# Quinols as novel therapeutic agents. Part 8.[1] Applications of the Sonogashira route to thioredoxin-inhibitory indolyl-substituted quinols

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**Abstract**
Molecular modelling suggested that polar groups appended to the arylsulfonyl residue in indoles **2**, which are potential anticancer agents, could aid pharmaceutical properties without adversely affecting activity. A variety of substituted indoles were prepared using a one-pot Sonogashira-type method. A related indole, containing three Michael acceptor groups, has also been prepared.

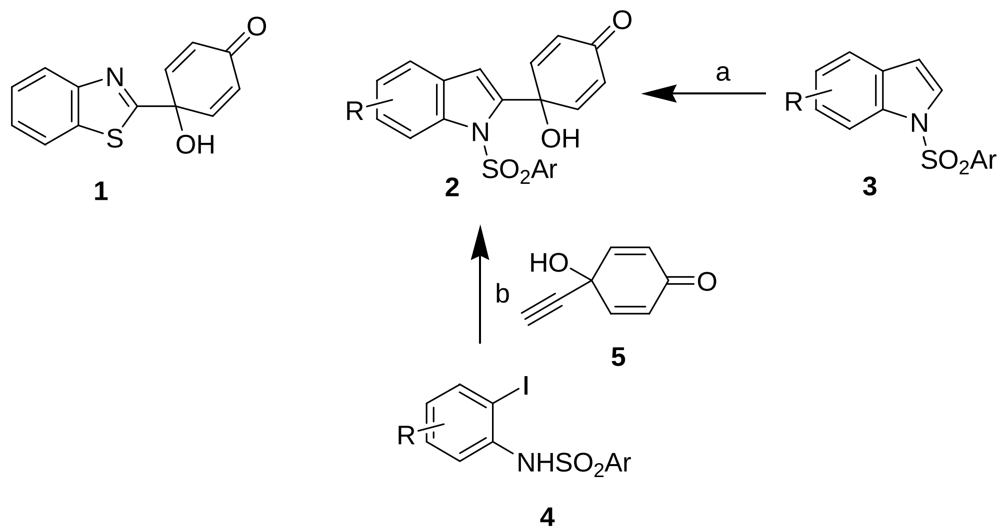
**Keywords:** Indoles, Sonogashira, 4-hydroxycyclohexa-2,5-dienones

## Introduction

Investigations on heterocycles substituted with the 4-hydroxycyclohexa-2,5-dien-1-one (‘quinol’) fragment (a new pharmacophore in anticancer drug development) has led to the discovery of a number of potential therapeutic agents with novel biological properties. The prototypic benzothiazole-substituted quinol **1**, where the quinol fragment acts as a double Michael acceptor, displayed selective antitumor activities against colon, renal, and breast cancer cell lines[2] with the small redox-regulatory protein thioredoxin (Trx) being the primary molecular target.[3] As expected, this agent also perturbs signalling events modulated by downstream Trx effectors (eg Hif-1 [4] and VEGf [5]) which have a major role in the tumor angiogenesis process triggered by cellular hypoxia. Subsequent investigations identified a more potent series of indolyl-quinols **2** which maintain the selectivity fingerprint against colon, renal and breast cancer cell lines in vitro.[6] Moreover, certain of the indole series show significant in vivo antitumor activity in mice bearing human mammary MDA-MB-435, colon HCT 116 and renal CAK-1 xenografts.[6]

The original synthesis of indoles **2** was accomplished by lithiation of a substituted 1-arylsulfonylindole **3** with n-butyllithium in THF at -78 $^{o}$C followed by addition to 4,4-

dimethoxycyclohexa-2,5-dien-1-one with subsequent acid hydrolysis of the ketal protecting group.[6] We have recently described a more versatile route, employing a Sonogashira coupling with sequential cyclisation, from sulfonylated iodoanilines **4** and 4-ethynyl-4-hydroxycyclohexa-2,5-dienone **5** (Scheme 1).[1]



Conditions: a: i) n-BuLi, THF; ii) 4,4-Dimethoxycyclohexa-2,5-dienone; iii) AcOH;
b: $Pd(PPh_3)_4$, CuI, $N(i\text{-}Pr)_2H$, $H_2O$, DMAC.

**Scheme 1**

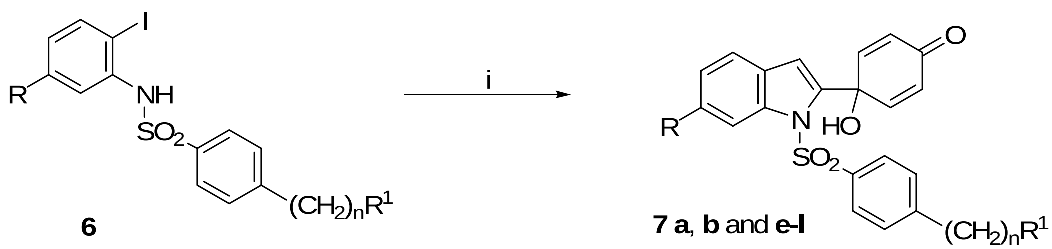
One of the limitations of the previously synthesised quinols was their limited water solubility. Preliminary molecular modelling suggested that polar groups appended to the arylsulfonyl residue in the indolyl-quinol series **2** would project outside the binding cavity of the Trx protein and be potentially available for profitable solvent interactions. One objective of the present work was to devise syntheses of variants of **2** with potentially improved pharmaceutical properties, based on the Sonogashira key step. In addition, molecular dynamics based docking studies were performed in order to analyse the non-covalent interactions of the indolyl-quinol (**2**: R = H, Ar = Ph) for its hypothesised Trx target. Observations of the resulting orientations adopted by the ligand in the human protein active site identified a non-active site cysteine specific to this protein which might be intercepted by an additional Michael acceptor fragment attached to the arylsulfonyl moiety. A route to such a compound has been achieved.

## Results and Discussion

Our chosen strategy was to incorporate additional substitutents at the protected aniline stage prior to the Sonogashira step, starting from the previously described precursors **6a** and **6b**.[1]

The methyl esters **6a,b** were efficiently hydrolysed (> 95%) in 10% aqueous KOH to the corresponding propanoic acids **6c,d** and thence re-esterified to the *t*-butyl esters **6e,f** with DMF di-*t*-butyl acetal.[7] Coupling of acid **6c** to morpholine or 1-methylpiperazine with dicyclohexylcarbodiimide in a DMAP/DCM medium gave the amides **6g** and **6h** in 65 and 57% yields, respectively. Borane-dimethyl sulfide reduction of **6a** in THF[8] yielded the propanol **6i** (66%), which was oxidized to the corresponding aldehyde **6j** (80%) with Dess-Martin periodinane. Reductive amination of the aldehyde with morpholine or 1-methylpiperazine yielded the amines **6k** and **6l** in 95 and 72 % yields respectively.[9]

Microwave-promoted Sonogashira cyclization of the sulfonamides **6** with alkyne **5** afforded the indolyl-quinols **7** in yields generally < 50% (Scheme 2), but no indoles **7c,d** were obtained from the corresponding carboxylic acids **6c,d**. (The preparation of the free acids **7c** and **7d** from **7a** and **7b**, respectively is described in the previous paper in the series.)[1]




a: R = H, $R^1 = CO_2Me$, n = 2

b: R = F, $R^1 = CO_2Me$, n = 2

c: R = H, $R^1 = CO_2H$, n = 2

d: R = F, $R^1 = CO_2H$, n = 2

e: R = H, $R^1 = CO_2{}^tBu$, n = 2

f: R = F, $R^1 = CO_2{}^tBu$, n = 2

g: R = H, $R^1 = CON(CH_2CH_2)_2O$, n = 2

h: R = H, $R^1 = CON(CH_2CH_2)_2NMe$, n = 2

i: R = H, $R^1 = OH$, n = 3

j: R = H, $R^1 = CHO$, n = 2

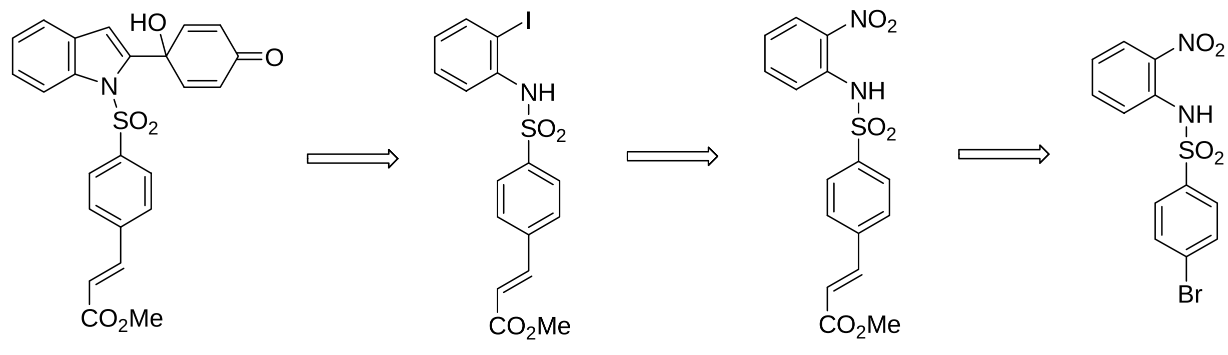
k: R = H, $R^1 = N(CH_2CH_2)_2O$, n = 3

l: R = H, $R^1 = N(CH_2CH_2)_2NMe$, n = 3

Conditions: a: KOH, $H_2O$; b: DMF di-t-butyl acetal, toluene; c: DCC, DMAP, morpholine, DCM; d: DCC, DMAP, 1-methylpiperazine, DCM; e: $BH_3$.DMS, THF; f: Dess-Martin periodinane, DCM; g: morpholine, $Na(OAc)_3BH$, 1,2-DCE; h: 1-methylpiperazine, $Na(OAc)_3BH$, 1,2-DCE; i **5**, $Pd(PPh_3)_4$, CuI, $N(i\text{-}Pr)_2H$, $H_2O$, DMAC.

**Scheme 2**

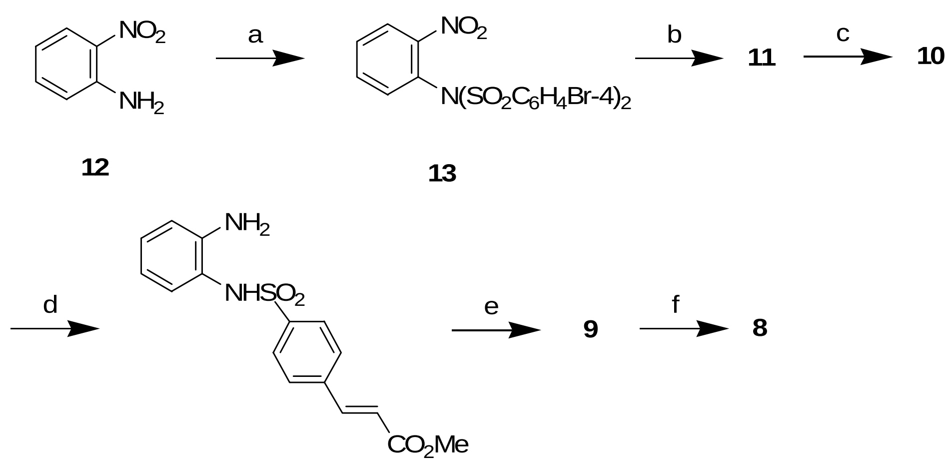
We then sought to prepare the quinol **8**, substituted with the methyl acrylate residue to act as a third Michael acceptor. The retrosynthetic analysis is shown in Scheme 3 wherein the iodo group required for Sonogashira coupling is introduced at the penultimate stage of the sequence and the methylacrylate functionality is appended from a bromo precursor by a Heck reaction.



**8** **9** **10** **11**

**Scheme 3**

Starting from 2-nitroaniline **12** preparation of the sulphonamide **11** was not trivial. Anilines containing electron-withdrawing groups are known to yield significant amounts of disulfonylated products,[10] and this proved to be the case with 2-nitroaniline, so a two step process to **11**, via the disulfonylated aniline **13** (87%) followed by TBAF mediated monodesulfonylation[10] (57%) was employed (Scheme 4).



**12** **13** **14**

Conditions: a: p-$BrC_6H_4SO_2Cl$, pyr, DMAP, THF; b: TBAF, THF; c: $Pd(OAc)_2$, IPr.HCl, $Cs_2CO_3$, $CH_2$=$CHCO_2Me$, DMAC; d: Fe, $FeCl_3.6H_2O$, AcOH, EtOH; e: $NaNO_2$, $H_2SO_4$, KI; f: **5**, $Pd(PPh_3)_4$, CuI, N(i-$Pr_2$)H, DMAC, $H_2O$.

**Scheme 4**

The Heck reaction of **11** with methyl acrylate was performed using a variety of catalysts: the most successful was Nolan's palladium/imidazolium salt which yielded **10** in 52 % yield.[11] The nitro group was reduced to the corresponding amine **14** using iron(III) chloride[12] (69 %) and a Sandmeyer reaction furnished the iodide **9**. Application of the Sonogashira reaction between **9** and 4-ethynyl-4-hydroxy-cyclohexa-2,5-dienone **5** yielded the desired indolyl-quinol **8** but in only 10 % yield. In conclusion, the synthesis of a number of novel substituted indoles, which are potential anticancer agents, has been described. Investigations into the biological properties of these compounds are continuing.

## Experimental Section

**General Procedures.** 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 $\mu$M) was used for column chromatography.

**3-{4-[*N*-(2-Iodophenyl)sulfamoyl]phenyl}propanoic acid (6c).** Ester **6a** (2.0 g; 4.5 mmol) was added to 10 % aqueous KOH (40 mL) and the mixture was refluxed for 0.5 h. The cooled solution was acidified with 1M HCl and the precipitate filtered, washed with water, and dried in a vacuum oven, yielding **6c** (1.88 g, 97%), mp 152-153.5 °C; $\nu_{max}$/cm$^{-1}$ 3290, 1797, 1596, 1474, 1335; $\delta_H$ (DMSO-$d_6$) 2.58 (2H, t, *J* = 7.5, $CH_2$), 2.90 (2H, t, *J* = 7.5, $CH_2$), 6.95-6.99 (2H, m, ArH), 7.30 (1H, td, *J* = 8.2, 1.4, ArH), 7.43 (2H, d, *J* = 8.4, ArH), 7.62 (2H, t, *J* = 8.4, ArH), 7.84 (1H, dd, *J* = 1.5, 8.2, ArH), 9.71 (1H, s, NH), 12.2 (1H, bs, $CO_2H$); $\delta_H$ (DMSO-$d_6$) 30.6, 35.1, 99.2, 127.3, 127.6, 128.9, 129.4, 129.5, 138.7, 138.9, 140.1, 146.8. Found C 41.5, H 3.1, N 3.7. Calc. for $C_{15}H_{14}INO_4S$ C 41.8, H 3.3, N 3.3%.

**3-{4-[*N*-(5-Fluoro-2-iodophenyl)sulfamoyl]phenyl}propanoic acid (6d).** Similarly prepared, by hydrolysis of ester **6b**, as a white powder (96%), mp 193-195 °C; $\nu_{max}$/cm$^{-1}$ 3300, 1705, 1596, 1480, 1335; $\delta_H$ (DMSO-$d_6$) 2.57 (2H, t, *J* = 7.6, $CH_2$), 2.90 (2H, t, *J* = 7.6, $CH_2$), 6.85 (1H, dd, *J* = 3.0, 10.2, ArH), 6.91 (1H, m, ArH), 7.44 (2H, d, *J* = 8.3, ArH), 7.65 (2H, d, *J* = 8.3, ArH), 7.84 (1H, dd, *J* = 6.5, 8.6, ArH), 9.90 (1H, s, NH), 12.20 (1H, bs, $CO_2H$). Found C 39.9, H 2.9, N 3.0. Calc. for $C_{15}H_{13}FINO_4S$ C 40.1, H 2.9, N 3.1%.

***t*-Butyl 3-{4-[*N*-(2-iodophenyl)sulfamoyl]phenyl}propanoate (6e).** To a stirred suspension of carboxylic acid **6c** (2.58 g, 6 mmol) in toluene (9 mL) at 60 °C was added dimethylformamide di-*t*-butyl acetal (4.92 g, 24 mmol) dropwise. The mixture was refluxed for 30 mins, allowed to cool to room temperature and washed with water (15 mL), saturated $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), concentrated, and the crude product recrystallised from aqueous ethanol to yield **6e** as white crystals (1.22 g, 47%), mp 87.5-88.5 °C; $\nu_{max}$/cm$^{-1}$ 3272, 2979, 1721, 1584, 1474, 1340, 1170; $\delta_H$ ($CDCl_3$) 1.38 (9H, s, *t*-Bu), 2.53

(2H, t, $J$ = 7.6, $CH_2$), 2.93 (2H, t, $J$ = 7.6, $CH_2$), 6.78 (1H, s, NH), 6.81-6.85 (1H, td, $J$ = 7.7, 1.5, ArH), 7.25-7.29 (3H, m, ArH), 7.33 (1H, td, J = 7.8, 1.3, ArH), 7.63-7.67 (3H, m, ArH); $\delta_C$ ($CDCl_3$) 28.1, 30.9, 36.3, 80.8, 92.4, 122.6, 126.9, 127.6, 129.0, 129.5, 136.7, 137.4, 139.1, 147.0, 171.5. Found C 46.9, H 4.6, N 2.7. Calc. for $C_{19}H_{22}INO_4S$ C 46.8, H 4.6, N 2.9%.

***t*-Butyl 3-{4-[*N*-(5-fluoro-2-iodophenyl)sulfamoyl]phenyl}propanoate (6f).** Similarly prepared by esterification of **6d** according to the method (above), mp 87-87.5 °C; $\nu_{max}/cm^{-1}$ 3269, 1723, 1597, 1482, 1343; $\delta_H$ ($CDCl_3$) 1.37 (9H, s, *t*-Bu), 2.54 (2H, t, $J$ = 7.6, $CH_2$), 2.94 (2H, t, $J$ = 7.6, $CH_2$), 6.60 (1H, m, ArH), 6.90 (1H, s, NH), 7.29 (2H, d, $J$ = 8.4, ArH), 7.43 (1H, dd, $J$ = 10.3, 2.9, ArH), 7.58 (1H, dd, $J$ = 6.0, 8.8), 7.71 (2H, d, 8.4, ArH). Found C 45.1, H 4.2, N 2.8. Calc. for $C_{19}H_{21}FINO_4S$ C 45.2, H 4.2, N 2.8%.

***N*-(2-Iodophenyl)-4-(3-morpholino-3-oxopropyl)benzenesulfonamide (6g).** To a stirred mixture of **6c** (2.15 g, 5 mmol), morpholine (0.435 g, 5 mmol) and DMAP (0.05 g) in DCM (18 mL) at 0 °C, was added dicyclohexylcarbodiimide (1.03 g, 5 mmol). The mixture was stirred for 16 h at 25 °C, then cooled in an ice bath and filtered. The solvent was reduced under reduced pressure, and the product crystallised from EtOH/water to give **6g** as white plates (1.63 g, 65%), mp 101-102 °C; $\nu_{max}/cm^{-1}$ 3245, 1645, 1160; $\delta_H$ ($d_6$-DMSO) 2.66 (2H, t, $J$ = 7.6, $CH_2$), 2.90 (2H, t, $J$ = 7.6, $CH_2$), 3.32 (8H, m, $N(CH_2CH_2)_2O$), 6.94-7.01 (2H, m, ArH), 7.29 (1H, t, $J$ = 7.7, ArH), 7.44 (2H, d, $J$ = 8.3, ArH), 7.63 (2H, d, $J$ = 8.3, ArH), 7.83 (1H, dd, $J$ = 1.2, 7.8, ArH), 9.73 (1H, s, NH). $\delta_H$ ($d_6$-DMSO) 30.9, 33.6, 42.0, 45.8, 66.6, 99.1, 127.2, 127.3, 128.8, 129.4, 129.7, 138.8, 140.1, 147.3, 170.3. $\delta_C$ ($CDCl_3$) 31.0, 34.1, 42.0, 45.8, 66.5, 66.9, 92.2, 122.4, 126.9, 127.7, 129.2, 129.6, 136.7, 137.4, 139.2, 147.4, 170.0. Found C 45.8, H 4.2, N 5.7. Calc. for $C_{19}H_{21}IN_2O_4S$ C 45.6, H 4.2, N 5.6%.

***N*-(2-Iodophenyl)-4-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]benzene-sulfonamide (6h).** Similarly prepared from **6c** and 1-methylpiperazine as described (above) as a white powder (1.46 g, 57%), mp 131.5-135.5 °C; $\nu_{max}/cm^{-1}$ 3126, 1634, 1471, 1448, 1340, 1163; $\delta_H$ ($CDCl_3$) 2.28 (3H, s, $CH_3$), 2.30 (2H, t, $J$ = 5.2), 2.34 (2H, t, $J$ = 5.2, $CH_2$), 2.59 (2H, t, $J$ = 7.7, $CH_2$), 3.01 (2H, t, $J$ = 7.7, $CH_2$), 3.39 (2H, t, $J$ = 5.1, $CH_2$), 3.62 (2H, t, $J$ = 5.1, $CH_2$), 6.81-6.85 (2H, m, NH, ArH), 7.26-7.33 (3H, m, ArH), 7.64-7.68 (4H, m, ArH); $\delta_C$ ($CDCl_3$) 31.1, 34.2, 41.7, 45.3, 46.0, 54.7, 55.0, 92.4, 122.5, 126.9, 127.7, 129.2, 129.6, 136.7, 137.4, 139.1, 147.6, 169.7. Found C 47.2, H 4.8, N 8.0. Calc. for $C_{20}H_{24}IN_3O_3S$ C 46.8, H 4.7, N 8.2%.

**4-(3-Hydroxypropyl)-*N*-(2-iodophenyl)benzenesulfonamide (6i).** To a round- bottomed flask with attached distillation apparatus was added **6a** (4.45 g, 10 mmol), borane-dimethyl sulfide complex (1 mL) and tetrahydrofuran (1 mL). The mixture was refluxed for 3 h, with dimethyl sulfide (bp 38 °C) being removed by distillation. Water (10 mL) was added, followed by $K_2CO_3$ (1.5 g). The mixture was repeatedly extracted with $Et_2O$, which was dried ($MgSO_4$), concentrated, to give the crude product. Recrystallisation from aqueous ethanol gave **6i** (2.75 g, 66%) as white plates, mp 93.5-94.5 °C; $\nu_{max}/cm^{-1}$ 3244, 1336, 1160; $\delta_H$ ($CDCl_3$) 1.32 (1H, s, OH), 1.89 (2H, m, $CH_2$CH_2OH$), 2.77 (2H, t, $J$ = 7.7, $ArCH_2$), 3.64-3.69 (2H, m, $CH_2OH$), 6.80 (1H, s, NH), 6.86 (1H, td, $J$ = 7.5, 1.4, ArH), 7.26-7.36 (3H, m, ArH), 7.66-7.69 (4H, m, ArH),

$\delta_C$ ($CDCl_3$) 31.9, 33.6, 61.8, 92.5, 122.8, 127.0, 127.6, 129.1, 129.6, 136.4, 137.5, 139.1, 148.1. Found C 42.9, H 3.8, N 3.2. Calc. for $C_{15}H_{16}INO_3S$ C 43.2, H 3.9, N 3.4%.

***N*-(2-Iodophenyl)-4-(3-oxopropyl)benzenesulfonamide (6j).** To a solution of **6i** (2.08 g, 5 mmol) in DCM (50 mL) was added Dess-Martin periodinane (2.76 g, 6.50 mmol) and the mixture was stirred for 2 h at 25 °C, then washed (aqueous $Na_2S_2O_3$ followed by $NaHCO_3$), dried ($MgSO_4$) and concentrated. After purification by column chromatography (hexane/ethyl acetate: 3/1) the oxopropylbenzenesulfonamide **6j** was obtained as a white powder (1.66 g, 80%), mp 102.5-105.5 °C; $\nu_{max}/cm^{-1}$ 3251, 1712, 1333, 1160; $\delta_H$ ($CDCl_3$) 2.79 (2H, t $J$ = 7.4, $ArCH_2$), 2.98 (2H, t, $J$ = 7.4, $CH_2CHO$), 6.77 (1H, s, NH), 6.84 (1H, td, $J$ = 7.5, 1.4, ArH), 7.24-7.34 (3H, m, ArH), 7.64-7.67 (4H, m, ArH); $\delta_C$ ($CDCl_3$) 27.8, 44.6, 92.5, 122.8, 127.0, 127.8, 127.9, 129.1, 129.6, 136.8, 137.4, 139.1, 146.1. Found C 43.4, H 3.4, N 3.2. Calc. for $C_{15}H_{14}INO_3S$ C 43.4, H 3.4, N 3.4%.

***N*-(2-Iodophenyl)-4-(3-morpholinopropyl)benzenesulfonamide (6k).** To a stirred solution of **6j** (1.04 g, 2.5 mmol) and morpholine (0.218 g, 2.5 mmol) in 1,2-dichloroethane (10 mL) under an atmosphere of nitrogen, was added sodium (triacetoxy)borohydride (0.75 g, 3.5 mmol). The mixture was stirred at room temperature for 4 h, then quenched with saturated aqueous $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc, which was dried ($MgSO_4$) and concentrated, yielding **6k** (1.15 g, 95%), mp 111.5-113 °C; $\nu_{max}/cm^{-1}$ 2953, 1330, 1154; $\delta_H$ ($CDCl_3$) 1.79 (2H, m, $CH_2CH_2CH_2$), 2.30 (2H, t, $J$ = 7.5, $CH_2$), 2.40 (4H, m, 2 × $CH_2$), 2.68 (2H, t, $J$ = 7.5, $CH_2$), 3.70 (4H, t, $J$ = 4.6, 2 × $OCH_2$), 6.84 (1H, td, $J$ = 7.7, 1.5, ArH), 7.23 (2H, d, $J$ = 8.4, ArH), 7.30-7.34 (1H, m, ArH), 7.62-7.68 (4H, m, ArH); $\delta_C$ ($CDCl_3$) 27.6, 33.4, 53.6, 57.8, 66.9, 92.6, 122.9, 127.0, 127.5, 129.1, 129.6, 136.3, 137.5, 139.1, 148.3. HRMS Found 487.0547 (M + $H^+$); calc. for $C_{19}H_{24}INO_3S$ 487.0552.

***N*-(2-Iodophenyl)-4-(3-(4-methylpiperazin-1-yl)propyl)benzenesulfon-amide (6l).** Similarly prepared (above) from **6j** and 1-methylpiperazine followed by crystallisation from aqueous ethanol (72%), mp 97-99.5 °C; $\nu_{max}/cm^{-1}$ 3548, 1458; $\delta_H$ ($CDCl_3$) 1.78 (2H, quin, $J$ = 7.6, $CH_2CH_2CH_2$), 2.22-2.45 (5H, m, $NCH_3$, $CH_2$), 2.45-2.64 (8H, bs, $N(CH_2CH_2)_2N$), 2.66 (2H, t, $J$ = 7.6, $CH_2$), 6.84 (1H, td, $J$ = 7.6, 1.5, ArH), 7.22 (2H, d, J = 8.4, ArH), 7.31 (1H, td, J = 7.8, 1.4, ArH), 7.57-7.67 (4H, m, ArH); $\delta_C$ ($CDCl_3$) 28.1, 33.5, 46.0, 53.1, 55.1, 57.4, 92.7, 123.0, 127.0, 127.5, 129.1, 129.5, 136.3, 137.5, 139.1, 148.4. HRMS Found 500.0866 (M + $H^+$); calc. for $C_{20}H_{27}IN_3O_2S$ 500.0869.

### Preparation of Indolyl-quinols

To a 10 mL microwave vial containing a magnetic stirrer bar was added 4-ethynyl-4-hydroxycyclohexa-2,5-dienone **5** (0.39 g, 2.9 mmol), activated 2-iodoaniline **6** (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, 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 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 recrystallisation with aqueous ethanol.

***t*-Butyl 3-{4-[2-(4-hydroxy-1-oxocyclohexa-2,5-dienyl)-1*H*-indol-1-ylsulfonyl]phenyl} propanoate (7e).** From **6e** and **5** (39%), mp 141.5-142.5 °C; $\nu_{max}/cm^{-1}$ 3437, 1720, 1668, 1627, 1374; $\delta_H$ ($CDCl_3$) 1.33 (9H, s, *t*-Bu), 2.50 (2H, t, *J* = 7.5, $CH_2$), 2.90 (2H, t, *J* = 7.5 $CH_2$), 5.53 (1H, s, OH), 6.34 (2H, d, *J* = 10.3, 2 × C(OH)C*H*), 6.80 (1H, d, *J* = 0.6, ArH), 7.20-7.32 (4H, m, ArH), 7.43 (1H, dd, *J* = 0.6, 7.2, ArH), 7.58 (2H, d, *J* = 10.3, 2 × CHC=O), 7.79 (2H, d, *J* = 8.5, ArH), 8.00 (1H, dd, *J* = 0.6, 8.5, ArH). Found C, 65.7, H, 5.4, N, 2.7. Calc. for $C_{27}H_{27}NO_6S$: C, 65.7, H, 5.5, N, 2.8%.

***t*-Butyl 3-{4-[6-fluoro-2-(4-hydroxy-1-oxocyclohexa-2,5-dienyl)-1*H*-indol-1-ylsulfonyl]phenyl} propanoate (7f).** From **6f** and **5** (44%), mp 138-139 °C; $\delta_H$ ($CDCl_3$) 1.31 (9H, s, *t*-Bu), 2.50 (2H, t, *J* = 7.5, $CH_2$), 2.90 (2H, t, *J* = 7.5 $CH_2$), 5.36 (1H, s, OH), 6.32 (2H, d, *J* = 10.3, 2 × C(OH)C*H*), 6.73 (1H, d, *J* = 0.6, ArH), 6.96 (1H, td, *J* = 8.8, 2.3, ArH), 7.28 (2H, d, *J* = 8.5, ArH), 7.35 (1H, dd, *J* = 8.6, 5.4), 7.53 (2H, d, *J* = 10.3, 2 × CHC=O), 7.73 (1H, dd, *J* = 10.2, 2.3), 7.79 (2H, d, *J* = 8.6, ArH). Found C, 63.3, H, 5.1, N, 2.7. Calc. for $C_{27}H_{26}FNO_6S$: C, 63.4, H, 5.1, N, 2.7%.

**4-Hydroxy-4-{1-[4-(3-morpholino-3-oxopropyl)phenylsulfonyl]-1*H*-indol-2-yl}cyclohexa-2,5-dien-1-one (7g).** From **6g** and **5** (40%), mp 173-174 °C; $\nu_{max}/cm^{-1}$ 3483, 1672, 1644, 1447, 1353, 1167; $\delta_H$ ($CDCl_3$) 2.54 (2H, t, *J* = 7.5, $ArCH_2$), 2.97 (2H, t, *J* = 7.5, $CH_2CO$), 3.29 (2H, t, *J* = 4.6, $CH_2$), 3.49 (2H, t, *J* = 4.6, $CH_2$), 3.56-3.59 (4H, m, 2 × $CH_2$), 5.47 (1H, s, OH), 6.34 (2H, d, *J* = 10.3, 2 × C(OH)C*H*), 6.78 (1H, d, *J* = 0.6, ArH), 7.20-7.33 (4H, m, ArH), 7.45 (1H, d, *J* = 7.7, ArH), 7.55 (2H, d, *J* = 10.3, 2 × CHC=O), 7.78 (2H, d, *J* = 8.5, ArH), 8.00 (1H, dd, *J* = 0.6, 8.6, ArH); $\delta_C$ ($CDCl_3$) 30.9, 33.6, 42.0, 45.8, 66.4, 66.8, 67.6, 113.5, 115.2, 121.7, 124.6, 126.2, 126.9, 127.7, 128.3, 129.5, 135.3, 138.2, 140.8, 147.5, 148.7, 169.7, 184.9. Found C 63.8, H 5.1, N 5.5. Calc. for $C_{27}H_{26}N_2O_6S$ C 64.0, H 5.2, N 5.5%.

**4-Hydroxy-4-{1-[4-(3-(4-methylpiperazin-1-yl)-3-oxopropyl)phenyl-sulfonyl]-1*H*-indol-2-yl}cyclohexa-2,5-dien-1-one (7h).** From **6h** and **5** (15%), mp 175-175.5 °C; $\nu_{max}/cm^{-1}$ 1670, 1636, 1444, 1370, 1173; $\delta_H$ ($CDCl_3$) 2.28 (3H, s, $CH_3$), 2.29 (2H, t, *J* = 5.2), 2.34 (2H, t, *J* = 5.2, $CH_2$), 2.55 (2H, t, *J* = 7.6, $CH_2$), 2.96 (2H, t, *J* = 7.6, $CH_2$), 3.35 (2H, t, *J* = 5.1, $CH_2$), 3.59 (2H, t, *J* = 5.1, $CH_2$), 5.52 (1H, s, OH), 6.34 (2H, d, *J* = 10.3, 2 × C(OH)C*H*), 6.78 (1H, d, *J* = 0.6, ArH), 7.20-7.33 (4H, m, ArH), 7.45 (1H, d, *J* = 7.8, ArH), 7.55 (2H, d, *J* = 10.3, 2 × CHC=O), 7.78 (2H, d, *J* = 8.5, ArH), 7.99 (1H, dd, *J* = 0.6, 8.5, ArH); $\delta_C$ ($CDCl_3$) 30.9, 33.9, 41.6, 45.2, 46.0, 54.6, 55.0, 67.5, 113.4, 115.2, 121.7, 124.5, 126.2, 126.9, 127.7, 128.3, 129.5, 135.2, 138.2, 140.7, 147.5, 148.9, 169.5, 184.9. Found C 64.4, H 5.6, N 7.9. Calc. for $C_{28}H_{29}N_3O_5S$ C 64.7, H 5.6, N 8.1%.

**4-Hydroxy-4-{1-[4-(3-hydroxypropyl)phenylsulfonyl]-1*H*-indol-2-yl}cyclohexa-2,5-dien-1-one (7i).** From **6i** and **5** (11%), mp 183-185.5 °C; $\nu_{max}/cm^{-1}$ 3478, 1670, 1625, 1344, 1166; $\delta_H$ ($CDCl_3$) 1.32 (1H, bs, $CH_2OH$), 1.80-1.87 (2H, m, C$H_2$$CH_2$OH), 2.73 (2H, t, *J* = 7.8, $ArCH_2$), 3.61-3.65 (2H, m, C$H_2$OH), 5.55 (1H, s, OH), 6.34 (2H, d, *J* = 10.3, 2 ×C(OH)C*H*), 6.78 (1H, d, *J* = 0.6, ArH), 7.22-7.34 (4H, m, ArH), 7.44 (1H, dd, *J* = 0.5, 7.3), 7.59 (2H, d, *J* = 10.3, 2 ×

CHC=O), 7.79 (2H, d, *J* = 8.5, ArH), 8.01 (1H, dd, *J* = 0.7, 8.5, ArH); $\delta_C$ ($CDCl_3$) 32.0, 33.3, 61.7, 67.5, 113.5, 115.2, 121.7, 124.6, 126.2, 126.8, 127.6, 128.3, 129.4, 134.9, 138.2, 140.7, 147.6, 149.4, 185.0.

**4-Hydroxy-4-{1-[4-(3-morpholinopropyl)phenylsulfonyl]-1*H*-indol-2-yl}-cyclohexa-2,5-dien-1-one (7k).** From **6k** and **5** (40%), mp 150-151 °C (dec.); $\delta_H$ ($CDCl_3$) 1.69-1.77 (2H, m, $CH_2CH_2CH_2$), 2.26 (2H, t, *J* = 7.4, $CH_2$), 2.35 (4H, m, 2 × $CH_2$), 2.63 (2H, t, *J* = 7.6, $CH_2$), 3.66 (4H, t, *J* = 4.6, 2 × $OCH_2$), 5.54 (1H, s, OH), 6.32 (2H, d, *J* = 10.3, 2 × C(OH)C*H*), 6.78 (1H, d, *J* = 0.6, ArH), 7.19-7.32 (4H, m, ArH), 7.42 (1H, d, *J* = 7.3, ArH), 7.57 (2H, d, *J* = 10.3, 2 × CHC=O), 7.76 (2H, d, *J* = 8.5, ArH), 7.98 (1H, dd, *J* = 0.6, 8.5, ArH).

**4-Hydroxy-4-{1-[4-(3-(4-methylpiperazin-1-yl)propyl)phenylsulfonyl]-1*H*-indol-2-yl}cyclohexa-2,5-dien-1-one (7l).** Prepared from **6l** and **5** according to General Method B, but with a different work up. The crude mixture was poured into DCM/water and extracted as before, but the product was purified by column chromatography using $CHCl_3$/MeOH (19/1) as eluant. The resulting brown oil was allowed to stand in a small amount of $CHCl_3$, then filtered. The filtrate was concentrated to an oil which was dissolved in EtOAc and product **7l** was precipitated as a fawn powder with hexane (18%), mp 65 °C (dec.); $\delta_H$ ($CDCl_3$) 1.69-1.75 (2H, m, $CH_2CH_2CH_2N$), 2.25-2.55 (13H, m), 2.61 (2H, t, *J* = 7.7, $CH_2$), 5.56 (1H, s, OH), 6.32 (2H, d, *J* = 10.3, 2 × C(OH)C*H*), 6.78 (1H, d, *J* = 0.6, ArH), 7.19-7.32 (4H, m, ArH), 7.42 (1H, d, *J* = 7.8, ArH), 7.57 (2H, d, *J* = 10.3, 2 × CHC=O), 7.76 (2H, d, *J* = 8.5, ArH), 7.98 (1H, dd, *J* 0.6, 8.5, ArH). HRMS Found 506.2037 ($M + H^+$); calc. for $C_{28}H_{32}N_3O_4S$ 506.2114.

**4-Bromo-*N*-(4-bromophenylsulfonyl)-*N*-(2-nitrophenyl)benzenesulfon-amide (13)** A mixture of 2-nitroaniline (24.54 g; 0.178 moles), 4-bromobenzenesulfonyl chloride (100.92 g; 0.395 moles) and dimethylaminopyridine (0.2 g) were stirred in pyridine (100 mL) and THF (100 mL) overnight. The mixture was concentrated, and recrystallised from ethanol, to give pure product as a pale yellow powder (88.7 g; 87 %), mp 242-243 °C. $\nu_{max}/cm^{-1}$ 1573, 1528, 1472, 1386, 1337. $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 7.13 (1H, dd, *J* 1.5, 7.8, ArH), 7.62 (1H, td, *J* 7.7, 1.8, ArH), 7.64-7.68 (1H, m, ArH), 7.70 (2H, d, *J* 8.8, ArH), 7.82 (2H, d, *J* 8.8, ArH), 8.06 (1H, dd, *J* 1.7, 7.8, ArH). $\delta_C$ 126.1, 127.1, 130.2, 130.8, 131.6, 132.3, 133.3, 134.6, 137.1, 148.1. Found C 37.2, H 2.1, N 5.2. Calc. for $C_{18}H_{12}Br_2N_2O_6S_2$ C 37.5, H 2.1, N 4.9%.

**4-Bromo-*N*-(2-nitrophenyl)benzenesulfonamide (11).** 4-Bromo-*N*-(4-bromophenyl sulfonyl)-*N*-(2-nitrophenyl)benzenesulfonamide (2.56 g; 5 mmol) was stirred in tetrabutylammonium fluoride (1M solution in THF; 5.5 mL; 5.5 mmol) for 2 hours. The mixture was diluted with water (25 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated, and the residue purified by column chromatography (hexane/ethyl acetate 10/1) to give **9** (1.02 g; 57 %) as bright yellow crystals, mp 128.5-130 °C. $\nu_{max}/cm^{-1}$ 3263, 3093, 1609, 1575, 1525, 1487, 1392, 1355. $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 7.22 (1H, td, *J* 7.9, 1.1, ArH), 7.61-7.63 (1H, m, ArH), 7.63 (2H, d, *J* 8.7, ArH), 7.74 (2H, d, *J* 8.7, ArH), 7.85 (1H, dd, *J* 1.0, 8.4, ArH), 8.16 (1H, dd, *J* 1.4, 8.4, ArH), 9.91 (1H, s, NH). $\delta_C$ 121.0, 124.3, 126.4, 128.7, 129.0, 132.8, 133.5, 136.0, 137.2, 137.7. Found C 40.1, H 2.5, N 7.8. Calc. for $C_{12}H_9BrN_2O_4S$ C 40.4, H 2.5, N 7.8%.

**(*E*)-Methyl 3-{4-[*N*-(2-nitrophenyl)sulfamoyl]phenyl}acrylate (10).** To tetrabutyl ammonium bromide (10 mg) in dimethylacetamide (20 mL) was added palladium(II) acetate (45 mg), IPr.HCl[13] (136 mg) and $Cs_2CO_3$ (6.52 g) and nitrogen gas was bubbled through the stirred mixture for 15 minutes. **11** (3.57 g; 10 mmol) was added, followed by methyl acrylate (1.43 mL; 1.37 g; 38 mmol), and the flask sealed with a septum, (pierced with a needle to release pressure), and heated at 140 °C for 1 hour. A further 0.5 mL methyl acrylate was added, and heating continued for a further hour. After this time, the mixture was cooled, added to water, and extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated, and purified by column chromatography (hexane/ethyl acetate 10/1) to give **10** (1.87 g; 52 %) as a pale yellow powder. Mp 134.5-135.5 °C. $\nu_{max}/cm^{-1}$ 3278, 1712, 1350, 1328. $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 3.82 (3H, s, $CH_3$), 6.49 (1H, d, *J* 16.0, CH=C*H*CO), 7.19 (1H, m, ArH), 7.58-7.66 (4H, m), 7.84-7.87 (3H, m), 8.12 (1H, dd, *J* 1.5, 8.4, ArH), 9.90 (1H, s, NH). Found C 52.2, H 3.8, N 7.9. Calc. for $C_{16}H_{14}N_2O_6S$ C 53.0, H 3.4, N 7.7.

**(*E*)-Methyl 3-{4-[*N*-(2-aminophenyl)sulfamoyl]phenyl}acrylate (14).** To a refluxing solution of **10** (1.84 g; 5.08 mmol) in ethanol (8 mL) and glacial acetic acid (1 ml) was added iron powder (2.06 g) portionwise followed by $FeCl_3.6H_2O$ (0.24 g). Refluxing was continued for 3 hours, then the reaction mixture was cooled and filtered. Water was added, and the mixture repeatedly extracted with ether. The ether layers were combined and concentrated to give a yellow oil. Addition of a small amount of ethanol led to the precipitation of a yellow solid after a short time, which was filtered to give title compound as a yellow crystals (1.16 g; 69 %). mp 163-164.5 °C $\nu_{max}/cm^{-1}$ 3498, 3392, 3141, 1692, 1637, 1610, 1499, 1326. $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 3.83 (3H, s, Me), 4.10 (2H, bs, $NH_2$), 6.00 (1H, s, NH), 6.44-6.55 (2H, m, ArH), 6.53 (1H, d, *J* = 16.1, CH=C*H*CO), 6.76 (1H, d, *J* = 8.0, ArH), 7.07 (1H, t, *J* = 7.0, ArH), 7.60 (2H, d, *J* = 6.4, ArH), 7.69 (1H, d, *J* = 16.1, C*H*=CHCO), 7.76 (2H, d, *J* = 8.4, ArH). $\delta_C$ 52.0, 117.3, 118.7, 120.5, 121.3, 128.2, 128.4, 128.6, 129.4, 138.9, 139.9, 142.5, 144.7, 166.7. Found C 57.4, H 4.8, N 8.3. Calc. for $C_{16}H_{16}N_2O_4S$ C 57.8, H 4.9, N 8.4%.

**(*E*)-Methyl 3-{4-[*N*-(2-iodophenyl)sulfamoyl]phenyl}acrylate (9).** To a stirred suspension of **14** (1.66 g; 5 mmol) in ice (2.5 g), water (2.5 mL) and $H_2SO_4$ (0.325 mL) at 0 °C was added a solution of $NaNO_2$ (0.36 g) in water (0.5 mL). The mixture was stirred for 20 mins at 0 °C, after which time further $H_2SO_4$ was added (0.5 mL). The mixture was poured into a solution of KI (1 g) in $H_2O$ (1 mL), and a catalytic amount of Cu powder was added. The mixture was warmed to 50 °C, then cooled. The solid was filtered, and purified by column chromatography to give **9** as a white powder (0.724 g; 33 %) mp 146-151 °C. $\nu_{max}/cm^{-1}$ 1728, 1640, 1589, 1396, 1318. $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 3.81 (3H, s, $CH_3$), 6.50 (1H, d, *J* = 16.0, CH=C*H*CO), 7.50 (1H, dt, *J* = 1.0, 8.2), 7.61-7.71 (4H, m, ArH), 8.08-8.14 (4H, m, C*H*=CHCO, ArH). $\delta_C$ 52.1, 112.0, 120.8, 122.6, 126.1, 128.6, 128.9, 130.5, 131.6, 137.7, 141.0, 141.7, 145.5, 166.3.

**(*E*)-Methyl 3-{4-[2-(1-hydroxy-4-oxocyclohexa-2,5-dienyl)-*1H*-indol-1-ylsulfonyl]phenyl}acrylate (8).** Prepared from **9** and **5** according to the standard method described above. (10%) mp 204.5-205.5 °C. $\nu_{max}/cm^{-1}$ 3942, 1720, 1672, 1629. $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 3.80 (3H, s, $CH_3$), 5.37 (1H, s, OH), 6.33 (2H, d, *J* = 10.3, C(OH)C*H*), 6.45 (1H, d, *J* = 16.0, CH=C*H*CO), 6.81 (1H, d, *J* =

0.5, ArH), 7.23 (1H, m, ArH), 7.32 (1H, td, *J* 7.3, 1.3, ArH), 7.43 (1H, d, *J* 7.8, ArH), 7.52-7.60 (5H, m), 7.88 (2H, d, *J* = 8.4, ArH), 8.00 (1H, dd, *J* 0.6, 8.5, ArH). $\delta_C$ 52.1, 67.5, 114.1, 115.2, 121.9, 122.1, 124.9, 126.4, 127.3, 127.8, 128.3, 128.6, 138.1, 138.2, 140.1, 140.7, 141.8, 147.3, 166.4, 184.1. Found C 63.7, H 4.3, N 3.3. Calc. for $C_{24}H_{19}NO_6S$ C 64.1, H 4.3, N 3.1.

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