Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 1773–1780

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis of Novel Analogues of Marine Indole Alkaloids: Mono(indolyl)-4-trifluoromethylpyridines and Bis(indolyl)-4-trifluoromethylpyridines as Potential Anticancer Agents

Wen-Nan Xiong, Cai-Guang Yang and Biao Jiang*

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

Received 17 January 2001; accepted 10 March 2001

Abstract—Mono(indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines were synthesized using Suzuki cross-coupling reaction between 2-chloro-4-trifluoromethylpyridine **9**, 2,6-dichloro-4-trifluoromethylpyridine **6** or 2,6-dichloro-3-cyano-4-trifluoromethylpyridine **23** and *N*-tosyl-3-indolylboronic acid **10**. They were evaluated for cytotoxic activity against P388 and A-549 cells with IC_{50} values. 4-Trifluoromethyl-2,6-bis[3′-(*N*-tosyl-6′-methoxylindolyl)]pyridine **18** was identified as the most potent in this series.

Introduction

Marine natural products are very important source of novel bioactive compounds for anticancer drug development. Marine indole alkaloids have emerged as an important structural class based upon their high degree of biological activities including antimicrobial, antiviral and antitumor properties.[1] Bis(indole) alkaloids, dragmacidin D and topsentins and their analogues exhibited activities in vitro and in vivo against P388 murine and human tumor cells.[2] Monoindole alkaloids, meridianins B–E showed cytotoxity toward LMM3 (murine mamarian adenocarcinoma cell line) with IC_{50} values between 9.3 and 33.9 μM.[3] A common structural feature of this kind of compound incorporates an extra five-, six- or seven-membered heterocyclic ring with one or two indole rings. In our previous studies, we have reported the synthesis of bis(indolyl)thiazoles,[4] mono and bis(indolyl)pyrimidines, mono and bis(indolyl)pyrazines,[5] bis(indolyl)pyrazinones[6] (Fig. 1). They acted as very powerful inhibitors of growth for many types of human tumor cells in vitro. These results promoted us to design new analogues with further modification of indole alkloids to optimize the structure–activity relationships (SAR) and to develop the more potent and selective antitumor agents. As a part of our ongoing structure–activity relationship study on indole alkaloids, we incorporated fluorines into indole alkaloids to investigate the effects of fluorine on cytotoxity. A range of trifluoromethyl containing indole alkaloids were designed and synthesized.

In this paper, we wish to report the synthesis of mono(-indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-

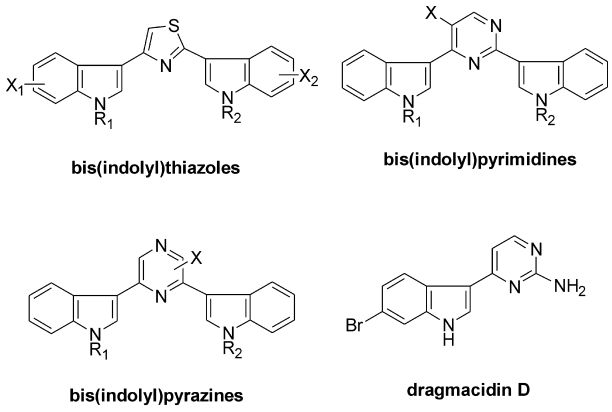


Figure 1.

*Corresponding author. Tel; + 86-21-6416-3300; fax: 86-21-6416-6128; e-mail: jlang@pub.sioc.ac.cn

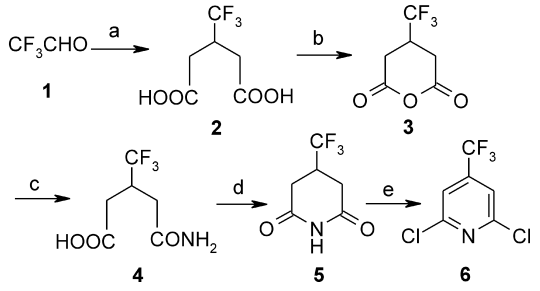
0968-0896/01/$ - see front matter
PII: S0968-0896(01)00070-0

trifluoromethylpyridines. Their cytotoxicity toward P388 and human tumor cell A-549 was described.

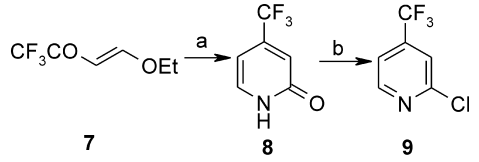
Chemistry

Mono(indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines were conveniently prepared by using palladium catalyzed Suzuki cross-coupling reaction of 3-indolylboronic acids with 4-trifluoromethyl-halogenopyridines. The key intermediates are 4-trifluoromethyl-2-chloropyridine and 4-trifluoromethyl-2,6-dichloropyridine that would lead themselves to cross-coupling with various 3′-indolylboronic acids.

The synthetic route to the key intermediate 2,6-dichloro-4-trifluoromethylpyridine was outlined in Scheme 1. Condensation of trifluoroacetaldehyde **1** with two molar cyanacetamide and subsequent hydrolysis afforded the diacid **2**[7] which was dehydrated to give cyclic anhydride **3**. Amination of cyclic anhydride **3** lead to monoamide **4** of glutaric acid, subsequent dehydration gave glutarimide **5**.[8] Treatment of glutarimide **5** with phosphorus pentachloride and phosphorus oxychloride gave 2,6-dichloro-4-trifluoromethylpyridine **6**.[9]



Scheme 1. Reagents and conditions: (a) cyanacetamide, EtOH, pyridine, rt, then 3 N HCl, reflux; (b) Ac_2O, reflux; (c) $NH_3{\cdot}H_2O$, rt; (d) 220–230 °C, 1.5 h; (e) $POCl_3$, reflux, 10 h.



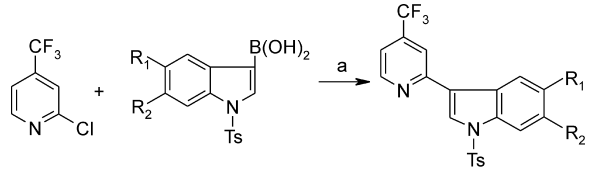
Scheme 2. Reagents and conditions: (a) $ClCH_2CN$, Zn, TMSCl, THF, 3 h, concn HCl, reflux; (b) $POCl_3$, PCl_5, 3 h.

A versatile and short-step synthetic approach to 2-chloro-4-trifluoromethylpyridine has been achieved (Scheme 2). Addition of chloroacetonitrile to trifluoroacetylvinyl ether **7** in the presence of zinc and trimethylchlorosilane afforded 4-trifluoromethyl-2-pyridone **8** in one pot.[10,11] Chlorization of pyridone resulted the desired 2-chloro-4-trifluoromethylpyridine **9** in good yield.

Mono(indolyl)-4-trifluoromethylpyridines **11**–**16** were prepared by Suzuki cross-coupling reaction between 2-chloro-4-trifluoromethylpyridine **9** with 1.1 molar equiv of *N*-tosyl-3-indolylboronic acid **10**[12] in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium[13] and aqueous sodium carbonate in a mixture of benzene and methanol under refluxing for 6 h in good yields (Scheme 3).

When 2,6-dichloro-4-trifluoromethylpyridine **6** was reacted with 2.2 molar equiv of *N*-tosyl-6-methoxyl-3-indolylboronic acid **10e** under above-mentioned condition, bis(6′-methoxylindolyl)-4-trifluoromethylpyridines **18** was obtained in 51% yield along with mono(-indolyl)pyridine **17** in 33% yield. Extending the reaction time to 10 h, the reaction was completely to produce compound **18** in 78% yield. Bis(indolyl)-4-trifluoromethylpyridines **19**–**22** were gained by coupling of **6** with corresponding 3-indolylboronic acids **10** under the same conditions (Scheme 4).

2,6-Dichloro-3-cyano-4-trifluoromethylpyridine **23**[14] was refluxed with 1.1 molar equiv of *N*-tosyl-3-indolylboronic acid **10a**, **10d** or **10e** in a mixture of benzene and methanol for 10 h in the presence of palladium

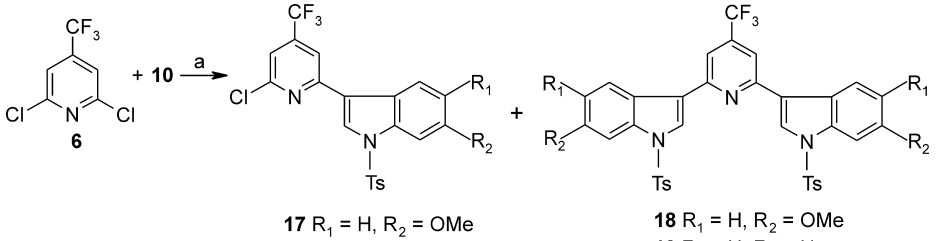


9

10a R_1 = H, R_2 = H
10b R_1 = Br, R_2 = H
10c R_1 = H, R_2 = Br
10d R_1 = OMe, R_2 = H
10e R_1 = H, R_2 = OMe
10f R_1 = OBn, R_2 = H

11 R_1 = H, R_2 = H
12 R_1 = Br, R_2 = H
13 R_1 = H, R_2 = Br
14 R_1 = OMe, R_2 = H
15 R_1 = H, R_2 = OMe
16 R_1 = OBn, R_2 = H

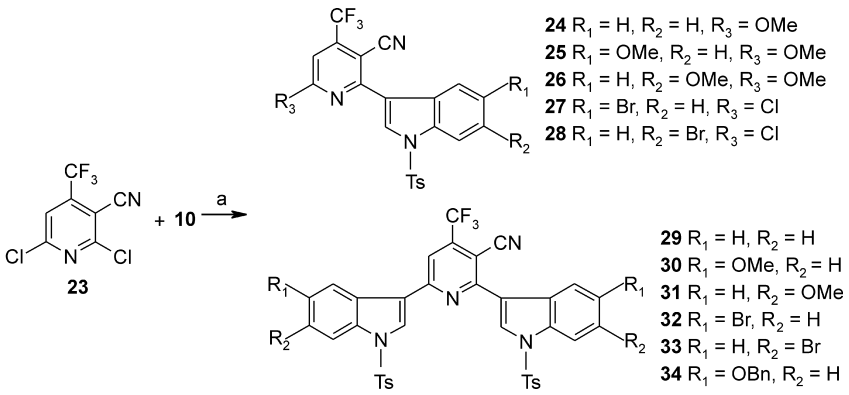
Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, benzene/MeOH.



17 R_1 = H, R_2 = OMe

18 R_1 = H, R_2 = OMe
19 R_1 = H, R_2 = H
20 R_1 = H, R_2 = Br
21 R_1 = OMe, R_2 = H
22 R_1 = OBn, R_2 = H

Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, benzene, MeOH.



Scheme 5. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, benzene, MeOH or DME.

catalyst and aqueous sodium carbonate to produce 2-indolyl-6-methoxyl-4-trifluoromethylpyridines **24**–**26** regioselectively in good yields (Scheme 5). The structure of compound **25** was confirmed by X-ray single crystal analysis (Fig. 2). The carbon–chloride bond at the 2-position in **23** was more reactive than that at the 6-position. While **23** was coupled with **10b** or **10c** by using dimethoxyethane (DME) as solvent instead of methanol, 2-indolyl-6-chloro-4-trifluoromethylpyridines **27**–**28** were obtained. Treatment of dichloropyridine **23** with 2 molar equiv of 3-indolylboronic acids **10** in a mixture of benzene and DME for 10 h afforded corresponding bis(indolyl)-4-trifluoromethylpyridines **29**–**34** in moderate yields (Scheme 5).

Pharmacological Results and Discussion

The prepared indolyl–trifluoropyridine compounds were submitted to the Shanghai Institute of Materia Medica for testing their cytotoxicity. Growth inhibition on murine leukemia cells P388 was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT, Sigma Chemical Co.) assay[15] with minor modification,[16] and human lung tumor cells A-549 was measured by the sulforhodamine B dye-staining (SRB) method.[17] The cytotoxicity screening results are shown in Table 1 as IC_{50} values.

Compounds **14**, **16**, **19**, **20**, **21**, **30**, **31**, **33** were inactive against P388 and A-549 tumor cells with IC_{50} values exceeded 100 μM. Compounds **11**, **19**, **28** and **32** were inactive against P388 cells and showed weak cytotoxicity toward A-549 with IC_{50} exceeded 10 μM. Compounds **12**, **17**, **25**, **27** were inactive against P388 cells ($IC_{50} > 100$ μM) and showed cytotoxicity toward A-549, the IC_{50} values of which were, respectively, 4.1, 6.4, 5.0, 7.7 μM. Compound **13** exhibited moderate inhibitory activities against P388 cell lines with IC_{50} value of 11 μM and A-549 cell lines with IC_{50} value of 48 μM. Compound **18** exhibited strong inhibitory activities against P388 cell lines with IC_{50} values of 4.3 μM and A-549 cell lines with IC_{50} values of 1.7 μM, which was identified as the most potent in this series.

It can be seen, compared to our previously reported bis(indolyl)thiazoles,[4] mono and bis(indolyl)pyrimidines, mono and bis(indolyl)pyrazines,[5] bis(indolyl)pyrazinones,[6] the prepared indolylpyridine compounds containing trifluoromethyl group showed weaker antitumor activity. To some extent, it revealed that the central heterocyclic moiety between the indole rings took an important role in the antitumor activity. On the other hand, the introduction of fluorine as a highly electronegative center seemed to not improve the biological properties of these molecules as expected.

In conclusion, we have synthesized a series of mono(-indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines. The preliminary screening shows this set of compounds exhibited weak cytotoxicity toward murine leukemia cells (P388), and some compounds displayed moderate inhibitory activity against human lung cancer cells (A-549).

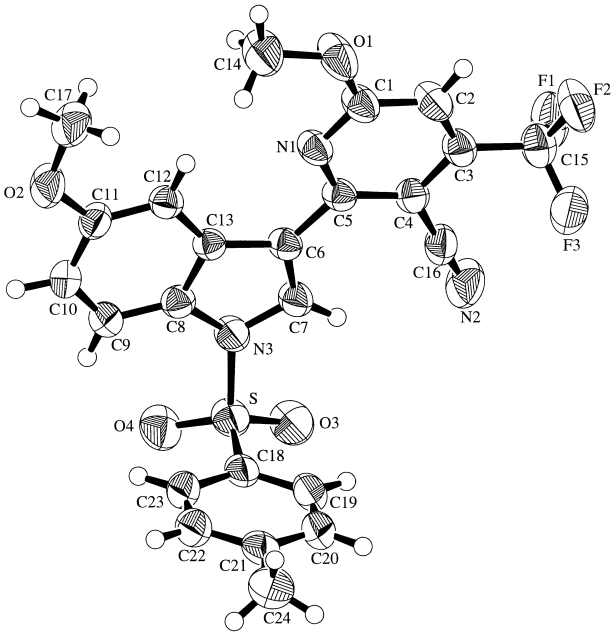


Figure 2. ORTEP drawing of the X-ray crystal structure of compound **25**.

Table 1. In vitro cytotoxicity against the P388 and A-549 cell lines

Concn (μM)	P388				CTX[a] P388 IC_{50} (μM)	A-549				CTX[b] A-549 IC_{50} (μM)
	100	10	1	0.1		100	10	1	0.1	
11	49.9	—	10.5	—	>100	68.4	30.5	35.0	29.2	25
12	32.6	21.9	17.8	9.7	>100	98.0	20.6	32.8	38.9	4.1
13	95.2	43.3	35.2	8.0	11	91.6	9.0	0	0	48
14	15.6	—	—	—	>100	51.8	14.1	19.7	24.5	>100
16	2.2	—	—	—	>100	35.9	9.9	23.2	16.9	>100
17	47.7	8.2	6.4	13.2	>100	68.1	55.7	25.7	31.0	6.4
18	99.9	92.8	—	—	4.3	97.1	45.7	28.8	35.5	1.7
19	14.7	23.5	20.9	15.7	>100	69.3	27.6	36.7	37.5	23
20	8.9	15.1	10.0	8.1	>100	49.2	32.0	30.7	25.8	>100
21	13.8	5.0	7.0	9.3	>100	41.7	22.2	7.1	16.7	>100
25	54.1	21.6	11.2	6.1	>100	91.7	40.6	20.7	20.6	5.0
27	50.4	19.2	9.4	13.2	>100	98.8	21.1	26.4	8.5	7.7
28	22.5	1.9	0.6	—	>100	85.7	18.0	34.4	13.7	14
30	—	3.5		1.7	>100	17.7	25.2	24.4	25.0	>100
31	3.8	10.1	9.1	5.1	>100	21.2	13.3	26.7	33.0	>100
32	8.2	—	3.7	—	>100	70.6	9.6	17.4	9.8	78
33	1.3	5.7	1.7	3.1	>100	48.1	27.6	18.8	23.8	>100

[a]Cytotoxicity (CTX) against murine leukemia cells (P388) was measured by the microculture tetrazolium-formazan method.
[b]CTX against human lung cancer cells (A-549) was measured by the sulforhodamine B dye-staining method.

Experimental

All melting points were measured with a WRS-1A digital melting point apparatus, without correction. IR spectra were determined with a Shimadzu IR-440 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument. The chemical photo shifts are expressed in ppm and coupling constants are given in Hz. Low-resolution MS spectra were obtained on a VG-Quattro or HP-5969A spectrometer and high-resolution MS spectra were recorded on a Finnigan MAT-95 spectrometer. Elemental analyses were carried out on a Heraeus Rapid-CHNO instrument. Column chromatography was performed on silica gel H (10–40 μm). Reagents purchased commercially were used without further purification. Solvents were dried using standard procedures.

4-Trifluoromethyl-2,6-piperidinedione (5). A mixture of Trifluoroacetaldehyde **1** (1.96 g, 20 mmol) and cyanacetamide (2.8 g, 40 mmol) was refluxed in ethanol (15 mL) with piperidine as a catalyst for 10 h. Then the ethanol was removed in vacuo. Hydrochloric acid (2 N, 20 mL) was added. The resulting mixture was refluxed for another 6 h, diluted with ethyl ether, washed with brine, dried over Na_2SO_4 and concentrated in vacuo to obtain crude product **2**. A mixture of **2** (4 g, 20 mmol) and acetic anhydride (15 mL) was refluxed for 14 h. The excess acetic anhydride was removed in vacuo. Then ammonia water (30 mL) was added and the mixture stirred at room temperature overnight. The aqueous layer was extracted with ethyl acetate (3×80 mL). The combined organic extract was washed with 1 N HCl (75 mL) and brine (2×50 mL), dried (anhydrous Na_2SO_4) and concentrated to give a crude reaction mixture which was directly used in the next reaction without purification. The crude product was heated at 220–230 °C until water was no longer distilled. The reaction mixture was cooled to ambient temperature and dissolved in water (10 mL). The solution was boiled for 30 min with about 0.5 g of charcoal. The charcoal is removed by filtration. The dry residue was crystallized from 95% ethanol to give product **5** (1.1 g, 30%): mp 136–138 °C; IR (KBr) ν_{max} 3202, 3098, 1698, 1130 cm^{-1}; MS (EI) m/e 181 (M^+, 12), 138 (23), 69 (8), 42 (100); ^{19}F NMR ($CDCl_3$) δ −3.4 (d, J=6.6 Hz); ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 2.85–3.03 (m, 4H), 2.62–2.7 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.2, 125.6 (q, J=276.7 Hz), 35.1 (q, J=29.8 Hz), 30.6; HRMS (EI) calcd for $C_5H_5F_3O$: 138.02925; found: 138.02948.

2,6-Dichloro-4-trifluoromethylpyridine (6). A mixture of **5** (5.43 g, 30 mmol) and phosphorus oxychloride (30 mL) was heated to reflux for 8 h. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was poured into ice water and extracted with CH_2Cl_2 (3×50 mL). The organic phase was washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). After being dried over Na_2SO_4, concentration in vacuo afforded a residue that was purified by flash chromatography to give **6** (4.2 g, 65%): MS (EI) m/e 215 (M^+, 10), 217 (6), 196 (6), 180 (100), 182 (32), 160 (29), 144 (8), 110 (15); ^{19}F NMR ($CDCl_3$) δ −13 (s); ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1H).

4-Trifluoromethyl-2(1*H*)-pyridinone (8). Trimethylchlorosilane (5.3 mL, 30 mmol) was added to the solution of zinc powder (2 g, 30 mmol) in anhydrous THF (30 mL) under N_2. After stirred for 0.5 h, a solution of chloroacetonitrile (1.27 mL, 20 mL) and trifluoroacetylvinyl ether (1.68 g, 10 mmol) in anhydrous THF (15 mL) was added dropwise slowly to keep the temperature at 40 °C. The mixture was refluxed for 2 h. After being cooled to room temperature, concd. HCl (5 mL) was added. The mixture was refluxed for 1 h, then cooled to room temperature and poured into ice water. The product was extracted with EtOAc (3×50 mL), and the combined extract was washed with brine. The organic layer was dried over anhydrous

Na_2SO_4, filtered, and evaporated to dryness to give the residue that could be used in the next reaction without further purification. The residue was purified by column chromatography to afford **8** (1.2 g, 74%): IR (KBr) ν_{max} 3151 (N-H), 2851, 1664 (C=O), 1621, 1072 (CF_3) cm^{-1}; MS (EI) m/e 163 (M^+, 100), 144 (M^+-F, 12), 135 (83), 116 (99), 85 (25), 69 (CF_3, 15), 57 (15), 43 (15); ^{19}F NMR ($CDCl_3$) δ −13 (s); ^1H NMR ($CDCl_3$) δ 6.49 (dd, $J=1.6$ and 6.9 Hz, 1H), 6.78 (d, $J=0.85$ Hz, 1H), 7.75 (d, $J=7.0$ Hz, 1H).

2-Chloro-4-trifluoromethylpyridine (9). A mixture of **8** (3 g, 18.4 mmol) and phosphorus oxychloride (30 mL) was heated to reflux for 3 h. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was poured into ice water and extracted with CH_2Cl_2 (3×50 mL). The organic phase was washed with satd $NaHCO_3$ (20 mL) and brine (30 mL). After drying (Na_2SO_4), concentration in vacuo afforded a residue that was purified by flash chromatography to give the desired **9** (2.0 g, 60%) as a colorless oil: IR (KBr) ν_{max} 1450, 1334, 1146 cm^{-1}; MS (EI) m/e 181 (M^+, 3.58), 146 (M^+ −Cl, 100), 69 (CF_3, 54), 126 (25); ^{19}F NMR −13 (s, CF_3); ^1H NMR ($CDCl_3$) δ 8.61 (d, $J=5.13$ Hz, 1H), 7.58 (s, 1H), 7.47 (d, $J=5.08$ Hz, 1H).

General procedure for *N*-tosyl-3-indolylboronic acids (10a–f). A mixture of mercuric acetate (20 mmol) and 150 mL of glacial HOAc was stirred at room temperature for 30 min. The insoluble material was removed by filtration. To the filtrate was added substituted *N*-tosylindole (20 mmol). The clear solution was stirred at room temperature overnight and became white slurry. Filtration gave a white heavy solid, which was used directly in the next reaction without purification.

To a solution of 3-acetoxymercurio-*N*-tosylindole (10 mmol) in 120 mL of dried THF purged with Ar_2 was added borane solution (10 M in Me_2S, 10 mL, 100 mmol) at room temperature and the mixture was stirred for 1 h, followed by the addition of 8 mL of water carefully. A clear solution and elemental mercury were obtained. The mercury was removed by filtration, and the solvent was evaporated at 40 °C under reduced pressure. To the white residue was then added 300 mL of THF/EtOAc (1:9) and the insoluble material was removed by filtration. The filtrate was washed with water and brine, and concentrated to give a white solid **10a–f**, which was pure enough for the cross-coupling reaction without further purification.

General procedure for the synthesis of mono(indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines. *N*-Tosyl-3-indolylboronic acid **10** (1.1 or 2.2 mmol) was added to the solution of 2-chloropyridine **9**, 2,6-dichloropyridine **6** or 2,6-dichloro-3-cyanopyridine **23** (0.1 mmol), aqueous sodium carbonate (2 mL, 2 M) and tetrakis(triphenylphosphine)palladium (0.2 mmol) in benzene (10 mL), methanol or DME (2 mL). The mixture was refluxed under an argon atmosphere. After stirring for 6 or 10 h, anhydrous sodium sulfate was added. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, eluting with ethyl acetate/hexane to give the corresponding mono(indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines **26–48**.

4-Trifluoromethyl-2-(*N*-toluenesulfonyl-3′-indolyl)pyridine (11). Yield 92%; mp 141–143 °C ($CHCl_3$); IR (KBr) ν_{max} 1611, 1561, 1379, 1174, 1141 cm^{-1}; MS (EI) m/e 416 (M^+, 63), 417 ($M^+ + 1$, 18), 262 (20), 261, (100), 234 (46), 155 (13); ^{19}F NMR δ −12 (s); ^1H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.72 (s, 1H), 8.11–7.99 (m, 4H), 7.66 (s, 1H), 7.45–7.27 (m, 5H), 2.35 (s, 3H); anal. calcd for $C_{21}H_{15}F_3N_2O_2S$: C, 60.58; H, 3.61; N, 6.73. Found: C, 60.19; H, 3.35; N, 6.78.

4-Trifluoromethyl-2-[3′-(*N*-toluenesulfonyl-5′-bromoindolyl)]-pyridine (12). Yield 85%; mp 195–197 °C ($CHCl_3$); IR (KBr) ν_{max} 1610, 1553, 1438, 1344, 1174, 1131 cm^{-1}; MS (EI) m/e 496 (M^+, 100), 497 (27), 341 (47), 339 (47), 260 (33), 233 (17), 155 (25); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.81 (d, $J=4.77$ Hz, 1H), 8.54 (d, $J=1.8$ Hz, 1H), 8.07 (s, 1H), 7.85–7.73 (m, 4H), 7.44–7.36 (m, 2H), 7.19 (m, 2H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.9, 150.6, 145.8, 134.3, 134.3, 130.2 129.9, 128.4, 127.0, 126.7, 125.4, 117.9, 117.3, 117.2, 116.5, 116.4, 114.9, 29.7, 21.6; HRMS (EI) calcd for $C_{21}H_{14}BrF_3N_2O_2S$: 493.99115; found: 493.99006.

4-Trifluoromethyl-2-[3′-(*N*-toluenesulfonyl-6′-bromoindolyl)]-pyridine (13). Yield 87%; mp 215–217 °C ($CHCl_3$); IR (KBr) ν_{max} 1611, 1551, 1428, 1318, 1180, 1147 cm^{-1}; MS (EI) m/e 496 (M^+, 100), 494 (M^+, 93.9), 477 (3.8), 475 (3.7), 341 (70.4), 339 (71.9), 314 (17.7), 312 (18.6), 260 (42.4), 233 (23.2), 155 (11.9); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.9 (s, 1H), 8.59 (s, 1H), 8.26 (d, $J=1.47$ Hz, 1H), 8.04–7.96 (m, 4H), 7.64 (s, 1H), 7.50 (dd, $J=1.4$ and 8.5 Hz, 1H), 7.32 (m, 2H); 2.37 (s, 3H); HRMS (EI) calcd for $C_{21}H_{14}BrF_3N_2O_2S$: 493.99115; found: 493.98842.

4-Trifluoromethyl-2-[3′-(*N*-toluenesulfonyl-5′-methoxylindolyl)]pyridine (14). Yield 90%; mp 146–148 °C ($CHCl_3$); IR (KBr) ν_{max} 2833, 1612, 1592, 1480, 1320, 1172, 1141 cm^{-1}; MS (EI) e/e 446 (M^+, 92), 291 (100), 276 (42), 264 (11), 247 (17), 155 (3); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.91 (s, 1H), 8.31 (s, 1H), 7.95–7.66 (m, 5H), 7.50 (s, 1H), 7.26–7.24 (m, 2H), 7.02 (dd, $J=1.8$ and 9.0 Hz, 1H), 3.87 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.2, 153.7, 149.5, 145.6, 134.8,130.3, 130.1, 128.8, 128.0, 127.2, 119.4, 117.4, 117.3, 114.6, 114.5, 104.4, 55.9, 21.6; HRMS (EI) calcd for $C_{22}H_{17}F_3N_2O_3S$: 446.09120; found 446.09605.

4-Trifluoromethyl-2-[3′-(*N*-toluenesulfonyl-6′-methoxylindolyl)]pyridine (15). Yield 90%; mp 159–161 °C ($CHCl_3$); IR (KBr) ν_{max} 2839, 1612, 1561, 1492, 1320, 1170, 1128 cm^{-1}; MS (EI) e/e 446 (M^+, 40.5), 291 (100), 276 (5.4), 264 (9.6), 247 (8.1); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.22–8.15 (m, 2H), 7.89–7.83 (m, 3H), 7.56 (d, $J=1.9$ Hz, 1H), 7.43 (d, $J=3.2$ Hz, 1H), 7.23 (m, 1H), 6.98 (dd, $J=1.9$ and

8.8 Hz, 1H), 3.90 (s, 3H), 2.34 (s, 3H); HRMS (EI) calcd for $C_{22}H_{17}F_3N_2O_3S$: 446.09120; found: 446.09410.

4-Trifluoromethyl-2-[3′-(*N*-toluenesulfonyl-5′-benzoxylindolyl)]pyridine (16). Yield 87%; mp 169–171 °C ($CHCl_3$); IR (KBr) ν_{max} 2928, 1556, 1444, 1378, 1173 cm^{-1}; MS (EI) m/e 522 (M^+, 7.7), 431 (5.5), 367, (23), 368 (6.4), 276 (15), 155 (14), 91 (100); ^{19}F NMR δ −13 (s); ^1H NMR ($CDCl_3$) δ 8.85 (d, J = 5.1 Hz, 1H), 8.10 (s, 1H), 7.99 (d, J = 2.6 Hz, 1H), 7.94 (s, 1H), 7.91 (s, 1H), 7.81 (m, 3H), 7.45–7.21 (m, 7H), 7.09 (dd, J = 2.6 and 9.08 Hz, 1H), 5.12 (s, 2H), 2.34 (s, 3H); anal. calcd for $C_{28}H_{21}F_3N_2O_3S$: C, 64.36; H, 4.05; N, 5.36. Found: C, 64.18; H, 3.98; N, 5.68.

6-Chloro-4-trifluoromethyl-2-[3′-(*N*-toluenesulfonyl-6′-methoxylindolyl)]pyridine (17). Yield 33%; mp 130–132 °C ($CHCl_3$); IR (KBr) ν_{max} 1624, 1579, 1482, 1363, 1173, 1112 cm^{-1}; MS (EI) e/e 480 (M^+, 38), 481 (13), 482 (16), 361 (24), 359 (36), 326 (26), 327 (36), 325 (100); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 7.75 (s, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.44 (d, J = 3.63 Hz, 1H), 7.37 (d, J = 8.62 Hz, 1H), 7.26–7.19 (m, 3H), 6.85 (dd, J = 2.32 and 8.62 Hz, 1H), 6.56 (d, J = 3.65 Hz, 1H), 3.87 (s, 3H), 2.33 (s, 3H); HRMS (EI) calcd for $C_{22}H_{16}ClF_3N_2O_3S$: 480.05223; found: 480.05016.

4-Trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-6′-methoxylindolyl)]pyridine (18). Yield 78%; mp 221–223 °C ($CHCl_3$); IR (KBr) ν_{max} 1614, 1534, 1436, 1307, 1173, 1120 cm^{-1}; MS (EI) e/e 745 (M^+, 36), 590 (50), 445 (100), 435 (37), 290 (63), 262 (23); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 3.53 Hz, 1H), 7.55 (d, J = 8.62 Hz, 1H), 7.43–7.24 (m, 3H), 6.85 (d, J = 3.50 Hz, 1H), 6.71 (s, 1H), 3.93 (s, 3H), 2.35 (s, 3H); HRMS (EI) calcd for $C_{38}H_{30}F_3N_3O_6S_2$: 745.1528; found: 745.1505.

4-Trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonylindolyl)]pyridine (19). Yield 83%; mp 229–231 °C ($CHCl_3$); IR (KBr) ν_{max} 1598, 1568, 1446, 1370, 1172, 1135 cm^{-1}; MS (EI) e/e 685 (M^+, 100), 686 (46), 530 (60), 531 (24), 375 (44), 374 (28), 348 (14), 155 (3); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.37 (s, 1H), 8.23 (m, 2H), 8.07 (d, J = 8.3 Hz, 2H), 7.89–7.79 (m, 6H), 7.44–7.26 (m, 8H), 2.35 (s, 6H); HRMS (EI) calcd for $C_{36}H_{26}F_3N_3O_4S_2$: 685.1296; found: 685.1299.

4-Trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-6′-bromoindolyl)]pyridine (20). Yield 60%; mp 260–262 °C ($CHCl_3$); IR (KBr) ν_{max} 1598, 1549, 1415, 1382, 1174, 1141 cm^{-1}; MS (EI) e/e 843 (M^+, 100), 844 (65), 845 (61), 841 (51), 688 (79), 689 (48), 690 (46), 533 (42), 373 (29), 155 (15); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.23–8.13 (m, 6H), 7.87–7.74 (m, 6H), 7.43–7.30 (m, 6H), 2.38 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.8, 145.9, 140.1, 139.6, 136.3, 134.8, 130.3, 127.6, 127.5, 127.1, 126.1, 123.7, 121.4, 119.3, 116.7, 114.5, 21.7; HRMS (EI) calcd for $C_{36}H_{24}Br_2F_3N_3O_4S_2$: 840.9537; found: 840.9532.

4-Trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-5′-methoxylindolyl)]pyridine (21). Yield 76%; mp 195–198 °C ($CHCl_3$); IR (KBr) ν_{max} 1475, 1439, 1354, 1268, 1179, 1150 cm^{-1}; MS (EI) e/e 745 (M^+, 100), 746 (45), 590 (14) 591 (12), 420 (7), 69 (4); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.18 (s, 2H), 7.95–7.92 (m, 4H), 7.84–7.81 (m, 4H), 7.75 (s, 2H), 7.26–7.24 (m, 4H), 7.01 (dd, J = 2.6 and 9.0 Hz, 2H), 3.72 (s, 6H), 1.17 (s, 6H); HRMS (EI) calcd for $C_{38}H_{30}F_3N_3O_6S_2$: 745.1528; found: 745.1523.

4-Trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-5′-benzoxylindolyl)]pyridine (22). Yield 79%; mp 235–237 °C ($CHCl_3$); IR (KBr) ν_{max} 1477, 1449, 1376, 1271, 1175, 1151 cm^{-1}; MS (EI) e/e 897 (M^+, 26.76), 898 (15), 807 (18), 806 (33), 743 (55), 742 (100), 652 (23), 588 (33), 497 (28), 496 (53), 468 (9), 155 (5); ^{19}F NMR δ−13 (s); ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 8.04 (d, J = 2.45 Hz, 1H), 7.95 (d, J = 9.07 Hz, 1H), 7.82 (d, J = 8.35 Hz, 1H), 7.72 (s, 1H), 7.23–7.19 (m, 8H), 7.08 (dd, J = 2.55 and 9.07 Hz, 1H), 4.85 (2H, s), 2.30 (s, 3H); anal. calcd for $C_{50}H_{38}F_3N_3O_6S_2$: C, 66.88; H, 4.27; N, 4.68. Found: C, 66.45; H, 4.59; N, 4.36.

2-Methoxy-3-cyano-4-trifluoromethyl-6-[3′-(*N*-toluenesulfonylindolyl)]pyridine (24). Yield 69%; mp 178–180 °C (MeOH); IR (KBr) ν_{max} 3177, 2217, 1597, 1534, 1473, 1380, 1171, 1140 cm^{-1}; MS (EI) e/e 471 (M^+, 100), 472 (31), 316 (43), 317 (12), 301 (26), 155 (21); ^{19}F NMR δ −13 (s); ^1H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.15 (dd, J = 0.62 and 8.5 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.43–7.25 (m, 4H), 7.05 (s, 1H), 4.14 (s, 3H), 2.34 (s, 3H); HRMS (EI) calcd for $C_{23}H_{16}F_3N_3O_3S$: 471.08645; found: 471.08571.

2-Methoxy-3-cyano-4-trifluoromethyl-6-[3′-(*N*-toluenesulfonyl-5′-methoxylindolyl)]pyridine (25). Yield 67%; mp 199–201 °C; IR (KBr) ν_{max} 3167, 2219, 1612, 1537, 1477, 1382, 1174, 1145 cm^{-1}; MS (EI) e/e 501 (M^+, 86), 502 (26), 346 (100), 347 (24), 316 (20), 288 (5), 155 (5); ^{19}F NMR δ−14 (s); ^1H NMR ($CDCl_3$) δ 8.57 (s, 1H), 7.98–7.88 (m, 3H), 7.66 (d, J = 2.39 Hz, 1H), 7.28–7.26 (m, 3H), 7.04–7.00 (m, 2H), 4.15 (s, 3H), 3.81 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.2, 157.3, 157.0, 145.5, 134.6, 130.2, 130.1, 129.9, 129.6, 129.5, 127.3, 117.8, 115.3, 114.7, 114.4, 107.2, 107.1, 104.6, 55.6, 55.1, 21.6; HRMS (EI) calcd for $C_{24}H_{18}F_3N_3O_4S$: 501.09701; found: 501.09413.

2-Methoxy-3-cyano-4-trifluoromethyl-6-[3′-(*N*-toluenesulfonyl-6′-methoxylindolyl)]pyridine (26). Yield 66%; mp 208–210 °C (MeOH); IR (KBr) ν_{max} 3136, 2928, 2229, 1615, 1596, 1464, 1372, 1174 cm^{-1}; MS (EI) e/e 501 (M^+, 40.9), 380 (3.4), 346 (100), 347 (23.6), 155 (0.7); ^{19}F NMR δ−14 (s); ^1H NMR ($CDCl_3$) δ 8.25 (d, J = 8.9 Hz, 1H), 8.16 (s, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.58–7.52 (m, 2H), 7.30–7.26 (m, 2H), 7.0 (dd, J = 2.2 and 8.9 Hz, 1H), 4.23 (s, 3H), 3.91 (s, H), 2.37 (s, 3H); HRMS (EI) calcd for $C_{24}H_{18}F_3N_3O_4S$: 501.09701; found: 501.09669.

2-Chloro-3-cyano-4-trifluoromethyl-6-[3′-(*N*-toluenesulfonyl-5′-bromoindolyl)]pyridine (27). Yield 75%; mp 261–263 °C (MeOH); IR (KBr) ν_{max} 2236, 1597, 1533, 1440, 1372, 1165, 1122 cm^{-1}; MS (EI) e/e 555 (M^+, 100), 553

(71) 556 (34), 557 (33), 400 (18), 398 (13), 319 (19), 155 (97), 91 (97); ^{19}F NMR δ−14 (s); ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.32 (s, 1H), 7.9–7.8 (m, 4H), 7.55 (d, J = 8.66 Hz, 1H), 7.31 (m, 2H), 2.39 (s, 3H); HRMS (EI) calcd for $C_{22}H_{12}BrClF_3N_3O_2S$: 552.94743; found: 552.94587.

2-Chloro-3-cyano-4-trifluoromethyl-6-[3′-(*N*-toluenesulfonyl-6′-bromoindolyl)]pyridine (28). Yield 72%; mp 248–251 °C (MeOH); IR (KBr) ν_{max} 2234, 1599, 1523, 1409, 1309, 1152 cm^{-1}; MS (EI) e/e 555 (M^+, 100), 553 (72) 556 (34), 557 (33), 400 (36), 398 (26), 319 (22), 155 (80), 91 (80), 69 (1); ^{19}F NMR δ−14 (s); ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 8.16 Hz, 1H), 8.30 (s, 1H), 8.19 (s, 1H), 7.91–7.85 (m, 3H), 7.54 (s, 1H), 7.33 (d, J = 8.25 Hz, 1H), 7.27 (s, 1H), 2.40 (s, 3H); HRMS (EI) calcd for $C_{22}H_{12}BrClF_3N_3O_2S$: 552.94743; found: 552.94909.

3-Cyano-4-trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonylindolyl)]pyridine (29). Yield 69%; mp 228–230 °C (MeOH); IR (KBr) ν_{max} 2927, 2226, 1595, 1447, 1378, 1176, 1141 cm^{-1}; MS (EI) e/e 710 (M^+, 100), 711 (45), 555 (48), 556 (27), 400 (37), 373 (12), 155 (9); ^{19}F NMR δ−13 (s); ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.37 (s, 1H), 8.13–8.09 (m, 2H), 8.03 (d, J = 8.35 Hz, 1H), 7.96–7.93 (m, 3H), 7.89–7.86 (m, 2H), 7.45–7.38 (m, 2H), 7.30–7.24 (m, 7H), 2.36 (s, 3H), 2.35 (s, 3H); HRMS (EI) calcd for $C_{37}H_{25}F_3N_4O_4S_2$: 710.12693; found: 710.12727.

3-Cyano-4-trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-5′-methoxylindolyl)]pyridine (30). Yield 65%; mp 230–232 °C (MeOH); IR (KBr) ν_{max} 2230, 1594, 1537, 1479, 1380, 1172, 1141 cm^{-1}; MS (EI) e/e 770 (M^+, 100), 771 (49), 615 (31), 616 (20), 461 (11), 460 (21), 445 (39), 446 (12), 155 (2); ^{19}F NMR δ −13.5 (s); ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.32 (s, 1H), 7.99–7.84 (m, 9H), 7.60 (d, J = 2.37 Hz, 1H), 7.29–7.26 (m, 3H), 7.03–6.97 (m, 2H), 3.57 (s, 3H), 3.44 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.3, 157.2, 157.0, 145.9, 145.5, 134.6, 130.3, 130.2, 129.7, 129.5, 128.6, 128.5, 127.3, 127.1, 119.8, 118.4, 115.7, 115.1, 114.9, 114.5, 114.3, 113.8, 113.7, 105.1, 104.4, 55.4, 55.2, 21.7, 21.6; HRMS (EI) calcd for $C_{39}H_{29}F_3N_4O_6S_2$: 770.14807; found: 770.14824.

3-Cyano-4-trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-6′-methoxylindolyl)]pyridine (31). Yield 61%; mp 249–251 °C (MeOH); IR (KBr) ν_{max} 3141, 2229, 1616, 1596, 1492, 1376, 1179 cm^{-1}; MS (EI) e/e 770 (M^+, 100), 771 (47), 616 (51), 615 (89), 461 (45), 460 (58), 445 (36), 446 (15); ^{19}F NMR δ−14 (s); ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 8.27 (d, J = 8.9 Hz, 1H), 8.22 (s, 1H), 8.00–7.84 (m, 6H), 7.61 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1 H), 7.31–7.26 (m, 4H), 6.91–6.86 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.7, 158.6, 157.1, 156.9, 145.9, 145.6, 136.8, 136.1, 134.7, 134.6, 130.3, 130.2, 127.6, 127.3, 127.1, 126.9, 123.8, 122.9, 122.3, 121.2, 120.3, 118.6, 115.1, 114.1, 114.0, 113.9, 113.5, 113.4, 97.8, 97.5, 55.9, 55.8, 21.7; HRMS (EI) calcd for $C_{39}H_{29}F_3N_4O_6S_2$: 770.14807; found: 770.14605.

3-Cyano-4-trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-5′-bromoindolyl)]pyridine (32). Yield 50%; mp 275–277 °C (MeOH); IR (KBr) ν_{max} 2230, 1596, 1542, 1439, 1174, 1130 cm^{-1}; MS (EI) e/e 868 (M^+, 100), 869 (73), 867 (71) 870 (64) 866 (46) 714 (52), 713 (45), 91 (45); ^{19}F NMR δ−15 (s); ^{1}H NMR (DMSO-d_6) δ 9.34 (s, 1H), 8.78 (s, 1H), 8.72 (s, 1H), 8.61 (s, 1H), 8.15 (s, 1H), 8.04–7.95 (m, 6H), 7.64–7.58 (m, 2H), 7.46 (m, 4H), 2.28 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 20.9, 114.9, 115.0, 116.1, 117.4, 118.2, 124.0, 125.4,126.9, 128.2, 128.3, 128.8, 129.7, 130.1, 130.3, 130.4, 132.1, 132.8, 133.2, 133.3, 133.5, 139.9, 146.3; HRMS (EI) calcd for $C_{37}H_{23}Br_2F_3N_4O_4S_2$: 865.94795; found: 865.94539.

3-Cyano-4-trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-6′-bromoindolyl)]pyridine (33). Yield 52%; mp 276–278 °C (MeOH); IR (KBr) ν_{max} 2225, 1594, 1532, 1405, 1382, 1149 cm^{-1}; MS (EI) e/e 868 (M^+, 100), 869 (73), 870 (68), 866 (48), 713 (54), 712 (40), 559 (27), 155 (21), 91 (38); ^{19}F NMR δ−15 (s); ^{1}H NMR (DMSO-d_6) δ 9.29 (s 1H), 8.76 (s, 1H), 8.72 (s, 1H), 8.28 (d, J = 9 Hz, 1H), 8.18–8.00 (m, 6H), 7.53–7.41 (m, 6H), 7.87 (d, J = 8.4 Hz, 1H), 2.35 (s, 6H); HRMS (EI) calcd for $C_{37}H_{23}Br_2F_3N_4O_4S_2$: 865.94795; found: 865.95243.

3-Cyano-4-trifluoromethyl-2,6-bis[3′-(*N*-toluenesulfonyl-5′-benzoxylindolyl)]pyridine (34). Yield 54%; mp 288–290 °C (MeOH); IR (KBr) ν_{max} 2224, 1610, 1595, 1539, 1449, 1376, 1191, 1127 cm^{-1}; MS (EI) e/e 923 (M^+ + 1, 6), 400 (27), 402 (16), 319 (29), 239 (100), 209 (27), 165 (28); ^{19}F NMR δ−14 (s); ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.97–7.74 (m, 7H), 7.24–7.01 (m, 16H); anal. calcd for $C_{51}H_{37}F_3N_4O_6S_2$: C, 66.37; H, 4.04; N, 6.07. Found: C, 66.05; H, 4.41; N, 6.38.

X-ray crystallgraphic analysis. Colorless prismatic crystals of **25** were obtained from ethyl acetate. They were stable without the mother liquor in air and were selected at room atmosphere for X-ray crystallography. Formula $C_{24}H_{18}O_4N_3F_3S$, space group P1 (No. 2), a = 11.372(2), b = 11.765(3), c = 8.564(2) Å, α = 93.75(2)°, β = 99.34(1), γ = 87.07(1), V = 1127.2 (4) Å^3, Z = 2, No. of observations 3024; No. of variables 317; Residuals: R; Rw 0.041; 0.051; Goodness of fit indicator 1.87. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo-K_α radiation.

Acknowledgements

The authors express deep thanks to Dr. Jian Ding, Dr. Dong Xiao and their colleagues of the Shanghai Institute of Materia Medica for conducting the in vitro disease-orient primary antitumor screen. This work was financially supported by grant from Shanghai Municipal Committee of Science and Technology.

References and Notes

1. (a) Nishizawa, Y. *Nature* **1984**, *308*, 693. (b) Nishizawa, Y. *Science* **1986**, *233*, 305. (c) Nishizawa, Y. *Nature* **1988**, *334*, 661. (d) Stewart, A. F.; Schultz, G. *Cell* **1987**, *50*, 1109. (e)

Wu, H. Y.; Shyy, S. H.; Wang, J. C.; Liu, L. F. *Cell* **1988**, *53*, 433. (f) Merino, A.; Madden, K. R.; Lane, W. S.; Champoux, J. J.; Deinberg, D. *Nature* **1993**, *365*, 227.
2. (a) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772. (b) Tsujii, S.; Rinehart, K. L. *J. Org. Chem.* **1988**, *53*, 5446.
3. Franco, L. H.; Joffé, E. B. K.; Puricelli, L.; Tatian, M.; Seldes, A. M.; Palermo, J. A. *J. Nat. Prod.* **1998**, *61*, 1130.
4. Gu, X.-H.; Wan, X.-Z.; Jiang, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 569.
5. Jiang, B.; Gu, X.-H. *Bioorg. Med. Chem.* **2000**, *8*, 363.
6. (a) Jiang, B.; Yang, C.-G. *Heterocycles* **2000**, *53*, 1489. (b) Jiang, B.; Gu, X.-H. *Heterocycles* **2000**, *53*, 1559.
7. Gootjes, J.; Nauta, W. T. *Recueil* **1965**, *84*, 1183.
8. Rabjohn, N. (Ed) *Org. Syn.* Vol. IV, John Wiley & Sons, New York: **1963**: 496.
9. Choi, Y. M.; Kucharczyk, N.; Sofia, R. D. *J. Labelled Compd. Radiopharm.* **1987**, *24*, 1.
10. Brown, S. M.; Bowden, M. C.; Parsons, T. J.; McNeilly, P.; Fraine, P. J. *Org. Process Res. Dev.* **1997**, *1*, 370.
11. Bernard, A. M.; Piras, P. P. *J. Heterocyclic Chem.* **1996**, *33*, 1771. (c) Cocco, M. T.; Congiu, C.; Onnis, V. *J. Heterocyclic Chem.* **1995**, *32*, 543.
12. Zheng, Q.; Yang, Y.; Martin, A. R. *Heterocycles* **1994**, *37*, 1761.
13. Coulson, D. R. *Inorg. Syn.* **1972**, *13*, 121.
14. Grozinger, K. G. WO patent 22532, **1992**; *Chem. Abstr.* **1992**, *118*, 191556.
15. (a) Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L. *Cancer Res.* **1988**, *48*, 589. (b) Mosmman, T. *J. Immunol. Meth.* **1983**, *65*, 55.
16. Qing, C.; Zhang, J.-S.; Ding, J. *Acta Pharmacol Sin.* **1999**, *20*, 297.
17. Skehan, P.; Storeng, R.; Scudiero, D. A.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.