DOI: 10.1002/ejoc.200800929

New Route to the Synthesis of the Isocryptolepine Alkaloid and Its Related Skeletons Using a Modified Pictet–Spengler Reaction[‡]

Piyush K. Agarwal,[a] Devesh Sawant,[a] Sunil Sharma,[a] and Bijoy Kundu*[a]

Keywords: Cyclization / Natural products / Polycycles / Nitrogen heterocycles

A new route to the synthesis of the isocryptolepine alkaloid with antimalarial activity using a modified Pictet–Spengler reaction has been devised. The strategy was then used to generate libraries based on three structural variants of the alkaloid. Compounds based on these three variants in general were accessed in three steps through a modified Pictet–Spengler cyclization reaction as the key step. The C-2-, C-3-, or N-1-linked (aminoaryl)indoles (**8**, **12**, **13**) required for cyclization were obtained by treating the corresponding indoles with *o*-halonitrobenzene using either nucleophilic replacement or Pd-based chemistry (Heck/Suzuki reaction) followed by reduction of the nitroaryl functionality. The substrates **8**, **12**, and **13** were then subjected to the Pictet–Spengler reaction to furnish polycyclic structures, indolo-quinolines **4** and **19** and indolo-quinoxalines **20** with three-point diversity in high yields and purities. One of the indolo-quinolines **4a** after treatment with CH_3I furnished the isocryptolepine alkaloid in excellent yield.

Introduction

The indole ring system is an important structural component in many clinically used therapeutic drugs[1] and in several thousand indole alkaloids[2] with important physiological activity. It has been estimated that more than one quarter of all known alkaloids are indole derivatives.[3] Numerous methods have been developed for the synthesis of substituted indoles[4] and indole-containing polycyclic ring systems.[5] Of the polycyclic alkaloids based on indoles, β-carbolines (**1**),[6] γ-carbolines (**2**),[7] and isocryptolepine (**3**) (Figure 1) have remained interesting synthetic targets owing to their various biological activities,[8] including antimalarial activity.[9] Isocryptolepine (Figure 1) has been isolated from the roots of the plant *Cryptolepis sanguinolenta*, which displays antimalarial properties[10] and bears a strong structural resemblance to γ-carboline. However, despite exhibiting promising activity, few attempts have been made to optimize its antimalarial activity by synthesizing its analogues.[11] Although there are several reports in the literature dealing with the synthesis of isocryptolepine,[12] a general strategy for generating a library based on this alkaloid with both structural and chemical diversity has not yet been described.

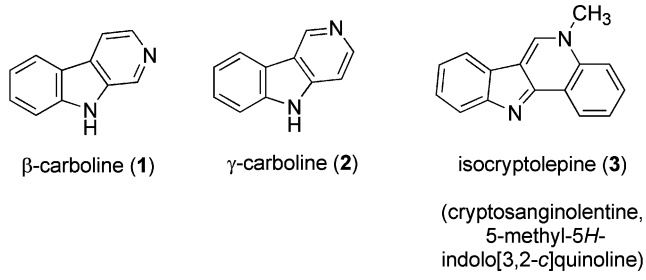


Figure 1. Polycyclic structures based on indoles.

Recently, we reported a modified strategy of the Pictet–Spengler reaction using substrates with an arylamine linked to an activated heterocyclic ring leading to the formation of either six-membered quinolines and quinoxalines or seven-membered diazepines fused to the heterocyclic ring.[13] In contrast, the substrates used in the traditional Pictet–Spengler reaction are based on an aliphatic amine linked to an activated heterocyclic ring, which results in pyridines fused to the heterocyclic ring. Following the disclosure of our methodology, several groups[14] have successfully demonstrated the application of our modified Pictet–Spengler strategy using novel substrates derived from arylamines for the synthesis of fused six-, seven-, and eight-membered rings.

As the isocryptolepine alkaloid is based on the indolo[3,2-*c*]quinoline framework, we decided to apply our modified Pictet–Spengler reaction[13] to its synthesis. In this paper we report a new route to the synthesis of the isocryptolepine alkaloid and a library based on three structural variants of the alkaloid. These studies represent a continua-

[‡] CDRI communication No. 7582.

[a] Medicinal and Process Chemistry Division, Central Drug Research Institute,
Lucknow 226001, India
Fax: +91-522-2623405
E-mail: bijoy_kundu@yahoo.com

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

tion of our interest in the search for novel natural-product-inspired nitrogen-rich polycyclic structures with antimalarial activity.[15]

Results and Discussion

A retrosynthetic analysis of isocryptolepine suggests three possible routes for its synthesis, as depicted in Figures 2 and 3. Out of the three routes, routes A and B are based on strategies reported in the literature[12] (Figure 2) and involve the formation of the indole ring in the final step, whereas route C (Figure 3) is based on our modified Pictet–Spengler strategy and leads to the formation of the quinoline ring in the final step.

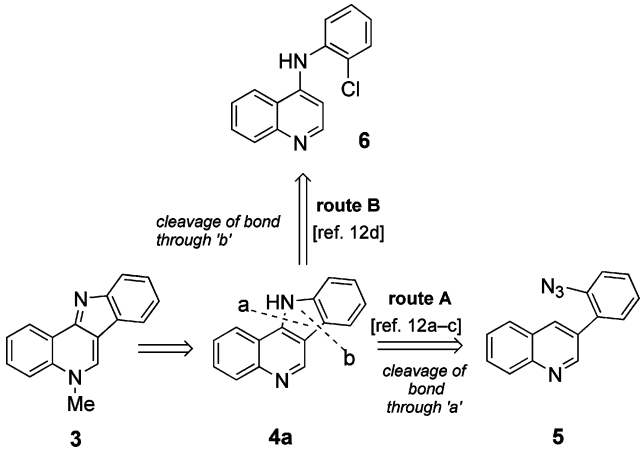


Figure 2. Retrosynthetic analysis of isocryptolepine based on reported strategies involving indolization.

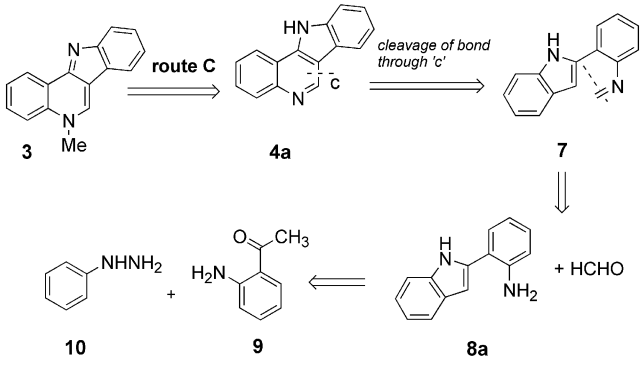


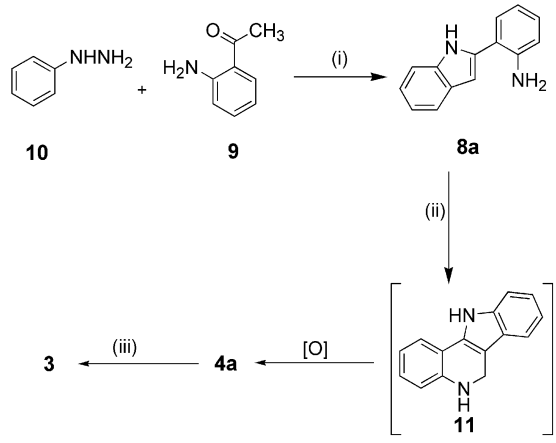
Figure 3. Retrosynthetic analysis of isocryptolepine involving formation of the quinoline ring.

The strategies reported for the synthesis of isocryptolepine as the target structure generally involved indolization by insertion of the nitrene,[12a–12c] photocyclization of anilinoquinoline[12d] or a Schiff base,[12h] modified Fischer indole synthesis,[12i] or Pd-catalyzed Buchwald–Hartwig amination of 4-chloroquinoline with 2-chloroaniline followed by Pd-catalyzed intramolecular arylation.[12j] An alternate strategy involved the application of the Vilsmeier methodology to an intramolecular reaction to produce the 3-aminoalkylidene-3*H*-indole unit of the alkaloid.[12k] Miki et al.[12l] reported the synthesis of isocryptolepine by the intramolecular decarboxylative Heck-type reaction of indolecarboxylic acids. Molina et al.[12m] reported the synthesis of the isocryptolepine by cyclization of a 4-(1*H*-benzotriazol-1-yl)-quinoline using the Grabe–Ullmann reaction. Surprisingly, despite being a compound of great biological significance, the reported strategies are not amenable to the generation of a library based on isocryptolepine with the exception of the procedures designed by Cheng[11a] and Maes[11b] and their co-workers. Cheng and co-workers described two synthetic approaches to the preparation of 11*H*-indolo[3,2-*c*]-quinoline derivatives using the Fischer indole synthesis, whereas Maes and co-workers applied their palladium-driven strategy published earlier[12j] to generate a library. However, both these methods were restricted exclusively to arene rings with no structural diversity in the pyridyl ring of the quinoline moiety.

Unlike the strategies reported in the literature for the synthesis of isocryptolepine, which rely predominantly on the formation of the indole by ring closure in the final step, we focused our attention on the formation of the quinoline ring in the final step. Retrosynthetic analysis by route C suggests that the isocryptolepine could be derived by methylation of **4a** (Figure 3). Cleavage of the C-6–C-6a bond in the quinoline ring (indicated by line "c") in **4a** suggests that it can be derived by 6-*endo* cyclization (π cyclization) from the corresponding Schiff base **7**, which in turn could be obtained by condensation of the arylamine substrate **8a** and formaldehyde. The key intermediate, arylamine derivative **8a**, can be obtained by the Fischer indole synthesis involving *o*-aminoacetophenone (**9**) and phenyl hydrazine (**10**). Note that although π cyclization of **7** is expected to proceed via the formation of a dihydro derivative of **4a** in the first instance, subsequent oxidation[13,14] can then be affected to furnish **4a**.

The synthetic strategy for the preparation of the isocryptolepine is depicted in Scheme 1. Our synthesis commenced with the Fischer indole synthesis of the indole intermediate **8a** by reacting phenylhydrazine (**10**) with *o*-aminoacetephenone (**9**) in two steps following the procedure reported in the literature.[16] The resulting key intermediate **8a** was subjected to the Pictet–Spengler reaction by treating it with paraformaldehyde in the presence of TFA as Brønsted acid to furnish the indolo-quinoline **4a**. As reported earlier by us[13c–13e] and others,[14] indolo-quinoline **4a** was formed by Pictet–Spengler cyclization of the imine **7** to form **11** followed by spontaneous aerial oxidation. The latter was then subjected to *N*-methylation[11b] by treatment with methyl iodide to furnish the desired isocryptolepine alkaloid **3**.

After successfully establishing the synthetic protocol for isocryptolepine we then decided to generate a library around it for our ongoing antimalarial program. As the key intermediate involved in the synthesis of the isocryptolepine alkaloid is substrate **8**, with an arylamine linked to C-2 of the indole, we envisaged that by taking into account the susceptibility of both C-3 and C-2 of the indole moiety to electrophilic attack, novel structural variants of **8** as additional substrates could be designed. We proposed to

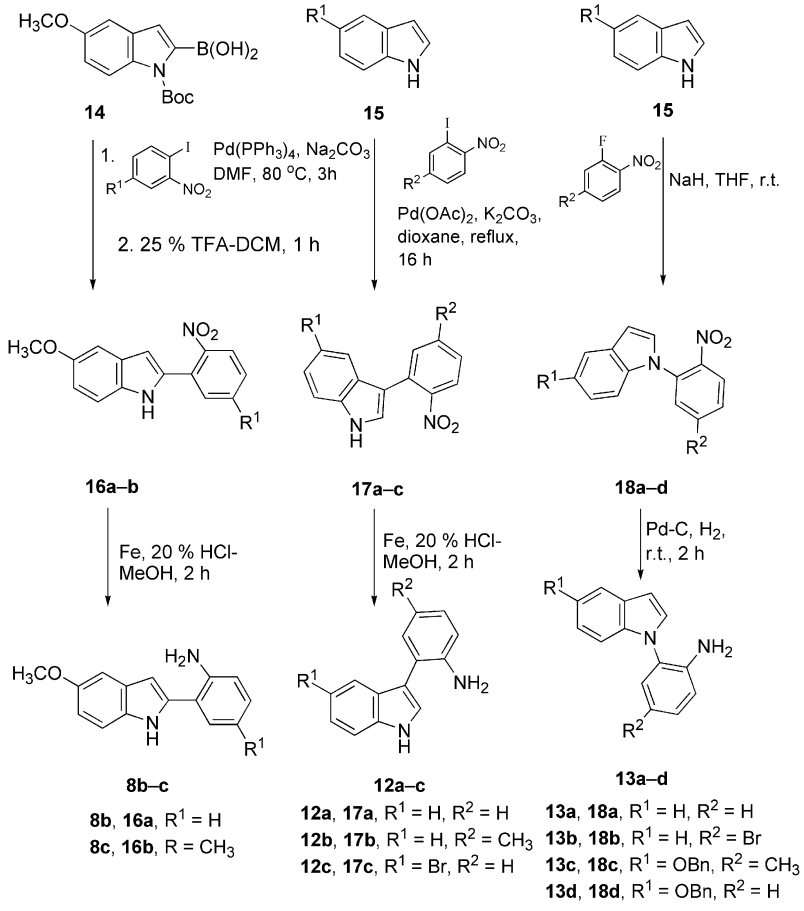


Scheme 1. Synthesis of isocryptolepine alkaloid **3**. Reagents and conditions: (i) (a) AcOH (5 mol-%), EtOH, 6 h; (b) PPA, 100 °C, 10 min; (ii) $(CH_2O)_n$, TFA, CH_3CN, 80 °C, sealed tube, 2 h; (iii) MeI, toluene, reflux, 2 h.

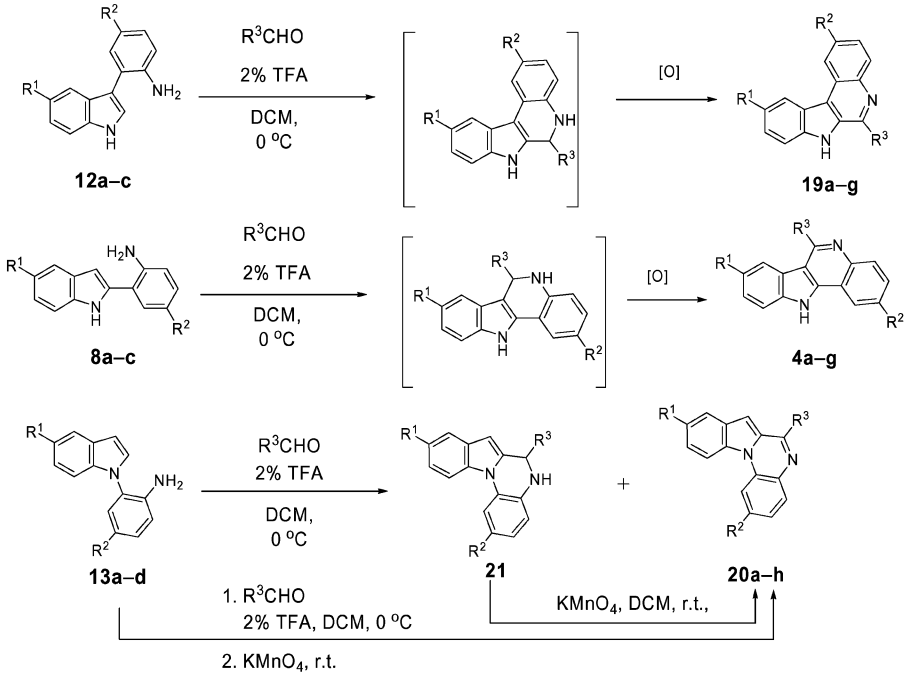
achieve this by shifting the arylamine from C-2 in **8** to either C-3 or N-1 of the indole ring thereby furnishing two new substrates **12** and **13**, respectively, as structural variants of the substrate **8**. Interestingly, the three substrates **8b**,**c**, **12a**–**c**, and **13a**–**d** all offer scope for introducing diversity into both the indole ring as well as the aminoarene moiety attached to it (Scheme 2).

Keeping the electrophilic substitution pattern of the indole moiety[17] in mind, we envisioned that an arylamine at C-3 in substrates **12** would undergo the Pictet–Spengler cyclization at C-2 to furnish indolo-quinolines **19**, whereas substrates **13** with an arylamine at N-1 would undergo the Pictet–Spengler cyclization at C-2 to furnish indolo-quinoxalines **20** (Scheme 3).

A literature search for the synthesis of 7*H*-indolo[2,3-*c*]-quinolines **19** revealed few papers[18] dealing with the preparation of the target structure and those that did gave products of limited diversity. A search for reports on the synthesis of indolo[1,2-*a*]quinoxalines **20** revealed only two papers. The first paper reported a condensation of 2-arylindoles with α-bromocyclohexanone dimethyl ketal to give 1,2,3,4-tetrahydroindolo[1,2-*a*]quinoxaline followed by dehydrogenation over a Raney nickel catalyst.[18] However, the difficulty in obtaining substituted 2-halocyclohexanones restricts the generality of this procedure. The second paper reported the preparation of 5-substituted indole-2-carboxylates by Fischer indolization of the appropriate phenylhydrazones followed by *N*-arylation with 2-bromonitroben-



Scheme 2. Synthetic strategy for substrates **8**, **12**, and **13**.



Entry	Pictet–Spengler substrate	Aldehyde R^3-CHO	Pictet–Spengler product				Time (min)	Isolated yield (%)
			No.	R^1	R^2	R^3		
1	**12a**	4-OEt-C_6H_4-CHO	**19a**	H	H	4-OEt-C_6H_4	15	88
2	**12a**	4-NO_2-C_6H_4-CHO	**19b**	H	H	4-NO_2-C_6H_4	30	75
3	**12a**	2-OH-C_6H_4-CHO	**19c**	H	H	2-OH-C_6H_4	10	91
4	**12b**	4-Cl-C_6H_4-CHO	**19d**	H	CH_3	4-Cl-C_6H_4	15	85
5	**12b**	4-$(CH_3)_2$N-C_6H_4-CHO	**19e**	H	CH_3	4-$(CH_3)_2$N-C_6H_4	15	81
6	**12b**	4-OMe-C_6H_4-CHO	**19f**	H	CH_3	4-OMe-C_6H_4	20	89
7	**12c**	4-$(CH_3)_2$N-C_6H_4-CHO	**19g**	Br	H	4-$(CH_3)_2$N-C_6H_4	30	84
9	**8b**	4-OEt-C_6H_4-CHO	**4b**	OCH_3	H	4-OEt-C_6H_4	15	81
10	**8b**	4-NO_2-C_6H_4-CHO	**4c**	OCH_3	H	4-NO_2-C_6H_4	20	79
11	**8b**	2-OH-C_6H_4-CHO	**4d**	OCH_3	H	2-OH-C_6H_4	30	84
12	**8c**	4-$(CH_3)_2$N-C_6H_4-CHO	**4e**	OCH_3	CH_3	4-$(CH_3)_2$N-C_6H_4	15	76
13	**8c**	4-CH_3-C_6H_4-CHO	**4f**	OCH_3	CH_3	4-CH_3-C_6H_4	10	78
14	**8c**	C_6H_5-CHO	**4g**	OCH_3	CH_3	C_6H_5	20	72
15	**13a**	C_6H_5-CHO	**20a**	H	H	C_6H_5	330	81
16	**13a**	4-$(CH_3)_2$N-C_6H_4-CHO	**20b**	H	H	4-$(CH_3)_2$N-C_6H_4	480	80
17	**13a**	4-NO_2-C_6H_4-CHO	**20c**	H	H	4-NO_2-C_6H_4	180	70
18	**13a**	4-Br-C_6H_4-CHO	**20d**	H	H	4-Br- C_6H_4	300	76
19	**13b**	4-OMe-C_6H_4-CHO	**20e**	H	Br	4-OMe-C_6H_4	480	77
20	**13b**	2-OH-C_6H_4-CHO	**20f**	H	Br	2-OH-C_6H_4	600	75
21	**13c**	C_6H_5-CHO	**20g**	benzyloxy	CH_3	C_6H_5	360	70
22	**13d**	4-CH_3-C_6H_4-CHO	**20h**	benzyloxy	H	4-Me-C_6H_4	300	69

Scheme 3. Pictet–Spengler reaction of substrates **8**, **12**, and **13** to furnish **4**, **19**, and **20**, respectively.

zene using Ullman chemistry.[19] Thus, the literature survey for all three prototypes revealed that although target structures based on **4**, **19**, and **20** have been synthesized, none of the methods deal with the generation of libraries with chemical diversity for medicinal chemistry purposes.

The synthetic strategies for the key intermediates **8**, **12**, and **13** are depicted in Scheme 2. For the synthesis of **8b**,**c**, *N*-(*tert*-butoxycarbonyl)-5-methoxyindole-2-boronic acid (**14**) was treated with 2-iodonitrobenzene following the Suzuki procedure reported in the literature.[20] The resulting

coupled derivative was first deprotected by using 25% TFA in DCM to furnish the nitroarene derivative **16**, which was then subjected to reduction using Fe/HCl to give **8b**,**c**. The substrate **12** was synthesized by treating indole **15** with 2-iodonitrobenzene following the Heck procedure reported in the literature.[21] The resulting nitroarene derivative **17** was subjected to reduction with Fe/HCl to give **12**. Finally, the substrate **13** was synthesized by treating indole **15** with 2-fluoronitrobenzene in the presence of NaH by the procedure reported in the literature.[22] The resulting nitroarene derivative **18** was subjected to reduction by catalytic hydrogenation to give **13**.

For the Pictet–Spengler cyclization, **12a** was initially treated with salicylaldehyde under a variety of traditional Pictet–Spengler protocols involving *p*TsOH in toluene at reflux, 2% TFA in DCM at 0 °C, AcOH in ethanol at reflux, neat toluene at 80 °C and $Yb(OTf)_3$. Interestingly, *endo* cyclization resulting in indolo-quinoline **19c** occurred under all conditions, but the best results were obtained with 2% TFA in DCM at 0 °C and it took 10 min for completion of the reaction (Scheme 3). The crude product obtained after work-up was purified by silica gel column chromatography using EtOAc/hexane as eluent and was isolated in 91% yield. Note that although **12a** successfully underwent the Pictet–Spengler reaction, its aliphatic amine analogue tryptamine (generally used as a substrate in the traditional Pictet–Spengler reaction) failed to undergo *endo* cyclization under a similar protocol. Cook and co-workers[23] circumvented this problem by using *N*-benzyltryptamine, which furnished an iminium ion intermediate with enhanced electrophilicity compared with the imine obtained from tryptamine and in turn facilitated *endo* cyclization. Based on this information it can be inferred that for the substrate **12a**, the imine intermediate derived from the aldehyde with an electron-donating group is relatively more electrophilic than the imine derived from tryptamine using the same aldehyde. This is supported by the observation of Cook and co-workers that it is the electrophilicity of the imine double bond resulting from the condensation of amines with aldehydes that acts as the limiting factor for the Pictet–Spengler cyclization and the pK_a values of amines could be used to compare the electrophilicities of the "imines".[24] Thus, the pK_a values of tryptamine (10.2) and aniline (in the absence of a pK_a value for **12a**, the pK_a value for aniline was taken into account; 4.2) clearly suggest that the carbon–nitrogen double bond derived from substrate **12a** is highly electrophilic because the nitrogen has a smaller electron density than that of the imines derived from tryptamine. These findings support our earlier observations[13] that arylamine-derived substrates undergo the Pictet–Spengler reaction faster than the substrates derived from aliphatic amines. The scope and limitation of our strategy with substrates based on **12a**–**c** was established by synthesizing six compounds based on indolo-quinolines **19a**,**b**,**d**–**g** using six aromatic aldehydes (Scheme 3). For the Pictet–Spengler cyclization, the protocol involving 2% TFA/DCM at 0 °C was used and in all cases cyclization was found to be complete within 30 min. The purities of the crude products were typically in excess of 90% based on HPLC analysis and substituents on either **12a**–**c** or the aldehydes had no affect on the rates and yields of the *endo*-cyclized products. Aldehydes with an electron-donating group had no adverse effect on the rate of cyclization.

After successfully establishing the Pictet–Spengler reaction for substrates **12**, we shifted our attention to substrate **8c** (Scheme 3). The substrate was initially treated with *p*-(dimethylamino)benzaldehyde with 2% TFA/DCM at 0 °C. The progress of the reaction was monitored by TLC and HPLC. As expected, cyclization of the substrate **8c** to give **4e** was found to be complete within 15 min.

Next we subjected **13a** to the Pictet–Spengler cyclization reaction by treating it with *p*-(dimethylamino)benzaldehyde (Scheme 3). Surprisingly, unlike substrates **8** and **12**, the reaction with **13a** took 8 h to reach completion and furnished two products with similar R_f values on TLC and similar retention times on HPLC. ESMS of the crude product showed signals at 340.4 and 338.4 Da, which corresponded to the desired product **20b**. We attributed the component with the higher mass to the dihydro product **21**. Of these two compounds, the dihydro product **21** had moderate stability because, even after purification, it had a tendency to undergo slow oxidation to **20b**. Such an oxidation has been reported earlier by us[13a,13c,13d] and others.[25] We envisioned that by using oxidizing agents in the final step, **20b** could be synthesized in quantitative yields. Accordingly, compound **13a**, after the Pictet–Spengler reaction with an aldehyde, was further treated with $KMnO_4$ for 15 min at room temperature to furnish **20b** as the only product in excellent yield. Based on our previous reports[13] and present observation, we hypothesize that when an arylamine is linked to the carbon atom of an activated heterocyclic skeleton, it results in the formation of the oxidized product by spontaneous aerial oxidation. However, when an arylamine is attached to the nitrogen atom, it results in a mixture of oxidized and dihydro derivatives. In contrast, condensation of traditionally used indole-based substrates, tryptamine with an aliphatic amine at C-3 of the indole, with aldehydes invariably furnished tetrahydro-β-carbolines (THBC).[26] Indeed, spontaneous oxidation of THBC to β-carbolines has been reported both on prolonged heating and by the addition of an oxidizing agent.[27]

The scope and limitation of our strategy with substrates based on **8b**,**c** and **13a**–**d** were established by synthesizing 12 compounds based on indolo-quinolines **4b**–**d**,**f**,**g** and indolo-quinoxalines **20a**,**c**–**h** using eight aromatic aldehydes (Scheme 3). For the substrates **8b**,**c**, the Pictet–Spengler cyclization was found to be complete within 30 min, however, for **13a**–**d**, it ranged from 180 to 600 min. The purities of the crude products were typically in excess of 90% based on HPLC analysis and substituents on either the substrates or the aldehydes had no affect on the rates and yields of the *endo*-cyclized products.

Although the three substrates **8**, **12**, and **13** successfully underwent Pictet–Spengler cyclization, we observed that the rate of the reaction with the *N*-linked arylamine substrate **13** was significantly slower (15–20 times) than the rates of

the reaction with the *C*-linked arylamine substrates **8** and **12**. This may be attributed to the fact that because the indole is an activated heterocyclic ring, C-2 and C-3 in substrates **8** and **12** act as powerful nucleophiles in the absence of *N*-substitution, whereas in substrate **13**, the nucleophilicity of C-2 decreases because of the presence of an aryl ring at the N-1 position.

Conclusions

We have developed a mild and efficient protocol for the synthesis of the isocryptolepine alkaloid using our modified Pictet–Spengler strategy. The efficacy of the strategy was further established by generating a library with three-point diversity based on three structural variants of the alkaloid. The broad substrate scope and reactivity of our strategy suggest wider application of this powerful reaction to the synthesis of novel polycyclic skeletons based on privileged structures. Work is in progress in our laboratory on several second-generation substrates for the application of the Pictet–Spengler reaction and will be reported soon.

Experimental Section

General: All solvents were commercially available and used without purification. All products were characterized by ^{1}H and ^{13}C NMR, ESMS, IR, and HPLC. Analytical TLC was performed using 2.5 × 5 cm plates 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 by using Thomas Baker silica gel 60 (100–200 mesh). ^{1}H NMR spectra (200, 300 MHz) are reported as follows: chemical shifts in ppm downfield from TMS as internal standard (δ scale), multiplicity [br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, o = overlapped, coupling constant (Hz), integration, and assignment]. All ^{13}C NMR spectra (50, 75 MHz) were recorded at 25 °C with complete proton decoupling and are reported in ppm except for compounds **4b**, **4c**, **12a**, and **14c**, which are insoluble at higher concentrations. The purity and characterization of these compounds were further established by HR/EI mass spectroscopy. Elemental analyses were performed with a Carlo–Erba 1108 microanalyzer or an Elementar Vario EL III microanalyzer. The microanalyses were performed at the Sophisticated Analytical Instrument Facility Division, CDRI. Analytical HPLC was performed with a C-18 reversed-phase column (250 mm × 4.6 mm). Mass spectra were recorded with a Merck MS-8000 spectrometer and HR/EI mass spectra were with a JEOL-600H spectrometer at 70 eV. Melting points are uncorrected.

Synthesis of 2-(2′-Aminophenyl)indole (8a): This was synthesized according to the procedure published in the literature[22] by treating phenylhydrazine (**10**) with *o*-aminoacetophenone (**9**) followed by heating the resulting phenylhydrazone with polyphosphoric acid to about 100 °C in an oil bath. The crude thus obtained was purified by silica gel chromatography using hexane/EtOAc (20:80, v/v) as eluent to afford **8a** with a melting point of 146–148 °C (ref.[22a] 148–150 °C).

Synthesis of 11*H*-Indolo[3,2-*c*]quinoline (4a): TFA (100 μL) was added in one portion to a suspension of paraformaldehyde (36 mg, 1.2 mmol), 2-(2′-aminophenyl)indole (**8a**; 0.21 g, 1 mmol), and acetonitrile (6 mL) in a sealed tube. The suspension was stirred at 80 °C for 2 h. After cooling to room temperature, the solvent was removed by evaporation in vacuo. The reaction mixture was dissolved in EtOAc (30 mL) and washed with aq. $NaHCO_3$ (2 × 20 mL), water (2 × 20 mL), and brine (20 mL). The combined organic layer was dried with $MgSO_4$. The solvent was removed in vacuo and then purified by column chromatography on silica gel (EtOAc/hexane, 1:9 to 2:3) to give the desired compound **4a** (0.18 g, 86%) as a white solid; m.p. >250 °C (ref.[28] 339–341 °C); R_f = 0.42 (2:3 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3421, 3021, 1595, 1427 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.75 (br. s, 1 H, NH), 9.60 (s, 1 H, ArH), 8.53 (dd, J = 1.0, 7.5 Hz, 1 H, ArH), 8.32 (d, J = 7.7 Hz, 1 H, ArH), 8.14 (d, J = 8.4 Hz, 1 H, ArH), 7.77–7.67 (m, 3 H, ArH), 7.50 (d, J = 8.2 Hz, 1 H, ArH), 7.34 (d, J = 7.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 145.7, 145.2, 140.2, 139.2, 129.9, 128.5, 126.2, 126.0, 122.5, 122.3, 121.1, 120.5, 117.5, 114.7, 112.3 ppm. MS (ES$^+$): m/z = 219.5 [M + 1]$^+$. HRMS (EI): calcd. for [M]$^+$ 218.0844; found 218.0842. $C_{15}H_{10}N_2$ (218.08): calcd. C 82.55, H 4.62, N 12.84; found C 82.63, H 4.55, N 12.86.

Synthesis of Isocryptolepine (3): Compound **4a** was methylated by treating it with methyl iodide in toluene at reflux for 2 h according to the procedure published in the literature.[11b] The crude thus obtained was purified by silica gel chromatography using MeOH/$CHCl_3$ (1:4, v/v) as eluent to afford **3**.

Yield 91%, yellow solid, m.p. 192–193 °C (ref.[29] 194–195 °C); R_f = 0.28 (1:19 MeOH/$CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3032, 2984 1605 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.27 (s, 1 H, ArH), 8.78 (dd, J = 1.2, 7.9 Hz, 1 H, ArH), 8.09 (d, J = 7.6 Hz, 1 H, ArH), 7.99 (d, J = 8.5 Hz, 1 H, ArH), 7.82–7.77 (m, 2 H, ArH), 7.67 (d, J = 7.2 Hz, 1 H, ArH), 7.43 (t, J = 8.0 Hz, 1 H, ArH), 7.24 (t, J = 7.1 Hz, 1 H, ArH), 4.22 (s, 3 H, NCH_3) ppm. ^{1}H NMR (75 MHz, CD_3OD): δ = 152.5, 151.8, 136.5, 134.8, 128.8, 125.5, 124.6, 123.3, 120.0, 119.6, 118.9, 116.9, 116.2, 115.7, 41.1 ppm. MS (ES$^+$): m/z = 233.1 [M + 1]$^+$. $C_{16}H_{12}N_2$ (232.10): calcd. C 82.73, H 5.21, N 12.06; found C 82.83, H 5.31, N 12.16.

General Procedure for the Synthesis of 5-Methoxy-2-(2-nitrophenyl)-1*H*-indole 16: A solution of *o*-iodonitrobenzene (4.4 mmol) in DMF (50 mL) was degassed with nitrogen for 15 min and then Na_2CO_3 (10.5 mL, 2 M) was added under the continuous flow of nitrogen. After 10 min, *N*-(*tert*-butoxycarbonyl)-5-methoxyindole-2-boronic acid (**14**) (1 g, 4.0 mmol) and [Pd(Ph$_3$)$_4$] (0.46 g, 0.4 mmol) were added to the reaction mixture under nitrogen. The reaction mixture was stirred at 80 °C for 3 h. The solution was diluted with H_2O (5 mL) and then the product was extracted three times with EtOAc (20 mL). The combined organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (95:5, v/v) as eluent to afford *tert*-butyl 5-methoxy-2-(2-nitrophenyl)indole-1-carboxylate, which was subsequently treated with a 25% solution of trifluoroacetic acid in DCM (25 mL) at 0 °C. The mixture was stirred further for 20 min. After completion of the reaction, the DCM was evaporated in vacuo, and the crude was extracted with ethyl acetate (30 mL) and subsequently washed with aq. $NaHCO_3$ (20 mL). The combined organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (9:1, v/v) as eluent to afford **16**.

5-Methoxy-2-(2-nitrophenyl)-1*H*-indole (16a): Yield 65%, yellow solid, m.p. 105–107 °C; R_f = 0.64 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3411, 2930, 1728, 1610, 1533, 1345, 1216 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.38 (br. s, 1 H, NH), 7.95 (d, J = 7.9 Hz, 1 H, ArH), 7.78 (d, J = 3.7 Hz, 2 H, ArH), 7.63–7.58 (m,

1 H, ArH), 7.30 (d, J = 8.7 Hz, 1 H, ArH), 7.07 (d, J = 2.3 Hz, 1 H, ArH), 7.80 (dd, J = 2.4, 8.8 Hz, 1 H, ArH), 6.45 (d, J = 1.5 Hz, 1 H, ArH), 3.75 (s, 3 H, OCH_3) ppm. MS (ES^+): m/z 269.2 $[M + 1]^+$. $C_{15}H_{12}N_2O_3$ (268.08): calcd. C 67.16, H 4.51, N 10.44; found C 67.28, H 4.46, N 10.29.

5-Methoxy-2-(5-methyl-2-nitrophenyl)-1*H*-indole (16b): Yield 70%, brown oil; R_f = 0.69 (1:9 EtOAc/hexane). IR (neat): $\tilde{\nu}_{max}$ = 3420, 3021, 2923, 1721, 1588, 1518 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.09 (m, 2 H, ArH), 7.36 (d, J = 7.3 Hz, 2 H, ArH), 7.32 (br. s, 1 H, NH), 7.04 (d, J = 2.3 Hz, 1 H, ArH), 6.98 (dd, J = 2.5, 9.0 Hz, 1 H, ArH), 6.46 (s, 1 H, ArH), 3.87 (s, 3 H, OCH_3), 2.50 (s, 3 H, CH_3) ppm. MS (ES^+): m/z 283.3 $[M + 1]^+$. $C_{16}H_{14}N_2O_3$ (282.10): calcd. C 68.07, H 5.00, N 9.92; found C 68.29, H 4.89, N 10.02.

General Procedure for the Synthesis of 2-(5-Methoxy-1*H*-indol-2-yl)-phenylamines 8b,c: A solution of 5-methoxy-2-(2-nitrophenyl)-1*H*-indole (**16**, 2.09 mmol) and Fe (2.36 g, 10.45 mmol) in acidic ethanol (1:4 aq. HCl/EtOH, 40 mL) was heated at reflux under nitrogen for 1.5 h. The solution was cooled down and then poured into ice. The pH was made slightly basic (pH 8) by the addition of 5% aqueous $NaHCO_3$. EtOAc (50 mL) was added to the mixture and filtered through a bed of Celite. The organic layer was finally washed with water (50 mL) and then brine (50 mL) and dried with anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The crude product was purified on a silica gel column using hexane/ethyl acetate (9:1, v/v) as eluent to afford **8b** (or **8c**).

2-(5-Methoxy-1*H*-indol-2-yl)phenylamine (8b): Yield 87%, white solid, m.p. 196–198 °C; R_f = 0.50 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3426, 2928, 1612 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 11.06 (br. s, 1 H, NH), 7.33 (dd, J = 1.2, 7.7 Hz, 1 H, ArH), 7.26 (d, J = 8.7 Hz, 1 H, ArH), 7.06–7.03 (m, 2 H, ArH), 6.82 (d, J = 7.3 Hz, 1 H, ArH), 6.74–6.67 (m, 2 H, ArH), 6.59 (d, J = 1.4 Hz, 1 H, ArH), 5.16 (br. s, 2 H, NH_2), 3.76 (s, 3 H, OCH_3) ppm. MS (ES^+): m/z = 239.2 $[M + 1]^+$. $C_{15}H_{14}N_2O$ (238.11): calcd. C 75.61, H 5.92, N 11.76; found C 70.48, H 5.88, N 11.61.

2-(5-Methoxy-1*H*-indol-2-yl)-4-methylphenylamine (8c): Yield 91%, brown oil; R_f = 0.50 (1:4 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3422, 3021, 2975, 1633 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 11.00 (br. s, 1 H, NH), 7.26 (d, J = 8.7 Hz, 1 H, ArH), 7.17 (s, 1 H, ArH), 7.02 (d, J = 2.2 Hz, 1 H, ArH), 6.88 (dd, J = 1.4, 8.1 Hz, 1 H, ArH), 6.74–6.70 (m, 2 H, ArH), 6.58 (d, J = 8.1 Hz, 1 H, ArH), 4.93 (br. s, 2 H, NH_2), 3.75 (s, 3 H, OCH_3), 2.22 (s, 3 H, CH_3) ppm. MS (ES^+): m/z = 253.1 $[M + 1]^+$. $C_{16}H_{16}N_2O$ (252.12): calcd. C 76.16, H 6.39, N 11.10; found C 76.34, H 6.43, N 11.06.

General Procedure for the Synthesis of 8-Methoxy-11*H*-indolo-[3,2-*c*]quinoline 4b–g: A mixture of **8b** (or **8c**) (0.39 mmol) and aldehyde (0.39 mmol) in DCM (2 mL) was treated with 2% TFA in DCM (2 mL). Completion of the Pictet–Spengler cyclization was monitored by TLC. After 30 min, the solvent was evaporated and the residue thus obtained was triturated with aq. $NaHCO_3$ (10 mL). It was then extracted with EtOAc (20 mL), washed with brine (10 mL), and dried with sodium sulfate. EtOAc was evaporated to dryness under reduced pressure and the crude product was purified on a silica gel column using hexane/ethyl acetate (1:4, v/v) as eluent to afford **4b**–**g**.

6-(4-Ethoxyphenyl)-8-methoxy-11*H*-indolo[3,2-*c*]quinoline (4b): Yield 81%, white solid, m.p. 215–217 °C; R_f = 0.46 (1:4 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3422, 1538, 1226 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.5 Hz, 1 H, ArH), 7.45 (d, J = 9.0 Hz, 1 H, ArH), 7.32 (d, J = 8.3 Hz, 1 H, ArH), 7.23 (d, J = 8.5 Hz, 2 H, ArH), 7.18 (d, J = 8.6 Hz, 1 H, ArH), 7.10 (t, J = 7.7 Hz, 1 H, ArH), 7.03 (br. s, 1 H, NH), 6.89 (d, J = 9.0 Hz, 1 H, ArH), 6.81 (t, J = 7.8 Hz, 3 H, ArH), 3.90 (q, J = 6.8 Hz, 2 H, OCH_2CH_3), 3.79 (s, 3 H, OCH_3), 1.38 (t, J = 6.9 Hz, 3 H, OCH_2CH_3) ppm. MS (ES^+): m/z = 369.3 $[M + 1]^+$. HRMS (EI): calcd. for $[M]^+$ 368.1525; found 368.1528. $C_{24}H_{20}N_2O_2$ (368.15): calcd. C 78.24, H 5.47, N 7.60; found C 78.18, H 5.55, N 7.61.

8-Methoxy-6-(4-nitrophenyl)-11*H*-indolo[3,2-*c*]quinoline (4c): Yield 79%, white solid, m.p. >250 °C; R_f = 0.51 (1:4 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3415, 1518, 1345 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$-DMSO): δ = 12.85 (br. s, 1 H, NH), 8.57 (d, J = 7.6 Hz, 1 H, ArH), 8.50 (d, J = 8.7 Hz, 2 H, ArH), 8.14 (d, J = 8.4 Hz, 3 H, ArH), 7.80–7.70 (m, 2 H, ArH), 7.67 (d, J = 8.8 Hz, 1 H, ArH), 7.13 (dd, J = 2.4, 7.7 Hz, 1 H, ArH), 6.95 (d, J = 2.2 Hz, 1 H, ArH), 3.65 (s, 3 H, OCH_3) ppm. MS (ES^+): m/z = 370.2 $[M + 1]^+$. HRMS (EI): calcd. for $[M]^+$ 369.1113; found 369.1121. $C_{22}H_{15}N_3O_3$ (369.11): calcd. C 71.54, H 4.09, N 11.38; found C 71.45, H 4.06, N 11.34.

2-(8-Methoxy-11*H*-indolo[3,2-*c*]quinolin-6-yl)phenol (4d): Yield 84%, white solid, m.p. 223–225 °C; R_f = 0.40 (1:4 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3413, 3020, 1590 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$-DMSO): δ = 12.67 (br. s, 1 H, NH), 8.53 (d, J = 8.4 Hz, 1 H, ArH), 8.10 (d, J = 8.0 Hz, 1 H, ArH), 7.75 (t, J = 8.0 Hz, 1 H, ArH), 7.68 (t, J = 6.8 Hz, 1 H, ArH), 7.61 (d, J = 8.8 Hz, 1 H, ArH), 7.54 (dd, J = 1.2, 7.4 Hz, 1 H, ArH), 7.43 (t, J = 8.7 Hz, 1 H, ArH), 7.11–7.03 (m, 3 H, ArH), 6.88 (d, J = 2.2 Hz, 1 H, ArH), 3.62 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + 20 μL CF_3COOD): δ = 155.6, 153.3, 148.0, 143.8, 134.6, 134.4, 134.2, 132.2, 130.8, 128.2, 122.0, 121.4, 120.3, 117.7, 116.9, 116.7, 114.0, 113.5, 112.6, 105.0, 55.6 ppm. MS (ES^+): m/z = 341.3 $[M + 1]^+$. HRMS (EI): calcd. for $[M]^+$ 340.1212; found 340.1201. $C_{22}H_{16}N_2O_2$ (340.12): calcd. C 77.63, H 4.74, N 8.23; found C 77.71, H 4.79, N 8.26.

***N*-[4-(8-Methoxy-2-methyl-11*H*-indolo[3,2-*c*]quinolin-6-yl)phenyl]-*N*,*N*-dimethylamine (4e):** Yield 76%, white solid, m.p. 253–255 °C; R_f = 0.53 (1:4 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3021, 1483, 1427, 1215 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 12.54 (br. s, 1 H, NH), 8.26 (s, 1 H, ArH), 7.96 (d, J = 8.5 Hz, 1 H, ArH), 7.72 (d, J = 8.7 Hz, 2 H, ArH), 7.60 (d, J = 8.7 Hz, 1 H, ArH), 7.52 (dd, J = 1.7, 8.6 Hz, 1 H, ArH), 7.26 (d, J = 2.3 Hz, 1 H, ArH), 7.07 (dd, J = 2.4, 8.8 Hz, 1 H, ArH), 6.92 (d, J = 8.8 Hz, 2 H, ArH), 3.68 (s, 3 H, OCH_3), 3.41 (s, 6 H, $2 \times CH_3$), 2.57 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 154.0, 151.2, 143.9, 141.6, 134.6, 134.3, 130.4, 129.3, 128.4, 123.0, 121.2, 116.5, 114.2, 112.7, 112.3, 111.9, 105.2, 55.7, 40.3, 21.8 ppm. MS (ES^+): m/z = 382.4 $[M + 1]^+$. $C_{25}H_{23}N_3O$ (381.18): calcd. C 78.71, H 6.08, N 11.02; found C 78.78, H 6.06, N 11.09.

8-Methoxy-2-methyl-6-(*p*-tolyl)-11*H*-indolo[3,2-*c*]quinoline (4f): Yield 78%, white solid, m.p. 248–250 °C; R_f = 0.56 (1:4 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3405, 2923, 2855, 1588, 1464, 1205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.55 (br. s, 1 H, NH), 8.16 (d, J = 8.6 Hz, 1 H, ArH), 7.91 (s, 1 H, ArH), 7.79 (d, J = 7.9 Hz, 2 H, ArH), 7.48 (d, J = 8.7 Hz, 2 H, ArH), 7.38 (d, J = 7.8 Hz, 2 H, ArH), 7.13 (d, J = 2.3 Hz, 1 H, ArH), 7.06 (dd, J = 2.5, 8.8 Hz, 1 H, ArH), 3.72 (s, 3 H, OCH_3), 2.57 (s, 3 H, CH_3), 2.49 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 154.0, 143.8, 141.5, 138.6, 138.2, 135.1, 134.4, 130.6, 129.5, 129.3, 129.2, 122.8, 121.3, 116.7, 114.3, 112.8, 112.3, 104.9, 55.68, 21.8, 21.4 ppm. MS (ES^+): m/z = 353.3 $[M + 1]^+$. $C_{24}H_{20}N_2O$ (352.15): calcd. C 81.79, H 5.72, N 7.95; found C 81.71, H 5.75, N 8.03.

8-Methoxy-2-methyl-6-phenyl-11*H*-indolo[3,2-*c*]quinoline (4g): Yield 72%, white solid, m.p. 232–233 °C; R_f = 0.62 (1:4 EtOAc/hexane).

IR (KBr): $\tilde{\nu}_{max}$ = 3454, 2926, 1594, 1442, 1205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 12.65 (br. s, 1 H, NH), 8.30 (s, 1 H, ArH), 8.01 (d, J = 8.5 Hz, 1 H, ArH), 7.80 (dd, J = 1.6, 7.8 Hz, 2 H, ArH), 7.66–7.56 (m, 5 H, ArH), 7.08 (dd, J = 2.4, 8.8 Hz, 1 H, ArH), 6.94 (dd, J = 2.3, 8.8 Hz, 1 H, ArH), 3.60 (s, 3 H, OCH_3), 2.60 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 154.1, 143.8, 141.5, 141.1, 135.3, 134.3, 130.6, 129.6, 129.3, 129.2, 128.7, 122.7, 121.3, 116.7, 114.6, 112.9, 112.3, 104.5, 55.5, 21.8 ppm. MS (ES^+): m/z = 339.4 $[M + 1]^+$. $C_{23}H_{18}N_2O$ (338.14): calcd. C 81.63, H 5.36, N 8.28; found C 81.81, H 5.33, N 8.39.

General Procedure for the Synthesis of 3-(2-Nitrophenyl)-1*H*-indole 17: A solution of *o*-iodonitrobenzene (10.2 mmol) and indole **15** (8.5 mmol) in dioxane (30 mL) was degassed with nitrogen for 15 min and K_2CO_3 (3.27 g, 25.6 mmol) and $Pd(OAc)_2$ (0.19 g, 0.85 mmol) were added under a continuous flow of nitrogen. The reaction mixture was stirred at 100 °C for 16 h. The solution was passed through Celite, which was thoroughly washed with dioxane. The combined filtrate was evaporated to dryness and then diluted with H_2O (5 mL) followed by extraction of the product with EtOAc (2 × 20 mL) three times. The combined organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified on a silica gel column using hexane/ethyl acetate (90:10, v/v) as eluent to afford **17**.

3-(2-Nitrophenyl)-1*H*-indole (17a): Yield 43%, yellow solid, m.p. 112–114 °C; R_f = 0.68 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3403, 2926, 1610, 1533, 1350 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 11.51 (br. s, 1 H, NH); 7.95 (dd, J = 0.9, 8.1 Hz, 1 H, ArH), 7.76–7.67 (m, 2 H, ArH), 7.56–7.51 (m, 2 H, ArH), 7.47 (d, J = 8.1 Hz, 1 H, ArH), 7.31 (d, J = 7.9 Hz, 1 H, ArH), 7.16 (t, J = 7.0 Hz, 1 H, ArH), 7.04 (t, J = 7.0 Hz, 1 H, ArH) ppm. MS (ES^+): m/z = 239.3 $[M + 1]^+$. $C_{14}H_{10}N_2O_2$ (238.07): calcd. C 70.58, H 4.23, N 11.76; found C 70.44, H 4.25, N 11.49.

3-(5-Methyl-2-nitrophenyl)-1*H*-indole (17b): Yield 46%, yellow solid, m.p. 101–102 °C; R_f = 0.60 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3472, 3021, 1594, 1527, 1352 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.38 (br. s, 1 H, NH), 7.68 (s, 1 H, ArH), 7.56–7.49 (m, 2 H, ArH), 7.44 (d, J = 8.1 Hz, 1 H, ArH), 7.33 (d, J = 2.3 Hz, 1 H, ArH), 7.25 (d, J = 8.1 Hz, 2 H, ArH), 7.16 (t, J = 7.9 Hz, 1 H, ArH), 2.49 (s, 3 H, CH_3) ppm. MS (ES^+): m/z = 253.1 $[M + 1]^+$. $C_{15}H_{12}N_2O_2$ (252.08): calcd. C 71.42, H 4.79, N 11.10; found C 71.48, H 4.75, N 11.11.

5-Bromo-3-(2-nitrophenyl)-1*H*-indole (17c): Yield 81%, yellow solid, m.p. 118–119 °C; R_f = 0.54 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3467, 3021, 1594, 1526, 1433, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.43 (br. s, 1 H, NH), 7.87 (d, J = 8.4 Hz, 1 H, ArH), 7.68–7.61 (m, 3 H, ArH), 7.51–7.46 (m, 1 H, ArH), 7.36–7.30 (m, 3 H, ArH) ppm. MS (ES^+): m/z = 317.1 $[M + 1]^+$. $C_{14}H_9BrN_2O_2$ (315.98): calcd. C 53.02, H 2.86, N 8.83; found C 53.11, H 2.93, N 8.79.

General Procedure for the Synthesis of 2-(1*H*-Indol-3-yl)phenylamine 12: A solution of **17** (4.62 mmol) and Fe (1.3 g, 23.1 mmol) in acidic ethanol (1:4 HCl/EtOH, 20 mL) was heated at reflux under nitrogen for 2 h. The solution was cooled down and then poured into ice. The pH was made slightly basic (pH 8) by the addition of 5% aqueous $NaHCO_3$ (20 mL). Subsequently, EtOAc (50 mL) was added to the mixture and filtered through a bed of Celite. The organic layer was finally washed with water (50 mL), brine (50 mL), and dried with 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 (1:4, v/v) as eluent to afford **12**.

2-(1*H*-Indol-3-yl)phenylamine (12a): Yield 83%, colorless oil; R_f = 0.40 (1:9 EtOAc/hexane). IR (neat): $\tilde{\nu}_{max}$ = 3386, 2936, 1608, 1528, 1350 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 8.32 (br. s, 1 H, NH), 7.66 (d, J = 7.9 Hz, 1 H, ArH), 7.46 (d, J = 8.1 Hz, 1 H, ArH), 7.35–7.14 (m, 5 H, ArH), 6.86 (t, J = 7.6 Hz, 2 H, ArH) ppm. MS (ES^+): m/z = 209.2 $[M + 1]^+$. $C_{14}H_{12}N_2$ (208.10): calcd. C 80.74, H 5.81, N 13.45; found C 80.82, H 5.66, N 13.52.

2-(1*H*-Indol-3-yl)-4-methylphenylamine (12b): Yield 79%, brown oil; R_f = 0.69 (1:9 EtOAc/hexane). IR (neat): $\tilde{\nu}_{max}$ = 3420, 3021, 2923, 1721, 1588, 1518 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32 (br. s, 1 H, NH), 7.64 (d, J = 7.9 Hz, 1 H, ArH), 7.46 (d, J = 8.1 Hz, 1 H, ArH), 7.31 (dd, J = 2.4, 7.9 Hz, 1 H, ArH), 7.27–7.14 (m, 2 H, ArH), 6.85 (d, J = 7.7 Hz, 1 H, ArH), 6.70–6.69 (m, 2 H, ArH), 2.51 (s, 3 H, CH_3) ppm. MS (ES^+): m/z = 223.2 $[M + 1]^+$. $C_{15}H_{14}N_2$ (222.11): calcd. C 81.05, H 6.35, N 12.60; found C 81.25, H 6.24, N 12.51.

2-(5-Bromo-1*H*-indol-3-yl)phenylamine (12c): Yield 90%, white solid, m.p. 141–143 °C; R_f = 0.46 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3369, 3021, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.38 (br. s, 1 H, NH), 7.77 (s, 1 H, ArH), 7.34–7.32 (m, 3 H, ArH), 7.29–7.26 (m, 1 H, ArH), 7.29–7.26 (m, 1 H, ArH), 6.86 (t, J = 7.9 Hz, 2 H, ArH) ppm. MS (ES^+): m/z = 287.3 $[M + 1]^+$. $C_{14}H_{11}BrN_2$ (286.01): calcd. C 58.56, H 3.86, N 9.76; found C 58.68, H 3.82, N 9.59.

General Procedure for the Synthesis of 7*H*-Indolo[2,3-*c*]quinoline 19: A mixture of **12** (0.48 mmol) and aldehyde (0.48 mmol) in DCM (2 mL) was treated with 2% TFA in DCM (2 mL). Completion of the Pictet–Spengler cyclization was monitored by TLC. After 30 min, the reaction mixture was evaporated and the residue thus obtained was triturated with aq. $NaHCO_3$ (10 mL). It was then extracted with EtOAc (20 mL), washed with brine (10 mL), and dried with sodium sulfate. The organic layer was concentrated to dryness under reduced pressure and the crude obtained was purified by column chromatography to afford **19**.

6-(4-Ethoxyphenyl)-7*H*-indolo[2,3-*c*]quinoline (19a): Yield 88%, white solid, m.p. 219–221 °C; R_f = 0.76 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3401, 3019, 1603, 1368 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.85 (br. s, 1 H, NH), 8.74 (dd, J = 1.7, 8.2 Hz, 1 H, ArH), 8.64 (d, J = 8.0 Hz, 1 H, ArH), 8.36 (dd, J = 7.8, 1.5 Hz, 1 H, ArH), 8.00 (d, J = 8.7 Hz, 2 H, ArH), 7.74–7.57 (m, 4 H, ArH), 7.46 (t, J = 8.0 Hz, 1 H, ArH), 7.14 (d, J = 8.7 Hz, 2 H, ArH), 4.15 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 1.49 (t, J = 6.9 Hz, 3 H, OCH_2CH_3) ppm. MS (ES^+): m/z = 339.3 $[M + 1]^+$. HRMS (EI): calcd. for $[M]^+$ 338.1419; found 338.1415. $C_{23}H_{18}N_2O$ (338.14): calcd. C 81.63, H 5.36, N 8.28; found C 81.80, H 5.21, N 8.11.

6-(4-Nitrophenyl)-7*H*-indolo[2,3-*c*]quinoline (19b): Yield 75%, yellow solid, m.p. >250 °C; R_f = 0.74 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3456, 3021, 1671, 1598 cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 12.08 (br. s, 1 H, NH), 8.89 (d, J = 8.1 Hz, 1 H, ArH), 8.76 (d, J = 8.1 Hz, 1 H, ArH), 8.52 (d, J = 8.8 Hz, 2 H, ArH), 8.38 (d, J = 8.7 Hz, 2 H, ArH), 8.26 (dd, J = 0.8, 8.1 Hz, 1 H, ArH), 7.82–7.79 (m, 2 H, ArH), 7.73 (t, J = 7.8 Hz, 1 H, ArH), 7.63 (t, J = 8.1 Hz, 1 H, ArH), 7.44 (t, J = 7.7 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO + 20 μL CF_3COOD): δ = 149.1, 142.8, 142.6, 139.4, 137.3, 131.8, 130.1, 129.6, 129.1, 128.4, 125.6, 125.1, 124.4, 124.2, 124.1, 123.8, 122.0, 121.1, 117.7, 113.8 ppm. MS (ES^+): m/z = 340.3 $[M + 1]^+$. HRMS (EI): calcd. for $[M]^+$ 339.1008; found 339.1020. $C_{21}H_{13}N_3O_2$ (339.10): calcd. C 74.33, H 3.86, N 12.38; found C 74.48, H 3.84, N 12.44.

2-(7*H*-Indolo[2,3-*c*]quinolin-6-yl)phenol (19c): Yield 91%, yellow solid, m.p. 219–220 °C; R_f = 0.65 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$

= 3407, 3020, 1609 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.28 (br. s, 1 H, OH), 11.90 (br. s, 1 H, NH), 8.86 (d, J = 7.4 Hz, 1 H, ArH), 8.72 (d, J = 8.1 Hz, 1 H, ArH), 8.21 (d, J = 8.0 Hz, 1 H, ArH), 7.99 (dd, J = 1.2, 7.6 Hz, 1 H, ArH), 7.86 (d, J = 8.1 Hz, 1 H, ArH), 7.78 (t, J = 7.1 Hz, 1 H, ArH), 7.69 (t, J = 6.8 Hz, 1 H, ArH), 7.60 (t, J = 7.3 Hz, 1 H, ArH), 7.49–7.43 (m, 2 H, ArH), 7.13 (t, J = 7.9 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 157.8, 146.8, 140.8, 140.6, 131.4, 130.8, 130.6, 129.7, 127.5, 127.3, 126.4, 123.5, 123.3, 122.5, 121.7, 121.0, 119.6, 117.5, 113.6 ppm. MS (ES$^+$): m/z = 311.4 [M + 1]$^+$. HRMS (EI): calcd. for [M]$^+$ 310.1106; found 310.1107. $C_{21}H_{14}N_2O$ (310.11): calcd. C 81.27, H 4.55, N 9.03; found C 81.33, H 4.56, N 8.97.

6-(4-Chlorophenyl)-2-methyl-7*H*-indolo[2,3-*c*]quinoline (19d): Yield 85%, white solid, m.p. 156–158 °C; R_f = 0.61 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3417, 3020, 1586, 762 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.86 (br. s, 1 H, NH), 8.74 (d, J = 8.4 Hz, 1 H, ArH), 8.69 (d, J = 8.1 Hz, 1 H, ArH), 8.11 (d, J = 8.5 Hz, 2 H, ArH), 8.01 (s, 1 H, ArH), 7.77 (d, J = 8.3 Hz, 1 H, ArH), 7.73 (d, J = 8.5 Hz, 2 H, ArH), 7.59 (t, J = 8.4 Hz, 2 H, ArH), 7.39 (t, J = 7.2 Hz, 1 H, ArH), 2.58 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 145.6, 142.8, 141.0, 137.1, 131.1, 130.7, 130.5, 130.3, 129.4, 129.2, 127.2, 126.1, 124.1, 123.5, 123.2, 122.9, 121.8, 120.8, 119.8, 113.1, 21.6 ppm. MS (ES$^+$): m/z = 343.4 [M + 1]$^+$. $C_{22}H_{15}ClN_2$ (342.09): calcd. C 77.08, H 4.41, N 8.17; found C 76.99, H 4.45, N 8.10.

Dimethyl[4-(2-methyl-7*H*-indolo[2,3-*c*]quinolin-6-yl)phenyl]amine (19e): Yield 81%, yellow solid, m.p. 208–210 °C; R_f = 0.58 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3021, 1605 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.92 (br. s, 1 H, NH), 8.63–8.58 (m, 2 H, ArH), 8.17 (s, 1 H, ArH), 7.96 (d, J = 8.7 Hz, 2 H, ArH), 7.69–7.52 (m, 3 H, ArH), 7.43 (t, J = 8.1 Hz, 1 H, ArH), 6.89 (d, J = 8.6 Hz, 2 H, ArH), 3.05 [s, 6 H, N(CH$_3$)$_2$], 2.56 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 153.2, 143.8, 143.6, 139.3, 134.8, 130.0, 130.7, 130.1, 128.4, 125.7, 124.6, 124.1, 120.8, 122.2, 120.6, 120.1, 115.6, 114.0, 112.3, 40.4, 21.8 ppm. MS (ES$^+$): m/z = 352.4 [M + 1]$^+$. HRMS (EI): calcd. for [M]$^+$ 351.1735; found 351.1739. $C_{24}H_{21}N_3$ (351.17): calcd. C 82.02, H 6.02, N 11.96; found C 82.19, H 5.93, N 11.88.

6-(4-Methoxyphenyl)-2-methyl-7*H*-indolo[2,3-*c*]quinoline (19f): Yield 89%, white solid, m.p. 156–158 °C; R_f = 0.52 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3417, 3020, 1586, 762 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.70 (d, J = 8.5 Hz, 1 H, ArH), 8.06 (d, J = 8.6 Hz, 2 H, ArH), 7.99 (br. s, 1 H, NH), 7.78 (d, J = 8.3 Hz, 1 H, ArH), 7.57 (t, J = 5.8 Hz, 2 H, ArH), 7.38 (t, J = 7.8 Hz, 2 H, ArH), 7.23 (d, J = 8.7 Hz, 3 H, ArH), 3.90 (s, 3 H, OCH$_3$), 2.57 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 146.6, 143.0, 140.4, 136.7, 135.2, 131.1, 130.6, 129.4, 128.9, 126.9, 123.4, 123.1, 122.8, 121.9, 121.8, 121.4, 120.7, 114.6, 113.5, 55.8, 21.6 ppm. MS (ES$^+$): m/z = 339.4 [M + 1]$^+$. $C_{23}H_{18}N_2O$ (338.14): calcd. C 81.63, H 5.36, N 8.28; found C 81.81, H 5.45, N 8.19.

***N*-[4-(10-Bromo-7*H*-indolo[2,3-*c*]quinolin-6-yl)phenyl]dimethylamine (19g):** Yield 84%, white solid, m.p. 220–222 °C; R_f = 0.62 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3233, 1632, 1217, 757 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.77 (br. s, 1 H, NH), 8.20 (d, J = 8.5 Hz, 1 H, ArH), 7.98 (dd, J = 1.2, 7.7 Hz, 3 H, ArH), 7.56–7.51 (m, 4 H, ArH), 7.46 (d, J = 8.5 Hz, 1 H, ArH), 7.07–7.03 (m, 2 H, ArH), 3.68 (s, 3 H, CH$_3$), 2.57 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 147.3, 142.7, 139.0, 138.2, 131.4, 130.3, 129.8, 129.7, 129.3, 127.6, 126.4, 125.2, 123.8, 123.6, 123.5, 120.6, 115.5, 113.2, 40.6 ppm. MS (ES$^+$): m/z = 416.2 [M + 1]$^+$. $C_{23}H_{18}BrN_3$ (415.06): calcd. C 66.36, H 4.36, N 10.09; found C 66.24, H 4.39, N 10.21.

General Procedure for the Synthesis of 1-(2-Nitrophenyl)-1*H*-indole 18: Indole **15** (8.5 mmol) was treated with NaH (0.38 g in 60% oil, 12.8 mmol) in DMF (10 mL) at room temp. for 15 min. Then *o*-fluoronitrobenzene (8.5 mmol) was added portionwise over a period of 5 min. The reaction was monitored by TLC and after completion of the reaction; the mixture was poured into ice-cold water (50 mL) and was extracted with EtOAc (2 × 25 mL). The EtOAc layer was washed with water (2 × 10 mL) and brine (1 × 10 mL). The organic layers were combined and dried with anhydrous Na_2SO_4 and evaporated to obtain a yellow residue, which after column chromatography on silica gel with hexane/EtOAc (20:80, v/v) as eluent afforded **18**.

1-(2-Nitrophenyl)-1*H*-indole (18a): Yield 72%, yellow solid, m.p. 85–87 °C; R_f = 0.50 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3036, 1612, 1530, 1313 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.02 (d, J = 7.86 Hz, 1 H, ArH), 7.76–7.66 (m, 2 H, ArH), 7.59–7.53 (m, 2 H, ArH), 7.20–7.11 (m, 4 H, ArH), 6.72 (d, J = 3.7 Hz, 1 H, ArH) ppm. MS (ES$^+$): m/z = 239.2 [M + 1]$^+$. $C_{14}H_{10}N_2O_2$ (238.07): calcd. C 70.58, H 4.23, N 11.76; found C 70.71, H 4.28, N 11.71.

1-(5-Bromo-2-nitrophenyl)-1*H*-indole (18b): Yield 67%, yellow solid, m.p. 101–103 °C; R_f = 0.54 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3018, 1598, 1533, 1323 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.08 (d, J = 6.9 Hz, 1 H, ArH), 7.76–7.68 (m, 4 H, ArH), 7.56–7.72 (m, 2 H, ArH), 7.21 (d, J = 8.1 Hz, 1 H, ArH), 6.72 (d, J = 2.8 Hz, 1 H, ArH) ppm. MS (ES$^+$): m/z = 317.2 [M + 1]$^+$. $C_{14}H_9BrN_2O_2$ (317.13): calcd. C 53.02, H 2.86, N 8.83; found C 53.23, H 3.01, N 8.63.

5-Benzyloxy-1-(5-methyl-2-nitrophenyl)-1*H*-indole (18c): Yield 75%, yellow solid, m.p. 98–99 °C; R_f = 0.48 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3043, 1608, 1531, 1331 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.50 (d, J = 6.9 Hz, 2 H, ArH), 7.43–7.28 (m, 5 H, ArH), 7.20–7.13 (m, 3 H, ArH), 7.06–6.93 (m, 2 H, ArH), 6.64 (d, J = 3.2 Hz, 1 H, ArH), 5.14 (s, 2 H, CH$_2$), 2.51 (s, 3 H, CH$_3$) ppm. MS (ES$^+$): m/z = 359.3 [M + 1]$^+$. $C_{22}H_{18}N_2O_3$ (358.13): calcd. C 73.73, H 5.06, N 7.82; found C 73.91, H 4.96, N 7.69.

5-Benzyloxy-1-(2-nitrophenyl)-1*H*-indole (18d): Yield 81%, yellow solid, m.p. 102–104 °C; R_f = 0.42 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3056, 2986, 1608, 1530, 1313 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.02 (dd, J = 2.0, 8.2 Hz, 1 H, ArH), 7.72 (dd, J = 2.3, 9.2 Hz, 1 H, ArH), 7.60–7.55 (m, 2 H, ArH), 7.52–7.31 (m, 4 H, ArH), 7.20 (d, J = 3.2 Hz, 1 H, ArH), 7.13 (d, J = 4.9 Hz, 2 H, ArH), 7.03 (s, 1 H, ArH), 6.95 (d, J = 3.5 Hz, 1 H, ArH), 6.64 (dd, J = 1.0, 4.9 Hz, 1 H, ArH), 5.11 (s, 2 H, CH$_2$) ppm. MS (ES$^+$): m/z = 345.3 [M + 1]$^+$. $C_{21}H_{16}N_2O_3$ (344.16): calcd. C 73.24, H 4.68, N 8.13; found C 73.36, H 4.71, N 8.23.

General Procedure for the Synthesis of 2-(Indol-1-yl)phenylamine 13: A mixture of compound **18** (5.8 mmol) and Pd/C (100 mg) in methanol (10 mL) was subjected to hydrogenation for 2 h in a Parr apparatus at 35 psi at room temperature. Thereafter, the catalyst was removed by vacuum filtration of the reaction mixture through a Celite bed with methanol. The filtrate was evaporated to obtain an oily residue, which was taken up in EtOAc (2 × 20 mL) and washed with water (20 mL). The organic layers were evaporated in vacuo to obtain the crude oil, which was purified by column chromatography using EtOAc/hexane (1:4) as eluent to obtain **13**.

2-(Indol-1-yl)phenylamine (13a): Yield 86%, colorless oil; R_f = 0.48 (1:9 EtOAc/hexane). IR (neat): $\tilde{\nu}_{max}$ = 3372, 1616, 1508 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.74 (d, J = 7.86 Hz, 1 H, ArH), 7.31–7.17 (m, 6 H, ArH), 6.92–6.86 (m, 2 H, ArH), 6.73 (d, J = 3.2 Hz, 1 H, ArH), 3.60 (br. s, 2 H, NH$_2$) ppm. MS (ES$^+$): m/z = 209.3 [M + 1]$^+$. $C_{14}H_{12}N_2$ (208.25): calcd. C 80.74, H 5.81, N 13.45; found C 80.69, H 5.79, N 13.52.

4-Bromo-2-(indol-1-yl)phenylamine (13b): Yield 91%, yellow oil; R_f = 0.53 (1:9 EtOAc/hexane). IR (neat): $\tilde{\nu}_{max}$ = 3412, 1596, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 4.9 Hz, 1 H, ArH), 7.24–7.13 (m, 4 H, ArH), 7.06–7.04 (m, 2 H, ArH), 6.97 (dd, J = 0.9, 8.2 Hz, 1 H, ArH), 6.72 (d, J = 3.1 Hz, 1 H, ArH) ppm. MS (ES^+): m/z = 287.2 $[M + 1]^+$. $C_{14}H_{11}BrN_2$ (286.01): calcd. C 58.56, H 3.86, N 9.76; found C 58.68, H 3.81, N 9.87.

2-(5-Benzyloxyindol-1-yl)-4-(methylphenyl)amine (13c): Yield 72%, brown oil; R_f = 0.48 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3412, 1596, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.1 Hz, 2 H, ArH), 7.56–7.46 (m, 5 H, ArH), 7.35–7.02 (m, 5 H, ArH), 6.66 (d, J = 3.1 Hz, 1 H, ArH), 5.14 (s, 2 H, CH_2), 3.42 (s, 2 H, NH_2), 2.53 (s, 3 H, CH_3) ppm. MS (ES^+): m/z = 329.3 $[M + 1]^+$. $C_{22}H_{20}N_2O$ (328.15): calcd. C 80.46, H 6.14, N 8.53; found C 80.64, H 6.08, N 8.68.

2-(5-Benzyloxyindol-1-yl)phenylamine (13d): Yield 78%, yellow oil; R_f = 0.46 (1:9 EtOAc/hexane). IR (neat): $\tilde{\nu}_{max}$ = 3396, 1608, 1523 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, J = 6.8 Hz, 1 H, ArH), 7.44–7.34 (m, 3 H, ArH), 7.25–7.19 (m, 5 H, ArH), 7.07 (d, J = 8.8 Hz, 1 H, ArH), 6.97–6.83 (m, 3 H, ArH), 6.63 (d, J = 3.0 Hz, 1 H, ArH), 5.15 (s, 2 H, CH_2) ppm. MS (ES^+): m/z = 315.2 $[M + 1]^+$. $C_{21}H_{18}N_2O$ (314.14): calcd. C 80.23, H 5.77, N 8.91; found C 80.15, H 5.82, N 8.88.

General Procedure for the Synthesis of Indolo[1,2-*a*]quinoxaline 20: A mixture of **13** (0.36 mmol) and benzaldehyde (0.36 mmol) in DCM (2 mL) was treated with 2% TFA in DCM. Completion of the Pictet–Spengler cyclization was monitored by TLC. After complete consumption of the amine (by TLC) the mixture was treated with $KMnO_4$ (50 mg) for 15 min, the reaction mixture was then evaporated, and the residue thus obtained was triturated with aq. $NaHCO_3$. It was then extracted with EtOAc, washed with brine (10 mL), and dried with sodium sulfate. EtOAc was evaporated to dryness under reduced pressure and the crude obtained was purified by column chromatography using EtOAc/hexane (1:9) to afford **20**.

6-Phenylindolo[1,2-*a*]quinoxaline (20a): Yield 81%, white solid, m.p. 169–172 °C; R_f = 0.65 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3021, 2965, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.54 (t, J = 8.3 Hz, 2 H, ArH), 8.11 (dd, J = 1.2, 7.9 Hz, 1 H, ArH), 8.06–8.03 (m, 2 H, ArH), 7.96 (d, J = 7.9 Hz, 1 H, ArH), 7.67–7.56 (m, 5 H, ArH), 7.50–7.44 (m, 2 H, ArH), 7.28 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 156.1, 138.3, 136.3, 133.0, 130.5, 130.1, 130.0, 129.0, 129.1, 128.6, 128.2, 124.3, 124.1, 122.7, 122.6, 114.6, 114.5, 102.4 ppm. MS (ES^+): m/z = 295.4 $[M + 1]^+$. HRMS (EI): calcd. for $[M]^+$ 294.1157; found 294.1165. $C_{21}H_{14}N_2$ (294.11): calcd. C 85.69, H 4.79, N 9.52; found C 85.78, H 4.72, N 9.50.

***N*-(4-Indolo[1,2-*a*]quinoxalin-6-ylphenyl)dimethylamine (20b):** Yield 80%, yellow solid, m.p. 145–147 °C; R_f = 0.38 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3020, 2924, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 8.2 Hz, 1 H, ArH), 8.07 (dd, J = 1.2, 7.9 Hz, 1 H, ArH), 8.03 (d, J = 8.8 Hz, 2 H, ArH), 7.96 (d, J = 7.8 Hz, 1 H, ArH), 7.75 (d, J = 8.9 Hz, 1 H, ArH), 7.61–7.54 (m, 2 H, ArH), 7.45 (t, J = 7.4 Hz, 1 H, ArH), 7.36 (s, 1 H, ArH), 6.90 (d, J = 8.8 Hz, 2 H, ArH), 6.72 (d, J = 8.8 Hz, 1 H, ArH), 3.10 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.6, 133.0, 131.9, 130.1, 129.9, 129.8, 129.4, 129.3, 127.6, 126.1, 124.0, 122.6, 122.4, 114.6, 114.5, 111.8, 110.9, 102.3, 40.5 ppm. MS (ES^+): m/z = 338.4 $[M + 1]^+$. $C_{23}H_{19}N_3$ (337.15): calcd. C 81.87, H 5.68, N 12.45; found C 81.78, H 5.69, N 12.53.

6-(4-Nitrophenyl)indolo[1,2-*a*]quinoxaline (20c): Yield 70%, red solid, m.p. 213–214 °C; R_f = 0.56 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3016, 1595, 1350 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.62 (t, J = 8.5 Hz, 1 H, ArH), 8.46 (d, J = 10.8 Hz, 2 H, ArH), 8.24 (d, J = 9.0 Hz, 2 H, ArH), 8.10 (dd, J = 1.5, 6 Hz, 1 H, ArH), 7.98 (d, J = 9.0 Hz, 1 H, ArH) 7.73–7.60 (m, 2 H, ArH), 7.54–7.48 (m, 2 H, ArH), 7.25 (d, J = 9.0 Hz, 2 H, ArH) ppm. MS (ES^+): m/z = 340.2. HRMS (EI): calcd. for $[M]^+$ 339.1008; found 339.1012. $C_{21}H_{13}N_3O_2$ (339.10): calcd. C 74.33, H 3.86, N 12.38; found C 74.24, H 3.76, N 12.30.

6-(4-Bromophenyl)indolo[1,2-*a*]quinoxaline (20d): Yield 76%, yellow solid, m.p. 219–221 °C; R_f = 0.60 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3021, 2965, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.54 (t, J = 8.3 Hz, 2 H, ArH), 8.09 (dd, J = 1.2, 7.9 Hz, 1 H, ArH), 7.95–7.93 (m, 3 H, ArH), 7.74 (d, J = 7.9 Hz, 2 H, ArH), 7.68–7.57 (m, 2 H, ArH), 7.48 (t, J = 7.9 Hz, 2 H, ArH), 7.23 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.0, 135.8, 133.0, 131.6, 130.9, 130.2, 130.1, 129.5, 129.4, 127.5, 126.5, 125.9, 125.1, 124.4, 123.1, 117.2, 115.8, 114.9, 114.7 ppm. MS (ES^+): m/z = 375.4. HRMS (EI): calcd. for $[M]^+$ 373.03404; found 373.03046. $C_{21}H_{13}BrN_2$ (372.02): calcd. C 67.58, H 3.51, N 7.51; found C 67.66, H 3.58, N 7.54.

2-Bromo-6-(4-methoxyphenyl)indolo[1,2-*a*]quinoxaline (20e): Yield 77%, yellow solid, m.p. 234–236 °C; R_f = 0.48 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3413, 2921, 1094, 1389 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.43 (d, J = 8.6 Hz, 1 H, ArH), 8.38 (d, J = 8.8 Hz, 1 H, ArH), 8.23 (d, J = 2.2 Hz, 1 H, ArH), 8.03 (d, J = 8.8 Hz, 2 H, ArH), 7.96 (d, J = 7.9 Hz, 1 H, ArH), 7.69 (dd, J = 2.3, 8.8 Hz, 1 H, ArH), 7.59 (t, J = 7.0 Hz, 1 H, ArH), 7.47 (t, J = 7.5 Hz, 1 H, ArH), 7.32 (s, 1 H, ArH), 7.12 (d, J = 8.8 Hz, 2 H, ArH) 3.94 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 155.3, 135.8, 133.7, 132.0, 130.5, 130.2, 127.9, 125.9, 125.8, 125.2, 124.8, 124.6, 120.3, 118.9, 117.0, 116.1, 115.5, 114.6, 55.8 ppm. MS (ES^+): m/z = 405.3 $[M + 1]^+$. $C_{22}H_{15}BrN_2O$ (402.03): calcd. C 65.52, H 3.75, N 6.95; found C 65.48, H 3.81, N 6.89.

2-(2-Bromoindolo[1,2-*a*]quinoxalin-6-yl)phenol (20f): Yield 75%, yellow solid, m.p. 159–161 °C; R_f = 0.59 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3428, 2928, 1669, 1595, 1478 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, J = 8.7 Hz, 1 H, ArH), 8.34 (d, J = 8.9 Hz, 1 H, ArH), 8.23 (dd, J = 1.5, 7.9 Hz, 1 H, ArH), 8.04 (d, J = 2.3 Hz, 1 H, ArH), 7.98 (d, J = 8.0 Hz, 1 H, ArH), 7.69 (dd, J = 2.3, 8.9 Hz, 1 H, ArH), 7.62–7.57 (m, 2 H, ArH), 7.51–7.44 (m, 2 H, ArH), 7.17 (d, J = 8.3 Hz, 1 H, ArH), 7.06 (t, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 153.2, 136.4, 135.8, 134.0, 131.1, 127.9, 128.9, 125.9, 125.3, 125.1, 124.74, 124.7, 121.1, 118.9, 118.1, 117.0, 116.6, 114.7, 114.5 ppm. MS (ES^+): m/z = 389.3 $[M + 1]^+$. $C_{21}H_{13}BrN_2O$ (388.02): calcd. C 64.80, H 3.37, N 7.20; found C 64.60, H 3.17, N 7.30.

9-Benzyloxy-2-methyl-6-phenylindolo[1,2-*a*]quinoxaline (20g): Yield 70%, yellow solid, m.p. 172–173 °C; R_f = 0.62 (1:19 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3020, 1597, 1381 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, J = 9.0 Hz, 1 H, ArH), 8.26 (s, 1 H, ArH), 8.04–7.97 (m, 3 H, ArH), 7.59–7.51 (m, 5 H, ArH), 7.46–7.26 (m, 6 H, ArH), 7.15 (s, 1 H, ArH), 5.20 (s, 2 H, CH_3), 2.65 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9, 138.9, 138.6, 137.2, 134.3, 130.0, 129.9, 128.8, 128.7, 128.5, 128.1, 127.7, 125.2, 115.9, 115.7, 114.6, 103.9, 101.6, 70.5, 22.3 ppm. MS (ES^+): m/z = 415.2 $[M + 1]^+$. $C_{29}H_{22}N_2O$ (414.17): calcd. C 84.03, H 5.35, N 6.76; found C 84.18, H 5.25, N 6.56.

9-Benzyloxy-6-(*p*-tolyl)indolo[1,2-*a*]quinoxaline (20h): Yield 69%, yellow solid, m.p. 153–155 °C; R_f = 0.58 (1:9 EtOAc/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3021, 1600, 1441, 1382 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, J = 8.2 Hz, 1 H, ArH), 8.42 (d, J = 9.2 Hz, 1 H, ArH), 8.09 (dd, J = 1.4, 7.9 Hz, 1 H, ArH), 7.94 (d, J = 8.0 Hz,

2 H, ArH), 7.62 (t, J = 8.5 Hz, 1 H, ArH), 7.52 (d, J = 6.9 Hz, 2 H, ArH), 7.48–7.28 (m, 8 H, ArH), 7.18 (s, 1 H, ArH), 5.20 (s, 2 H, CH_2), 2.50 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 154.7, 140.0, 137.0, 136.2, 135.5, 130.4, 130.1, 129.6, 129.1, 129.3, 128.6, 128.5, 128.4, 128.1, 128.0, 127.5, 123.9, 116.0, 115.5, 114.2, 103.7, 101.8, 70.4, 21.5 ppm. MS (ES^+): m/z = 415.2 [M + 1]$^+$. $C_{29}H_{22}N_2O$ (414.17): calcd. C 84.03, H 5.35, N 6.76; found C 84.23, H 5.41, N 6.82.

Supporting Information (see also the footnote on the first page of this article): The NMR and MS spectroscopic data for the representative compounds is provided.

Acknowledgments

P. K. A., D. S. and S. S. are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for providing fellowships.

[1] for reviews, see: a) A. R. Katritzky, A. F. Pozharskii in *Handbook of Heterocyclic Chemistry*, Pergamon Press, Oxford, **2000**; b) H. Takayama, S. I. Tsutsumi, M. Kitajima, D. Santiarworn, B. Liawruangrath, N. Aimi, *Chem. Pharm. Bull.* **2003**, *51*, 232–233; c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911.

[2] a) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761–793; b) K. Higuchi, T. Kawasaki, *Nat. Prod. Rep.* **2007**, *24*, 843–868; c) S. Hibino, T. Choshi, *Nat. Prod. Rep.* **2001**, *18*, 66–87.

[3] T. Robinson, *The Biochemistry of Alkaloids*, Springer, New York, **1981**.

[4] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559–568; c) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621–6622; d) A. D. Batcho, W. Leimgruber, *Org. Synth.* **1985**, *63*, 214–220; e) A. D. Batcho, W. Leimgruber, U.S. Patent 3732245, **1973** [*Chem. Abstr.* **1973**, *79*, 29624]; f) G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129–2132; g) G. Bartoli, M. Bosco, R. Dalpozzo, G. Palmieri, E. Marcantoni, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2757–2761; h) A. Dobbs, *J. Org. Chem.* **2001**, *66*, 638–641; i) A. Bischler, P. Firemann, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1336–1349; j) P. G. Gassman, T. J. van Bergen, G. Gruetzmacher, *J. Am. Chem. Soc.* **1973**, *95*, 6508–6509; k) H. Hemetsberger, D. Knittel, *Monatsh. Chem.* **1972**, *103*, 194–204; l) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662; m) C. D. Nenitzescu, *Bull. Soc. Chim. Romania* **1929**, *11*, 37–43; n) A. Reissert, *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1030–1053.

[5] G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045–1075.

[6] a) T. Hino, M. Nakagawa, *J. Heterocycl. Chem.* **1994**, *31*, 625–630; b) B. J. Baker, *Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 357–407; c) B. E. Love, *Org. Prep. Proceed. Int.* **1996**, *28*, 1–64; d) E. Magnier, Y. Langlois, *Tetrahedron* **1998**, *54*, 6201–6258; e) M. Nakagawa, *J. Heterocycl. Chem.* **2000**, *37*, 567–581; f) T. Ohmoto, K. Koike in *The Alkaloids* (Ed.: A. Brossi), Academic Press, San Diego, **1989**, vol. 36, pp. 135–150.

[7] a) N. Matsukura, T. Kawachi, K. Morino, H. Ohgaki, T. Sugimura, S. Takayama, *Science* **1981**, *213*, 346–347; b) S. Hibino, E. Sugino, N. Sgura, Y. Shintani, K. Sato, *Heterocycles* **1990**, *30*, 271–273.

[8] a) G. W. Gribble in *The Alkaloids* (Ed.: A. Brossi), Academic Press, San Diego, **1990**, vol. 39, chapter 7; b) J. M. Pezzuto in *Chemistry and Toxicology of Diverse Classes of Alkaloids* (Ed.: M. S. Blum), Alaken, Ft. Collins (Colorado, USA), **1996**, pp. 1–119; c) for a recent report, see: C. H. Nguyen, F. Lavelle, J.-F. Riou, M.-C. Bissery, C. Huel, E. Bisagni, *Anti-Cancer Drug Des.* **1992**, *7*, 235–251.

[9] a) R. B. Turner, R. B. Woodward in *The Alkaloids* (Ed.: R. H. F. Manske), Academic Press, New York, **1953**, Vol. 3, Chapter 16; b) M. R. Uskoković, G. Grethe in *The Alkaloids* (Ed.: R. H. F. Manske), Academic Press, New York, **1973**, vol. 14, pp. 181–223; c) S. Schwikkard, F. R. van Heerden, *Nat. Prod. Rep.* **2002**, *19*, 675–692; d) J. C. P. Steele, N. C. Veitch, G. C. Kite, M. S. J. Simmonds, D. C. Warhurst, *J. Nat. Prod.* **2002**, *65*, 85–88; e) M. Souvain, C. Moretti, J.-A. Bravo, J. Collapa, V. Munoz, E. Ruiz, B. Richard, L. Le Man-Oliver, *Phytother. Res.* **1996**, *10*, 198–201; f) C. Ancolio, N. Azas, V. Mahiou, E. Ollivier, C. Di Giorgio, A. Keita, P. Timon-David, G. Balansard, *Phytother. Res.* **2002**, *16*, 646–649; g) K. Pavanand, K. Yongvanitchit, H. K. Webster, T. Dechatiwongse, W. Nutakul, Y. Jewvachdamrongkul, J. Bansiddhi, *Phytother. Res.* **1988**, *2*, 33–36; h) for akagerine, see: C. W. Wright, D. H. Bray, M. J. O'Neill, D. C. Warhurst, J. D. Phillipson, J. Quetin-Leclercq, L. Angenot, *Planta Med.* **1991**, *57*, 337–340; i) P.-C. Kuo, [1].-S. Shi, A. G. Damu, C.-R. Su, C. H. Huang, C.-H. Ke, J. B. Wu, A. J. Lin, K. F. Bastow, K. H. Lee, T. S. Wu, *J. Nat. Prod.* **2003**, *66*, 1324–1327; j) J. R. F. Allen, B. R. Holmstedt, *Liebigs Ann. Chem.* **1980**, *19*, 1573–1582; k) C. Braestrup, M. Nielsen, C. E. Olsen, *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 2288–2292; l) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis* **1995**, 1225–1227; m) P. Molina, P. M. Fresneda, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1819–1822; n) P. Molina, P. M. Fresneda, S. Garcia-Zafra, P. Almendros, *Tetrahedron Lett.* **1994**, *35*, 8851–8854; o) K. Takasu, T. Shimogama, C. Saiin, H. S. Kim, Y. Wataya, M. Ihara, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1689–1692; p) Y. Boursereau, I. Coldham, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5841–5844; q) Y. Wu, M. Zhao, C. Wang, S. Peng, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2331–2333; r) P. Molina, P. M. Fresneda, S. Garcia-Zafra, *Tetrahedron Lett.* **1995**, *36*, 3581–3582; s) M. Tsuda, J. Kobayashi, *Heterocycles* **1997**, *46*, 765–794; t) A. Batch, R. H. Dodd, *J. Org. Chem.* **1998**, *63*, 872–877; u) G. M. Konig, A. D. Wright, O. Sticher, C. K. Angerhofer, J. M. Pezzuto, *Planta Med.* **1994**, *60*, 532–537; v) R. Sakai, T. Higa, C. W. Jefford, G. Bernardinelli, *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405.

[10] P. Grellier, L. Ramiaramanana, V. Millerioux, E. Deharo, J. Schrevel, F. Frappier, F. Trigalo, B. Bodo, J.-L. Pousset, *Phytotherapy Res.* **1996**, *10*, 317–321.

[11] a) L. He, H. X. Chang, T. C. Chou, N. Savaraj, C. C. Cheng, *Eur. J. Med. Chem.* **2003**, *38*, 101–107; b) C. Meyers, G. Rombouts, K. T. J. Loones, A. Coelho, B. U. W. Maes, *Adv. Synth. Catal.* **2008**, *350*, 465–470.

[12] a) G. Timari, T. Soos, G. Hajos, *Synlett* **1997**, 1067–1068; b) P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron* **2001**, *57*, 6197–6202; c) P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron Lett.* **1999**, *40*, 7275–7278; d) T. Dhanabal, R. Sangeetha, P. S. Mohan, *Tetrahedron* **2006**, *62*, 6258–6263; e) G. Timari, T. Soos, G. Hajos, *Synlett* **1997**, 1067–1068; f) P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron* **2001**, *57*, 6197–6202; g) P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron Lett.* **1999**, *40*, 7275–7278; h) R. N. Kumar, T. Suresh, P. S. Mohan, *Tetrahedron Lett.* **2002**, *43*, 3327–3328; i) T. Dhanabal, R. Sangeetha, P. S. Mohan, *Tetrahedron Lett.* **2005**, *46*, 4509–4510; j) T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemiere, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommisse, *Synlett* **2003**, 615–618; k) P. E. Murray, K. Mills, J. A. Joule, *J. Chem. Res. (S)* **1998**, 377–377; l) Y. Miki, M. Kuromatsu, H. Miyatake, H. Hamamoto, *Tetrahedron Lett.* **2007**, *48*, 9093–9095; m) A. Molina, J. J. Vaquero, J. L. García-Navio, J. Alvarez-Builla, *Tetrahedron Lett.* **1993**, *34*, 2673–2676.

[13] a) B. Kundu, D. Sawant, R. Chhabra, *J. Comb. Chem.* **2005**, *7*, 317–321; b) B. Kundu, D. Sawant, P. Partani, A. P. Kesarwani, *J. Org. Chem.* **2005**, *70*, 4889–4892; c) S. Duggineni, D. Sawant, B. Saha, B. Kundu, *Tetrahedron* **2006**, *62*, 3228–3241; d) S. Sharma, B. Saha, D. Sawant, B. Kundu, *J. Comb. Chem.* **2007**, *9*, 783–792; e) B. Saha, S. Sharma, D. Sawant, B. Kundu, *Tetrahedron* **2008**, *64*, 8676–8684.

[14] a) M. A. J. Duncton, L. M. Smith, S. Burdzovic-Wizeman, A. Burns, H. Liu, Y. Mao, W. C. Wong, A. S. Kiselyov, *J. Org. Chem.* **2005**, *70*, 9629–9631; b) L. Zheng, J. Xiang, Q. D. Daang, X. Bai, *J. Comb. Chem.* **2005**, *7*, 813–815; c) E. David, S. Pellet-Rostaing, M. Lemaire, *Tetrahedron* **2007**, *63*, 8999–9006; d) X. L. Wang, X. F. Zheng, R. H. Liu, J. Reiner, J. B. Chang, *Tetrahedron* **2007**, *63*, 3389–3394; e) S. Gracia, J. Schulz, S. Pellet-Rostaing, M. Lemaire, *Synlett* **2008**, 1852–1856; f) X. Che, L. Zheng, Q. Dang, X. Bai, *J. Org. Chem.* **2008**, *73*, 1147–1149.

[15] a) T. Srinivasan, G. K. Srivastava, A. Pathak, S. Batra, S. K. Puri, K. Raj, B. Kundu, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2803–2806; b) A. Pathak, S. K. Singh, M. A. Farooq Biabani, S. Srivastava, D. K. Kulshreshtha, S. K. Puri, B. Kundu, *Comb. Chem. High Throughput Screening* **2002**, *5*, 241–248; c) B. Saha, R. Kumar, P. R. Maulik, B. Kundu, *Tetrahedron Lett.* **2006**, *47*, 2765–2769.

[16] a) A. K. Kiang, A. F. Mann, A. F. Prior, A. Topham, *J. Chem. Soc.* **1956**, 1319–1331; b) R. L. Duncan, G. C. Helsey, R. F. Boswell, *J. Heterocycl. Chem.* **1973**, *10*, 65–70.

[17] a) R. S. Kusurkar, N. A. H. Alkobati, A. S. Gokule, V. G. Puranik, *Tetrahedron* **2008**, *64*, 1654–1662; b) R. A. Jones in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, London, **1984**, vol. 4, pp. 205–206.

[18] V. I. Shvedov, L. B. Altukhova, V. V. Alekseev, N. Grinev, *Chem. Heterocycl. Compd.* **1970**, *6*, 1255–1259.

[19] M. S. Joseph, L. D. Basanagoudar, *Synth. Commun.* **2003**, *33*, 851–862.

[20] a) N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513–519; b) N. M. Elwan, H. A. Abdelhadi, T. A. Abdullah, H. M. Hassaneen, *Tetrahedron* **1996**, *52*, 3451–3456; c) A. N. C. Lotter, R. Pathak, T. S. Sello, M. A. Fernandes, W. A. L. van Otterlo, C. B. de Koning, *Tetrahedron* **2007**, *63*, 2263–2274.

[21] a) G. Cusati, L. Djakovitch, *Tetrahedron Lett.* **2008**, *49*, 2499–2502; b) K. Ferre-Filmon, L. Delaude, A. Demonceau, A. F. Noels, *Coord. Chem. Rev.* **2004**, *248*, 2323–2336.

[22] R. S. Stabler, Jahangir, *Synth. Commun.* **1994**, *24*, 123–129.

[23] a) J. Sandrin, D. Soerens, L. Hutchins, F. Richfield, F. Ungemach, J. M. Cook, *Heterocycles* **1976**, *4*, 1101–1105; b) J. Sandrin, D. Soerens, P. Mokry, J. M. Cook, *Heterocycles* **1977**, *6*, 1133–1139.

[24] D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiePierro, J. M. Cook, *J. Org. Chem.* **1979**, *44*, 535–545.

[25] R. E. Tenbrink, W. B. Im, V. H. Sethy, A. H. Tang, D. B. Carter, *J. Med. Chem.* **1994**, *37*, 758–768.

[26] E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797–1842.

[27] H. E. Shannon, F. Guzman, J. M. Cook, *Life Sci.* **1984**, *35*, 2227–2236.

[28] E. E. Garcia, J. G. Riley, R. Ian Fryer, *J. Org. Chem.* **1968**, *33*, 2868–2874.

[29] W. O. Kermack, N. E. Storey, *J. Chem. Soc.* **1950**, 607–612.

Received: September 23, 2008
Published Online: November 28, 2008

