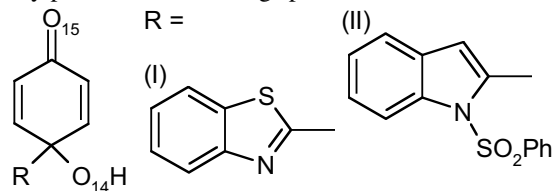


W0145

Crystal Structures of Two Anti-Cancer Quinols and Models of Their Thioredoxin Binding. C.H. Schwalbe,¹ R. Ren,¹ D.L. Rathbone,¹ P.R. Lowe,¹ A.D. Westwell,² M.F.G. Stevens,² ¹Aston Pharmacy School, Aston Univ., Birmingham B4 7ET, UK, ²The Pharmacy School, Univ. of Nottingham, University Park, Nottingham NG7 2RD, UK.

Quinols with a 6/5-heterobicyclic substituent have shown selectivity against renal and colon cancer cell lines. The cyclohexadienone moiety can act as a "double Michael acceptor". Database mining of the NCI 60 cell screening panel suggests that the protein thioredoxin with two active-site cysteine residues 3.9 Å apart (PDB structure 1ERT) may provide the attacking species.



Structure determination was facile for (I). However, (II) has $Z' = 2$ in space group $P2_1/c$ with similarity of a and c that leads to twinning and partial overlap of hkl and $l-kh$ reflections. Eventually a specimen was found with twin component fraction < 0.05 . The quinol geometry is similar in both compounds; however, N-C-C-O14 is $-168.8(2)^\circ$ in (I) but $-68.3(5)$ and $-74.5(5)^\circ$ in (II), which places one sulfonyl O atom near O14-H. This OH group also interacts intermolecularly with O15, via a water bridge in (I) and directly in (II). Michael adducts of 2 x MeSH and various dithiols including the Cys-Gly-Pro-Cys fragment from 1ERT have been built, leading to a thioredoxin adduct model that can accommodate (I) and (II).