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Antitumour Benzothiazoles. Part 10: The Synthesis and Antitumour Activity of Benzothiazole Substituted Quinol Derivatives

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Abstract—The synthesis of a series of new antitumour agents, the benzothiazole substituted quinol ethers and esters, is reported via the hypervalent iodine mediated oxidation of hydroxylated 2-phenylbenzothiazoles. The products were found to be active in vitro against human colon and breast cancer cell lines with IC_{50} values in the nanomolar range.

The hypervalent iodine reagent, [di(acetoxy)iodo]-benzene (DAIB) and its trifluoroacetate analogue, have emerged in recent years as mild and selective oxidising agents for a wide range of phenolic substrates.[1] In addition, it has recently been reported that the oxidation products of bioactive phenols may be more active as antitumour agents than their reduced counterparts.[2] With these observations in mind, we initiated a program of research looking into the antitumour activity of novel chemically diverse oxidation products of biologically active phenols.[3] As an extension to our interest in the area of hydroxylated tyrosine kinase inhibitors,[4] we have recently described how control of structural diversity can be achieved for the oxidation of tyrphostins using DAIB[5] according to the reaction conditions employed and the choice of phenol.

In this paper, the novel products arising from the oxidation of 2-(4-hydroxyphenyl)benzothiazole (**1**), namely quinol ester **3a** and ethers **3b–e**, and their potent and selective in vitro activity against human tumour cell lines is described. Products of type **3** represent a distinct, but structurally related, series of antitumour agents compared to the 2-(4-aminophenyl)benzothiazoles discovered and under development in our laboratories.[6] The oxidation of 2-(3-hydroxyphenyl)benzothiazole (**2**) and 6-hydroxy-2-phenylbenzothiazole (**5**) under analogous conditions to give 4,4-dialkoxy-3-(benzothiazol-2-yl)cyclohexa-2,5-dienones (**4a**,**b**) and 7,7-dialkoxy-6,7-dihydro-6-oxo-2-phenylbenzothiazoles (**6a**,**b**) respectively and evaluation of their antitumour properties is also described.

Chemistry

The precursor phenols for the oxidation studies are readily synthesised via condensation of *o*-aminothiophenol with 4- or 3-hydroxybenzaldehyde[7] under Dean–Stark conditions to give the product 2-(4-hydroxyphenyl)- and 2-(3-hydroxyphenyl)benzothiazoles **1** and **2** respectively. Treatment of 2-(4-hydroxyphenyl)-benzothiazole **1** with DAIB in acetic acid and in a range of alcohols as shown in Scheme 1 gives rise to a series of novel benzothiazole-substituted quinol ester and ether derivatives.[8] Although the yields for the oxidation reactions described are modest, the products resulting from the oxidation represent unusual examples of heteroaromatic quinol derivatives and are stable solids at ambient temperature. Previous examples of this type of oxidation reaction have been confined to the corresponding alkyl-[9] or phenyl-substituted quinol methyl ethers prepared from the precursor phenols via DAIB[10] or electrochemical[11] oxidation.

The corresponding oxidation of 2-(3-hydroxyphenyl)-benzothiazole (**2**) using two equivalents of DAIB in methanol or ethanol to give 4,4-dimethoxy- or 4,4-diethoxy-3-(benzothiazol-2-yl)cyclohexa-2,5-dienone **4a** or **4b** respectively[12] is outlined in Scheme 2.

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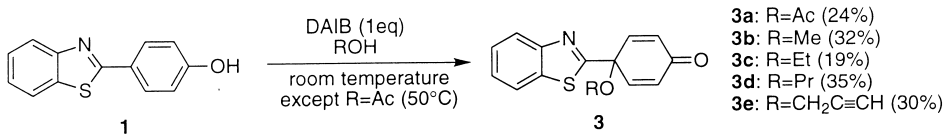
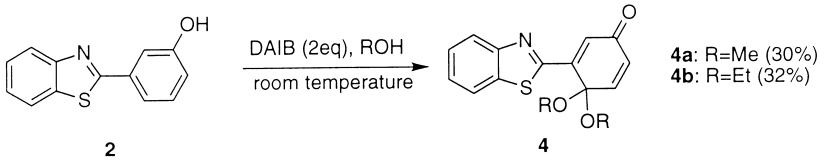
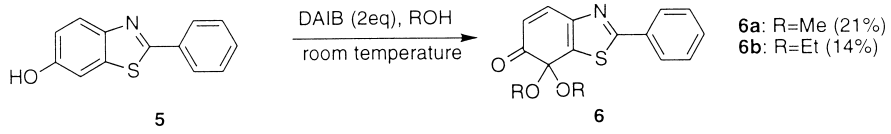


Scheme 1. DAIB oxidation of 2-(4-hydroxyphenyl)benzothiazole **1**.



Scheme 2. DAIB oxidation of 2-(3-hydroxyphenyl)benzothiazole **2**.



Scheme 3. DAIB oxidation of 6-hydroxy-2-phenylbenzothiazole **5**.

DAIB oxidation of 6-hydroxy-2-phenylbenzothiazole (**5**)[13] gave similar results; the major product arising from oxidation (two equivalents of DAIB) in methanol or ethanol being 7,7-dialkoxy-6,7-dihydro-6-oxo-2-phenylbenzothiazoles **6a** or **6b**[14] (Scheme 3).

Biological Results

Compounds **3a**–**e** and **4a**,**b** have been evaluated for in vitro antitumour activity in the human colon cancer cell lines HCT-116 (wt p53, mutant *ras)* and HT29 (mutant p53, wt *ras)* and also in the breast cell lines MCF-7 (oestrogen receptor positive) and MDA468 (oestrogen receptor negative). IC_{50} values (μM) for each cell line were determined using the three day MTT assay previously used for studies on the antitumour 2-(4-aminophenyl)benzothiazole series.[5] IC_{50} values for the phenolic starting materials were also determined. The results of these studies are shown in Table 1.

A number of interesting conclusions can be drawn from the results shown in Table 1:

Table 1. IC_{50} (μM) values for compounds **1**,**2**, **3a**–**e** and **4a**,**b** against colon (HCT-116 and HT29) and breast (MCF-7 and MDA468) cell lines in vitro (3 day assay)[a]

Compound	HCT-116	HT29	MCF-7	MDA468
1	>100	83.7	53.4	0.14[b]
2	>100	78.7	51.8	0.05[b]
3a	0.24	0.52	0.23	0.09
3b	0.60	2.6	0.56	0.51
3c	0.89	1.98	0.51	0.74
3d	0.27	1.10	0.31	0.19
3e	0.53	1.81	0.28	0.77
4a	22.2	40.5	19.1	15.4
4b	1.18	14.7	1.80	3.7

[a]Values are the mean of three experiments.
[b]Indicates biphasic dose–response relationship.[6]

(i) In both colon cell lines tested quinol ester compound **3a** was the most potent (0.24 μM for HCT-116). All the oxidation products tested were found to be more active in the HCT-116 cell line (wt p53, mutant *ras*) than the HT29 (mutant p53, wt *ras*).

(ii) In three of the four cell lines tested the oxidation product quinol derivatives **3**–**4** were found to be significantly more active than the phenols from which they were derived, providing some validation of our original hypothesis that the oxidation products would show increased antitumour activity. The exception to this observation was the breast cell line MDA468 (oestrogen receptor negative), where compounds **1** and **2** were found to be potent and to exhibit an unusual biphasic dose–response relationship.[6]

Conclusions

A novel series of antitumour quinol derivatives has been synthesised and evaluated in vitro against human colon and breast cancer cell lines. The most potent compounds in the series exhibit nanomolar activity in these cells. Further work is underway to build on these exciting preliminary findings through the synthesis and evaluation of new examples of this class of compound and through biological mechanism of action studies.

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References and Notes

1. Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1891.
2. Rambas, L.; McMurray, J. S.; Budde, R. J. A. *Cancer Res.* **1994**, *54*, 867.
3. Wells, G. PhD thesis, University of Nottingham, 1998.
4. Stevens, M. F. G.; McCall, C. J.; Lelieveld, P.; Alexander, P.; Richter, A.; Davies, D. E. *J. Med. Chem.* **1994**, *37*, 1689.
5. Wells, G.; Seaton, A.; Stevens, M. F. G. *J. Med. Chem.*, in press.
6. Bradshaw, T. D.; Wrigley, S.; Shi, D.-F.; Schultz, R. J.; Paull, K. D.; Stevens, M. F. G. *Brit. J. Cancer* **1998**, *77*, 745.
7. Ben-Allum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395.
8. ^{1}H NMR data for compounds of type **3: 4-(benzothiazol-2-yl)-4-acetoxycyclohexa-2,5-dienone (3a).** ^{1}H NMR (DMSO-d_6) δ 8.18 (1H, m, ArH), 8.04 (1H, m, ArH), 7.54 (2H, m, H-5′, H-6′), 7.37 (2H, d, *J* 10.1 Hz, H-2′, H-6′), 6.45 (2H, d, *J* 10.1 Hz, H-3′, H-5′), 2.22 (3H, s, CH_3CO); **4-(benzothiazol-2-yl)-4-methoxycyclohexa-2,5-dienone (3b).** ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, d, *J* 7.8 Hz, ArH), 7.94 (1H, d, *J* 8.0 Hz, ArH), 7.49 (1H, td, *J* 1.3, 7.8 Hz, ArH), 7.47 (1H, td, *J* 1.3, 7.5 Hz, ArH), 6.98 (2H, d, *J* 9.5 Hz, H-3′, H-5′), 6.57 (2H, d, *J* 9.0 Hz, H-2′, H-6′), 3.51 (3H, s, CH_3O); **4-(benzothiazol-2-yl)-4-ethoxycyclohexa-2,5-dienone (3c).** ^{1}H NMR ($CDCl_3$) δ 8.04 (1 H, dd, *J* 1.0, 7.0 Hz, ArH), 7.94 (1H, dd, *J* 1.3, 8.0 Hz, ArH), 7.51 (1H, td, *J* 1.5, 7.8 Hz, ArH), 7.44 (1H, td, *J* 1.5, 7.8 Hz, ArH), 7.01 (2H, d, *J* 10.3 Hz, H-3′, H-5′), 6.53 (2H, d, *J* 10.3 Hz, H-2′, H-6′), 3.70 (2H, q, *J* 6.8 Hz, CH_2), 1.32 (3H, t, *J* 7.0 Hz, CH_3); **4-(benzothiazol-2-yl)-4-propyloxycyclohexa-2,5-dienone (3d).** ^{1}H NMR ($CDC1_3$) δ 8.00 (1H, m, ArH), 7.90 (1H, m, ArH), 7.43 (2H, m, ArH), 6.94 (2H, d, *J* 10.3 Hz, H-3′, H-5′), 6.50 (2H, d, *J* 10.3 Hz, H-2′, H-6′), 3.55 (2H, t, *J* 6.5 Hz, OCH_2), 1.70 (2H, m, $CH_2CH_2CH_3$), 1.00 (3H, t, *J* 7.5 Hz, CH_3); **4-(benzothiazol-2-yl)-4-(2′-propynyloxy)cyclohexa-2,5-dienone (3e).** ^{1}H NMR ($CDCl_3$) δ 8.03 (1H, m, ArH), 7.93 (1H, m, ArH), 7.49 (2H, m, ArH), 7.06 (2H, d, *J* 10.3 Hz, H-3′, H-5′), 6.55 (2H, d, *J* 10.3 Hz, H-2′, H-6′), 4.31 (2H, d, *J* 2.3 Hz, OCH_2), 2.57 (1H, t, *J* 2.5 Hz, C≡CH).
9. Mitchell, A. S.; Russell, R. A. *Tetrahedron Lett.* **1993**, *34*, 545.
10. Callinan, A.; Chen, Y.; Morrow, G. W.; Swenton, J. S. *Tetrahedron Lett.* **1990**, *31*, 4551.
11. DeSchepper, R. E.; Swenton, J. S. *Tetrahedron Lett.* **1985**, *26*, 4831.
12. ^{1}H NMR data for compounds of type **4: 3-(benzothiazol-2-yl)-4,4-dimethoxycyclohexa-2,5-dienone (4a).** ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, dd, *J* 0.8, 7.8 Hz, H-4), 7.96 (1H, dd, *J* 0.8, 7.8 Hz, H-7), 7.50 (3H, m, H-5, H-6, H-2′), 6.87 (1H, d, *J* 10.3 Hz, H-5′), 6.58 (1H, dd, *J* 2.l, 10.5 Hz, H-6′), 3.34 (6H, s, 2×CH_3O); **3-(benzothiazol-2-yl)-4,4-diethoxycyclohexa-2,5-dienone (4b).** ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, m, H-4), 8.00 (1H, m, H-7), 7.55 (1H, d, *J* 2.3 Hz, H-2′), 7.53 (2H, m, H-5, H-6), 6.89 (1H, d, *J* 10.3 Hz, H-5′), 3.63 (2H, m, CH_2O), 3.44 (2H, m, CH_2O), 1.24 (6H, t, *J* 7.0 Hz, 2*x* CH_3O).
13. Shi, D.-F. PhD thesis, University of Nottingham, 1995.
14. ^{1}H NMR data for compounds of type **6: 6,7-dihydro-7,7-dimethoxy-6-oxo-2-phenylbenzothiazole (6a).** ^{1}H NMR($CDCl_3$) δ 8.00–7.92 (2H, m, H-2′, H6′), 7.63 (1H, d, *J* 10.1 Hz, H-5), 7.52–7.46 (3H, m, H-3′, H-4′, H-5′), 6.17 (1H, d, *J* 10.0 Hz, H-4), 3.45 (6H, s, 2×CH_3O); **7,7-diethoxy-6,7-dihydro-6-oxo-2-phenylbenzothiazole (6b).** ^{1}H NMR ($CDCl_3$) δ 8.00–7.93 (2H, m, H-2′, H6′), 7.64 (1H, d, *J* 10.1 Hz, H-5), 7.52–7.47 (3H, m, H-3′, H-4′, H-5′), 6.18 (1H, d, *J* 10.0 Hz, H-4), 3.68 (4H, dd, *J* 2.3, 7.0 Hz, 2×CH_2), 1.23 (6H, t, *J* 7.0 Hz, 2×CH_3).