

Synthesis and Biological Evaluation of Cicerfuran, an Antifungal Compound from Chickpea Roots

by

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ABSTRACT

Cicerfuran [2-(2'-methoxy-4',5'-methylenedioxyphenyl)-6-hydroxy-benzofuran] is a potently anti-fungal 2-arylbenzofuran previously isolated for the first time from roots of some species of *Cicer* (chickpea). This thesis describes the synthesis of the natural product and several analogues to evaluate their biological activity and determine any structure function relationships. A novel scheme was used comprising five steps involving the synthesis of hydroxylated styrenes by biotransformation after methylation their, palladium-catalysed coupling with multi-oxygenated aryl halides followed by epoxidation and acid-catalysed cyclisation. The styrenes were prepared synthetically through chemical processes because decarboxylation of hydroxylated cinnamic acid by Baker's yeast gave poor yields. Two analogues of cicerfuran, 2-(2'-methoxy-4',5'-methylenedioxyphenyl)benzofuran and 2-(2'-methyl-4',5'-methylenedioxyphenyl)benzofuran were prepared following the proposed synthetic scheme. However, Heck coupling failed for the synthesis of stilbenes required for cicerfuran. Synthesis of arylbenzofuran structures was successfully attempted by palladium-catalysed heteroannulation reaction of acetylenes with oxygenated aryl halides and three arylbenzofurans, 2-phenylbenzofuran, 2-(3',4'-methylenedioxyphenyl)benzofuran and 2-(2-methoxy-4',5'-methylenedioxyphenyl)benzofuran were synthesised. The synthesis of cicerfuran was also attempted by palladium-catalysed coupling, specifically of 2-methoxy-4,5-methylenedioxyacetylene with 2,4-diacetoxyiodobenzene. Although the presence of cicerfuran was confirmed in the reaction mixture by GC linked-mass spectrometry it could not be purified. Finally, using sesamol (3,4-methylenedioxyphenol) as the starting material, cicerfuran was successfully synthesised *via* a series of eight reactions. The key intermediate, 1-(2'-methoxy-4',5'-methylenedioxyphenyl)-2-(2,4-di-*o-tert*-butyldimethylsiloxyphenyl)ethene, was obtained *via* a Wittig reaction between 2-methoxy-4',5'-methylenedioxybenzyltriphenylphosphonium bromide and 2,4-di-*o-tert*-butyldimethylsiloxybenzaldehyde. This was epoxidised and after removing the protecting groups, it was finally treated with *p*-toluene sulphonic acid to give cicerfuran. The chromatographic and spectroscopic properties of natural and synthetic cicerfuran were identical, confirming the structure proposed for the natural compound. The biological activity of cicerfuran and analogues was evaluated against four fungal species and two bacterial species. The biological activity of arylbenzofuran structures was found to be associated with the presence of a hydroxy group at the 6-position. Cicerfuran was found to be active against *B. cinerea* a causative agent of botrytis grey mold and *A. niger* a causative agent of plant wilting. Cicerfuran also showed activity against both gram-positive and gram-negative bacteria. The biological activity of some stilbene intermediates was also evaluated.