Quinols As Novel Therapeutic Agents. 7.[1] Synthesis of Antitumor 4-[1-(Arylsulfonyl-1*H*-indol-2-yl)]-4-hydroxycyclohexa-2,5-dien-1-ones by Sonogashira Reactions

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Interaction of 2-iodoaniline or 5-fluoro-2-iodoaniline with a range of arylsulfonyl chlorides affords sulfonamides that undergo Sonogashira couplings under thermal or microwave conditions with the alkyne 4-ethynyl-4-hydroxycyclohexa-2,5-dien-1-one followed by cyclization to 4-[1-(arylsulfonyl-1*H*-indol-2-yl)]-4-hydroxycyclo-hexa-2,5-dien-1-ones. This method allows for incorporation of a range of substituents into the arylsulfonyl moiety, and compounds showed selective in vitro inhibition of cancer cell lines of colon and renal origin, a feature of compounds bearing the quinol pharmacophore.

Introduction

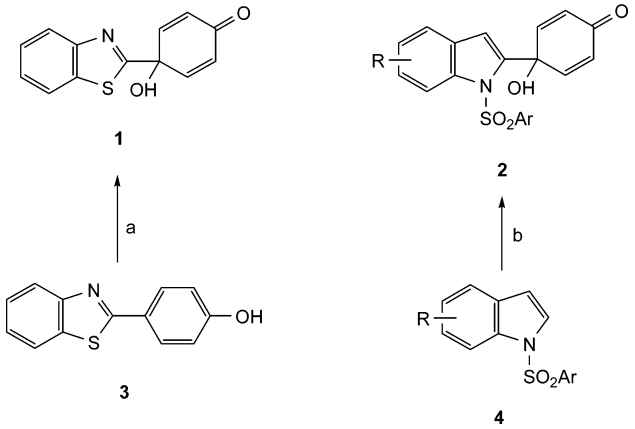
Our interest in the generation of novel and structurally diverse chemical oxidation products of bioactive phenols as potential therapeutic agents with enhanced biological properties has led to the discovery of 4-hydroxycyclohexa-2,5-dien-1-ones ("quinols") substituted with a heterocyclic fragment in the 4-position, a new pharmacophore in anticancer drug development. The prototypic benzothiazole-substituted quinol **1** displayed selective antitumor activity against colon, renal, and breast cancer cell lines,[2] and by a combination of biochemical and biophysical methods we have identified the redox homeostasis-controlling protein thioredoxin (Trx) as a primary molecular target.[3] As expected, this agent also perturbs signaling events modulated by downstream Trx effectors (eg Hif-1α[4] and VEGF[5]) that have a major role in the tumor angiogenesis process triggered by cellular hypoxia. Subsequently, we have identified a second more potent series of indolyl-quinols **2**, which maintain the selectivity fingerprint against colon, renal, and breast cell lines in vitro and show significant in vivo antitumor activity in mice bearing human mammary MDA-MB-435, colon HCT-116, and renal CAKI-1 xenografts.[6]

The original synthesis of **1** was achieved by a phenyliodonium diacetate (or trifluoroacetate) oxidation of a precursor phenol, 2-(4-hydroxyphenyl)benzothiazole **3**.[2] A more versatile one-pot synthesis of indoles **2** was accomplished by lithiation of a 1-(arylsulfonyl)indole **4** with *n*-butyllithium in THF at −78 °C, followed by addition to 4,4-dimethoxycyclohexa-2,5-dien-1-one, with subsequent acidic removal of the ketal protecting group (Scheme 1).[6] Both methods gave variable yields generally <40%, and in some cases reactions failed to deliver isolable products, probably because of stability issues in workup. Accordingly, we sought an alternative synthetic methodology to increase the range of quinols available for biological evaluation as well as to identify agents with better solubility properties than the original series **2**.

The use of transition metallic reagents, such as copper acetylides, in the construction of an indole ring from 2-iodoanilines dates back to the 1960s.[7] Taylor and McKillop were the first to use palladium chemistry in this type of synthesis when they reported the addition of copper acetylides to *o*-thallated anilides, with the subsequent cyclization mediated by palladium chloride.[8] In 1988, Sakamoto et al. described a significant advance in the one-pot Sonogashira synthesis of indoles from 2-iodoanilines and alkynes activated by electron-withdrawing substituents on the amino group.[9] Since then, a substantial body of work has been carried out on related reactions, and the subject has been covered in several reviews.[10] Methods have been developed for conducting indole syntheses on polymer supports by Zhang et al., where an arylsulfonyl group activates the amine and also acts as a traceless linker.[11] Kabalka adapted Sonogashira conditions to secure indole formation on alumina under microwave conditions, and the sulfonamide was the most successful activating group;[12] also, Sakamoto showed that the reaction could be performed using mono- or bismesylated iodoanilines in the reaction when TBAF was used as base.[13]

One possible reason for the limited use of the sulfonamide activating/protecting group in palladium(0)-mediated syntheses is the difficulty of its removal once the reaction is complete. However, as our past work has shown that the arylsulfonyl moiety actually enhances activity in indolyl-quinols **2**,[6] our new strategy was to react *N*-arylsulfonyl-2-iodoanilines with an alkynyl-substituted quinol under Sonogashira conditions.

Scheme 1. Synthesis of 4-Substituted 4-Hydroxycyclohexa-2,5-dien-1-ones[a]



[a] Reagents and conditions: (a) [bis(trifluoroacetoxy)iodo]benzene, TEMPO, in MeCN/H_2O; (b) *n*-BuLi, THF, −78 °C, 4,4-dimethoxy-2,5-cyclohexadien-1-one, then 10% aq. AcOH.

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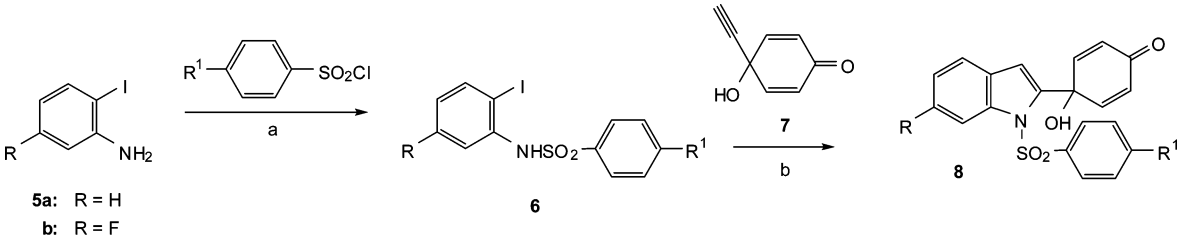
Scheme 2. Synthesis of Indol-2-yl-substituted 4-Hydroxycyclohexa-2,5-dien-1-ones[a]



	R	R^1		R	R^1
a:	H	H	**h:**	H	$(CH_2)_2NHAc$
b:	F	H	**i:**	H	$(CH_2)_2CO_2Me$
c:	H	Me	**j:**	F	$(CH_2)_2CO_2Me$
d:	H	$NHCO_2Et$	**k:**	H	Cl
e:	H	NHAc	**l:**	H	Br
f:	H	SO_2Me	**m:**	H	$(CH_2)_2CO_2H$
g:	H	CN	**n:**	F	$(CH_2)_2CO_2H$

c, d

[a] Reagents and conditions: (a) pyridine/THF, 25 °C; (b) $(i\text{-Pr})_2NH$, tetrakis(triphenylphosphine)palladium, CuI, DMAC, H_2O, 100 °C, 100W MW; (c) **8i**, Me_3SnOH, DCE, 120 °C, 100W MW; (d) as (c) from **8j**.

Table 1. Yields and Melting Points of Products of Sonogashira Reactions

	yield (%)	m.p. °C (lit.)		yield (%)	m.p. °C (lit.)
8a	49	170−172 (170−172)[a]	**8h**	28	64.5 (dec)
8b	44	185−187[b]	**8i**	20	137−138
8c	45	159−161 (159−161)[a]	**8j**	48	129.5−130.5
8d	38	226−228 (dec)	**10**	24	173−174 (dec)
8e	27	109−115 (dec)	**12a**	14	170 (dec)
8f	23	95−105 (dec)	**12b**	32	201−202
8g	10	213−215	**14**	70	96.5−103

[a] Reference 6. [b] This compound was reported in ref 6, but no mp was recorded.

Results and Discussion

A series of 2-iodoanilines **6a**−**l** activated by *N*-arylsulfonyl residues was prepared from arylsulfonyl chlorides and 2-iodoaniline **5a** or 5-fluoro-2-iodoaniline **5b** in pyridine. In a model experiment, the reaction between *N*-(2-iodophenyl)benzenesulfonamide **6a** and phenylacetylene gave 1-benzenesulfonyl-2-phenylindole in a satisfactory 70% yield employing conditions reported by Kotschy [Pd/C catalyst, copper iodide, diisopropylamine base in dimethylacetamide (DMAC) containing 5% water].[14] However, this approach, and use of other catalyst/solvent combinations, to pilot reactions between **6a**−**c** and 4-ethynyl-4-hydroxycyclohexa-2,5-dien-1-one **7** (prepared by addition of ethynylmagnesium bromide to 4,4-dimethoxycyclohexa-2,5-dienone)[15,16] gave only poor yields of products **8a**−**c**. After considerable experimentation, it was found that use of the homogeneous catalyst tetrakis(triphenylphosphine)palladium and copper iodide in a diisopropylamine/aqueous DMAC medium at 100 °C afforded indoles **8a**−**g** in only 10 min with microwave irradiation (Scheme 2, Table 1); again, yields were generally low possibly because of losses sustained during isolation. These standardized conditions were used to prepare indolyl-quinols bearing aliphatic side chains **8h**−**j**, but disappointingly, the halo-substituted *N*-(2-iodophenyl)benzenesulfonamides **6k**,**l** failed to furnish isolable quinols **8k**,**l** presumably because the halogen substituents provide additional sites for palladium(0)-mediated couplings. The reactions also proceeded in 10 min under thermal conditions at 100 °C (or in some cases at 80 °C) with similar yields, but the microwave conditions were more convenient for small-scale reactions.

The indolyl-quinols as a class are only poorly soluble in water and we were interested to prepare agents with appended polar groups which might impart more tractable pharmaceutical properties. Hydrolysis of the esters **8i**,**j** to yield the corresponding propionic acids **8m**,**n** could not be accomplished under basic saponification conditions without degradation of the quinol moiety. A method modified from that described by Nicolaou,[17] involving application of excess trimethyltin hydroxide in 1,2-dichloroethane (DCE) for 0.5 h at 120 °C under microwave conditions, was successfully employed to effect hydrolysis of methyl esters **8i**,**j** to the corresponding propanoic acids **8m**,**n**.

Having achieved Sonogashira indole cyclizations on a small scale under microwave conditions, the conversion of **6b** to the most potent indolyl-quinol **8b** on a larger scale (20 mmol) was investigated: a yield of 53% was obtained in just 10 min under thermal conditions. Compound **8c** was prepared similarly (72% yield) from **6c**. Yields of **8b**,**c** by this process were superior to that achieved in the lithiation/addition route.[6]

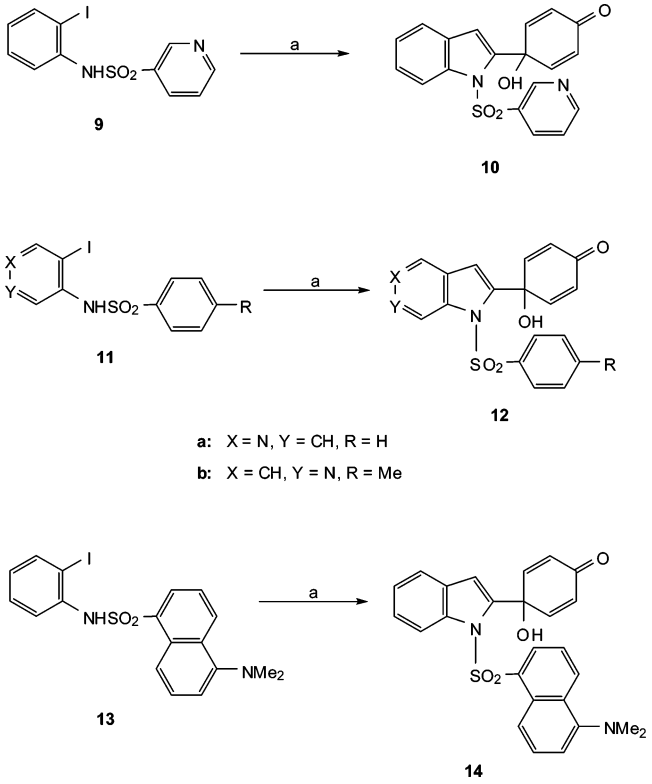
The 3-pyridosulfonyl-activated iodoaniline **9** was successfully cyclized to **10** (24%) using homogeneous catalyst with microwave activation. The preparation of 5- and 6-azaindoles bearing the quinol group was also investigated. The desired aminoiodopyridine starting materials were not commercially available and were prepared by *ortho*-lithiation/iodination of pivaloylated aminopyridines with subsequent acid hydrolysis.[18] Surprisingly, addition of the arylsulfonyl group to 3-iodo-4-aminopyridine was unsuccessful under the normal conditions, so the sulfonamide **11a** was prepared using KOH and a phase-transfer catalyst in DCM. Cyclization of the activated iodopyridylamines **11a**,**b** with alkyne **7** to the 5- and 6-azaindolyl-quinols **12a**,**b**, respectively, was achieved under microwave conditions although yields of these isolated aza-analogs were only modest (<35%). The dansyl-substituted indole **14**, which was required as a potential fluorescent probe to explore

Table 2. Activity of Compounds in the NCI In Vitro 60-Cell Panel[a]

cmpd	mean GI_{50} (μM)	mean LC_{50} (μM)	most sensitive cell lines (LC_{50}, μM)[b,c]
1	0.23[d]	3.39	HCT−116 (0.43), RXF393 (0.58)
8a	0.039[d]	2.95	HCT−116 (0.03), CAKI−1 (0.05)
8b	0.016[d]	2.24	HCT−116 (<0.01), ACNH (0.02)
8c	0.11	7.24	HCT−116 (<0.01), LOX IMVI (<0.01), ACHN (0.04)
8d	0.19	7.58	HCT−116 (0.295), ACHN (0.60)
8i	0.68	22.9	HCT−116 (0.02), SK-MEL−5 (0.60)
8j	0.50	10.5	HCT−116 (0.72), LOX IMVI (0.81), BT−549 (0.74)
8m	2.34	23.4	*e*
8n	2.5	29.5	*e*
10	0.41	14.1	HCT−116 (0.29)
12a	0.34	13.8	HCT−116 (0.93), CAKI−1 (0.47)
12b	0.17	5.75	HCT−116 (<0.01), LOX IMVI (0.06), ACHN (0.05)
14	0.19	13.2	A498 (0.06), ACHN (0.41)

[a] For definitions of GI_{50} and LC_{50}, see ref 19. [b] Cell lines with LC_{50} < 1 μM. [c] Cancer cell line origin: HCT-116 (colon); RXF 393, CAKI-1, ACHN and A498 (renal); LOX IMVI and SK-MEL-5 (melanoma); BT-549 (breast). [d] Data from ref 6. [e] No cell lines with LC_{50} < 1 μM.

Scheme 3. Synthesis of 4-Substituted 4-Hydroxycyclohexa-2,5-dien-1-ones with Additional Hetero Atoms and Benzene Rings[a]



[a] Reagents and conditions: (a) **7**, $(i\text{-Pr})_2$NH, tetrakis(triphenylphosphine)palladium, CuI, DMAC, H_2O, 100 °C, 100W MW.

biological mechanisms in this series, but which also has the structural requirements for bioactivity in its own right (see Table 2), was similarly prepared from the dansyl-activated iodoaniline **13** (70%; Scheme 3).

Certain indolyl-quinols (**8f**−**h** and **10**) showed evidence of instability and gave substantial $(M-H_2O+H)^+$ ions in their HRMS (ES) spectra; they also gave unreliable CHN analytical data. However, all the indolyl-quinol series showed characteristic absorptions in their ^{1}H NMR spectra. The (exchangeable) 4-OH proton absorbs at δ 5.11−5.56, the cyclohexadienone 3-CH within a tight range at δ 6.32−6.37, and H-2 of the indole at δ 6.74−6.90, as a doublet with a small (∼ 0.5 Hz) coupling constant.

Biological Results and Discussion

The growth-inhibitory activities of new quinols were initially monitored in a preliminary screen comprising a panel of human colon (HCT-116 and HT29), breast (MCF-7 and MDA 468), and nonsmall cell lung (A549) cancer cell lines in 72 h drug exposure MTT assays. The most sensitive cell line was colon HCT-116, giving IC_{50} values over a 10-fold range (0.03−0.2 μM); the least sensitive cell line was A549 (IC_{50} values 0.5−4 μM) with the other cell lines of intermediate sensitivity (data not shown). Activities of new indolyl-quinols were compared with those of lead structures in the U.S. National Cancer Institute (NCI) in vitro 60-cell panel.[19] With the exception of the propanoic acids **8m**,**n**, the mean GI_{50} values (Table 2) were in the range 0.1−0.68 μM, but new compounds were less potent than the previously synthesized indolyl-quinols **8a**,**b** (mean GI_{50} 0.039 and 0.016 μM, respectively). Because of the tight range of activities, it was not possible to discern a meaningful structure−activity relationship in this series, but clearly, the presence of the 6-F substituent in **8b** confers high potency at the GI_{50} level. The mean potencies and pattern of selectivities at the LC_{50} level were similar across the series of compounds with colon (HCT-116) and renal cells lines (ACNH, CAKI-1, and RXF-393) being particularly sensitive, a feature of this novel class of agents bearing the quinol pharmacophore.[2,6] This selectivity is a property of compounds of the quinol class that inhibit the thioredoxin signaling pathway.[3] However, conversion of the propionate esters **8i**,**j** to more polar propanoic acids **8m**,**n** was accompanied by an overall loss of in vitro activity, especially against the normally sensitive cell lines. Possibly, introduction of a residue charged at physiological pH has an adverse effect on cellular penetration, although this has not been investigated.

In summary, we have shown that Sonogashira coupling chemistry can be employed to construct a new series of indolyl quinols **8b**−**j**, which show selective in vitro activities especially against cancer cells of colon, renal, and melanoma origin. However, new compounds prepared by this route were less potent than other congeners in this series.[6]

Experimental Section

Melting points were recorded on a Stuart Scientific SMP3 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FT−IR. Mass spectra were recorded on a Micromass LCT spectrometer using electrospray. NMR spectra were recorded on a Bruker Avance 400 instrument at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C) in [$^2H_6$]DMSO) or $CDCl_3$; coupling constants are in Hz. Merck silica gel 60 (40−60 μM) was used for column chromatography. 2-Iodoaniline was purchased from Avocado and recrystallized from hexane prior to use, and 5-fluoro-2-iodoaniline was purchased from Lancaster and used as received.

General Method A: Preparation of Arylsulfonamides. A solution of an arylsulfonyl chloride (10 mmol) and 2-iodoaniline **5a** or 5-fluoro-2-iodoaniline **5b** (10 mmol) in pyridine (4 mL) and tetrahydrofuran (4 mL) was stirred overnight at 25 °C. The mixture was concentrated under reduced pressure, and the products were purified either by recrystallization from aqueous ethanol or by column chromatography (hexane/ethyl acetate, 3/1).

General Method B: Preparation of Indolyl-quinols. To a 10 mL microwave vial containing a magnetic stirrer bar was added 4-ethynyl-4-hydroxycyclohexa-2,5-dienone **7** (0.39 g, 2.9 mmol), an activated 2-iodoaniline (2.5 mmol), DMAC (2.5 mL), diisopropylamine (0.5 mL), and water (0.1 mL). Nitrogen gas was gently

bubbled through for 10 min, and then tetrakis(triphenylphosphine)-palladium (160 mg, 0.15 mmol) and copper iodide (48 mg, 0.25 mmol) were added. The vial was sealed, shaken, and heated at 100 °C (100 W) for 10 min under microwave conditions. The cooled mixture was diluted with DCM/water (200 mL, 1/1). The aqueous layer was extracted with DCM, and the combined organic layers were dried and concentrated. The residue was passed through a pad of silica (hexane/ethyl acetate, 1/1) and purified further by column chromatography and/or recrystallization with aqueous ethanol.

3-{4-[2-(4-Hydroxy-1-oxocyclohexa-2,5-dienyl)-1*H*-indol-1-yl-sulfonyl]-phenyl}propanoic Acid 8m. A mixture of ester **8i** (0.132 g) and trimethyltin hydroxide (0.30 g) in 1,2-dichloroethane (3 mL) was heated in a sealed vial under microwave conditions at 120 °C for 0.5 h. The cooled mixture was filtered, concentrated in vacuo, and purified by column chromatography (EtOAc) to yield the propanoic acid **8m** (0.05 g, 39%), mp 193−194 °C.

3-{4-[6-Fluoro-2-(4-hydroxy-1-oxocyclohexa-2,5-dienyl)-1*H*-indol-1-ylsulfonyl]phenyl}propanoic Acid 8n. Similarly prepared from **8j** and trimethyltin hydroxide, followed by recrystallization from hexane/EtOAc, was the propanoic acid **8n** as white crystals (65%), mp 70−71 °C.

Larger Scale Preparation of 4-(1-Benzenesulfonyl-6-fluoro-1*H*-indol-2-yl)-4-hydroxycyclohexa-2,5-dien-1-one 8b Under Thermal Conditions. Nitrogen gas was bubbled through a stirred mixture of *N*-(5-fluoro-2-iodophenyl)benzenesulfonamide **6b** (7.56 g, 20 mmol), 4-ethynyl-4-hydroxy-cyclohexa-2,5-dienone (**7**, 3.12 g), diisopropylamine (4 mL), DMAC (20 mL), and water (0.8 mL) for approximately 10 min, and then tetrakis(triphenyl-phosphine)-palladium(0) (1.28 g) and copper(I) iodide (0.384 g) were added. The flask was sealed with a subaseal containing a needle to relieve pressure, the mixture was heated at 80 °C for 10 min and then allowed to cool, and the products were partitioned in DCM/water (1/1). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was passed through a short silica plug with EtOAc. Column chromatography (hexane/ethyl acetate, 3/1) yielded the indolyl-quinol **8b** as white crystals, recrystallized from EtOH (4.08 g, 53%), identical (^{1}H NMR) to the sample prepared previously.[6]

Similarly, on the same scale, 4-hydroxy-4-[1-(toluene-*p*-sulfonyl)-1*H*-indol-2-yl]cyclohexa-2,5-dien-1-one **8c** was prepared (72%) from **6c** and **7** under thermal conditions.

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Supporting Information Available: Spectroscopic properties (IR, ^{1}H NMR, and ^{13}C NMR) for sulfonamides **6a**−**l**, **9**, **11a**,**b**, and **13** and for quinols **8a**−**j**, **8m**,**n**, **10**, **12a**,**b**, and **14**. CHN elemental analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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