

**P006** Identification and characterisation of non-competitive antagonists of the CB1 cannabinoid receptor  
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The cannabinoid receptors continue to stimulate much research interest, and CB1 antagonists may have therapeutic application in the treatment of obesity and cognitive disorders. To date, reports of CB1 antagonists have focused around diarylpyrazole derivatives which act as competitive antagonists at the binding site for the CB1 agonist, CP-55-940. By screening of the Organon compound collection with a functional assay of CB1 antagonism (based on regulation of luciferase reporter gene expression by the human CB1 receptor) we discovered a new class of compounds, subsequently shown to act as non-competitive CB1 antagonists. Org 144881 is a potent antagonist of CP-55-940-induced luciferase activity ( $pEC_{50} = 7.5$ ). However, in contrast to other CB1 antagonists (e.g. SSR141716), Org 144881 was unable to displace [ $^3$ H]CP-55-940 binding to the CB1 receptor. Here we present data confirming that Org 14488 acts as non-competitive antagonist of the [ $^3$ H]CP-55-940 binding site of the CB1 receptor. To our knowledge, this is the first example of a non-competitive antagonist for the CB1 receptor and suggests that multiple binding sites exist that may be exploited for the development of novel, selective ligands.