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Synthesis of novel diaryl ethers and their evaluation as antimitotic agents

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Abstract—A series of novel diaryl ethers possessing various functional groups were synthesized and evaluated for antiproliferative activity in human myeloid leukemia HL-60 cells. Among the compounds examined, compounds **10**, **17**, **20**, **24**, and **33** showed moderate to potent antiproliferative activity. These derivatives were further examined in terms of their abilities to inhibit tubulin polymerization; however, all of the tested compounds were relatively ineffective. The reference compound E7010 with an IC_{50} of 0.34 μM exhibited potent antiproliferative activity and significantly inhibited tubulin polymerization in a dose-dependent manner.

Antimitotic agents, which arrest cells in mitosis (the M phase of the cell cycle), can be classified as tubulin interactive agents (TIAs).[1] These tubulin-targeting agents are generally divided into two major classes: microtubule-stabilizing agents, like taxanes, epothilones, and discodermolide, and microtubule-destabilizing agents, like colchicine, vinca alkaloids, and cryptophycins.[2,3] Although taxanes and vinca alkaloids are widely used clinically to treat cancer, their structural complexities, difficult formulations, lack of oral availability, and more importantly, acquired and intrinsic resistance render these drugs suboptimum for clinical treatment of cancer.[4] Consequently, considerable interest is being shown in the discovery and development of novel small molecule inhibitors of tubulin polymerization that can circumvent the difficulties of natural products. In this context, progress has recently been made on the development of highly potent tubulin inhibitors and currently, several compounds are undergoing clinical trials.[5–10]

Diaryl ethers represent an important class of synthetic compounds recognized as potential anticancer drugs. Experimental and pre-clinical models have demonstrated that a number of these compounds elicit outstanding anticancer activity through the significant inhibition of tubulin assembly accompanied by potent antiproliferative activity.[11,12] Moreover, the diaryl ether scaffold is found in a number of natural products and biologically important molecules.[13] In this context, several reports have recently described various pharmacological evaluations of compounds possessing diaryl ether motifs.[14–16] As a result of our continuing studies aimed at the discovery and development of potential antimitotic agents, herein we report the synthesis, antiproliferative activities, and tubulin polymerization inhibitions of a series of novel diaryl ethers.

A variety of substituted diaryl ethers, **3**–**25** and **28**–**33**, were prepared as outlined in Schemes 1–3. To facilitate the efficient and diverse synthesis of the key diaryl ether skeleton,[17] the approach that emerged as being most attractive was the $Cu(OAc)_2$-mediated coupling reaction developed by the Evans group,[18] due to its mild reaction conditions as compared with alternatives[17] (room temperature versus higher temperature, >80 °C). Thus, treatment of 4- or 3,4-substituted arylboronic acids **1** and appropriate phenols **2** with $Cu(OAc)_2$ in the

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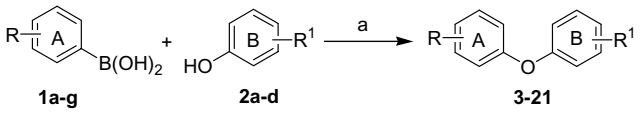
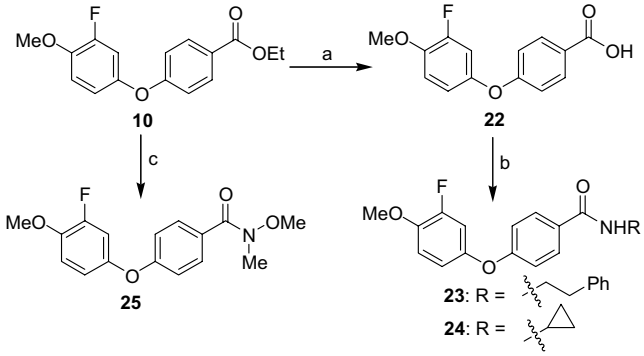


R = 4-CN, 4-Cl, 4-NMe_2, 3-F,4-OMe, 4-OMe, 3,4-di-OMe, 3,4-di-F.
R^1 = 3-CO_2Me, 4-COOEt, 3-OH-4-COOEt, 2,5-di-OMe.

Scheme 1. Reagents and condition: (a) $Cu(OAc)_2$, Et_3N, CH_2Cl_2, rt 42–84%.

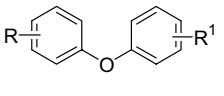


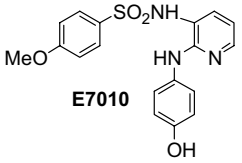
Scheme 2. Reagents: (a) LiOH, H_2O–THF, 86%; (b) phenethylamine, DCC, DMAP, THF, 53% for **23**; cyclopropylamme, DCC, DMAP, THF, 77% for **24**; (c) Me(MeO)NH · HCl, *i*-PrMgCl, THF, 63%.

presence of Et_3N and molecular sieve at room temperature afforded the desired diaryl ethers **3**–**21**[19] in modest to high yields (Scheme 1).[20]

As shown in Scheme 2, amide derivatives **23**–**25**[19] were also prepared starting from ester **10**, which appeared to have promising antiproliferative activity (*vide infra*, Table 1). To this end, ester **10** was subjected to alkaline hydrolysis to give the corresponding acid **22**. DCC-mediated coupling of the resulting **22** with appropriate amines provided the amide analogues **23** and **24**, in 53% and 77% yields, respectively. Reaction of ester **10** with *N*,*O*-dimethylhydroxylamine in the presence of isopropyl magnesium chloride[21] provided the *N*-methoxy-*N*-methylamide derivative **25**.

Table 1. In vitro antiproliferative activities of diaryl ethers **3**–**21** and E7010 in HL-60 cells[a]

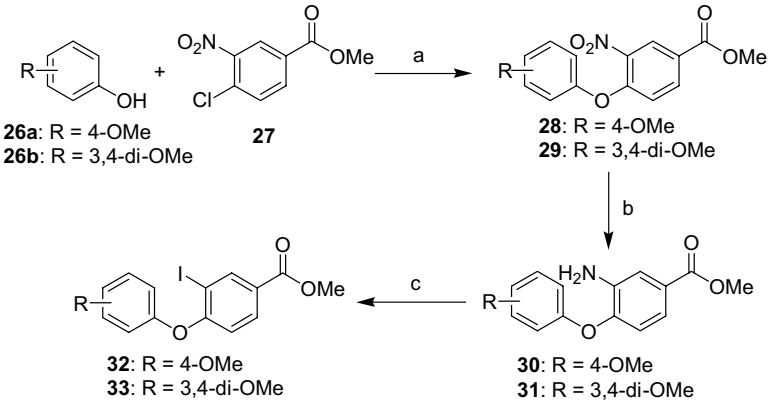




Compound	R	R^1	IC_{50}[a] (μM)
3	4-CN	3-COOMe	>20
4	4-$N(Me)_2$	3-COOMe	>20
5	4-OMe	3-COOMe	>20
6	3-F,4-OMe	3-COOMe	>20
7	4-CN	4-COOEt	>20
8	4-$N(Me)_2$	4-COOEt	>20
9	4-OMe	4-COOEt	>20
10	3-F,4-OMe	4-COOEt	3.5
11	4-Cl	4-COOEt	>20
12	3,4-Di-OMe	4-COOEt	>20
13	3,4-Di-F	4-COOEt	>30
14	4-$N(Me)_2$	3-OH, 4-COOEt	>30
15	4-OMe	3-OH, 4-COOEt	>30
16	3-F,4-OMe	3-OH, 4-COOEt	>30
17	3,4-Di-OMe	3-OH, 4-COOEt	1.5
18	3,4-Di-F	3-OH, 4-COOEt	>30
19	4-CN	2,6-Di-OMe	>20
20	4-$N(Me)_2$	2,6-Di-OMe	11.4
21	3-F,4-OMe	2,6-Di-OMe	>20
E7010			0.34

[a] All experiments were independently performed at least three times.

To identify the effect of *ortho*-substitution of the B-ring on antiproliferative activity, *ortho*-substituted diaryl ethers **28**–**33** were obtained by utilizing a sequence of reactions (Scheme 3). Ullmann coupling[17] of the potassium salts of appropriate phenols **26** with methyl 4-chloro-3-nitrobenzoate (**27**) gave the corresponding diaryl ethers **28** and **29** possessing an *ortho*-nitro group, which were subsequently reduced to the related aniline derivatives **30** and **31**. Diazotization followed by iodination of these anilines, **30** and **31**, gave the respective iodinated diaryl ethers **32** and **33**[19] in good yields.



Scheme 3. Reagents and conditions: (a) aq KOH, reflux, 76–88%; (b) Pd/C, H_2AcOH, rt; (c) (i) $NaNO_2$, concd H_2SO_4, 0–5 °C; (ii) KI, H_2O, rt-70 °C, 55–71% for two steps.