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Synthesis of novel benzo[*b*]furans and benzo[*b*]thiophenes: analogs of combretastatin and resveratrol

Jay Chauhan, Alexandre R. Monteil and Steven E. Patterson*

Center for Drug Design, Academic Health Center, University of Minnesota, 516 Delaware St SE, Minneapolis, MS 55455, USA

*Corresponding author
e-mail: Patte219@umn.edu

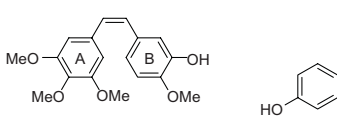
Abstract

A rapid and efficient synthesis of fused polyphenolic/polymethoxy benzofurans and benzothiophenes that have potential as antitumor agents and components of anti-HIV combination therapy has been achieved.

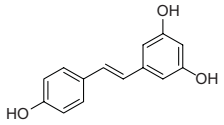
Keywords: benzofuran; benzothiophene; cancer; combretastatin; HIV; polyphenol; resveratrol.

Introduction

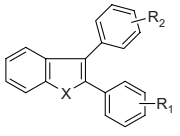
The potent antineoplastic drug combretastatin A4 and its phosphate prodrug have generated much recent interest owing, at least in part, to their dual function as anti-angiogenesis and antimitotic agents (Cirla and Mann, 2003; Siemann et al., 2009). Combretastatin A4 has therefore recently served as a lead molecule for generation of a large number of analogs as potential anticancer agents (Odlo et al., 2008, 2010; Ducki et al., 2009a,b; Liu et al., 2009; Schobert et al., 2009, 2010; Biersack et al., 2010a,b; Brachet et al., 2010; Chen et al., 2010; Lee et al., 2010; Lorion et al., 2010; Ty et al., 2010; Zoldakova et al., 2010). SAR studies have demonstrated that the cisoid conformation and the 3,4,5-trimethoxyphenyl moiety (ring A) are required for potent activity (Cirla and Mann, 2003; Hsieh et al., 2005; Hu et al., 2006).



Combretastatin A4



Resveratrol



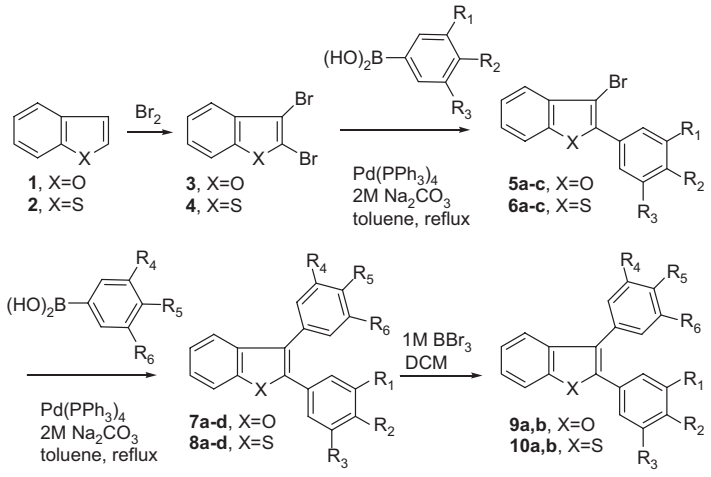
X=O, Benzo[*b*]furans
X=S, Benzo[*b*]thiophenes
R_1=R_2=OMe, OH

There is also much interest in the hydroxylated *trans*-stilbenes, such as resveratrol, which have a wide range of potential therapeutic uses in experimental systems such as anti-aging, anti-HIV and cancer chemoprevention. Resveratrol produces a cascade of events resulting from a broad range of cellular targets including oxidative pathways (Xia et al., 2010), ribonucleotide reductase (Fontecave et al., 1998), SIRT1 (Baur and Sinclair, 2006), glycosylation (Zhang et al., 2010), and cholesterol synthesis (Macarulla et al., 2009). We recently reported that combination of the ribonucleotide reductase inhibitor gemcitabine with decitabine results in potent inhibition of HIV replication in cell culture (Clouser et al., 2010) and have recently demonstrated that combination of resveratrol and decitabine also has anti-HIV activity (Chauhan and Patterson, unpublished). Here, we report the synthesis of benzo[*b*]furan and benzo[*b*]thiophene hydroxylated stilbene derivatives that could serve as either anticancer agents or components of HIV combination therapy with decitabine.

Results and discussion

Synthesis of the target molecules was performed by treatment of commercially available benzofuran (**1**) and benzothiophene (**2**) with bromine to yield 2,3-dibromoheteraromatics **3** and **4**, respectively (Hussain et al., 2009a,b) (Scheme 1). Monocoupling under Suzuki-Miyaura conditions with 3,5-dimethoxyphenylboronic acid was highly selective for the 2-position (Heynderickx et al., 2002; Hung et al., 2010), providing **5a** and **6a**, followed by a second coupling of the remaining aryl bromide with 4-methoxyphenylboronic acid to give oxygen and sulfur derivatives **7a** and **8a**. Finally, global deprotection of the methoxy groups was achieved by treatment with boron tribromide (Roberti et al., 2006) to give 2,3-diphenylheteroaryl analogs **9a** and **10a**, accordingly. In a similar manner, regioisomers **9b** and **10b** of compounds **9a** and **10a** were also synthesized by inverting the order of the boronic acid coupling partner in the established route. Thus, coupling with 4-methoxyphenylboronic acid followed by a second coupling with 3,5-dimethoxyphenylboronic acid and standard deprotection (Roberti et al., 2006) gave regioisomeric resveratrol analogs **9b** and **10b**, respectively.

SAR studies have shown that a 3,5-dimethoxy motif in resveratrol derivatives (Fulda, 2010) and a 3,4,5-trimethoxy motif in combretastatin (Cirla and Mann, 2003; Hsieh et al., 2005; Hu et al., 2006) was found to be essential for potent pro-apoptotic activity. Thus, compounds **7c**, **8c** and their regioisomers **7d**, **8d** were synthesized employing a similar strategy to that shown above. In conclusion, we have synthesized 12



	R_1	R_2	R_3	R_4	R_5	R_6
5a/6a	OMe	H	OMe	-	-	-
5b/6b	H	OMe	H	-	-	-
5c/6c	OMe	OMe	OMe			
7a/8a	OMe	H	OMe	H	OMe	H
7b/8b	H	OMe	H	OMe	H	OMe
7c/8c	OMe	OMe	OMe	OMe	H	OMe
7d/8d	OMe	H	OMe	OMe	OMe	OMe
9a/10a	OH	H	OH	H	OH	H
9b/10b	H	OH	H	OH	H	OH

Scheme 1 Synthesis of the title compounds.

resveratrol/combretastatin analogs (compounds **7–10**) that feature either a benzo[*b*]furan or benzo[*b*]thiophene backbone. The biological activity of these individual compounds and their combination with decitabine will be reported in due course.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian Unity Plus 600 MHz NMR (Varian, Inc., Santa Clara, CA, USA). High resolution mass spectra were acquired on an Agilent G1969-TOF system (Agilent Technologies, Inc., Palo Alto, CA, USA).

General procedure for Suzuki-Miyaura coupling

Aryl halide (2.00 mmol) and boronic acid (1.2 equiv., 2.40 mmol) were dissolved in toluene/ethanol (10: 3/20 ml). Aqueous Na_2CO_3 (2 M, 3 equiv.) was added and the resulting mixture was deoxygenated with a stream of argon. After 10 min, $Pd(PPh_3)_4$ (5 mol%) was added and the reaction mixture was heated to reflux for 6 h. After cooling, the reaction mixture was quenched with sat. NH_4Cl (3 ml) and partitioned between EtOAc (50 ml) and H_2O (20 ml). The aqueous phase was extracted with EtOAc (3×20 ml) and the organic portions combined, washed with H_2O (20 ml), sat. NaCl (20 ml), dried (Na_2SO_4) and reduced *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc) to produce the desired compounds.

General procedure for methoxy group deprotection

Protected aryl (1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 ml). Boron tribromide (1 M in CH_2Cl_2, 3.2 mmol) was added to the solution at -78°C and the resulting mixture was allowed to warm to room temperature and stirred for 20 h. The solution was poured into H_2O (20 ml) and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 ml), and the organic portions combined and washed with 1 M sodium thiosulfate (10 ml), followed by H_2O (10 ml). The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc) to produce the desired compound.

Representative data for the synthesis of compound 10b

6b; ^{1}H NMR ($CDCl_3$) δ 7.81 (1 H, d, *J*=8.0, Ar), 7.73 (1 H, d, *J*=8.0, Ar), 7.67 (2 H, d, *J*=8.5, Ar), 7.42 (1 H, t, *J*=7.6, Ar), 7.33 (1 H, t, *J*=7.6, Ar), 6.96 (2 H, d, *J*=8.5, Ar), 3.80 (3 H, s, OMe). ^{13}C NMR ($CDCl_3$) δ 160.3, 139.5, 138.4, 137.7, 131.2, 125.6, 125.5, 125.4, 123.3, 122.4, 114.3, 104.5, 55.6.

8b; ^{1}H NMR ($CDCl_3$) δ 7.83 (1 H, d, *J*=9.1, Ar), 7.62 (1 H, d, *J*=9.1, Ar), 7.41–7.26 (4 H, m, Ar), 6.79 (2 H, d, *J*=8.6, Ar), 6.49 (2 H, d,

J=1.7, Ar), 6.47 (1 H, t, *J*=1.7, Ar), 3.77 (3 H, s, OMe), 3.71 (6 H, s, 2×OMe). ^{13}C NMR ($CDCl_3$) δ 161.2, 159.5, 141.1, 139.7, 138.7, 137.9, 132.4, 130.9, 126.8, 124.7, 124.5, 123.4, 122.2, 114.1, 108.6, 105.8, 100.0, 55.6.

10b; ^{1}H NMR (acetone-d_6) δ 8.62 (1 H, s, OH), 8.34 (2 H, s, OH), 7.91 (1 H, d, *J*=9.1, Ar), 7.57 (1 H, d, *J*=9.1, Ar), 7.37–7.32 (2 H, m, Ar), 7.26 (2 H, d, *J*=8.4, Ar), 6.79 (2 H, d, *J*=8.4, Ar), 6.39 (1 H, d, *J*=2.1, Ar), 6.31 (2 H, d, *J*=2.1, Ar). ^{13}C NMR (acetone-d_6) δ 159.1, 157.7, 141.4, 139.3, 138.4, 137.8, 132.3, 130.7, 125.6, 124.6, 124.5, 123.2, 122.1, 115.6, 108.9, 102.2; *m/z* (ESI): 333 (100%, M-H$^+$), 667 (70%, 2M-H$^+$); HRMS: *m/z* [M-H]$^+$ calc. for $C_{20}H_{13}O_3S$: 333.0591, found: 333.0586.

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