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## **MDM2 inhibitors from natural products, results of a HTS screen using electrochemiluminescent detection.**

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### **Abstract:**

MDM2 is a ring finger E3 ubiquitin ligase that regulates both level and location of p53 within cells. Approximately half of all cancers have dysfunctionally low levels of p53, half of this set can be attributed to increased function of MDM2 making inhibition of this enzyme a desirable goal. Data from 143,874 unique extracts from the National Cancer Institute natural products extract library screened for inhibition of MDM2 self-ubiquitination using electrochemiluminescent detection technology will be presented. Briefly, MDM2-GST fusion was bound to glutathione-coated plates, a pre-incubated solution of E1, E2 (UbCH5B), Ub and ATP was added to the plate with extract, after incubation the plates were washed, ruthenylated anti-polyUb Ab was added and the plates were read. Of the 74,832 aqueous and 69,042 organic extracts tested, 2835 (1401 aqueous, 1434 organic) were found to inhibit MDM2 mediated self-ubiquitination, a summary of the taxonomy of these extracts will be presented. We also tested 3523 unique pure natural product compounds from the NCI repository and identified 31 'hits' of which five inhibited MDM2 ubiquitination greater than 50%.