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# PICTET-SPENGLER SYNTHESIS OF SOME NEW INDOLO[2,3-*c*]-QUINOLINES

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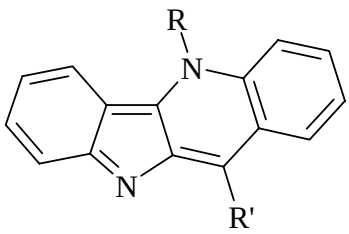
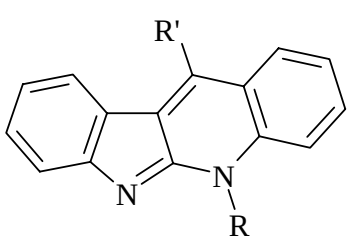
**Abstract**– A synthesis of some new indolo[2,3-*c*]quinolines (**16a-c**) is achieved by cyclocondensation of 3-[2-amino-(4-trifluoromethyl)phenyl]indole (**15**) with the appropriate aldehyde under Pictet-Spengler reaction conditions. Regio-selective cyclization occurred at the usual indolic C-2 position as evidenced from NMR spectral data of **16a-c**, and confirmed by X-ray crystal structure determination for **16c**.

## INTRODUCTION

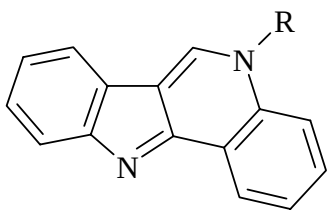
Indoloquinoline ring systems are receiving considerable interest as they constitute the skeleton of several cryptolepine alkaloids, exemplified by cryptolepine **1**, neocryptolepine **2**, and isocryptolepine (cryptosanguinolentine) **3** (Figure 1), isolated from the roots of the West African shrub *Cryptolepis sanguinolenta*.[1] The alkaloidal extracts of this shrub have for long been used in African folk medicine,




indolo[3,2-*b*]quinoline
**1** ( R = Me; R' = H )




indolo[2,3-*b*]quinoline
**2** ( R = Me; R' = H )




indolo[3,2-*c*]quinoline
**3** ( R = Me )

**Figure 1**

exhibiting a multiplicity of host-mediated biological activities including antiviral, antitumor, antibacterial, and anti-malarial properties.[2,3] On the other hand, synthetic studies of the angularly-fused isomeric indolo[2,3-*c*]quinolines have been confined to few reports.[4-9] A series of substituted indolo[2,3-*c*]quinolin-6-ones, such as the antitumor agent **4,**[4,5] was prepared by thermal cyclization of the respective 3-azidocarbostyrils,[4] while derivatives **5** (Figure 2) were obtained *via* the reaction of 3-formyl-1-methylindolin-2-one with $N_1$-substituted phenylhydrazine.[6] Various tetrahydroindolo[2,3-*c*]quinolines e.g. **6-9** (Figure 2), were also reported.[7-9] Thus, compound **6** was obtained by photocyclization of 3-(3-quinolinyl)benzylaminocyclohex-2-en-1-one,[7] while **7** and **8** were produced by photocyclization of the respective indole-2-carboxanilides,[8] and the synthesis of **9** was described.[9]

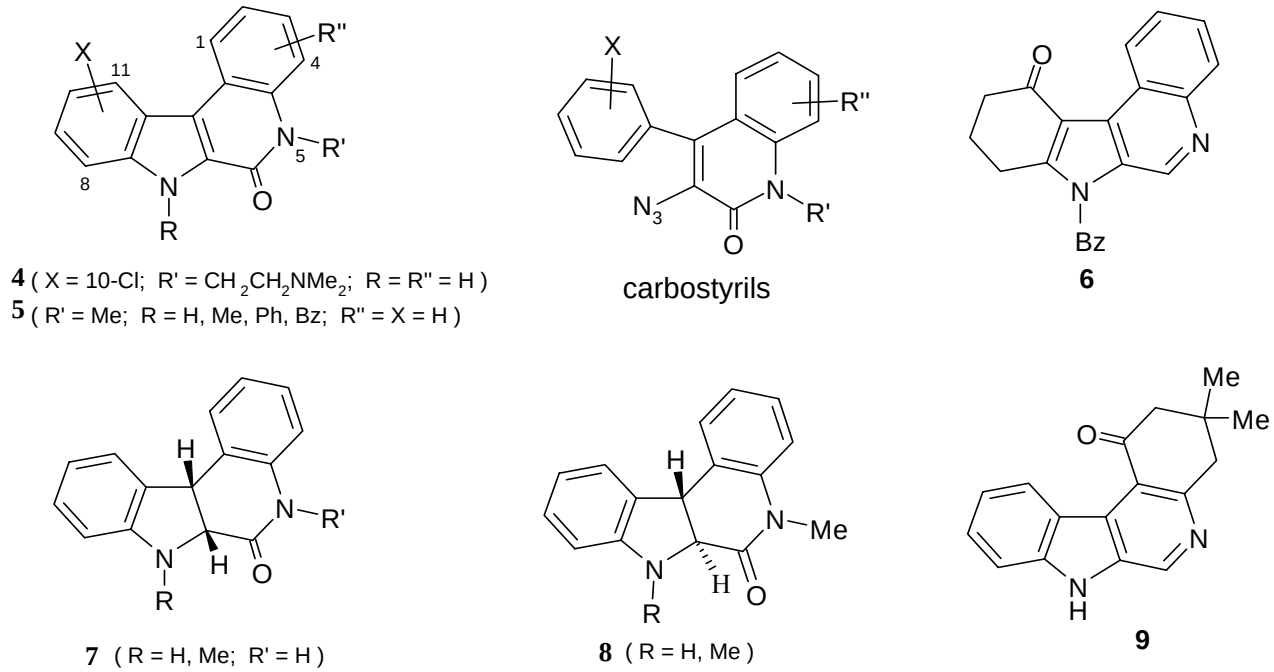
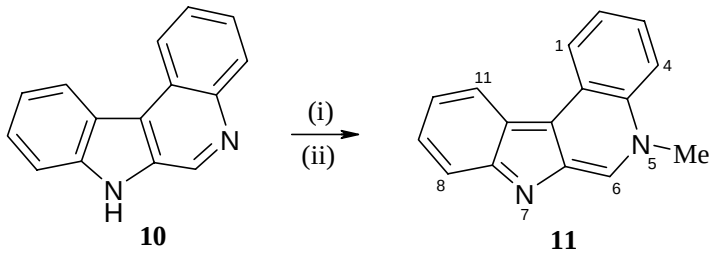



**Figure 2**

The non-oxygenated fully unsaturated 7*H*-indolo[2,3-*c*]quinoline system **10** has been prepared and selectively methylated at N(5) to produce **11**[10,11] for which the trivial name 'isoneocryptolepine' has been adopted[10] (Scheme 1). Although compound **11** has not been isolated from natural resources, yet preliminary *in vitro* screening results indicate that it exhibits selectivity index (ratio antiplasmodial activity / cytotoxicity) superior to the reported indices of the naturally occurring isomeric indoloquinolines (**1** – **3**), and is consequently becoming an interesting lead compound in the search for new antimalarial drugs.[10]

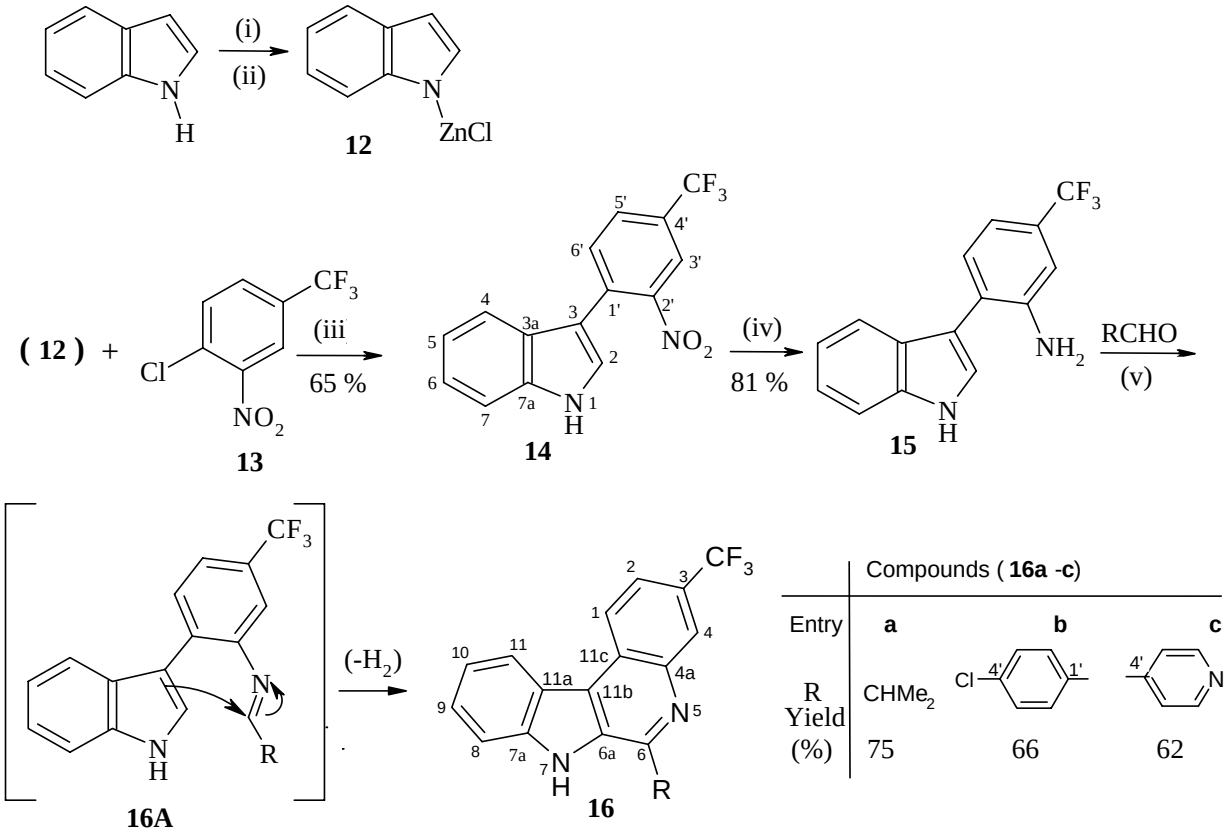
A recent synthesis of **10** started from 3-bromoquinoline and annulating the indole nucleus thereupon *via* amination with 2-bromoaniline (or 2-chloroaniline or aniline ) and subsequent cyclization by Heck-type reaction[10] (or by photochemical irradiation[11]). Conversely, an earlier preparative route utilized

3-(2-nitrophenyl)indole and constructed the quinoline ring thereupon, a process which entails sequential reduction of the nitro group into amino group, formamide formation thereat using formic acid, and subsequent Bischler-Napieralski type ring closure.[12]




**Scheme 1.** (i) MeI, toluene / reflux; (ii) conc. $NH_4OH$

Accordingly, alternative new short-cut preparative routes toward this interesting heterocyclic *'benzo-β-carboline'* system are, in effect, desirable. Herein, we wish to report on the synthesis of **16a-c** utilizing 3-[2-amino-4-(trifluoromethyl)phenyl]indole **15** as substrate in the Pictet-Spengler reaction, and for which avenue the steps are shown in Scheme 2.




**Scheme 2.** (i) MeMgI (3.0 *M* in $Et_2O$); (ii) $ZnCl_2$ (1.0 *M* in $Et_2O$); (iii) $Et_2O$ / 20 °C; (iv) $NaBH_4$, $Cu(OAc)_2$, MeOH / Δ; (v) $BF_3.OEt_2$, $CH_2ClCH_2Cl$ / Δ

## RESULTS AND DISCUSSION

In this study the required synthon, 3-[2-nitro-4-(trifluoromethyl)phenyl]indole (**14**), is readily prepared *via* direct coupling of N-indolylzinc chloride (**12**, acting as C-3 carbanion)[13] with 1-chloro-2-nitro-4-(trifluoromethyl)benzene (**13**) (Scheme 2), following similar procedure previously reported for the production of 3-[2,6-dinitro-4-(trifluoromethyl)phenyl]indole.[14] This reaction follows an $S_N$-*Ar* (addition–elimination) path and is facilitated by the presence of the electron withdrawing C(2)-nitro and C(4) - trifluoromethyl groups in **13**. Chemical reduction of the nitro group in **14**, using Copper (II) acetate / sodium borohydride system,[15] afforded the corresponding 3-[2-amino-4-(trifluoromethyl)phenyl]indole (**15**) (Scheme 2). The latter compound was subsequently reacted with the appropriate aldehyde, in presence of boron trifluoride etherate under Pictet-Spengler reaction conditions. In this reaction, the main isolable products were identified as the respective indolo[2,3-*c*]quinolines (**16a-c** / Scheme 1) on the basis of their spectral data and X-ray structure determination for **16c** (*vide infra*). The formation of **16a-c** implies the intermediacy of the corresponding imino derivatives (**16A**); the electrophilic nature of the imino carbon in the latter intermediate, enhanced by the lewis acid catalyst, provides the driving force for attack of indolic C2 - C3 double bond and consequent cyclization. Aromatization of the resulting tetracyclic intermediate, *via* air–oxidation, yielded the respective indoloquinolines (**16a-c**) as the final products. This result is in accordance with the established pathway for Pictet-Spengler type reactions.[16-18]

The new compounds (**14-16**) were characterized by elemental analyses, IR and NMR spectral data. These data, detailed in the Experimental part, are consistent with the assigned structures. DEPT and 2D (COSY, HMQC and HMBC) experiments showed correlations that helped in the $^1$H- and $^{13}$C- signal assignments to the various hydrogens and carbons. Herein, long range correlations are observed in HMBC experiments between: H-2 and C–1'/ C-3a as will as H-6' and C-3 for **14** and **15**; the *iso*propyl $Me_2C$-*H* proton and C-6a together with the isopropyl ($CH_3$)$_2$ protons and C-6 for **16a**; H-2' and C-6 for **16b**; H-3' and C-6 for **16c**.

The present study also deals with structural determination of the indoloquinoline ring system by X-ray crystal structure measurements for **16c.** A summary of data collection and refinement parameters is given in Table 1, and selected bond lengths and angles are provided in Table 2. The molecular structure of **16c**, based on crystallographic data, is displayed in Figures 3-5. The crystallographic data confirm the proposed indolo[2,3-*c*]quinoline structure for **16c** (and, by inference, for **16a**, **b** ). In the solid state, the molecules are associated through intermolecular hydrogen bonding involving N(7)-H(7)… N(15A)(Figure 2): (D = 3.086 (5) Å, d = 2.28 Å, Θ = 155.5 $^O$ #). [19]

**Table 1**. Summary of the crystal data and structure refinement parameters for **16c**

| | |
|---|---|
| Empirical formula | $C_{21}H_{12}F_3N_3$ |
| Formula weight | 363.34 Da |
| Temperature ( K) | 293(2) |
| Wavelength (Å) | 0.71073 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | |
| *a* (Å) | 7.588(3) |
| *b* (Å) | 20.843(7) |
| *c* (Å) | 10.460(4) |
| β(°) | 104.219(5) |
| Volume (Å$^3$) | 1603.6(9) |
| Z | 4 |
| Calculated density (mg / m$^3$) | 1.505 |
| Absorption coefficient ( mm$^{-1}$) | 0.115 |
| *F* (000) | 744 |
| Theta range for data collection(°) | 1.95 - 27.84 |
| completeness to theta = 27.84° | 52.9 % |
| Index range | $-8 \le h \le 8$; $-16 \le k \le 27$ ; $-10 \le 1 \le 13$ |
| Reflections collected | 4511 |
| Independent reflections | 2017 [ $R_{int}$ = 0.0376] |
| Weight scheme | Calcd $w = 1 / [\sigma^2 (F_0)^2 + (0.0701P)^2$ $0.0000P]$ where $P = [(F_0)^2 + 2(F_c)^2] / 3$ |
| Data / restraints / parameters | 2017 / 0 / 245 |
| Goodness-of-fit on $F^2$ | 0.893 |
| Final *R* indices [ $I > 2\sigma(I)$] | $R_1 = 0.0509$, $wR_2 = 0.1173$ |
| *R* indices ( all data) | $R_1 = 0.1104$, $wR_2 = 0.1360$ |
| Largest difference peak (e. Å$^{-3}$) | 0.248 |
| Largest difference hole (e. Å$^{-3}$) | -0.212 |

**Table 2.** Selected bond lengths (Å) and angles (°) for **16c**

| | | | |
|---|---|---|---|
| N(15)-C(14) | 1.328(5) | C(14)-N(15)-C(16) | 114.8(4) |
| N(5)-C(6) | 1.328(4) | C(6)-N(5)-C(4A) | 119.7(4) |
| N(5)-C(4A) | 1.379(4) | C(6A)-N(7)-C(7A) | 109.1(3) |
| N(7)-C(6A) | 1.376(4) | C(6A)-N(7)-H(7) | 125.4 |
| N(7)-C(7A) | 1.390(5) | C(7A)-N(7)-H(7) | 125.4 |
| N(7)-H(7) | 0.8600 | N(5)-C(6)-C(6A) | 120.6(4) |
| C(6)-C(6A) | 1.410(5) | N(5)-C(6)-C(12) | 113.6(4) |
| C(6)-C(12) | 1.482(5) | C(6A)-C(6)-C(12) | 125.7(4) |
| C(4A)-C(11C) | 1.415(5) | N(5)-C(4A)-C(4) | 117.1(4) |
| C(11B)-C(6A) | 1.407(5) | N(7)-C(6A)-C(11B) | 108.5(4) |
| C(11A)-C(7A) | 1.400(5) | N(7)-C(6A)-C(6) | 130.9(4) |
| C(11A)-C(11) | 1.408(5) | N(7)-C(7A)-C(8) | 129.1(4) |
| C(11B)-C(11A) | 1.427(5) | C(1)-C(11C)-C(11B) | 125.5(4) |
| C(11B)-C(11C) | 1.415(5) | C(11C)-C(11B)-C(11A) | 133.9(4) |
| C(11C)-C(1) | 1.411(5) | C(11)-C(11A)-C(11B) | 134.9(4) |

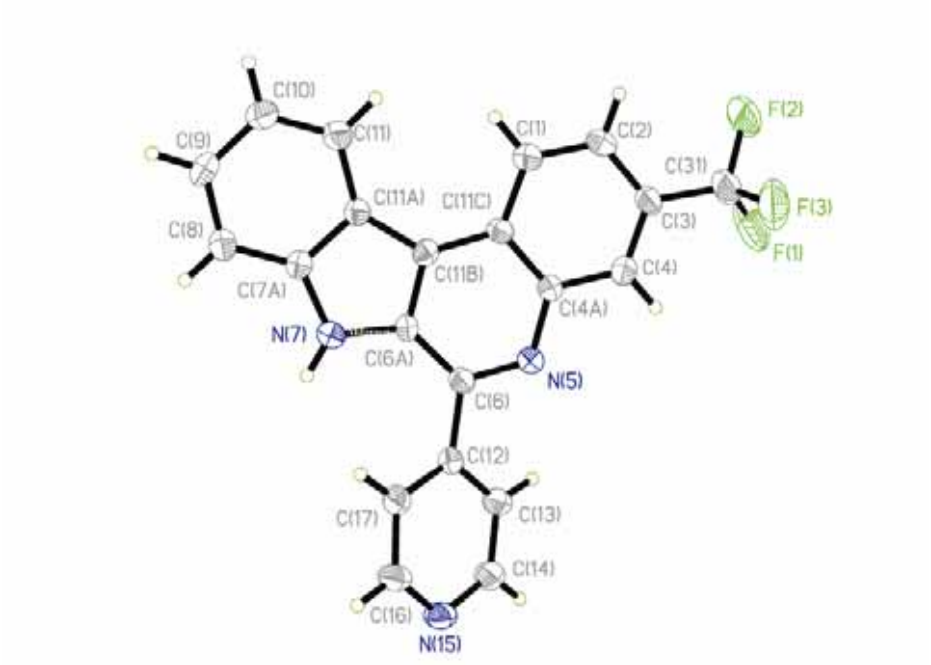



**Figure 3**. Asymmetric unit in $P2_1/c$ in **16c** (30% thermal ellipsoide)

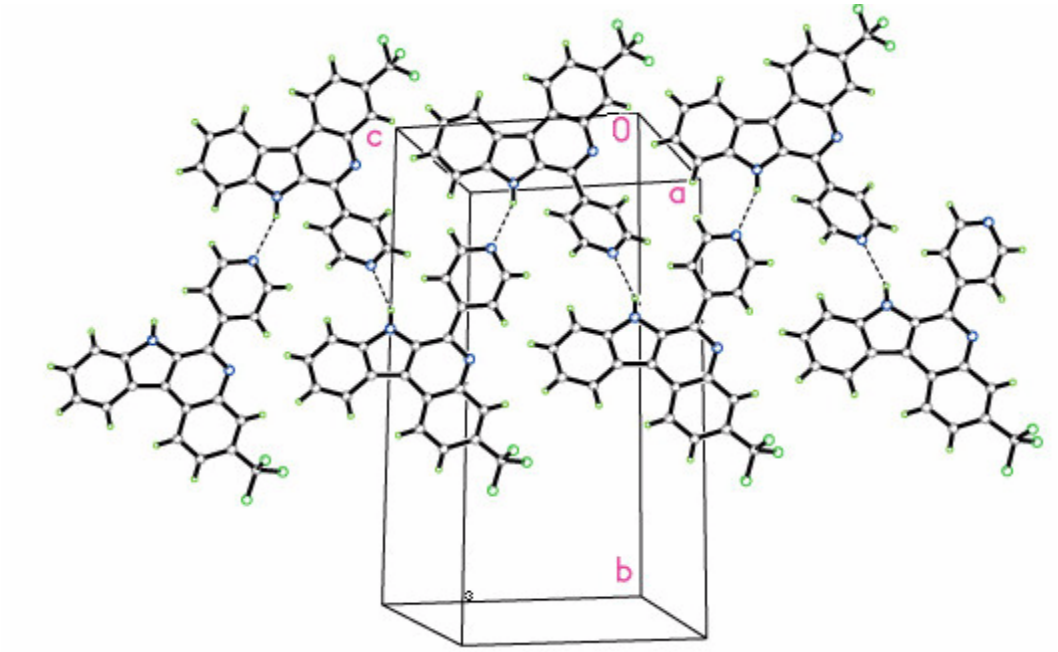



**Figure 4**. Intermolecular hydrogen bonding framework in **16c**

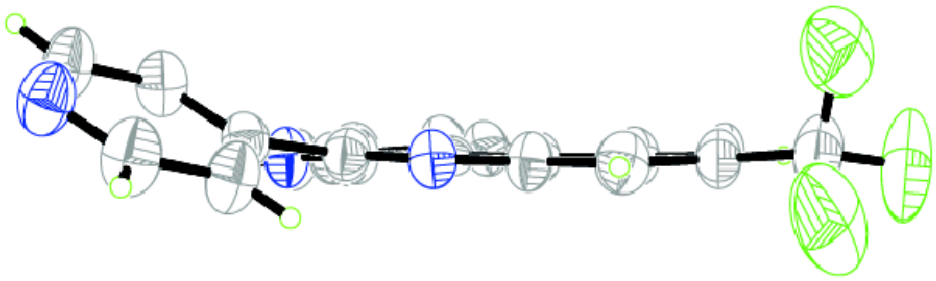


**Figure 5**. A 30% Thermal ellipsoid diagram showing a perpendicular view to the plane encompassing C(6), N(5), (4A), C(11C), C(11B) and C(6A) in **16c**

## EXPERIMENTAL

1-Chloro-2-nitro-4-(trifluoromethyl)benzene, *iso*butyraldehyde, 4-chlorobenzaldehyde, pyridine-4-carboxaldehyde and indole were purchased from Acros. $ZnCl_2$ (1.0 *M* in ether) and $BF_3.OEt_2$ were purchased from Aldrich. Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting temperature apparatus. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX-400 spectrometers using TMS as internal reference. Microanalyses were performed at the Microanalytical Laboratory, Chemistry Department, Al-albayt University, Jordan.

**3-[2-Nitro-4-(trifluoromethyl)phenyl]indole (14)**

To Mg (0.6 g, 25 mmol) in dry $Et_2O$ (40 mL), was added methyl iodide (3.55g, 25 mmol) with continuous stirring at rt for 30 min. A solution of indole (2.3 g, 20 mmol) in $Et_2O$ (20 mL) was then added and the resulting mixture was stirred at rt for 30 min. Thereafter, an ethereal solution of $ZnCl_2$ (1.0 *M*, 25mL) was added and stirred at rt for 30 min. generating indolylzinc chloride (**12**). A solution of 1-chloro-2-nitro-4-(trifluoromethyl)benzene **13** (2.3 g, 10 mmol) in $Et_2O$ (20 mL) was then added to the reaction mixture, and stirring was continued at rt for 6 h. The resulting mixture was then treated with water (100 mL) and stirred for 10 min. The ethereal layer was separated and the aqueous layer was extracted with $Et_2O$ (2 × 80 mL). The organic portions were combined, and the solvent was evaporated. The residual product was purified using silica gel column chromatography, eluting with $CH_2Cl_2$ to afford an orange solid. Yield of **14** = 2.0 g (65 %), mp 61-62 °C; *Anal.* Calcd for $C_{15}H_9F_3N_2O_2$ (306.25) : C, 58.83; H, 2.96; F, 18.61; N, 9.15 . Found : C, 59.02 ; H, 3.05 ; F, 18.44 ; N, 8.98; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.09 (dd, *J* = 7.7, 7.8 Hz, 1H, H-5), 7.20 (dd, *J* = 7.8, 8.0 Hz, 1H, H-6), 7.40 (d, *J* = 7.7 Hz, 1H, H-4), 7.55 (d, *J* = 8.0 Hz, 1H, H-7), 7.65 (d, *J* = 2.4 Hz, 1H, H-2), 7.95 (d, *J* = 8.1 Hz, 1H, H-6' ), 8.1 (dd, *J* = 8.1, 1.1 Hz, 1H, H-5' ), 8.4 (d, *J* = 1.1 Hz, 1H, H-3'), 11.75 (br s, 1H, N-H ); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ109.8 (C-3), 112.6 (C-7), 118.0 (C-4), 120.5 (C-5), 121.6 (q , $^3J_{C\text{-}F}$ = 3.6 Hz, C-3' ), 122.1 (C-1'), 122.4 (C-6), 125.3 (C-3a), 125.9 (C-2), 127.5 ( q , $^1J_{C\text{-}F}$ = 258 Hz, *C*$F_3$), 129.0 ( q , $^3J_{C\text{-}F}$ = 3.7 Hz, C-5' ), 133.2 (q, $^2J_{C\text{-}F}$ = 34 Hz, C- 4' ), 133.4 (C-6' ), 136.6 (C-7a), 148.9 (C-2').

**3-[2-Amino-4-(trifluoromethyl)phenyl]indole (15)**

To a stirred solution of 3-[2-nitro-4-(trifluoromethyl)phenyl]indole **14** (1.5 g, 4.9 mmol) in MeOH (60 mL) and 20 mL of saturated aqueous solution of $Cu(OAc)_2$, was added $NaBH_4$ (1.9 g, 40 mmol) portionwise at rt until the reduction was completed. This is followed by immediate addition of $Et_2O$ (100 mL), and the mixture was washed with 10 % aqueous $Na_2CO_3$. The ethereal layer was separated and the aqueous layer was further extracted with $Et_2O$ (40 mL). The combined ether fractions were dried ($MgSO_4$) and the solvent was removed whereby the title amino derivative was obtained as brown solid. Yield of **15** = 1.15 g (81 %), mp 132-134 °C; *Anal.* Calcd for $C_{15}H_{11}F_3N_2$ (276.26) : C, 65.22; H, 4.01; N, 10.14 . Found: C, 65.27 ; H, 4.05; N, 10.32; $^1$H NMR (400 MHz, DMSO-$d_6$) : δ 5.25 (s, 2H, $NH_2$), 6.92 (dd, *J* = 7.8, 1.2 Hz, 1H, H-5'), 7.06 (ddd, *J* = 7.9, 8.1, 1.1 Hz , 1H, H-5 ), 7.12 (d, *J* = 1.2 Hz, 1H, H-3' ), 7.17 (ddd, *J* = 8.0, 7.9, 1.1 Hz, 1H, H-6), 7.37 (d, *J* = 7.8 Hz, 1H, H-6' ), 7.48 (d, *J* = 8.1 Hz, 1H, H-4 ), 7.51 (d, *J* = 8.0 Hz, 1H, H-7 ), 7.59 (d, *J* = 2.5 Hz, 1H, H-2 ), 11.45 (br s, 1H, $N_1$-H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ110.8 (q , $^3J_{C\text{-}F}$ = 3.7 Hz, C-3' ), 111.7 (C-3), 112.1 (C-7), 112.4 (q , $^3J_{C\text{-}F}$ = 3.8 Hz, C-5' ), 119.3 (C-4), 119.4 (C-5), 121.7 (C-6), 123.6 ( q , $^2J_{C\text{-}F}$ = 32 Hz, C-4' ), 124.6 (C-2), 125.9 (C-3a ), 126.3 (C-1' ), 127.6 ( q , $^1J_{C\text{-}F}$ = 261 Hz, *C*$F_3$ ), 130.9 ( C- 6' ), 136.5 (C-7a), 146.5 (C-2' ).

**6-isoPropyl-3-trifluoromethyl-7H-indolo[2,3-c]quinoline (16a)**

A mixture of **15** (0.5 g, 1.8 mmol) and *iso*butyraldehyde (0.14 g, 1.9 mmol), dissolved in $CH_2Cl_2$ (50 mL) and few drops of glacial acetic acid, was stirred at rt for 1 h. $BF_3.OEt_2$ (4 mL) was added, and the mixture was heated at refluxed for 6 h. The solvent was then evaporated, the residual solid was soaked successively with 10% NaOH solution (20 mL) and water (2 x 20 mL), air-dried and then purified using silica gel chromatography, eluting with $CH_2Cl_2$ to give brown solid. Yield of **16a** = 0.44 g ( 75 %), mp 210 - 212 °C; *Anal.* Calcd for $C_{19}H_{15}F_3N_2$ (328.34) : C, 69.50 ; H, 4.60 ; N, 8.53 . Found : C, 69.54; H, 4.47; N, 8.48; $^1$H NMR ( 400 MHz, DMSO-$d_6$) : δ 1.45 (d, $J$= 6.5 Hz, 6H, -CH(C$H_3$)$_2$), 3.80 (septet, $J$ = 6.5 Hz, 1H, -C$H$Me$_2$), 7.46 (dd, $J$ = 7.6, 7.0 Hz , 1H, H-9), 7.65 (dd, $J$ = 7.8, 7.0 Hz, 1H, H-10 ), 7.83 (d, $J$ = 7.8 Hz, 1H, H-11), 7.93 (d, $J$ = 8.0 Hz, 1H, H-2), 8.43 (br s, 1H, H-4 ), 8.70 (d, $J$ = 7.6 Hz, 1H, H-8 ), 8.97 (d, $J$ = 8.0 Hz, 1H, H-1), 12.45 (s, 1H, N-H); $^{13}$C NMR ( 100 MHz, DMSO-$d_6$): δ 21.3 (-CH(C$H_3$)$_2$), 31.6 (-C$H$Me$_2$), 113.1 (C-11), 119.1 (C-11b), 120.9 (C-9), 121.5 (q, $^3J_{C\text{-}F}$ = 4.1 Hz, C-2), 121.6 (q, $^1J_{C\text{-}F}$ = 252 Hz,C$F_3$), 122.8 (C-8 ), 124.7 (C-1), 125.3 (C-6a), 125.6 (C-11c), 126.1 (q, $^2J_{C\text{-}F}$ = 26.6 Hz, C-3), 126.7 (q, $^3J_{C\text{-}F}$ = 4.2 Hz, C-4), 127.1 (C-10), 131.8 (C-7a), 139.5 (C-11a), 140.8 (C-4a), 156.8 (C-6).

**6-(4-Chlorophenyl)-3-trifluoromethyl-7H-indolo[2,3-c]quinoline (16b)**

This compound was prepared from **15** (0.5 g, 1.8 mmol) and 4-chlorobenzaldehyde (0.27 g, 1.9 mmol) by following the same procedure and experimental conditions described above for **16a**. The product was purified on silica gel column chromatography, eluting with $CH_2Cl_2$ **:** petroleum ether (1:1 v/v). Yield of **16b** = 0.46 g (66 %), mp 260 - 262 °C; *Anal.* Calcd for $C_{22}H_{12}ClF_3N_2$ (396.80) : C, 66.59; H, 3.05; Cl, 8.93; N, 7.06 . Found : C, 66.51; H, 3.02; Cl, 8.80; N, 6.97; $^1$H NMR (400 MHz, DMSO-$d_6$) : δ 7.38 (dd, $J$ = 8.0, 7.7 Hz, 1H, H-9), 7.58 (dd, $J$ = 8.2, 7.7 Hz, 1H, H-10), 7.66 (d, $J$ = 7.8 Hz, 2H, H-3'/ H-5'), 7.76 (d, $J$ = 8.2 Hz, 1H, H-11 ), 7.88 (d, $J$ = 8.6 Hz, 1H, H-2), 8.04 (d, $J$ = 7.8 Hz, 2H, H-2' / H-6'), 8.43 (br s, 1H, H-4 ), 8.66 (d, $J$ = 8.0 Hz, 1H, H-8 ), 8.92 (d, $J$ = 8.0 Hz, 1H, H-1), 12.09 (s, 1H, N-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ113.8 (C-11), 121.3 (C-11b), 121.5 (C-9), 121.7 (C-11c), 122.6 (q , $^3J_{C\text{-}F}$ = 4 Hz, C-2), 123.1 (C-8), 125.2 (C-1), 126.4 (C-6a ), 126.5 (q, $^2J_{C\text{-}F}$ = 25 Hz, C-3), 127.1 (q, $^1J_{C\text{-}F}$ = 248 Hz, C$F_3$ ), 127.5 (q, $^3J_{C\text{-}F}$ = 4 Hz, C-4), 127.7 (C-10), 129.4 (C-3' / C-5'), 131.2 (C-2' / C-6'), 131.7 (C-7a), 135.0 (C-4'), 136.6 (C-1'), 140.6 (C-11a), 141.3 (C-4a), 147.6 (C-6).

**6-(Pyridin-4-yl)-3-trifluoromethyl-7*H*-indolo[2,3-*c*]quinoline (16c)**

This compound was prepared from **15** (0.5 g, 1.8 mmol) and pyridine-4-carboxaldehyde (0.21 g, 2.0 mmol) by following the same procedure and experimental conditions described above for **16a**. The product was purified on silica gel column chromatography, eluting with $CH_2Cl_2$ **:** petroleum ether (1:1 v/v). Yield of **16c** = 0.41 g (62 %), mp 292 - 294 °C; *Anal.* Calcd for $C_{21}H_{12}F_3N_3$ (363.35) : C, 69.42 ; H, 3.33 ; N,

11.56. Found : C, 69.34 ; H, 3.35; N, 11.42; $^1$H NMR (400 MHz, DMSO-$d_6$) : δ 7.40 (dd, $J$ = 7.4 Hz, 7.9 Hz, 1H, H-9), 7.60 (dd, $J$ = 7.4, 8.0 Hz, 1H, H-10), 7.78 (d, $J$ = 8.0 Hz, 1H, H-11), 7.92 (dd, $J$ = 8.3, 1.5 Hz, 1H, H-2), 8.01(d, $J$ = 5.3 Hz, 1H, H-3'/ H-5'), 8.47(br s, 1H, H-4 ), 8.65 (d, $J$ = 7.9 Hz, 1H, H-8 ), 8.85 (d, $J$ = 5.3 Hz, 2H, H-2'/ H-6'), 8.96 (d, $J$ = 8.3 Hz, 1H, H-1), 12.23 (s, 1H, N(7)-H); $^{13}$C NMR ( 100 MHz, DMSO-$d_6$): δ 113.9 (C-11), 121.5 (C-11b), 121.6 (C-11c), 121.7 (C-9), 123.0 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C-2), 123.2 (C-8 ), 123.9 (br, C-3'/ C-5'), 124.9 (q, $^1J_{C\text{-}F}$ = 260 Hz, $C$F$_3$), 125.3 (C-1), 126.4 (q, $^2J_{C\text{-}F}$ = 30.8 Hz, C-3), 126.6 (C-6a), 127.8 (q, $^3J_{C\text{-}F}$ = 4.4 Hz, C-4), 128.0 (C-10), 131.6 (C-7a), 140.6 (C-11a), 141.5 (C-4a), 144.9 (C-4'), 146.3 (C-6), 150.8 (C-2'/ C-6').

## COLLECTION OF X-RAY DIFFRACTION DATA AND STRUCTURE ANALYSIS OF 16c

Crystals (yellow, parallelpiped) were obtained by allowing a hot solution of **16c** in ethanol / water (5:1, v/v) to stand at rt for 4-5 days; crystal dimensions: 0.20 x 0.10 x 0.10 mm. Data collection was made on a Rigaku Mercury diffractometer using graphite monochromated Mo-Kα radiation. The structure was solved by direct methods using the program SHELXS-97. [20] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedure based on $F^2$ using all unique data with SHELXL-97.[21] The hydrogen atoms were placed geometrically and then refined isotropically using a 'riding model' with $U_{iso}$ constrained to be 1.2 $U_{eq}$ of the carrier atom.

## SUPPLEMENTARY MATERIAL

Crysallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 265803 for compound **16c**. Copies of further information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (Fax: +44-1223-336033); e-mail: (deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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