Synthesis of Novel Fluorinated 11*H*-Azaindolo[3,2-*c*]isoquinolines

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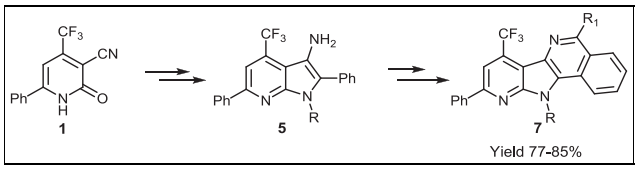

A series of novel fluorinated 11*H*-azaindolo[3,2-*c*]isoquinolines (**7**) have been synthesized starting from 2(1*H*)pyridones (**1**) via azaindoles (**5**). Initially, compound **1** was treated with $POCl_3$/DMF, and the resulting compound **2** was reacted with benzylamine to obtain compounds **3** that were subjected to cyclization after protecting the secondary amine to get azaindoles (**5**). Further, compounds **5** were subjected to cyclization as per Pictet–Spengler reaction condition. However, it was not successful. Subsequently, the azaindoles (**5**) were acetylated and then cyclized to give title compounds **7**. These compounds are new and well characterized by spectral data.

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INTRODUCTION

Pyrrolo[2,3-*b*]pyridines also known as azaindoles have received significant synthetic importance as they have been used as various pharmaceutical [1–4] and antipsychotic agents [5–9]. Tetracyclic ring systems similar to indoloquinolines and indoloisoquinolines have received considerable synthetic importance because of their interesting biological properties such as anti-inflammatory, antitumor, antibacterial, and fungicidalactivities [10–12]. Further, indoloisoquinolines constitute important structural moieties in natural products, and adoption of an additional nitrogen atom in the aromatic ring confers its own unique properties to the systems. In addition, the presence of fluorine at a specified position in a molecule alters the reactivity apart from liphophilicity. The synthesis of isoquinolines and indoloisoquinolines has been extensively reported in the literature [13]. However, no reports are available on the synthesis of azaindoloisoquinolines as availability of natural azaindoles is relatively scarce. Hence, the synthesis of azaindoloisoquinolines especially trifluoromethyl-substituted azaindoloisoquinolines is of significant importance.

RESULTS AND DISCUSSION

In continuation of our work on the synthesis of pyrazolopyridines [14] starting from 2(1*H*) pyridones (**1**), their subsequent utilization in ring fusion reactions has prompted us to synthesize 7-azaindoles and construct isoquinoline ring system over them. Therefore, we are reporting here a hitherto unreported trifluoromethyl-substituted azaindoloisoquinolines (**7**) by a novel method. In this instance, 3-amino-2,6-diphenyl-4-trifluoromethyl azaindoles (**5**) have been prepared starting from 3-cyano-4-trifluoromethyl-6-phenyl-2(1*H*) pyridones (**1**). Thus, compound **1** was reacted with benzylamine to obtain 2-*N*-benzylamino-3-cyano-4-trifluoromethyl-6-phenylpyridine (**3**) to prepare **5**.

Here, it is interesting to mention the important finding that NMR of the crude product 2(1*H*) pyridone and benzylamine reaction has shown the protons corresponding to benzyl function, but mass spectrum confirmed the molecular ion peak corresponding to benzylamine addition onto compound **1** instead of product **3**. However, when the crude product was passed through the column of silica gel, the starting material **1** was recovered (on the basis of NMR and mass data). To clear the ambiguity, the crude product was recrystallized and the X-ray crystallograph was recorded. Surprisingly, it was known by X-ray crystallography data that the benzyl amine functional and 2(1*H*) pyridone were in the form of a salt (Fig. 1).

It could be reasoned that the existence of salt form was attributed to the starting material **1** to come back when passed through column of silica gel that is of acidic nature. This was further confirmed by adding few drops of HCl to the crude product. Therefore, compound **3** was prepared by an alternate method where compound **1** was treated with $POCl_3$/DMF, and the resulted 2-chloro-3-cyano-4-trifluoromethyl-6-phenylpyridine (**2**) was then reacted with benzylamine to give compound **3** (Schemes 1).

Efforts to cyclize compound **3** onto nitrile group in the presence of a base to obtain azaindoles (**5**) were

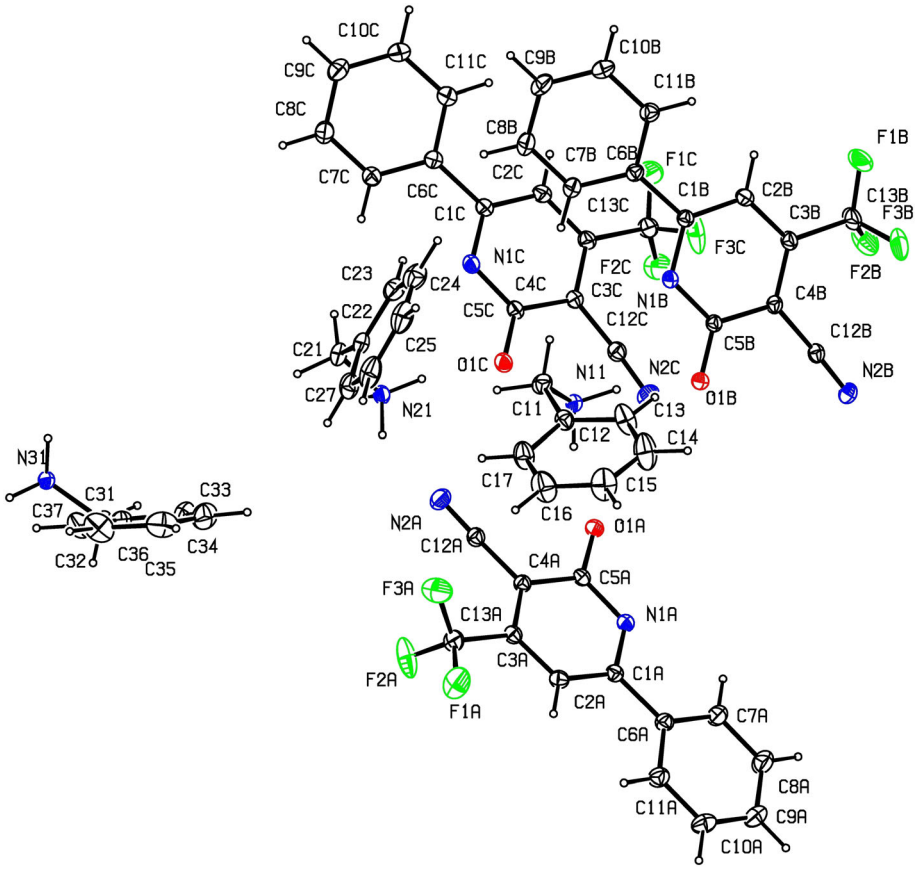
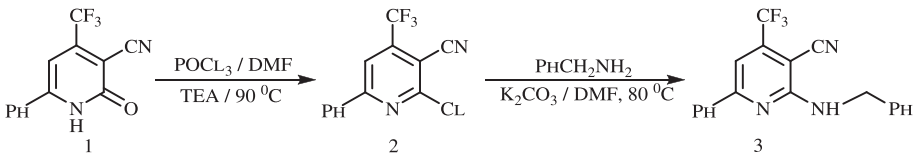
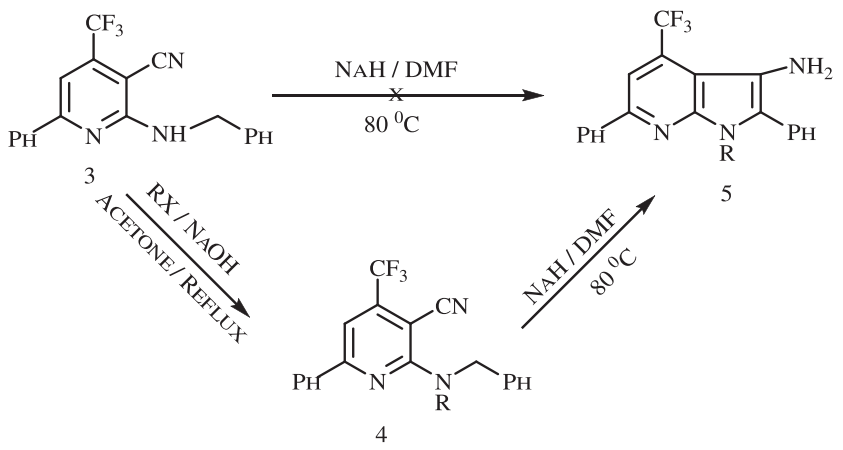


Figure 1. (X-ray crystallograph. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 1

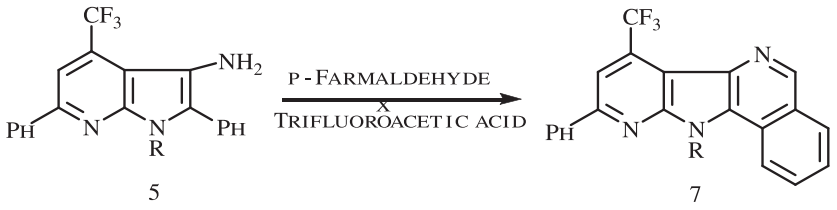


Scheme 2



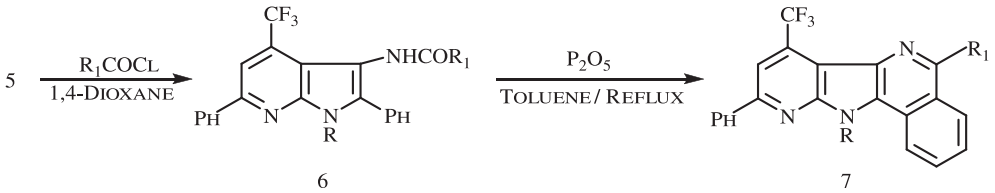
R=A)CH_3;B)CH_2CH_3;C)$CH_2C_6H_5$

Scheme 3



5 7

Scheme 4



6 7

A) $R=R_1=CH_3$; B) $R=CH_3, R_1=C_6H_5$; C) $R=CH_3, R_1=P\text{-}ClC_6H_4$;
D) $R=CH_2CH_3, R_1=CH_3$; E) $R=CH_2CH_3, R_1=C_6H_5$; F) $R=CH_2CH_3, R_1=P\text{-}ClC_6H_4$;
G) $R=CH_2C_6H_5, R_1=CH_3$; H)$R=CH_2C_6H_5, R_1=C_6H_5$; I) $R=CH_2C_6H_5, R_1=P\text{-}ClC_6H_4$;

unsuccessful. However, when the secondary amine was protected with alkyl or benzyl functional (**4**) and subjected to cyclization under basic condition, the desired compounds (**5**) were obtained (Schemes 2.

Further, compound **5** was unsuccessfully subjected to cyclization using, *p*-formaldehyde in the presence of trifluoroaceticacid to obtain title compounds (**7**) as per Pictet–Spengler reaction condition (Schemes 3.

Hence, compounds **5** were first acetylated and the resulted compounds **6** were then cyclized in the presence of P_2O_5 in toluene to afford 11*H*-azaindolo, [3,2-*c*]isoquinolines (**7**) in high yields (Schemes 4.

In conclusion, we have synthesized a number of new fluorinated azaindoloisoquinoline molecules, and the described methodologies are useful tools to synthesize a number of new heterocyclic compounds of biological interest.

EXPERIMENTAL

Melting points were determined in open glass capillaries on a Fischer-Johns melting point apparatus (Canada) and were uncorrected. ^{1}H NMR spectra were recorded on 300-MHz (Bruker, Switzerland) and 500-MHz (Varian, USA) spectrometers ($CDCl_3$/DMSO-d_6) with TMS as internal standard. IR spectra were recorded on Nicolet Nexus 670 spectrometer (USA) IR instrument on KBr pellets. Mass spectra were recorded on low resolution mass spectra (ESI-MS), and HRMS were recorded on MicroMass Quattro LC (Applied biosystems /MDS Sciex, USA) and QSTAR XL spectrometers(Manchester, UK), respectively. ^{13}C NMR spectra were recorded on 75-MHz and 125-MHz spectrometers. ^{19}F NMR spectra were recorded on 400-MHz spectrometer.

Preparation of 2-chlro-6-phenyl-4-trifluoromethyl-nicotinonitrile (2). To a solution of 2(1*H*) pyridone **1** (2.0 g, 7.5 mmol) in DMF (10 mL), triethylamine (0.40 ml) was added followed by $POCl_3$ (2.8 mL), and the reaction mass was heated to 90°C for 8 h while stirring. After completion of reaction, the mass was brought to room temperature and transferred on to crushed ice. The uniform aqueous mass was extracted with ethylacetate (3×50 mL) for desired compound. After evaporation of organic solvent under reduced pressure, the leftover residual mass was purified by column chromatography (silica gel 60–120) with the use of hexane and ethylacetate as eluent (90:10) to afford compound **2**.Yield 84%, mp 88–90 C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.12–8.08 (m, 2H, ArH), 8.0 (s, 1H, ArH), 7.57–7.50 (m, 3H, ArH) ppm. IR (KBr) 3087, 2922, 2234, 1595, 1376, 1314, 1262, 1144 cm^{-1}. MS (ESI) *m/z* 283 $(M+H)^+$.

Preparation of 2-benzylamino-6-phenyl-4-triflouromethyl-nicotinonitrile (3). To a solution of **2** (3.60 g, 12.76 mmol) in DMF (20 mL), benzylamine (1.636 g, 15.31 mmol) was added followed by K_2CO_3 (2.54 g, 25.53 mmol), and the reaction mixture was heated to 80°C for 2 h while stirring. After completion of reaction as indicated by TLC, the mass was allowed to come to room temperature and transferred on to crushed ice. The desired compound in aqueous mass was extracted with ethylacetate (3×50 mL), dried over anhydrous sodium sulfate, and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel 60–120) with the use of hexane and ethylacetate as eluent (90:10) to afford compound **3**. Yield 94%, mp 158–160°C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.0 (s, 1H, ArH), 7.56–7.39 (m, 5H, ArH), 7.38–7.20 (m, 5H, ArH), 4.80 (s, 2H, Ph–CH_2–N) ppm.IR (KBr) 3363, 3062, 2927, 2214, 1572, 1372, 1261, 1131, 1058 cm^{-1}. MS (ESI) *m/z* 354 $(M+H)^+$.

General procedure for the preparation of 2-(benzyl-substituted-amino)-6-phenyl-4-trifluoromethyl-nicotinonitrile (4a–4c). To a solution of compound **3** (1.0 g, 2.82 mmol) in acetone (10 mL), NaOH (0.224 g, 5.64 mmol) and methyl iodide (0.26 ml) was added, and the reaction mixture was heated to reflux while stirring. After completion of reaction

as indicated by TLC, the mass was cooled to room temperature and transferred on to crushed ice, and the separated solid was filtered and purified by column chromatography (silica gel 60–120) with the use of hexane and ethylacetate as eluent (90:10) to give compound **4a**. The yields are in the range of 88–96%.

2-(Benzyl-methyl-amino)-6-phenyl-4-trifluoromethyl nicotinonitrile (4a). Yield 96%, mp 85–87°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.96–7.92(m, 2H, ArH), 7.45–7.41 (m, 4H, ArH), 7.35–7.24 (m, 5H, ArH), 5.06 (s, 2H, Ph–CH_2–N), 3.38 (s, 3H, N–CH_3) ppm. IR (KBr) 2924, 2205, 1558, 1414, 1372, 1257, 1130, 1006 cm^{-1}. MS (ESI) *m/z* 368 $(M+H)^+$, 390 $(M+Na)^+$.

2-(Benzyl-ethyl-amino)-6-phenyl-4-trifluoromethyl nicotinonitrile (4b). Yield 95%, mp 78–80°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.91–7.86 (m, 2H, ArH), 7.45–7.38 (m, 4H, ArH), 7.34–7.22 (m, 5H, ArH), 5.04 (s, 2H, Ph–CH_2–N), 3.86 (q, J = 6.98 Hz, 2H, N–$\underline{CH_2}$–CH_3), 1.40 (t, J = 6.98 Hz, 3 H, N–CH_2–$\underline{CH_3}$) ppm. IR (KBr) 2925, 2854, 2207,1587, 1560,1495, 1371, 1259, 1140 cm^{-1}. MS (ESI) *m/z* 382 $(M+H)^+$, 404 $(M+Na)^+$.

2-Di-benzylamino-6-phenyl-4-trifluoromethyl nicotinonitrile (4c). Yield 88%, mp 90–93°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.94–7.89 (m, 2H, ArH), 7.47–7.39 (m, 4H, ArH), 7.35–7.22 (m, 10H, ArH), 5.01 (s, 4H, 2 Ph–CH_2–N) ppm. IR (KBr) 3030, 2925, 2217, 1583, 1553, 1443, 1373, 1257, 1133 cm^{-1}. MS (ESI) *m/z* 444 $(M+H)^+$, 466 $(M+Na)^+$.

General procedure for the preparation of 1-substituted-2,6-diphenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylamine (5a–5c). 2-(Benzyl-methyl-amino)-6-phenyl-4-trifluoromethyl-nicotinonitrile **4a** (1 g, 2.72 mmol) was added to a mixture of NaH (5 eq) (60% w/w in mineral oil) in DMF (4 mL) at room temperature and was stirred at 80°C for 1 h. After the reaction was completed (monitored by TLC), the mass was cooled to room temperature and transferred on to crushed ice. The desired compound was extracted into ethylacetate (3 × 20 mL); the combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The leftover residual mass was purified by column chromatography (neutral alumina) with the use of hexane as eluent to obtain compound **5a** as yellow color solid. The yields are in the range of 76–77%.

1-Methyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-ylamine (5a). Yield 76%, mp100–101°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.13 (d, J = 7.81 Hz, 2H, ArH), 7.74 (s, 1H, ArH), 7.54–7.48 (m, 4H, ArH), 7.46–7.34 (m, 4H, ArH), 3.82 (s, 3H, N–CH_3), 3.40 (br s, 2H, NH) ppm. IR (KBr) 3268, 3059, 2924, 1532, 1371, 1124 cm^{-1}. MS (ESI) *m/z* 368 $(M+H)^+$.

1-Ethyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-ylamine (5b). Yield 77%, mp 84–86°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.15 (d, J = 7.81 Hz, 2H, ArH), 7.75 (s, 1H, ArH), 7.60–7.30 (m, 8H, ArH), 4.45–4.35 (q, J = 6.98 Hz, 2H, N–$\underline{CH_2}$–CH_3), 3.35 (br s, 2H, NH), 1.25 (t, J = 6.98 Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. IR (KBr) 3338, 2928, 1623, 1460, 1367, 1261, 1115 cm^{-1}. MS (ESI) *m/z* 382 $(M+H)^+$.

1-Benzyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-ylamine (5c). Yield 77%, mp 98–100°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.10 (d, J = 7.36 Hz, 2H, ArH), 7.81 (s, 1H, ArH), 7.52–7.31 (m, 9H, ArH), 7.18–7.11 (m, 2H, ArH), 6.93–6.88 (m, 2H, ArH), 5.51(s, 2H, Ph–CH_2–N) ppm. IR (KBr) 3439, 3030, 2920, 1459, 1268, 1116 cm^{-1}. MS (ESI) *m/z* 444 $(M+H)^+$, 466 $(M+Na)^+$.

General procedure for the preparation of *N*-(1-substituted-2,6-diphenyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-benzamide/acetamide (6a–6i). To a solution of compound **5a** (0.1 g, 0.244 mmol) in 1,4-dioxane(5 mL), acetyl chloride(0.026 mL, 1.5 eq) (in the case of benzoyl chloride and *p*-chlorobenzoyl chloride (1.2 eq)) was slowly added at room temperature, and the reaction mass was heated to 90°C for 2 h while stirring. After completion of reaction as indicated by TLC, the 1,4-dioxane was removed under reduced pressure, and ethylacetate was added to the residue. The organic solution was washed with $NaHCO_3$ solution and dried over the anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography (silica gel 60–120) with the use of hexane and ethylacetate as eluent (80:20) to give compound **6a**. The yields are in the range of 72–85%.

N-(1-Methyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-yl)-acetamide (6a). Yield 85%, mp 221–223°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.10 (d, J = 7.17 Hz, 2H, ArH), 7.84 (s, 1H, ArH), 7.56–7.36 (m, 8H, ArH), 6.54 (br s,1H, NH–CO), 3.89 (s, 3H, N–CH_3) 2.12(s, 3H, $COCH_3$) ppm. IR (KBr) 3360, 3059, 2925, 1602, 1461, 1372, 1260, 1123 cm^{-1}. MS (ESI) *m/z* 410 $(M+H)^+$, 432 $(M+Na)^+$.

N-(1-Methyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-yl)-benzamide (6b). Yield 85%, mp 226–228°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.12 (d, J = 7.55 Hz, 2H, ArH), 7.86 (s, 1H, ArH), 7.78 (d, J = 6.79 Hz, 2H, ArH), 7.58 (d, J = 9.06 Hz, 2H, ArH), 7.52–7.39 (m, 9H, ArH), 7.23 (br s, 1H, NH–CO), 3.94 (s, 3H, N–CH_3) ppm. IR (KBr) 3413, 2925, 1674, 1474, 1366, 1260, 1129 cm^{-1}. MS (ESI) *m/z* 472 $(M+H)^+$, 494 $(M+Na)^+$.

4-Chloro-N-(1-methyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-benamide (6c). Yield 72%, mp 220–223°C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.10 (d, J = 7.55 Hz, 2H, ArH), 7.83 (s, 1H, ArH), 7.729 (d, J = 8.31 Hz, 2H, ArH), 7.56–7.36 (m, 10H, ArH), 7.24 (br s, 1H, NH–CO), 3.93 (s, 3H, N–CH_3)ppm. IR (KBr) 3217, 2922, 2851, 1649, 1528, 1460, 1368, 1211, 1133 cm^{-1}. MS (ESI) *m/z* 506 $(M+H)^+$, 528 $(M+Na)^+$.

N-(1-Ethyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-yl)-acetamide (6d). Yield 85%, mp 220–222°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.09 (d, J = 8.498 Hz, 2H, ArH), 7.84 (s, 1H, ArH), 7.55–7.39 (m, 8H, ArH), 6.50 (br s, 1H, NH–CO), 4.39 (q, J = 7.17 Hz, 2H, N–$\underline{CH_2}$–CH_3), 2.06 (s, 3H, $COCH_3$), 1.32 (t, J = 7.17 Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. IR (KBr) 3295, 2994, 2937, 1667, 1517, 1371, 1261, 1133 cm^{-1}. MS (ESI) *m/z* 424 $(M+H)^+$, 446 $(M+Na)^+$.

N-(1-Ethyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-yl)–benzamide (6e). Yield 87%, mp 210–212°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.10 (d, J = 7.36 Hz, 2H, ArH), 7.85 (s, 1H, ArH), 7.75 (d, J = 6.79 Hz, 2H, ArH), 7.60–7.55 (m, 2H, ArH), 7.51–7.37 (m, 9H, ArH), 7.18 (br s, 1H, NH–CO), 4.45 (q, J = 7.17 Hz, 2H, N–$\underline{CH_2}$–CH_3), 1.43 (t, J = 7.17 Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. IR (KBr) 3416, 3060, 2921, 2852, 1673, 1473, 1418, 1259, 1128 cm^{-1}. MS (ESI) *m/z* 486 $(M+H)^+$, 508 $(M+Na)^+$.

4-Chloro-N-(1-ethyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo [2,3-b]pyridin-3-yl)-benzamide (6f). Yield 75%, mp 216–217°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 9.79 (br s, 1H, NH–CO), 8.23 (d, J = 7.17 Hz, 2H, ArH), 7.98 (s, 1H, ArH), 7.86 (d, J = 8.49 Hz, 2H, ArH), 7.62 (d, J = 6.42 Hz, 2H, ArH), 7.57–7.43 (m, 8H, ArH), 4.48 (q, J = 6.98 Hz, 2H, N–$\underline{CH_2}$–CH_3), 1.33 (t, J = 6.98 Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. IR (KBr) 3228, 2926, 2855, 1652, 1530,

1421, 1373, 1300, 1256 cm^{-1}. MS (ESI) *m/z* 520 $(M+H)^+$, 542 $(M+Na)^+$.

N-(1-Benzyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-yl)-acetamide (6g). Yield 73%, mp 138–140°C; ^1H NMR($CDCl_3$; 500 MHz) δ 8.06 (d, $J=6.83$ Hz, 2H, ArH), 7.88 (s, 1H, ArH), 7.49–7.31 (m, 8H, ArH), 7.20–7.15 (m, 3H, ArH), 7.00–6.97 (m, 2H, ArH), 6.52 (br s, 1H, NH–CO), 5.55 (s, 2H, Ph–CH_2–N), 2.07 (s, 3H, $COCH_3$) ppm. IR (KBr) 3273, 2925, 2853, 1661, 1515, 1441, 1367, 1263, 1127, 766, 697 cm^{-1}. MS (ESI) m/z 486 $(M+H)^+$, 508 $(M+Na)^+$.

N-(1-Benzyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b] pyridin-3-yl)-benzamide (6h). Yield 81%, mp 166–169°C; ^1H NMR (DMSO-d_6; 300 MHz) δ 9.07 (br s, 1H, NH–CO), 8.09 (d, $J=7.17$ Hz, 2H, ArH), 7.89 (s, 1H, ArH), 7.83 (d, $J=6.98$ Hz, 2H, ArH), 7.51–7.36 (m, 11H, ArH), 7.20–7.17 (m, 3H, ArH), 7.04–6.99 (m, 2H, ArH), 5.65 (s, 2H, Ph–CH_2–N) ppm. IR (KBr) 3097, 2956, 1748,1660, 1414, 1254 cm^{-1}. MS (ESI) *m/z* 548 $(M+H)^+$, 570 $(M+Na)^+$.

4-Chloro-N-(1-benzyl-2,6-diphenyl-4-trifluoromethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-benzamide (6i). Yield 84%, mp 178–179°C; ^1H NMR ($CDCl_3$; 300 MHz) 8.07 (d, $J=8.12$ Hz, 2H, ArH), 7.90 (s, 1H, ArH), 7.70 (d, $J=8.49$ Hz, 2H, ArH), 7.50–7.33 (m, 10H, ArH), 7.23–7.15 (m, 3H, ArH), 7.04–6.97 (m, 2H, ArH), 5.60 (s, 2H, Ph–CH_2–N) ppm. IR (KBr) 3235, 2925, 1649, 1596, 1520, 1480, 1370, 1262, 1160, 1129 cm^{-1}. MS (ESI) *m/z* 582 $(M+H)^+$, 604 $(M+Na)^+$.

General procedure for the preparation of 5,11-disubstituted-9-phenyl-7-trifluoromethyl-11*H*-6,10,11-triaza-benzo[a]fluorine (7a–7i). Compound **6a** (0.1 g, 0.243 mmol) in toluene (15 mL) along with P_2O_5 (0.5 g) was refluxed for 18 h. Then the reaction mixture was cooled to room temperature and poured into ice cold water (30 mL).The solution was neutralized with 2*M* NaOH and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous sodium sulfate, the solvent evaporated, and the leftover residual mass purified by column chromatography (silica gel 60–120) with the use of hexane and ethyl acetate as eluent (90:10) to give compound **7a**.The yields are in the range of 77–85%.

5,11-Dimethyl-9-phenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7a). Yield 85%, mp 207–209°C; ^1H NMR ($CDCl_3$; 300 MHz) δ 8.69 (d, $J=8.49$ Hz, 1H, ArH), 8.30 (d, $J=8.31$ Hz, 1H, ArH), 8.22 (d, $J=8.49$ Hz, 2H, ArH), 8.00 (s, 1H, ArH),7.79 (t, $J=7.36$ Hz, 1H, ArH), 7.66 (t, $J=7.17$ Hz, 1H, ArH), 7.56–7.41 (m, 3H, ArH), 4.63 (s, 3H, N–CH_3), 3.11 (s, 3H, CH_3) ppm. ^{19}F NMR ($CDCl_3$; 400 MHz) δ −62.64. ^{13}C NMR ($CDCl_3$; 75 MHz) δ 152.38, 151.1, 138.88, 129.34, 129.39, 129.25, 128.49, 127.21, 127.10, 126.43, 121.92, 109.65(q, $J_{CF}=4.39$ Hz) 31.47, 23.41 ppm. IR (KBr) 2923, 2853, 1463, 1348, 1262, 1120, 1052 cm^{-1}. MS (ESI) *m/z* 392 $(M+H)^+$. HRMS Calcd for $C_{23}H_{16}F_3N_3$ $(M+H)^+$ 392.1374. Found 392.1374.

11-Methyl-5,9-diphenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7b). Yield 81%, mp 248–252°C; ^1H NMR ($CDCl_3$; 300 MHz) δ 8.72 (d, $J=8.31$ Hz, 1H, ArH), 8.40 (d, $J=8.31$ Hz,1H, ArH), 8.23 (d, $J=7.36$ Hz, 2H, ArH), 8.00 (s, 1H, ArH), 7.86–7.75 (m, 3H, ArH), 7.61–7.42 (m, 7H, ArH), 4.66 (s, 3H, N–CH_3) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.77. ^{13}C NMR ($CDCl_3$; 75 MHz) δ 154.52, 153.74, 151.27, 140.13, 138.76, 130.71, 129.40, 129.33, 129.25, 128.87, 128.53, 128.12, 127.79, 127.18, 126.37, 125.91, 125.44, 121.77, 109.85 (q, $J_{CF}=6.587$ Hz), 29.67 ppm. IR (KBr) 2924, 2853, 1460, 1135 cm^{-1}. MS (ESI) *m/z* 454 $(M+H)^+$, HRMS Calcd for $C_{28}H_{18}F_3N_3$ $(M+H)^+$ 454.1531. Found 454.1528.

5-(4-Chloro-phenyl)-11-methyl-9-phenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7c). Yield 83%, mp 276–278°C; ^1H NMR ($CDCl_3$; 300 MHz) δ 8.75 (d, $J=8.49$ Hz, 1H, ArH), 8.35 (d, $J=8.49$ Hz, 1H, ArH), 8.23 (d, $J=7.36$ Hz, 2H, ArH), 8.00 (s, 1H, ArH), 7.84–7.77 (m, 3H, ArH), 7.63–7.45 (m, 6H, ArH), 4.68(s, 3H, N–CH_3) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.92. ^{13}C NMR ($CDCl_3$; 75 MHZ) δ 155.70, 141.99, 139.67, 136.23, 134.60, 131.99, 129.98, 129.60, 129.48, 128.96, 128.90, 128.44, 127.33, 127.24, 126.63, 121.97, 109.9 (q, $J_{CF}=6.58$ Hz), 29.70 ppm. IR (KBr) 2926, 1460, 1339, 1218, 1130 cm^{-1}. MS (ESI) *m/z* 488 $(M+H)^+$, HRMS Calcd for $C_{28}H_{17}ClF_3N_3$ $(M+H)^+$ 488.1141. Found 488.1143.

11-Ethyl-5-methyl-9-phenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7d). Yield 78%, mp 202–205°C; ^1H NMR ($CDCl_3$; 300 MHz) δ 8.52 (d, $J=8.31$ Hz, 1H, ArH), 8.32 (d, $J=8.31$ Hz, 1H, ArH), 8.21 (d, $J=6.98$ Hz, 2H, ArH), 8.00 (s, 1H, ArH), 7.83 (t, $J=6.98$ Hz, 1H, ArH), 7.67 (t, $J=8.12$ Hz, 1H, ArH), 7.54–7.41 (m, 3H, ArH), 5.21 (q, $J=7.17$ Hz, 2H, N–$\underline{CH_2}$–CH_3), 3.11 (s, 3H, CH_3), 1.67 (t, $J=7.17$ Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. ^{19}F NMR ($CDCl_3$; 400 MHz) δ −62.70. ^{13}C NMR ($CDCl_3$ + DMSO-d_6; 100 MHz) δ 152.40, 151.44, 149.51, 145.22, 141.66, 131.58, 129.29, 129.23, 129.12, 128.62, 128.58, 128.54, 128.08, 128.04, 126.54, 126.29, 125.88, 125.82, 123.41, 121.23, 108.65 (q, $J_{CF}=4.50$ Hz), 37.72, 23.45, 14.27 ppm. IR (KBr) 2924, 2854, 1433, 1364, 1271, 1139 cm^{-1}. MS (ESI) *m/z* 406 $(M+H)^+$, HRMS Calcd for $C_{24}H_{18}F_3N_3$ $(M+H)^+$ 406.1531. Found 406.1517.

11-Ethyl-5,9-diphenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7e). Yield 85%, mp 228–230°C; ^1H NMR ($CDCl_3$; 300 MHz) δ 8.60 (d, $J=8.31$ Hz, 1H, ArH), 8.44 (d, $J=8.49$ Hz, 1H, ArH), 8.23 (d, $J=8.31$ Hz, 2H, ArH), 8.04 (s, 1H, ArH), 7.86–7.80 (m, 3H, ArH), 7.64–7.42 (m, 7H, ArH), 5.27 (q, $J=7.17$ Hz, 2H, N–$\underline{CH_2}$–CH_3), 1.73 (t, $J=7.17$ Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.79. ^{13}C NMR ($CDCl_3$;75 MHz) δ 153.97, 153.22, 151.07, 138.88, 138.76, 134.28, 131.97, 129.83, 129.46, 129.02, 128.93, 128.43, 127.23, 126.55, 125.72, 125.03, 121.95, 110.10 (q, $J_{CF}=4.39$ Hz), 38.71, 15.18 ppm. IR (KBr) 2928, 1727, 1594, 1462, 1433, 1366, 1342, 1225, 1134 cm^{-1}. MS (ESI) *m/z* 468 $(M+H)^+$. HRMS Calcd for $C_{29}H_{20}F_3N_3$ $(M+H)^+$ 468.1687. Found 468.1667.

5-(4-Chloro-phenyl)-11-ethyl-9-phenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7f). Yield 78%, mp 220–222°C; ^1H NMR ($CDCl_3$; 300 MHz) δ 8.58 (d, $J=9.06$ Hz, 1H, ArH), 8.38 (d, $J=8.31$ Hz, 1H, ArH), 8.22 (d, $J=8.31$ Hz, 2H, ArH), 8.03 (s, 1H, ArH), 7.86–7.77 (m, 3H, ArH), 7.64–7.43 (m, 6H, ArH), 5.27 (q, $J=6.79$ Hz, 2H, N–$\underline{CH_2}$–CH_3), 1.71 (t, $J=6.79$ Hz, 3H, N–CH_2–$\underline{CH_3}$) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.91. ^{13}C NMR ($CDCl_3$;75 MHz) δ 153.97, 153.22, 151.07, 138.88, 138.76, 134.28, 131.97, 129.83, 129.46, 129.02, 128.93, 128.43, 127.23, 126.55, 125.72, 125.03,121.95,110.08 (q, $J_{CF}=4.39$ Hz), 38.69, 15.20 ppm. IR (KBr) 2926, 1432, 1336, 1224, 1140 cm^{-1}. MS (ESI) *m/z* 502 $(M+H)^+$, 524 $(M+Na)^+$. HRMS Calcd for $C_{29}H_{19}ClF_3N_3$ $(M+H)^+$ 502.1297. Found 502.1281.

***11-Benzyl-5-methyl-9-phenyl-7-trifluoromethyl-11H*-6,10,11-triaza-benzo[a]fluorine (7g).** Yield 83%, mp 240–241°C;

^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.28–8.24 (m, 2H, ArH), 8.17 (d, J = 7.17 Hz, 2H, ArH), 8.06 (s, 1H, ArH), 7.60–7.57 (m, 2H, ArH), 7.49–7.37 (m, 3H, ArH), 7.29–7.21 (m, 3H, ArH), 7.18–7.14 (m, 2H, ArH) 6.37 (s, 2H, Ph–CH_2–N), 3.12 (s, 3H, CH_3) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.32. ^{13}C NMR ($CDCl_3$; 75 MHz) δ 137.21, 131.94, 129.93, 129.43, 129.01, 128.84, 128.41, 127.48, 127.33, 126.71, 126.05, 124.44, 122.50, 110.55 (q, J_{CF} = 4.39 Hz), 47.19, 29.69 ppm. IR (KBr) 2924, 2853, 1449, 1349, 1260, 1144, 1088, 1021, 802 cm^{-1}. MS (ESI) m/z 468 $(M+H)^+$. HRMS Calcd for $C_{29}H_{20}F_3N_3$ $(M+H)^+$ 468.1687. Found 468.1680.

11-Benzyl-5,9-diphenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7h). Yield 77%, mp 206–208°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.38–8.31 (m, 2H, ArH), 8.18 (d, J = 6.79 Hz, 2H, ArH), 8.08 (s, 1H, ArH), 7.83 (d, J = 7.55 Hz, 2H, ArH), 7.62–7.38 (m, 9H, ArH), 7.32–7.18 (m, 4H, ArH), 6.41 (s, 2 H, Ph–CH_2–N) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.59. ^{13}C NMR ($CDCl_3$ −75 MHz) δ 154.91, 153.98, 151.67, 140.25, 138.47, 137.16, 130.58, 129.42, 129.31, 129.03, 128.89, 128.69, 128.11, 128.03, 127.36, 127.09, 126.28, 126.22, 125.90, 122.06, 122.01, 110.25 (q, J_{CF} = 6.587 Hz), 47.01 ppm. IR (KBr) (cm^{-1}) 2924, 2854, 1450, 1346, 1261, 1144. MS (ESI) m/z 530 $(M+H)^+$. HRMS Calcd for $C_{34}H_{22}F_3N_3$ $(M+H)^+$ 530.1844. Found 530.1858.

11-Benzyl-5-(4-chloro-phenyl),9-diphenyl-7-trifluoromethyl-11H-6,10,11-triaza-benzo[a]fluorine (7i). Yield 84%, mp 232–235°C; ^{1}H NMR ($CDCl_3$; 500 MHz) δ 8.32 (t, J = 8.78 Hz, 2H, ArH), 8.18 (d, J = 7.81 Hz, 2H, ArH), 8.08 (s, 1H, ArH), 7.80 (d, J = 7.81 Hz, 2H, ArH), 7.61 (t, J = 8.78 Hz, 1H, ArH), 7.54–7.46 (m, 5H, ArH), 7.43–7.40 (m, 1H, ArH), 7.31–7.28 (m, 2H, ArH), 7.24–7.19 (m, 3H, ArH), 6.40 (s, 2H, Ph–CH_2–N) ppm. ^{19}F NMR($CDCl_3$; 400 MHz) δ −62.85.^{13}C NMR ($CDCl_3$; 75 MHz) δ 154.25, 153.66, 151.70, 138.65, 138.55, 137.12, 134.29, 131.93, 130.15, 129.58, 129.49, 129.09, 128.84, 128.67, 128.40, 128.13, 127.52, 127.23, 126.54, 125.99, 125.74, 124.86, 122.30, 110.51 (q, J_{CF} = 5.84 Hz), 42.2 ppm. IR (KBr) 2923, 2852, 1447, 1343, 1227, 1136, 1055 cm^{-1}. MS (ESI) m/z 564 $(M+H)^+$. HRMS Calcd for $C_{34}H_{21}ClF_3N_3$ $(M+H)^+$ 564.1463. Found 564.1457.

X-ray crystallographic analysis. X-ray data were collected at room temperature with the use of a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å) by the ω-scan method [15]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 7227 reflections in the range of $2.19 < \theta < 23.19°$.

Integration and scaling of intensity data were accomplished using the program SAINT [15]. The structures were solved by direct methods using SHELXS97 [16], and refinement was carried out by full-matrix least-squares technique using SHELXL97 [16]. Anisotropic displacement parameters were calculated for all nonhydrogen atoms. The hydrogen atoms attached to nitrogen atoms were located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms, with C–H distances of 0.93–0.96 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$. The anisotropic displacement parameters CF_3 were restrained to be similar (SIMU instruction in SHELXL97 [16]).

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