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Synthesis and Antitumor Evaluation of Novel Monoindolyl-4-trifluoromethylpyridines and Bisindolyl-4-trifluoromethylpyridines

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Abstract—A series of novel monoindolyl-4-trifluoromethylpyridines and bisindolyl-4-trifluoromethylpyridines was designed and synthesized as potential antitumor agents. They were evaluated for preliminary cytotoxic activity against P388 and A-549 cells with IC_{50} values. 4-Trifluoromethyl-2,6-bis[3′-(*N*-tosyl-6′-methoxyl-indolyl)] pyridine was identified as the most potent in this series.

Introduction

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] A common structural feature of these kinds of compounds incorporates an extra five-, six- or seven-membered heterocyclic ring with one or two indole rings. Bis(indole) alkaloids, dragmacidin D and nortopsentins A–C inhibited in vitro the growth of the P388 murine.[2] Monoindole alkaloids, meridianins B–E showed cytotoxity toward murine tumor cell lines.[3] One of the goals of our group is to develop novel antitumor agents by using marine indole alkaloids as the lead compounds. In a previous work, we have reported the synthesis of bis(indolyl)thiazoles,[4] mono(indolyl)pyrimidines and bis(indolyl)pyrimidines, mono(indolyl) pyrazines and bis(indolyl)pyrazines,[5] bis(indolyl)pyrazinones,[6] which exhibited significant cytotoxic activities against a variety of human cancer cell lines in vitro. These results promoted us to design new analogues with further modification of indole alkloids. On the basis of the well-known feature that the fluorine atom as a highly electronegative center alters significantly the physico-chemical properties of organic compounds, thereby modifying biological activity, we anticipated that if a fluorine atom was introduced into indole alkaloids, the resulting analogues might bring about significant biological consequence. A range of trifluoromethyl containing indole alkaloids were designed and synthesized.

In this communication, we wish to report the synthesis of monoindolyl-4-trifluoromethylpyridines and bisindolyl-4-trifluoromethylpyridines. Their preliminary cytotoxicity toward P388 and human tumor cell A-549 was described.

Chemistry

2-(3-Indolyl)-4-trifluoromethylpyridines and 2,6-bis(3-indolyl)-4-trifluoromethylpyridines were conveniently prepared by using the palladium catalyzed Suzuki cross-coupling reaction of 3-indolylboronic acids with 4-trifluoromethyl-halogenopyridines.

The synthetic route to the key intermediate 2-chloro-4-trifluoromethylpyridine **7** and 2,6-dichloro-4-trifluoromethylpyridine **10** is shown in Scheme 1. Commercially available trifluoroacetate **1** was reacted with allylmagnesium bromide to form trifluoromethyl-diallylcarbinol **3**.[7] Oxidation of alcohol **3** with ozone afforded dialdehyde **4**, which was cyclized in ammonia-saturated methanol solution to yield pyridine **5**. Oxidation of 4-trifluoromethylpyridine **5** with *m*-CPBA produced *N*-oxide **6**, which was chlorinated with thionyl chloride to give the

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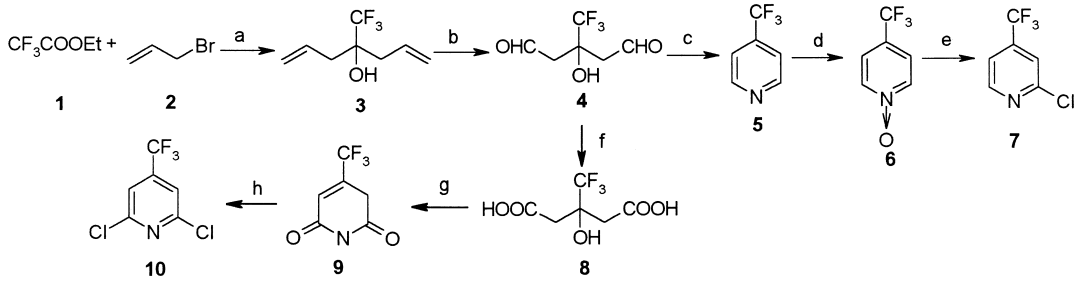


Scheme 1. Reagents and conditions: (a) Mg, THF, 50 °C, 3 h, 92%; (b) O_3, CH_2Cl_2/MeOH, −78 °C, 24 h, 90%; (c) NH_3/MeOH, reflux, 24 h, 70%; (d) MCPBA, CH_2Cl_2, rt, 10 h, 73%; (e) $SOCl_2$, reflux, 3 h, 42%; (f) 30% H_2O_2, HCOOH, 70 °C, 10 h, 68%; (g) NH_2CONH_2, 200 °C, 8 h; (h) $POCl_3$, reflux, 10 h, 30%.

desired 2-chloro-4-trifluoromethylpyridine **7**.[8] Dialdehyde **4** was refluxed with 30% hydrogen peroxide in formic acid to produce diacid **8**. Heating the diacid **8** with urea at high temperature led to imide **9**.[9] Chlorination of imide **9** with phosphorus oxychloride under refluxing afforded 2,6-dichloro-4-trifluoromethylpyridine **6**.[10]

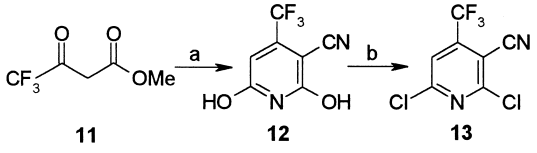
The synthesis of 2,6-dichloro-3-cyano-4-trifluoromethylpyridine is depicted in Scheme 2. Hydroxypyridine product **12** was synthesized from ethyl 4,4,4-trifluoroacetoacetate **11** and cyanoacetamide by adapting a literature method.[11] Chlorination of hydroxypyridine **12** with phosphorous oxychloride at 180 °C gave 2,6-dichloro-3-cyano-4-trifluoromethylpyridine **13**.

Finally the desired 2,6-bis(3-indolyl)-4-trifluoromethyl pyridines (**15**–**25**) were prepared, respectively, by Suzuki cross-coupling reaction of 2,6-dichloro-4-trifluoromethylpyridine **10** or 2,6-dichloro-3-cyano-4-trifluoromethylpyridine **13** with 2.2 molar equiv of *N*-tosyl-3-indolylboronic acid **14** in the presence of 10% tetrakis(triphenylphosphine) palladium and aqueous sodium carbonate in MeOH or DME under refluxing (Scheme 3).[12]

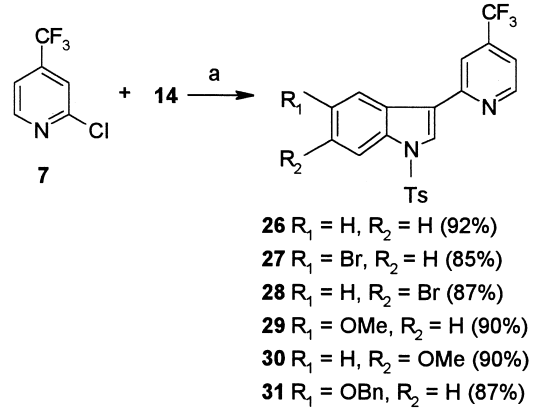
Suzuki coupling of **7** with 1.1 mol equiv of *N*-tosyl-3-indolylboronic acid **14** produced 2-indolyl-4-trifluoromethyl pyridines (**26**–**31**) in good yields (Scheme 4).[12]

Pharmacological Results and Discussion

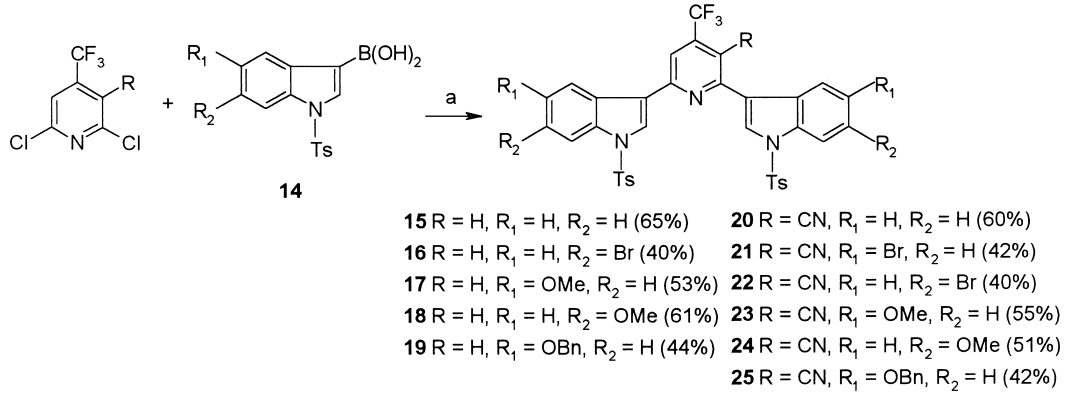
The prepared indolylpyridine compounds have been submitted to Shanghai Institute of Materia Medica for testing their cytotoxicity. The preliminary cytotoxicity



Scheme 2. Reagents and conditions: (a) cyanoacetamide, CH_3ONa, MeOH, 60 °C, 8 h, 63%; (b) $POCl_3$, 140 °C, 18 h, 80%.



Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, benzene, MeOH, 85–92%.



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, benzene, MeOH or DME, 40–65%.

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

	P388					A-549				
Concn (μM)	100	10	1	0.1	CTX[a] P388 IC_{50} (μM)	100	10	1	0.1	CTX[b] A-549 IC_{50} (μM)
15	14.7	23.5	20.9	15.7	>100	69.3	27.6	36.7	37.5	23
16	8.9	15.1	10.0	8.1	>100	49.2	32.0	30.7	25.8	>100
17	13.8	5.0	7.0	9.3	>100	41.7	22.2	7.1	16.7	>100
18	99.9	92.8	—	—	4.3	97.1	45.7	28.8	35.5	1.7
21	8.2	—	3.7	—	>100	70.6	9.6	17.4	9.8	78
22	1.3	5.7	1.7	3.1	>100	48.1	27.6	18.8	23.8	>100
23	—	3.5		1.7	>100	17.7	25.2	24.4	25.0	>100
24	3.8	10.1	9.1	5.1	>100	21.2	13.3	26.7	33.0	>100
26	49.9	—	10.5	—	>100	68.4	30.5	35.0	29.2	25
27	32.6	21.9	17.8	9.7	>100	98.0	20.6	32.8	38.9	4.1
29	15.6	—	—	—	>100	51.8	14.1	19.7	24.5	>100
31	2.2	—	—	—	>100	35.9	9.9	23.2	16.9	>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.

screening results agaist murine leukemia cells P388 and human lung tumor cells A-549 are shown in Table 1 as IC_{50} values.

Compounds **15**, **16**, **21**, **22**, **23**, **24**, **29**, and **31** were inactive against P388 and A-549 tumor cells. Compounds **15** and **26** were inactive against P388 cells and showed weak cytotoxicity toward A-549. Compound **27** was inactive agaist P388 cells and showed cytotoxicity toward A-549 with IC_{50} value of 4.1 μM. Compound **18** exhibited good 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.

In conclusion, we have designed and synthesized the trifluoromethyl containing indolylpyridines. The preliminary screening shows that 4-trifluoromethyl-2,6-bis[3′-(*N*-tosyl-6′-methoxylindolyl)]pyridine **18** was identified as the most potent in this series.

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12. Compounds **15**–**25** and **26**–**31** were fully characterized by ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, MS, HRMS and IR spectra.