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Synthesis of Substituted Benzoindolinothiazepines Using 5- and 6-Nitroindolines

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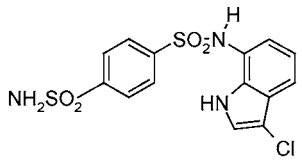
ABSTRACT: *Here is proposed a method of synthesis of benzoindolothiazepine compounds using Friedel-Crafts reactions conditions from indolines.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:39–43, 2005; Published online in Wiley InterScience (www. interscience. wiley.com). DOI 10.1002/hc.20063

INTRODUCTION

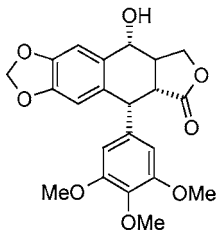
A new generation of molecular therapeutics targeted specifically to deregulated pathways involved in cell signal transduction and in cell fate regulation should be more effective and less toxic than the broadly antiproliferative cytotoxic drugs which dominate current therapy [1–3].

E7070 is a novel antitumor sulfonamide derived from a focused library of diarylsulfonamides through intensive chemical synthesis, antitumor screenings, and flow cytometric analyses. Preliminary data have indicated that E7070 may effect G1 progression of the cell cycle [4] and suppress CDK2 (cyclin-dependent kinases) activation and cyclin E expression in HCT116 (human colon carcinoma) [5]. A recent publication proved that this compound also acts as a potent carbonic anhydrase (CA) inhibitor [6,7].

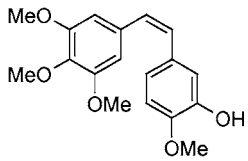
In order to design efficient products with antiproliferative activity, acting on reputation of cell cycle, we have designed tetracyclic compounds analogs of E7070 containing the trimethoxyphenyl moiety of podophyllotoxin [8] or combretastatin [9] which act as inhibitors of tubuline polymerization.



E7070



Podophyllotoxin



Combretastatin A-4

The central indole system, because of its inherent poor chemical stability, had to be generated at the end of the synthesis from an indoline precursor.

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Thus we have developed the synthesis of two tetracyclic benzoindolothiazepines. As depicted in the retrosynthesis (Fig. 1), we planned to synthesize benzo[*f*]indolo[5,6,*c*][1,2]thiazepine **1** from 5-nitroindoline and benzo[*f*]indolo[6,5,*c*][1,2]thiazepine **2** from 6-nitroindoline.

RESULTS AND DISCUSSION

At first it is necessary to protect the amine function of indolinic entity to avoid an alkylation of this function by methyl iodide used later during the synthesis. Exposure of acetic anhydride of the indoline nitrogen **3a** and **3b** followed by reduction of nitro group afforded the desired amines **4a** and **4b** in good yield (Scheme 1).

Treatment of both **4a,b** with commercially available methyl chlorosulfamoylbenzoate resulted in the formation of sulfonamide compounds **5a** and **5b** in good yield. Exposure of **5a** and **5b** to methyl iodide gave *N*-methylsulfonamide **6a** and **6b**. The protection of sulfonamide function was crucial for creation of the quadricycle benzoindolothiazepine, otherwise the Friedel-Crafts conditions gave the benzoisothiazolone by a reaction between the sulfonamide and the carboxylic acid functions. Exposure of **6a** and **6b** to potassium hydroxide gave the carboxylic acid **7a** and **7b** in good yield (Scheme 2). The cyclization of both **7a** and **7b** under Friedel-Crafts conditions with aluminum chloride and deprotection with concentrated HCl resulted in the formation of the desired tetracycles **8a** and **8b** in good yields (Scheme 3).

We have recently developed a one-pot method for oxidation-alkylation of N-substituted indolines that is especially effective to efficiently access to *N*-alkyl-6-nitroindoles at room temperature in DMF 6-nitroindoline with alkyl halide and NaH as basic catalyst [10].

In this approach applied to structure **8a**, use of NaH as a base in DMF was found to promote

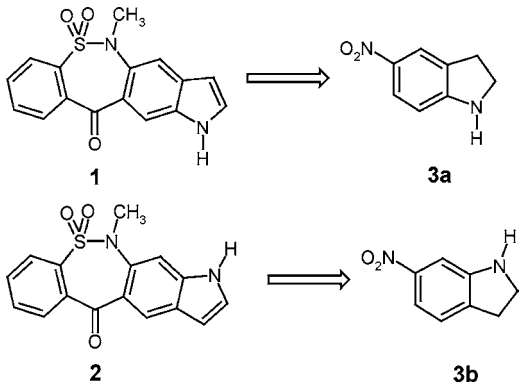
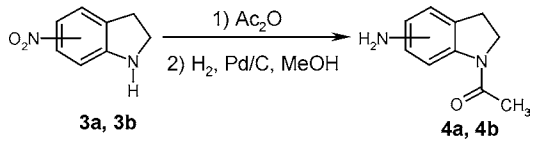


FIGURE 1 Retrosynthesis of indolothiazepines.



SCHEME 1

access to N-substituted indoles in an extremely efficient one-pot N-substitution-oxidation process **9** with good yields (Scheme 4) [11].

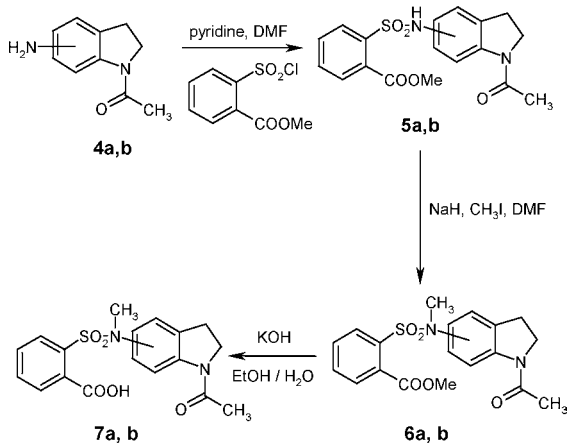
In the same way applying this method to **8b**, we access to N-substituted indolines and not N-substituted indoles. This observation allowed us to confirm our previous conclusions. The electron-withdrawing groups in 6th position favored this one-pot reaction. The oxidation of N-substituted indoline was finally realized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene to **10** (Scheme 5).

EXPERIMENTAL

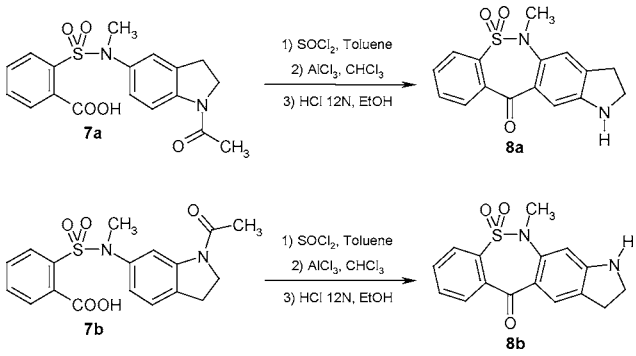
Melting points were determined on a Büchi SMP-540 apparatus. ^{1}H NMR spectra were recorded on an AC 300 P (300 MHz) spectrometer using d_6-DMSO or $CDCl_3$ as solvents. Chemical shifts are expressed downfield from the internal standard, tetramethylsilane. Coupling constants (J) are expressed in Hz. Key: t = triplet, s = singlet, d = doublet, dd = double doublet, m = multiplet. Mass spectra were recorded on a Funnigan Mat SSQ710 mass spectrometer.

*Methyl N-(1-Acetylindolin-5-yl)-2-sulfamoyl Benzoate (***5a***)*

Methyl 2-chlorosulfonylbenzoate (7.62 g, 0.033 mol) in DMF was added dropwise to a solution of



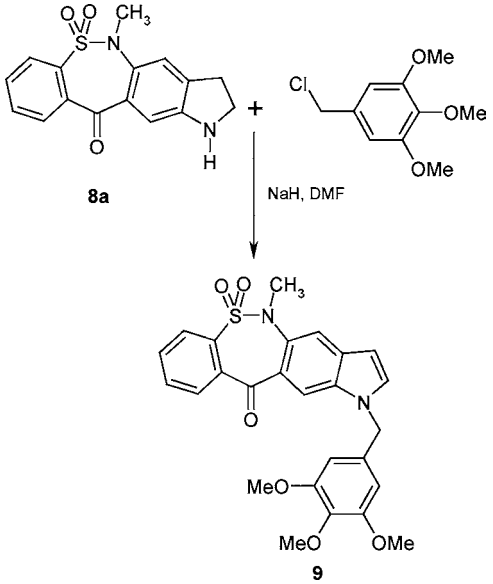
SCHEME 2



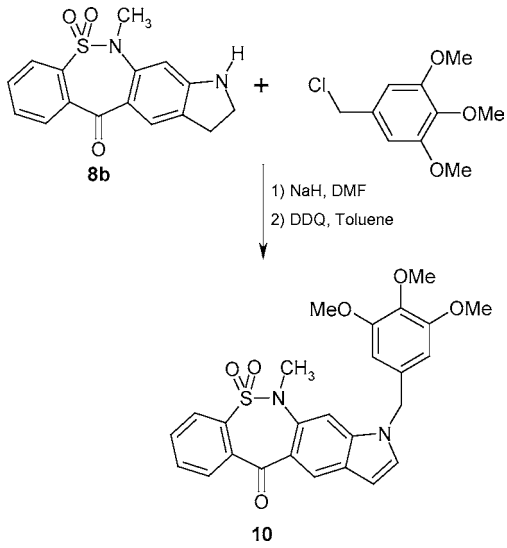
SCHEME 3

1-acetyl-5-aminoindoline (6.88 g, 0.039 mol) in DMF and pyridine (3.15 g, 0.039 mol) at room temperature. The reaction mixture was stirred at 60°C for 60 min and evaporated under reduced pressure. The residue was taken up in water, stirred at room temperature for 1 h, and the precipitate formed was filtered. The product was purified by recrystallization from methanol. **5a**: White crystals, yield 68%, mp 167–168°C. IR ν_{max} = 3240 (NH) and 1350,1170 (SO_2N) cm^{-1}. ^1H NMR δ = 2.19 (s, 3H, CH_3CO), 3.16 (t, 2H, J = 8.42 Hz, CH_2), 4.02 (t, 2H, J = 8.42 Hz, CH_2), 4.06 (s, 3H, $COOCH_3$), 6.76 (m, 1H, ArH), 7.16 (d, 1H, J = 1.88 Hz, ArH), 7.47 (m, 1H, ArH), 7.58 (m, 1H, ArH), 7.76 (m, 1H, ArH), 7.84 (m, 1H, ArH), 7.97 (m, 1H, ArH), 7.99 (s, 1H, NH). MS m/z (%) = 374 (100).

The preparation of **5b** was accomplished as **5a**. **5b**: White crystals, yield 72%, mp 165–166°C. IR



SCHEME 4



SCHEME 5

ν_{max} = 3230 (NH) and 1350,1160 (SO_2N) cm^{-1}. ^1H NMR δ = 2.16 (s, 3H, CH_3CO), 3.11 (t, 2H, J = 8.36 Hz, CH_2), 4.02 (t, 2H, J = 8.36 Hz, CH_2), 4.04 (s, 3H, $COOCH_3$), 7.05 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.86 (m, 3H, ArH), 8.10 (m, 1H, NH). MS: m/z (%) = 374 (100).

*Methyl N-(1-Acetylindolin-5-yl)-N-methyl-2-sulfamoyl Benzoate (**6a**)*

Methyl *N*-(1-acetylindolin-5-yl)-2-sulfamoyl benzoate **5a** (7.40 g, 0.019 mol) in DMF was added dropwise to a solution of NaH (1.52 g, 0.038 mol) in DMF. The solution was stirred at room temperature while a red color slowly developed. After 3 h, CH_3I diluted in DMF was added dropwise over 10 min and the mixture was stirred for 16 h at room temperature. The solution was evaporated under reduced pressure. The residue was taken up in water, was stirred at room temperature for 1 h, and the precipitate formed was filtered. The product was purified by recrystallization from methanol.

6a: White crystals, yield 89%, mp 177–178°C. IR (KBr): ν_{max} = 1360,1170 (SO_2N) cm^{-1}. ^1H NMR δ = 2.21 (s, 3H, CH_3CO), 3.19 (2H, t, J = 8.52 Hz, CH_2), 3.28 (3H, s, NCH_3), 3.90 (s, 3H, $COOCH_3$), 4.11 (t,2H, J = 8.52 Hz, CH_2), 6.81 (m, 1H, ArH), 7.19 (d, 1H, J = 2.20 Hz, ArH), 7.35 (m, 1H, ArH), 7.42 (m, 1H, ArH), 7.48 (m,1H, ArH), 7.59 (m, 1H, ArH), 8.09 (m, 1H, ArH). MS: m/z (%) = 388 (100).

The preparation of **6b** was accomplished as **6a**. **6b**: White crystals, yield 70%, mp 163–164°C. IR (KBr): ν_{max} = 1350,1170 (SO_2N) cm^{-1}. ^1H NMR δ = 2.20 (s, 3H, CH_3CO), 3.19 (t, 2H, J = 8.47 Hz, CH_2),

3.28 (s, 3H, NCH_3), 3.90 (s, 3H, $COOCH_3$), 4.11 (t, 2H, $J = 8.47$ Hz, CH_2), 7.05 (m, 1H, ArH), 7.15 (d, 1H, $J = 7.92$ Hz, ArH), 7.55 (m, 4H, ArH), 7.94 (m, 1H, ArH). MS: m/z (%) = 388 (100).

*N-(1-Acetylindolin-5-yl)-N-methyl-2-sulfamoyl Benzoic Acid (***7a***)*

Methyl *N*-(1-acetylindolin-5-yl)-*N*-methyl-2-sulfamoyl benzoate **6a** (5.00 g, 0.013 mol) in ethanol/water 1/1 was added potassium hydroxide (2.16 g, 0.038 mol). The resulting mixture was stirred at 100°C for 2 h. After cooling, the reaction medium was added to water and acidified with HCl 12 N for pH 1. The precipitate formed was filtered off and recrystallized from MeOH.

7a: White crystals, yield 89%, mp 227–228°C. IR (KBr): $\nu_{max} = 3400$ (OH) and 1360,1160 (SO_2N) cm^{-1}. ^1H NMR $\delta = 2.15$ (s, 3H, CH_3CO), 3.19 (t, 2H, $J = 8.52$ Hz, CH_2), 3.28 (s, 3H, NCH_3), 4.11 (t, 2H, $J = 8.52$ Hz, CH_2), 6.92 (m, 1H, ArH), 7.09 (m, 1H, ArH), 7.32 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.58 (m, 1H, ArH), 7.70 (m, 1H, ArH), 7.95 (m, 1H, ArH), 13.50 (m, 1H, COOH). MS: m/z (%) = 374 (100).

The preparation of **7b** was accomplished as **7a**. **7b**: White crystals, yield 92%, mp 228–229°C. IR (KBr): $\nu_{max} = 3420$ (OH) and 1350,1160 (SO_2N) cm^{-1}. ^1H NMR $\delta = 2.12$ (s, 3H, CH_3CO), 3.13 (t, 2H, $J = 8.49$ Hz, CH_2), 3.15 (s, 3H, NCH_3), 4.11 (t, 2H, $J = 8.49$ Hz, CH_2), 6.77 (m, 1H, ArH), 7.18 (m, 1H, ArH), 7.38 (m, 1H, ArH), 7.57 (m, 2H, ArH), 7.69 (m, 1H, ArH), 7.92 (m, 1H, ArH), 13.50 (m, 1H, COOH). MS: m/z (%) = 374 (100).

*5,11-Dihydro-5-methylbenzo[c]indolino[5,6,f][1,2]thiazepin-11-one 6,6-dioxide (***8a***)*

N-(1-acetylindolin-5-yl)-*N*-methyl-2-sulfamoyl benzoic acid **7a** (2.00 g, 0.005 mol) in toluene was added thionyl chloride (1.11 mL, 0.016 mol). The reaction was refluxed for 1 h. After cooling, the reaction medium was evaporated under reduced pressure. The resulting mixture was taken up in chloroform, added aluminum chloride (2.12 g, 0.016 mol), and refluxed for 1 h. After cooling, the reaction was evaporated under reduced pressure. The resulting mixture was taken up in water and extracted with dichloromethane. The organic layer was washed with NaOH 1 N, water, and dried with magnesium sulfate. The precipitate was taken up in ethanol and was added HCl 12 N. The reaction was refluxed for 2 h. After cooling to room temperature, the reaction was evaporated under reduced pressure. The resulting mixture was taken up in chloroform, added aluminum chloride, and was refluxed for 1 h. After cooling, the mixture was evaporated under reduced pressure. The resulting mixture was taken up in water and added NaOH 12 N having a pH of 10. The precipitate formed was filtered off and recrystallized from MeOH. The precipitate was recrystallized from EtOH.

8a: Yellow crystals, yield 36%, mp 205–206°C. IR (KBr): $\nu_{max} = 1650$ (CO) and 1340,1170 (SO_2N) cm^{-1}. ^1H NMR $\delta = 3.28$ (s, 3H, NCH_3), 3.30 (t, 2H, $J = 8.47$ Hz, CH_2), 4.14 (t, 2H, $J = 8.47$ Hz, CH_2), 7.13 (s, 1H, ArH), 7.72 (m, 1H, ArH), 7.98 (m, 1H, ArH), 8.97 (s, 1H, ArH). MS: m/z (%) = 314 (100).

The preparation of **8b** was accomplished as **8a**. **8b**: Yellow crystals, yield 44%, mp 212–213°C. IR (KBr): $\nu_{max} = 1640$ (CO) and 1340,1160 (SO_2N) cm^{-1}. ^1H NMR $\delta = 3.28$ (t, 2H, $J = 8.45$ Hz, CH_2), 3.31 (s, 3H, NCH_3), 4.17 (t, 2H, $J = 8.45$ Hz, CH_2), 7.72 (m, 2H, ArH), 7.97 (m, 2H, ArH), 8.15 (s, 1H, ArH), 8.21 (s, 1H, ArH). MS: m/z (%) = 314.

*5,11-Dihydro-5-methyl-1-(3,4,5-trimethoxy benzyl)benzo-[c]-1H-indolo[5,6,f][1,2] thiazepin-11-one 6,6-dioxide (***9***)*

1-Acetyl-5,11-dihydro-5-methylbenzo[*c*]indolino-[5,6,*f*] [1, 2] thiazepin-11-one 6,6-dioxyde **8a** (0.15 g, 1 mmol) in DMF was added dropwise to a solution of NaH (0.08 g, 2 mmol) in DMF. The solution was stirred at room temperature. After 3 h, 3,4,5-trimethoxybenzyl chloride (0.55 g, 2 mmol) in DMF was added dropwise over 10 min and the mixture was stirred for 16 h at room temperature. The solution was evaporated in vacuo to dryness and H_2O was added. The resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from ethanol.

9: Yellow crystals, yield 77%, mp 110–111°C. IR (KBr): $\nu_{max} = 1650$ (CO) and 1340,1170 (SO_2N) cm^{-1}. ^1H NMR $\delta = 3.30$ (s, 3H, NCH_3), 3.77 (s, 6H, m,m′-OCH_3), 3.82 (s, 3H, *p*-OCH_3), 5.31 (s, 2H, CH_2), 6.40 (s, 2H, ArH), 6.59 (d, 1H, $J = 3.17$ Hz, ArH), 7.37 (d, 1H, $J = 3.17$ Hz, ArH), 7.63 (s, 1H, ArH), 7.73 (m, 2H, ArH), 8.02 (m, 1H, ArH), 8.11 (m, 1H, ArH), 8.43 (s, 1H, ArH). MS: m/z (%) = 492 (100).

*5,11-Dihydro-5-methyl-1-(3,4,5-trimethoxy benzyl)benzo-[f]-1H-indolo[6,5,c][1,2]-thiazepin-11-one 6,6-dioxide (***10***)*

1-Acetyl-5,11-dihydro-5-methylbenzo[*c*]indolino-[5, 6, *f*][1, 2]thiazepin-11-one 6,6-dioxyde **8b** (0.30 g, 2 mmol) in DMF was added dropwise to a solution of NaH (0.16 g, 4 mmol) in DMF. The solution

was stirred at room temperature. After 3 h, 3,4,5-trimethoxybenzyl chloride (1.10 g, 4 mmol) in DMF was added dropwise over 10 min and the mixture was stirred for 16 h at room temperature. The solution was evaporated in vacuo to dryness and H_2O was added. The resulting precipitate was collected by filtration. The solid product was dissolved in toluene and was added DDQ (0.15 g, 2 mmol). The reaction mixture was heated under reflux for 2 h, cooled at room temperature, and filtered on celite. The solution was evaporated in vacuo and was purified via flash column chromatography to afford a yellow solid.

10: Yellow crystals, yield 81%, mp 118–119°C. IR (KBr): $\nu_{max} = 1650$ (CO) and 1330,1180 (SO_2N) cm^{-1}. ^1H NMR $\delta = 3.32$ (s, 3H, NCH_3), 3.78 (s, 6H, m,m′-OCH_3), 3.82 (s, 3H, *p*-OCH_3), 5.32 (s, 2H, CH_2), 6.40 (s, 2H, ArH), 6.59 (d, 1H, $J = 3.17$ Hz, ArH), 7.37 (d, 1H, $J = 3.17$ Hz, ArH), 7.63 (s, 1H, ArH), 7.73 (m, 2H, ArH), 8.02 (m, 1H, ArH), 8.11 (m, 1H, ArH), 8.43 (s, 1H, ArH). MS: *m/z* (%) = 492 (100).

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