileged structures. Currently work is in progress in our lab with several new substrates derived from deactivated heterosystems designed on the basis of our modified concept for the Pictet−Spengler reaction and will be reported soon.

Experimental Section

All solvents were commercially available and used without purification. All products were characterized by ^{1}H NMR, ^{13}C NMR, ESMS, IR, and HPLC. Analytical TLC was performed using 2.5 × 5 cm plated coated with a 0.25 mm thickness of silica gel (60F-254 Merck), and visualization was accomplished with UV light and iodine. Column chromatography was performed using silica gel 60 Thomas Baker (100−200 mesh). ^{1}H NMR spectra (300/200 MHz) are reported as follows: chemical shifts in parts per million downfield from TMS as internal standard (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, o = overlapped), integration, and coupling constant (Hz). All ^{13}C NMR spectra (50/75 MHz) are determined with complete proton decoupling and are reported in parts per million. All spectra were recorded at 25 °C. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. Analytical HPLC were performed on C-18 reverse-phase column (250 mm × 4.6 mm). Mass spectra were recorded on a Merck MS-8000 spectrometer. 2-Amino-pyridine, aldehydes, *o*-nitrophenacylbromide, tin chloride dihydrate, etc. were purchased from Aldrich and Lancaster. Melting points reported were uncorrected.

Table 4. Comparison of Reactivity of Monocyclic (**15**) and Bicyclic Substrates (**4** and **19**) toward *endo*-Cyclization with *p*-Tolualdehyde

Comp.	Time (h)	Yield (%) isolated	Cyclized product
 **15** R_1-(*p*-OMe)$CH_2C_6H_4$ R_2-$CH_2C_6H_5$	1h	61	 **16**
 **4**	3h	67	 **6c**
 **19**	7h	63	 **20**

2-(2-Nitro-phenyl)-imidazo[1,2-a]pyridine (3). A solution of 2-amino-pyridine **1** (500 mg, 5.31 mmol) and

2-bromo-1-(2-nitro-phenyl)-ethanone **2** (1.29 g, 5.31 mmol) in ethanol (20 mL) was refluxed for 4 h. After the solvent was removed, the residue was basified to pH 8 with $NaHCO_3$ solution and extracted with EtOAc (40 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (85/15, v/v) to afford 2-(2-nitro-phenyl)-imidazo[1,2-a]pyridine **3**.

Yield: 1.10 g (87%). Yellow solid. mp: 151−152 °C (lit.[16] value 151−153 °C). IR (KBr): ν 1620, 1595, 1525, 1360 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, 1H, $J = 6.8$ Hz), 8.01 (dd, 1H, $J = 7.8$, 1.3 Hz), 7.78 (s, 1H), 7.74−7.60 (m, 3H), 7.48 (dd, 1H, $J = 7.0$, 1.3 Hz), 7.24 (t, 1H, $J = 6.1$ Hz), 6.83 (t, 1H, $J = 6.0$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.7, 145.7, 140.6, 132.2, 131.7, 128.9, 128.1, 126.2, 125.6, 123.9, 118.3, 113.2, 111.0. MS (ES^+) *m*/*z* 240.2 ($M^+ + 1$). Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.57; H, 3.67; N, 17.45.

2-Imidazo[1,2-a]pyridin-2-yl-phenylamine (4). A solution of 2-(2-Nitro-phenyl)-imidazo[1,2-a]pyridine **3** (500 mg, 2.09 mmol) and $SnCl_2{\cdot}2H_2O$ (2.36 g, 10.45 mmol) in ethanol (40 mL) was refluxed under nitrogen for 1.5 h. The solution was allowed to cool down, and then it was poured into ice; the pH was made slighitly basic (pH 8) by addition of 5% aqueous $NaHCO_3$. EtOAc (50 mL) was added to the mixture, and it was filtered through a bed of celite. The organic layer was finally washed with water (50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (75/25, v/v) to afford 2-imidazo[1,2-a]pyridin-2-yl-phenylamine **4.**

Yield: 367 mg (84%). White solid. mp: 126−127 °C. IR (KBr): ν 3451, 3300, 1597 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, 1H, $J = 8.0$ Hz), 7.80 (s, 1H), 7.59−7.51 (m, 2H), 7.18−7.08 (m, 2H), 6.75−6.73 (m, 3H), 5.67 (br s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.0, 146.4, 144.9, 129.3, 128.6, 125.7, 124.6, 117.7, 117.5, 117.2, 112.8, 110.0, 108.8. MS (ES^+) *m*/*z* 210.1 (M^++1). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.77; H, 5.50; N, 20.38.

General Procedure for the Pictet−Spengler Reaction on Subtrate 4. A mixture of 2-imidazo[1,2-a]pyridin-2-yl-phenylamine **4** (100 mg, 0.48 mmol), salicyaldehyde (50 μL, 48 mmol), and *p*-tolylsulfonic acid (9.6 mg, 0.048 mmol) was refluxed in toluene (6 mL) until disappearance of amine on TLC. Toluene was evaporated in vacuo, and the residue was dissolved in ethyl acetate (40 mL). The organic layer was finally washed with water (25 mL) and brine (25 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (80/20, v/v) to afford desired product **6a** as white solid.

2-(5,6b,11-Triaza-benzo[a]fluoren-6-yl)-phenol (6a). Yield: 97 mg (65%). White solid. mp: 259−260 °C. IR (KBr): ν 3428, 1584 cm^{-1}. ^1H NMR (200 MHz, DMSO): δ 10.05 (br s, 1H), 8.71 (d, 1H, $J = 7.5$ Hz), 8.22 (dd, 1H, $J = 7.6$, 1.2 Hz), 8.11 (d, 1H, $J = 6.9$ Hz), 8.02 (d, 1H, $J = 8.0$ Hz), 7.90−7.71 (m, 4H), 7.62 (dd, 1H, $J = 7.6$, 1.4 Hz), 7.55 (t, 1H, $J = 7.8$ Hz), 7.18−7.11 (m, 2H). ^{13}C NMR (50 MHz, DMSO): δ 155.3, 149.2, 146.5, 146.1, 145.0, 131.5, 131.3, 131.0, 129.5, 128.8, 127.7, 126.6, 125.6, 122.6, 121.4, 120.2, 117.5, 116.1, 112.8. MS (FAB): *m*/*z* = 312 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{13}N_3O$: C, 77.16; H, 4.21; N, 13.50; Found: C, 77.42; H, 4.42; N, 13.36.

3-(5,6b,11-Triaza-benzo[a]fluoren-6-yl)-phenol (6b). Yield: 107 mg (72%). Orange solid. mp: 202−204 °C. IR (KBr): ν 3426, 1589 cm^{-1}. ^1H NMR (200 MHz, DMSO): δ 9.92 (br s, 1H), 8.65 (dd, 1H, $J = 8.3$, 1.4 Hz), 8.14 (t, 2H, $J = 7.4$ Hz), 7.97 (d, 1H, $J = 8.0$ Hz), 7.85−7.67 (m, 4H), 7.47 (t, 1H, $J = 7.7$ Hz), 7.16−6.98 (m, 3H). ^{13}C NMR (50 MHz, DMSO): δ 158.2, 149.6, 146.5, 145.0, 141.2, 139.5, 139.0, 131.2, 130.6, 129.6, 129.13, 127.5, 126.8, 122.7, 121.4, 119.5, 117.9, 116.9, 115.7, 113.0. MS (FAB): *m*/*z* 312 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{13}N_3O$: C, 77.16; H, 4.21; N, 13.50. Found: C, 77.36; H, 4.02; N, 13.75.

6-*p*-Tolyl-5,6b,11-triaza-benzo[a]fluorene (6c). Yield: 99 mg (67%). Pale-yellow solid. mp: 239−240 °C. IR (KBr): ν 2957, 2858, 1603 cm^{-1}. ^1H NMR (200 MHz, DMSO): δ 8.67 (dd, 1H, $J = 6.4$, 1.5 Hz), 8.17 (t, 2H, $J = 6.1$ Hz), 8.01 (d, 1H, $J = 8.8$ Hz), 7.85−7.77 (m, 3H), 7.70 (d, 2H, $J = 7.9$ Hz), 7.51 (d, 2H, $J = 8.0$ Hz), 7.09 (t, 1H, $J = 6.8$ Hz), 2.52 (s, 3H). ^{13}C NMR (50 MHz, DMSO): δ 153.1, 150.0, 146.2, 142.5, 137.6, 135.6, 132.1, 130.6, 129.6, 128.6, 128.4, 127.7, 123.4, 122.6, 120.4, 120.0, 118.3, 115.6, 21.6. MS (FAB): *m*/*z* = 310 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.77; H, 4.66; N, 13.33.

6-(2-Methoxy-phenyl)-5,6b,11-triaza-benzo[a]fluorene (6d). Yield: 109 mg (70%). Pale-yellow solid. mp: 240−241 °C. IR (KBr): ν 2924, 2828, 1598 cm^{-1}. ^1H NMR (200 MHz, DMSO): δ 8.89 (d, 1H, $J = 8.0$ Hz), 8.40 (d, 1H, $J = 8.3$ Hz), 8.29 (d, 1H, $J = 8.8$ Hz), 8.19−8.11 (m, 4H), 7.92 (d, 2H, $J = 8.0$ Hz), 7.58−7.43 (m, 3H), 3.80 (s, 3H). ^{13}C NMR (50 MHz, DMSO): δ 159.2, 158.5, 157.5, 153.2, 149.9, 142.8, 137.2, 136.0, 134.8, 132.4, 131.7, 129.0, 128.5, 123.5, 122.0, 120.7, 119.9, 118.1, 116.1, 112.9, 56.4. MS (FAB): *m*/*z* 326 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.74; H, 4.47; N, 12.76.

Dimethyl-[4-(5,6b,11-triaza-benzo[a]fluoren-6-yl)-phenyl]-amine (6e). Yield: 102 mg (63%). Orange solid. mp: >250 °C. IR (KBr): ν 2929, 2833, 1604 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.74 (dd, 1H, $J = 7.8$, 0.6 Hz), 8.34 (d, 1H, $J = 6.9$ Hz), 8.28 (d, 1H, $J = 8.1$ Hz), 7.87 (d, 1H, $J = 9.0$ Hz), 7.76 (t, 1H, $J = 6.9$ Hz), 7.68 (t, 1H, $J = 6.9$ Hz), 7.60 (d, 2H, $J = 8.7$ Hz), 7.51 (t, 1H, $J = 7.5$ Hz), 6.91 (d, 2H, $J = 8.7$ Hz), 6.80 (t, 1H, $J = 6.6$ Hz), 3.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.4, 149.7, 149.1, 147.4, 145.1, 130.2, 129.9, 129.2, 129.1, 129.0, 127.6, 126.3, 125.2, 122.7, 121.2, 117.7, 112.5, 112.1, 40.5. MS (ES^+): *m*/*z* 339.2 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{18}N_4$:C, 78.08; H, 5.36; N, 16.56. Found: C, 78.21; H, 5.60; N, 16.41.

6-(2-Chloro-phenyl)-5,6b,11-triaza-benzo[a]fluorene (6f). Yield: 114 mg (72%). Off-white solid. mp: 246−248 °C.

IR (KBr): ν 1594 cm^{-1}. ^{1}H NMR (200 MHz, DMSO): δ 8.69 (d, 1H, J = 7.2 Hz), 8.20 (dd, 1H, J = 7.3, 1.4 Hz), 7.99 (d, 1H, J = 8.0 Hz), 7.86−7.65 (m, 8H), 7.10 (t, 1H, J = 6.9 Hz). ^{13}C NMR (50 MHz, DMSO + TFA): δ 152.5, 149.1, 142.5, 138.5, 136.1, 134.1, 132.4, 132.1, 130.8, 129.9, 129.1, 129.0, 128.0, 123.5, 120.5, 120.1, 118.5, 118.0, 116.4, 112.8. MS (FAB): m/z 330 (M^+ + 1). Anal. Calcd for $C_{20}H_{12}ClN_3$: C, 72.84; H, 3.67; N, 12.74. Found: C, 72.58; H, 3.57; N, 12.94.

6-(4-Bromo-phenyl)-5,6b,11-triaza-benzo[a]fluorene (6g). Yield: 125 mg (70%). Off-white solid. mp: >250 °C. IR (KBr): ν 1605 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 8.83 (d, 1H, J = 7.8 Hz), 8.32 (d, 1H, J = 8.4 Hz), 8.22 (t, 2H, J = 8.1 Hz), 8.13−7.94 (m, 7H), 7.38 (t, 1H, J = 6.7 Hz). ^{13}C NMR (75 MHz, DMSO + TFA): δ 154.0, 150.8, 144.4, 136.7, 136.5, 133.4, 132.9, 131.9, 129.3, 129.2, 128.5, 126.9, 123.8, 121.6, 121.1, 118.4, 117.3, 116.4. MS (ES$^+$): m/z = 375.2 (M^+ + 1). Anal. Calcd for $C_{20}H_{12}BrN_3$: C, 64.19; H, 3.23; N, 11.23. Found: C, 64.39; H, 3.32; N, 11.39.

6-(4-Nitro-phenyl)-5,6b,11-triaza-benzo[a]fluorene (6h). Yield: 120 mg (74%). Pale-yellow solid. mp: >250 °C. IR (KBr): ν 1566, 1519, 1348 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 8.80 (d, 1H, J = 8.1 Hz), 8.63 (d, 2H, J = 8.7 Hz), 8.30 (d, 1H, J = 8.4 Hz), 8.24 (d, 2H, J = 8.7 Hz), 8.18−8.14 (m, 2H), 8.08−7.94 (m, 3H), 7.26 (t, 1H, J = 6.9 Hz). ^{13}C NMR (75 MHz, DMSO + TFA): δ 151.2, 148.7, 147.6, 142.6, 136.8, 135.5, 131.2, 130.2, 128.0, 127. 9, 123.8, 122.3, 122.0, 120.0, 118.4, 116.2, 115.0, 112.3. MS (ES$^+$): m/z = 341.3 (M^+ + 1). Anal. Calcd a $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.75; H, 3.44; N, 16.52.

6-Furan-2-yl-5,6b,11-triaza-benzo[a]fluorene (6i). Yield: 105 mg (77%). Off-white solid. mp: 165−166 °C. IR (KBr): ν 1598 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.78 (dt, 2H, J = 8.8, 1.4 Hz), 8.26 (d, 1H, J = 7.9 Hz), 7.93 (d, 1H, J = 8.8 Hz), 7.78−7.71 (m, 4H), 7.61 (t, 1H, J = 6.8 Hz), 6.96 (t, 1H, J = 6.7 Hz), 6.96−6.75 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.0, 150.1, 148.2, 145.2, 143. 9, 138.1, 130.5, 129.8, 129.3, 128.8, 127.1, 123.1, 122.0, 120.6, 118.1, 113.0, 112.5. MS (FAB): m/z = 286 (M^+ + 1). Anal. Calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.49; H, 3.77; N, 14.99.

6-Ethyl-5,6b,11-triaza-benzo[a]fluorene (6j). Yield: 83 mg (70%). White solid. mp: 144−145 °C. IR (KBr): ν 2928, 2854, 1598 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68−8.66 (m, 2H), 8.17 (d, 1H, J = 9.1 Hz), 7.89 (d, 1H, J = 9.1 Hz), 7.73 (dt, 1H, J = 7.6, 1.3 Hz), 7.63 (t, 1H, J = 7.1 Hz), 7.53 (t, 1H, J = 7.7 Hz), 7.03 (t, 1H, J = 6.6 Hz), 3.43 (q, 2H, J = 7.5 Hz), 1.53 (t, 3H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.8, 149.3, 146.9, 144.8, 129.4, 128.8, 128.7, 127.5, 126.1, 122.7, 121.2, 121.1, 118.3, 112.8, 30.1, 12.2. MS (FAB): m/z = 248 (M^+ + 1). Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.95; H, 5.47; N, 16.79.

5,6-Dihydro-5,6b,11-triaza-benzo[a]fluorene (7). Two drops of TFA was added to a solution of amine **4** (100 mg, 0.48 mmol) and acetophenone (60 μL, 0.48 mmol) in 5 mL of dry CH_3CN (6 mL). The solution was refluxed with stirring under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. CH_3CN was evaporated under reduced pressure. The residue was treated with an aqueous $NaHCO_3$ solution (25 mL). The reaction mixture was extracted with ethyl acetate (25 mL), washed with water (25 mL) and brine (25 mL), and dried over anhydrous Na_2SO_4 The organic layer was evaporated under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (80/20, v/v) to give triazabenzo[a]fluorines **7a** as gray solid.

6-Methyl-6-phenyl-5,6-dihydro-5,6b,11-triaza-benzo[a]fluorene (7a). Yield: 115 mg (77%). Gray solid. mp: 204−205 °C. IR (KBr): ν 3245, 2986, 2860, 1620, 1508, 1451, 1401 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (dd, 1H, J = 7.6, 1.3 Hz), 7.65−7.60 (m, 3H), 7.40−7.29 (m, 3H), 7.19 (d, 1 H, J = 7.0 Hz), 7.10−7.04 (m, 2H), 6.81 (dt, 1H, J = 7.5, 0.6 Hz), 6.52−6.48 (m, 2H), 4.22 (br s, 1H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.2, 144.2, 141.8, 137.9, 129.2, 129.1, 128.4, 127.1, 124.3, 123.4, 123.1, 120.5, 118.3, 117.3, 115.5, 113.1, 112.4, 59.0, 25.9. MS (ES$^+$): m/z 312.3 (M^+ + 1). Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.22; H, 5.31; N, 13.29.

6-(4-Methoxy-phenyl)-6-methyl-5,6-dihydro-5,6b,11-triaza-benzo[a]fluorene (7b). Yield: 108 mg (66%). Gray solid. mp: 248−249 °C. IR (KBr): ν 3233, 2925, 2855, 1607, 1508, 1455 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (dd, 1H, J = 6.0, 3.0 Hz), 7.61 (d, 1H, J = 9.0 Hz), 7.56 (d, 2H, J = 9.0 Hz), 7.17 (td, 1H, J = 6.0, 3.0 Hz), 7.10−7.02 (m, 2H), 6.87 (d, 2H, J = 9.0 Hz), 6.78 (dt, 1H, J = 6.0, 1.0 Hz), 6.51−6.46 (m, 2H), 4.05 (br s, 1H), 3.78 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8, 145.8, 143.3, 137.8, 137.7, 128.9, 127.8, 124.3, 122.3, 120.8, 117.0, 116.3, 115.1, 114.1, 113.0, 112.4, 58.0, 55.4, 26.4. MS (FAB): m/z 342 (M^+ + 1). Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.54; H, 5.71; N, 12.52.

6-Methyl-6-(4-nitro-phenyl)-5,6-dihydro-5,6b,11-triaza-benzo[a]fluorene (7c). Yield: 131 mg (77%). Gray solid. mp: 249−250 °C. IR (KBr): ν 3250, 2926, 2855, 1595, 1518, 1458 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.21 (d, 2H, J = 8.7 Hz), 7.85 (d, 1H, J = 6. 4 Hz), 7.69−7.58 (m, 4H), 7.25 (t, 1H, J = 7.0 Hz), 7.01 (t, 1H, J = 7.9 Hz), 6.79 (t, 1H, J = 6.9 Hz), 6.67−6.60 (m, 2H), 4.12 (br s, 1H), 2.19 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.6, 146.9, 146.1, 142.8, 138.0, 129.2, 127.7, 124.8, 124.5, 124.1, 122.4, 119.4, 117.2, 116.9, 115.1, 113.1, 112.8, 58.5, 26.2. MS (FAB): m/z = 357 (M^+ + 1). Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.64; H, 5.71; N, 12.52.

6,6-Dimethyl-5,6-dihydro-5,6b,11-triaza-benzo[a]fluorene (7d). Yield: 65 mg (55%). Gray solid. mp: >250 °C. IR (KBr): ν 3261, 2925, 2855, 1590, 1509, 1451 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 (d, 1H, J = 6.7 Hz), 7.85 (d, 1H, J = 7.5 Hz), 7.66 (d, 1H, J = 8.0 Hz), 7.19−7.02 (m, 2H), 6.82−6.74 (m, 2H), 6.55 (d, 1H, J = 7.9 Hz), 3.88 (br s, 1H), 1.76 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.6, 142.5, 137.7, 129.1, 124.1, 124.0, 123.2, 121. 8, 118.4, 118.1, 116.3, 113.3, 112.7, 54.5, 29.8. MS (ES$^+$): m/z = 250.2 (M^+ + 1). Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.28; H, 6.24; N, 16.66.

6-Ethyl-6-methyl-5,6-dihydro-5,6b,11-triaza-benzo[a]-fluorene (7e). Yield: 72 mg (57%). Gray solid. mp: 187−189 °C. IR (KBr): ν 3264, 2926, 2857, 1603, 1592, 1511, 1455 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (d, 1H, J = 6.8 Hz), 7.85 (d, 1H, J = 7.1 Hz), 7.68 (d, 1H, J = 9.0 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.05 (t, 1H, J = 7.5 Hz), 6.82−6.70 (m, 2H), 6.54 (d, 1H, J = 7.8 Hz), 3.75 (br s, 1H), 2.30 (q, 2H, J = 7.5 Hz), 1.73 (s, 3H), 0.88 (t, 3H, J = 7.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.5, 141.2, 135.7, 130.3, 129.2, 124.0, 123.1, 120.6, 118.5, 118.0, 117.8, 114.0, 112.8, 56.3, 35.5, 28.9, 9.2. MS (ES^+): m/z = 264.2 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: 77.77; H, 6.67; N, 15.76.

4-Phenyl-thiazol-2-ylamine (9). The phenacyl bromide **8** (500 mg, 2.51 mmol) was dissolved in ethanol (20 mL) and treated with thiourea (191 mg, 2.51 mmol). The reaction mixture was refluxed for 1 h. Ethanol was evaporated, and the resulting salt was refluxed with 30 mL of 1 N HCl for 30 min, followed by addition of aqueous NH_3 solution. The resulting solution was extracted with ethyl acetate (2 × 30 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification was carried out on a silica gel column using hexane−ethyl acetate (75/25, v/v) to afford **9**.

Yield: 433 mg (98%). White solid. mp: 154−156 °C (lit.[17] value 151−152 °C). IR (KBr): ν 3253, 3157, 1599, 1517, 1481, 1440 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (td, 2H, J = 7.1, 1.4 Hz), 7.39 (dt, 2H, J = 6.9, 1.2 Hz), 7.31 (td, 1H, J = 7.8 Hz), 6.75 (s, 1H), 5.07 (br s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.5, 151.2, 135.2, 128.9, 127.8, 126.2, 102.4. MS (ES^+): m/z = 177.2 ($M^+ + 1$). Anal. Calcd for $C_9H_8N_2S$: C, 61.33; H, 4.58; N, 15.90. Found: C, 61.21; H, 4.39; N, 15.78.

6-(2-Nitro-phenyl)-3-phenyl-imidazo[2,1-b]thiazole (10). A solution of 2-amino thiazole **9** (500 mg, 2.84 mmol) and 2-bromo-1-(2-nitro-phenyl)-ethanone **2** (693 mg, 2.84 mmol) in acetone (30 mL) was refluxed for 24 h. After removal of the solvent, the residue was refluxed for 1 h with 2 N HCl (50 mL). Then, the solution was basified with NH_4OH solution and extracted with EtOAc (2 × 40 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and evaporated to afford a residue, which was purified by column chromatography using hexane−ethyl acetate (80/20, v/v) to give **10**.

Yield: 182 mg (20%). Yellow oil. IR (neat): ν 1531, 1352 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90−7.84 (m, 2H), 7.72−7.59 (m, 3H), 7.55−7.42 (m, 4H), 7.35 (t, 1H, J = 6.8 Hz), 6.82 (s, 1H). MS (ES^+): m/z = 322.2 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.39; H, 3.66; N, 13.21.

2-(3-Phenyl-imidazo[2,1-b]thiazol-6-yl)-phenylamine (11). $SnCl_2 \cdot 2H_2O$ (1.41 g, 6.25 mmol) was added to a solution of 6-(2-nitro-phenyl)-3-phenyl-imidazo[2,1-b]thiazole **10** (400 mg, 1.25 mmol) in ethanol (20 mL). The reaction mixture was refluxed under a nitrogen atmosphere for 1 h. The solution was allowed to cool, and then it was poured into ice; the pH was made slighitly basic (pH 8) by the addition of 5% aqueous $NaHCO_3$. EtOAc (2 × 40 mL) was added to the mixture. The suspension was passed through a bed of celite. The organic layer was finally washed with water (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (70/30, v/v) to afford **11**.

Yield: 319 mg (88%). Colorless oil. IR (neat): 3352, 3297, 1604 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.70 (dd, 2H, J = 7.9, 1.6 Hz), 7.57−7.53 (m, 3H), 7.44 (dd, 1H, J = 7.7, 1.4 Hz), 7.11 (dt, 1H, J = 7.6, 1.5 Hz), 6.80 (s, 1H), 6.78−6.73 (m, 2H). MS (ES^+): m/z 292.3 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{13}N_3S$ C, 70.08; H, 4.50; N, 14.42. Found: C, 70.28; H, 4.62; N, 14.54.

General Procedure of the Pictet Spengler Reaction on Substrate 11. A mixture of 2-(3-phenyl-imidazo[2,1-b]-thiazol-6-yl)-phenylamine **11** (50 mg, 0.17 mmol), *p*-tolualdehyde (19 μL, 0.17 mmol), and *p*-tolylsulfonic acid (3.4 mg, 0.017 mmol) was refluxed in toluene (2 mL) for 8 h. Then toluene was evaporated in vacuo, and the residue was dissolved in ethylacetate (20 mL). The organic layer was finally washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (85/15, v/v) to afford **12** as a white solid.

7-Phenyl-6-p-tolyl-9-thia-5,6b,10-triaza-pentaleno[2,1-a]naphthalene (12a). Yield: 44 mg (65%). White solid. mp: >250 °C. IR (KBr): ν 2924, 2854, 1599 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (dd, 1H, J = 8.0, 1.3 Hz), 8.23 (dd, 1H, J = 8.4, 1.2 Hz), 7.75−7.68 (m, 2H), 7.33 (d, 2H, J = 8.0 Hz), 7.18−7.09 (m, 3H), 7.01−6.96 (m, 2H), 6.75−6.72 (m, 3H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 150.2, 146.1, 143.1, 137.2, 135.8, 135.7, 129.8, 127.9, 127.6, 127.5, 127.0, 126.8, 125.6, 124.9, 122.0, 120.8, 119.5, 108.7, 19.9. MS (ES^+): m/z = 392.4 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{17}N_3S$: C, 76.70; H, 4.38; N, 10.73. Found: C, 76.89; H, 4.21; N, 10.51.

6-(4-Nitro-phenyl)-7-phenyl-9-thia-5,6b,10-triaza-pentaleno[2,1-a]naphthalene (12b). Yield: 51 mg (71%). Yellow solid. mp: >250 °C. IR (KBr): ν 1598, 1515, 1345 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.81 (m, 3H), 7.64 (d, 1H, J = 9.0 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.25−7.20 (m, 4H), 7.04 (d, 1H, J = 7.0 Hz), 6.58−6.54 (m, 3H). MS (ES^+): m/z = 423.3 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{14}N_4O_2S$: C, 68.23; H, 3.34; N, 13.26. Found: C, 68.09; H, 3.56; N, 13.41.

Dimethyl-[4-(7-phenyl-9-thia-5,6b,10-triaza-pentaleno-[2,1-a]naphthalen-6-yl)-phenyl]-amine (12c). Yield: 43 mg (60%). Gray solid. mp: >250 °C. IR (KBr): ν 2924, 2841, 1601, 1501, 1451, 1413 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (dd, 1H, J = 7.9, 1.3 Hz), 8.21 (d, 1H, J = 8.1 Hz), 7.76−7.63 (m, 3H), 7.30 (d, 2H, J = 8.8 Hz), 7.17 (d, 1H, J = 8.4 Hz), 6.98−6.93 (m, 2H), 6.71−6.68 (m, 2H), 6.26 (d, 2H, J = 8.8 Hz), 2.89 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 150.0, 149.5, 146.5, 143.2, 135.9, 129.8, 128.5, 127.5, 127.3, 126.9, 126.8, 126.6, 125.7, 124.4, 122.1, 120.8, 119.2, 110.8, 109.7, 39.1. MS (ES^+): m/z = 421.4 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{20}N_4S$: C, 74.26; H, 4.79; N, 13.32. Found: C, 74.01; H, 4.56; N, 13.52.

6-(4-Bromo-phenyl)-7-phenyl-9-thia-5,6b,10-triaza-pentaleno[2,1-a]naphthalene (12d). Yield: 49 mg (63%). Yellow solid. mp: 122−124 °C. IR (KBr): ν 1595, 1463, 1351 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (d, 1H, J = 7.7 Hz), 8.45 (d, 1H, J = 8.3 Hz), 7.96−7.86 (m, 3H), 7.41−7.25 (m, 4H), 7.17 (d, 1H, J = 7.3 Hz), 7.08−7.06 (m, 3H), 6.74 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.1 148.9, 145.6, 144.6, 143.0, 137.6, 135.2, 129.9, 129.2, 127.9, 127.3, 127.2, 126.5, 125.8, 125.4, 124.7, 122.3, 120.9, 119.6, 108.9. MS (ES$^+$) m/z = 457.4 (M$^+$ + 1). Anal. Calcd for $C_{24}H_{14}BrN_3S$: C, 63.16; H, 3.09; N, 9.21. Found: C, 63.31; H, 3.26; N, 9.42.

2-(4-Methoxy-benzyl)-4-(2-nitro-phenyl)-1H-imidazole (13). Cesium carbonate (489 mg, 1.50 mmol) was added to a solution of 4-methoxyphenyl acetic acid (500 mg, 3.01 mmol) in methanol (20 mL). The reaction mixture was stirred for 1 h; the solvent was evaporated, and *o*-nitro phenacylbromide **2** (735 mg, 3.01 mmol) in DMF (10 mL) was added. The reaction mixture was stirred overnight at RT (room temperature). DMF was evaporated under reduced pressure, and xylene (30 mL) added to the residue. The cesium bromide salt was filtered; ammonium acetate (10 g) was added to the filtrate, and the reaction mixture was refluxed for 1.5 h using a Dean−Stark apparatus. After it was cooled, the reaction mixture was diluted with ice water and ethyl acetate (3 × 40 mL). The organic layer was washed with a saturated solution of sodium bicarbonate (50 mL), followed by brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. Purification was carried out on a silica gel column using hexane−ethyl acetate (80/20, v/v) to give **13**.

Yield: 186 mg (20%). Yellow solid. mp: 169−171 °C. IR (KBr): ν 3013, 2928, 2827, 1605, 1529, 1463, 1354 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, 1H, J = 7.6 Hz), 7.64 (d, 1H, J = 7.9 Hz), 7.54 (t, 1H, J = 7.6 Hz), 7.37−7.23 (m, 3H), 7.12 (s, 1H), 6.95 (d, 2H, J = 7.6 Hz), 4.12 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.3, 148.7, 135.0, 132.2, 131.9, 131.3, 130.9, 129.9, 129.0, 126.8, 123.9, 121.7, 111.3, 56.1, 30.5. MS (ES$^+$): m/z = 310.2 (M$^+$ + 1). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.88; H, 4.62; N, 13.41.

1-Benzyl-2-(4-methoxy-benzyl)-4-(2-nitro-phenyl)-1H-imidazole (14). 2-(4-Methoxy-benzyl)-4-(2-nitro-phenyl)-1H-imidazole **13** (200 mg, 0.65 mmol) was treated with NaH (17.0 mg, 0.71 mmol) in DMF (3 mL) at RT for 15 min; then benzyl bromide (79 μL, 0.65 mmol) was added portionwise over a period of 15 min. The reaction was monitored by TLC. After the completion of the reaction, the mixture was poured into ice-cold water (50 mL) and was extracted with ethyl acetate (25 mL). The ethyl acetate layer was washed with water (2 × 20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. Purification was carried out on a silica gel column with hexane/EtOAc (80/20, v/v) to afford **14**.

Yield: 212 mg (82%). Red oil. IR (neat): 2937, 2804, 1637, 1531, 1354 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (dd, 1H, J = 7.9, 1.4 Hz), 7.63 (dd, 1H, J = 8.0, 1.2 Hz), 7.55 (dt, 1H, J = 7.6, 1.3 Hz), 7.35 (dd, 1H, J = 7.8, 1.4 Hz), 7.32−7.28 (m, 3H), 7.20 (dt, 1H, J = 7.7, 1.7 Hz), 7.12−7.10 (m, 2H), 7.01−6.98 (m, 2H), 6.90 (dt, 1H, J = 7.5, 0.92 Hz), 6.84 (d, 1H, J = 8.2 Hz), 4.99 (s, 2H), 4.13 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.9, 148.2, 136.5, 132.0, 130.7, 130.3, 129.6, 129.2, 129.0, 128.4, 127.5, 127.3, 123.8, 121.8, 121.3, 119.4, 110.7, 55.7, 50.2, 27.0. MS (ES$^+$): m/z = 400.3 (M$^+$ + 1). Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.29; H, 5.57; N, 10.71.

2-[1-Benzyl-2-(4-methoxy-benzyl)-1H-imidazol-4-yl]-phenylamine (15). A solution of 1-benzyl-2-(4-methoxy-benzyl)-4-(2-nitro-phenyl)-1H-imidazole **14** (150 mg, 0.38 mmol) and $SnCl_2$•$2H_2O$ (429 mg, 1.90 mmol) was refluxed in ethanol (5 mL) under a nitrogen atmosphere for 1 h. The solution was allowed to cool, and then it was poured into ice; the pH is made slighitly basic (pH 8) by the addition of 5% aqueous $NaHCO_3$. EtOAc (40 mL) was added to the mixture. The suspension was passed through a bed of celite. The organic layer was finally washed with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (80/20, v/v) to afford **15**.

Yield: 122 mg (88%). Off-white solid. mp: >250 °C. IR (KBr): ν 3032, 2930, 2842, 1611, 1493, 1459, 1309 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.28 (m, 4H), 7.21 (t, 1H, J = 7.8 Hz), 7.12 (d, 1H, J = 7.2 Hz), 7.06−7.03 (m, 4H), 6.91−6.83 (m, 2H), 6.73−6.65 (m, 2H), 5.04 (s, 2H), 4.13 (s, 2H), 3.81 (s, 3H). MS (ES$^+$): m/z = 370.3 (M$^+$ + 1). Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.28; H, 6.10; N, 11.25.

3-Benzyl-2-(4-methoxy-benzyl)-4-p-tolyl-3H-imidazo-[4,5-c]quinoline (16). A mixture of 2-[1-benzyl-2-(4-methoxy-benzyl)-1H-imidazol-4-yl]-phenylamine **15** (50 mg, 0.14 mmol), *p*-tolualdehyde (15 μL, 0.14 mmol), and *p*-tolylsulfonic acid (2.7 mg, 0.014 mmol) was refluxed in toluene (2 mL) for 1 h. Then toluene was evaporated in vacuo, and the residue was dissolved in ethyl acetate (30 mL). The organic layer was finally washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (80/20, v/v) to afford **16**.

Yield: 39 mg (61%). White solid. mp: 168−169 °C. IR (KBr): ν 2932, 2847, 1603 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73−8.69 (m, 1H), 8.24−8.20 (m, 1H), 7.71−7.67 (m, 2H), 7.21−7.06 (m, 9H), 6.89 (dt, 1H, J = 7.5, 0.7 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.38 (d, 2H, J = 7.0 Hz), 5.13 (s, 2H), 4.36 (s, 2H), 3.74 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.4, 147.8, 145.2, 143.7, 138.4, 136.3, 135.5, 129.9, 129.4, 128.7, 128.3, 127.5, 127.2, 126.9, 126.4, 125.1, 124.2, 121.7, 120.9, 110.4, 100.0, 55.3, 48.2, 27.8, 21.3. MS (ES$^+$): m/z 470.4 (M$^+$ + 1). Anal. Calcd for $C_{32}H_{27}N_3O$: C, 81.85; H, 5.80; N, 8.95. Found: C, 81.79; H, 5.67; N, 8.71.

2-Amino-nicotinamide (17). A solution of nicotinic acid (500 mg, 3.62 mmol), *N*-methymorpholine (438 μL, 3.98 mmol), and isobutyl chloroformate (516 μL, 3.98 mmol) in

dry THF (15 mL) was stirred at −15 °C for 10 min. Then NH_4OH (40 mL) was added to reaction mixture. The reaction mixture was stirred for 1 h. After completion of the reaction, the solvent was evaporated, and residue was extracted with EtOAc (2 × 50 mL), washed with saturated $NaHCO_3$ solution (2 × 25 mL), water (30 mL), and brine (30 mL), and dried over Na_2SO_4. The organic layer was evaporated to obtain a residue, which was purified by column chromatography using $CHCl_3$−MeOH (95/05, v/v) to afford **17**.

Yield: 253 mg (51%). White solid. mp: 200−201 °C (lit.[18] value mp 199−202 °C). IR (KBr): ν 3456, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (dd, 1H, J = 3.8, 1.7 Hz), 7.92 (d, 1H, J = 7.6 Hz), 7.87−7.86 (m, 2H), 6.85 (br s, 2H), 6.56−6.52 (m, 1H). ^{13}C NMR (75 MHz, DMSO): δ 169.1, 158.3, 150.6, 136.3, 110.4, 108.0; MS (ES^+): m/z = 138.1 ($M^+ + 1$). Anal. Calcd. for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.46; H, 5.44; N, 30.57.

2-(2-Nitro-phenyl)-imidazo[1,2-a]pyridine-8-carboxylic Acid Amide (18). A solution of 2-amino-nicotinamide **17** (400 mg, 2.92 mmol) and 2-bromo-1-(2-nitro-phenyl)-ethanone **2** (713 mg, 2.92 mmol) in ethanol (10 mL) was refluxed for 7 h. After removal of the solvent, the residue was basified with $NaHCO_3$ solution (25 mL) and extracted with EtOAc (50 mL). The organic layer was washed with water (25 mL) and brine (25 mL), and dried over anhydrous Na_2SO_4; then, the organic layer was evaporated. The residue was purified by column chromatography using hexane−ethyl acetate (75/25, v/v) to afford **18**.

Yield: 552 mg (67%). Yellow solid. mp: 235−236 °C. IR (KBr): ν 3304, 1677, 1598, 1522, 1374 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.07 (br s, 1H), 8.79 (dd, 1H, J = 7.6, 1.2 Hz), 8.53 (s, 1H), 8.05 (dd, 1H, J = 7.2, 1.0 Hz), 8.00 (dd, 1H, J = 7.6, 1.1 Hz, br (o) 1H), 7.87 (dd, 1H, J = 7.9, 1.1 Hz), 7.76 (dt, 1H, J = 7.6, 1.5 Hz), 7.62 (dt, 1H, J = 7.7, 1,1 Hz), 7.14 (t, 1H, J = 7.0 Hz). ^{13}C NMR (75 MHz, DMSO): δ 163. 9, 149.2, 143.1, 139.4, 132.3, 130.8, 130.5, 129.8, 129.1, 125.5, 123.8, 120.7, 113.0, 112.4. MS (ES^+): m/z = 283.1 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.48; H, 3.49; N, 19.79.

2-(2-Amino-phenyl)-imidazo[1,2-a]pyridine-8-carboxylic Acid Amide (19). A solution of 2-(2-Nitro-phenyl)-imidazo[1,2-a]pyridine-8-carboxylic acid amide **18** (200 mg, 0.71 mmol) and $SnCl_2{\cdot}2H_2O$ (801 mg, 3.55 mmol) in ethanol (15 mL) was refluxed under nitrogen for 1 h. The solution was allowed to cool, and then it was poured into ice; the pH was made slighitly basic (pH 8) by addition of 5% aqueous $NaHCO_3$. EtOAc (35 mL) was added to the mixture. The suspension was passed through a bed of celite. The organic layer was finally washed with water (25 mL) and brine (25 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The crude material was purified by silica gel chromatography using hexane−ethyl acetate (70/30, v/v) to afford **19**.

Yield: 155 mg (87%). Yellow solid. mp: 223−225 °C. IR (KBr): ν 3458, 3398, 3338, 1699 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.20 (br s, 1H), 8.75 (d, 1H, J = 6.6 Hz), 8.40 (s, 1H), 8.08 (br s, 1H), 8.00 (d, 1H, J = 7.1 Hz), 7.59 (dd, 1H, J = 6.4, 1.3 Hz), 7.13−7.06 (m, 2H), 6.80 (d, 1H, J = 8.07 Hz), 6.66 (t, 1H, J = 7.4 Hz), 5.91 (br s, 2H). ^{13}C NMR (50 MHz, DMSO): δ 164.4, 146.5, 144.6, 142.4, 130.1, 129.3, 129.01, 128.0, 120.4, 116.8, 116.6, 116.1, 112.5, 110.9. MS (ES^+): m/z 253.2 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.54; H, 4.66; N, 22.08.

6-*p*-Tolyl-5,6b,11-triaza-benzo[a]fluorene-10-carboxylic Acid Amide (20). A mixture of 2-(2-amino-phenyl)-imidazo[1,2-a]pyridine-8-carboxylic acid amide **19** (50 mg, 0.20 mmol), *p*-tolualdehyde (22 μL, 0.20 mmol), and *p*-tolylsulfonic acid (3.8 mg, 0.02 mmol) was refluxed in toluene (3 mL) for 7 h. Then, the toluene was evaporated in vacuo, and the residue was dissolved in ethyl acetate (30 mL). The organic layer was finally washed with water (25 mL) and brine (25 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure to afford a crude material, which was purified by silica gel column using hexane−ethyl acetate (80/20, v/v) to afford **20**.

Yield: 44 mg (63%). Yellow solid. mp: >250 °C. IR (KBr): ν 2927, 2818, 1675, 1598 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.42 (br s, 1H), 8.79 (dd, 1H, J = 6.7, 1.3 Hz), 8.59 (dd, 1H, J = 5.9, 1.2 Hz), 8.36−8.30 (m, 2H), 7.85 (dt, 1H, J = 7.6, 1.5 Hz), 7.77 (dt, 1H, J = 7.2, 1.1 Hz), 7.64 (d, 2H, J = 7.9 Hz), 7.48 (d, 2H, J = 7.9 Hz), 6.98 (t, 1H, J = 7.1 Hz), 6.21 (br s, 1H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, DMSO): δ 161.8, 150.0, 148.2, 145.5, 141.5, 136.1, 131.4, 130.0, 129.4, 128.4, 127.8, 122.8, 121.6, 120.7, 119.2, 118.7, 116.4, 113.9, 112.6, 20.4. MS (ES^+): m/z = 353.5 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 74.84; H, 4.48; N, 15.77.

Acknowledgment. This is Central Drug Research Institute communication no. 7228. S.S., B.S., and D.S. are thankful to CSIR, New Delhi, India, for providing fellowships. We are grateful to the SAIF staff for providing MS and NMR data.

Supporting Information Available. Spectroscopic data of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Dolle, R. E.; Nelson, K. H., Jr. *J. Comb. Chem.* **1999**, *1*, 235−282. (b) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214. (c) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 1−41. (d) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854.

(2) (a) Borisov, A. V.; Dzhavakhishvili, S. G.; Zhuravel, I. O.; Kovalenko, S. M.; Nikitchenko, V. M. *J. Comb. Chem.* **2007**, *9*, 5−8. (b) Xie, F.; Li, S.; Bai, D.; Lou, L.; Hu, Y. *J. Comb. Chem.* **2007**, *9*, 12−13. (c) Liu, G.; Li, L.; Kou, B.; Zhang, S.; Zhang, L.; Yuan, Y.; Ma, T.; Shang, Y.; Li, Y. *J. Comb. Chem.* **2007**, *9*, 70−78. (d) Yang, T. M.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 86−95. (e) Carpenter, R. D.; DeBerdt, P. B.; Lam, K. S.; Kurth, M. L. *J. Comb. Chem.* **2006**, *8*, 907−914. (f) Ma, Z.; Xiang, Z.; Luo, T.; Lu, K.; Xu, Z.; Chen, J.; Yang, Z. *J. Comb. Chem.* **2006**, *8*, 696−704. (g) Jeon, H. S.; Kim, J. N.; Kim, T. H. *J. Comb. Chem.* **2006**, *8*, 799−801. (h) He, R.; Shi Min Ching, S. M.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 923−928. (i) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (i) Carroll,

C. D.; Johnson, T. O.; Tao, S.; Lauri, G.; Orlowski, M.; Gluzman, I. Y.; Goldberg, D. E.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3203−3206. (j) Labadie, G. R.; Choi, S. R.; Avery, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 615−619.

(3) For review on privileged structures as starting points for library synthesis, see: Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 93−930.

(4) For a recent review, see: Prien, O. *Chem. Bio. Chem.* **2005**, *6*, 500−505.

(5) (a) Kundu, B.; Sawant, D.; Chhabra, R. *J. Comb. Chem*. **2005**, *7*, 317−321. (b) Kundu, B.; Sawant, D.; Partani, P.; Kesarwani, A. P. *J. Org. Chem*. **2005**, *70*, 4889−4892. (c) Duggineni, S.; Sawant, D.; Saha, B.; Kundu, B. *Tetrahedron* **2006**, *62*, 3228−3241.

(6) (a) Duncton, M. A. J.; Smith, L. M.; Burdzovic-Wizeman, S.; Burns, A.; Liu, H.; Mao, Y.; Wong, W. C.; Kiselyov, A. S. *J. Org. Chem.* **2005**, *70*, 9629−9631. (b) Zheng, L.; Xiang, J.; Daang, Q. D.; Bai, X. *J. Comb. Chem*. **2005**, *7*, 813−815. (c) Zheng, L.; Xiang, J.; Dang, Q.; Guo, S.; Bai, X. *J. Comb. Chem*. **2006**, *8*, 381−387.

(7) (a) Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Ghelli, A.; Ratta, M.; Benelli, B.; Degli Espoti, M. *J. Med. Chem*. **1995**, *38*, 1090−1097. (b) Biftu, T.; Feng, D.; Fisher, M.; Liang, G.; Qian, X.; Scribner, A.; Dennis, R.; Lee, S.; Liberator, P. A.; Brown, C.; Gurnett, A.; Leavitt, P. S.; Thompson, D.; Mathew, J.; Misura, A.; Samaras, S.; Tamas, T.; Sina, J. F.; McNulty, K. A.; McKnight, C. G.; Schmatz, D. M.; Wyvrat, M. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2479−2483.

(8) (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R., Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1984; pp 41−110. (b) Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R., Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1984; pp 235−330.

(9) (a) Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2415−2434. (b) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev*. **2004**, *104*, 2777−2812.

(10) Yamanaka, M.; Miyake, K.; Suda, S.; Ohhara, H.; Ogawa, T. *Chem. Pharm. Bull*. **1991**, *39*, 1556−1567.

(11) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem*. **1979**, *44*, 535−545.

(12) (a) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Recanatini, M.; Lenaz, G.; Fato, R.; Bergamini, C. *Bioorg. Med. Chem*. **2004**, *12*, 5525−5532. (b) Abignente, E.; de Caprariis, P.; Sacchi, A.; Marmo, E.; Berrino, L.; Matera, M. G. *Farmaco IL* **1983**, *38*, 534−545. (c) Ostlind, D. A.; Cifelli, S.; Mickle, W. G.; Smith, S. K.; Ewanciw, D. V.; Rafalko, B.; Felfalko, B.; Misura, A. *J Helminthol*. **2006**, *80*, 393−396. (d) Naito, S.; Koike, K.; Ono, M.; Machida, T.; Tasaka, S.; Kiue, A.; Koga, H.; Kumazawa, J. *Oncol. Res*. **1998**, *10*, 123−132.

(13) Wang, X.; Xu, F.; Xu, Q.; Mahmud, H.; Houze, J.; Zhu, L.; Akerman, M.; Tonn, G.; Tang, l.; McMaster, B. E.; Dairaghi, d. J.; Schall, T. J.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2800−2803.

(14) Andreani, A.; Rambaldi, M.; Leoni, A.; Morigi, R.; Locatelli, A.; Ghelli, A.; Esposti, M. D.; Ratta, M.; Benelli, B.; Degli Espoti, M. *Eur. J. Med. Chem*. **1999**, *34*, 883−889.

(15) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Lenaz, G.; Fato, R.; Farruggia, B. *J. Med. Chem*. **2005**, *48*, 3085−3089.

(16) Teulade, J. C.; Gueiffier, A.; Chapat, J. P.; Grassy, G.; Carpy, A.; Naifi, A. H.; Perly, B.; Couquelet, J. *Chem. Pharm. Bull*. **1989**, *37*, 2293−2297.

(17) King, L. C.; Miller, F. M. *J. Am. Chem. Soc*. **1949**, *71*, 367−368.

(18) Okawa, T.; Toda, M.; Eguchi, S.; Kakehi, A. *Synthesis* **1998**, 1467−1475.

CC0700445