

NOVEL SULFONANILIDES SUPPRESS AROMATASE EXPRESSION IN BREAST CANCER CELLS BY TARGETING INTRACELLULAR SIGNALING PATHWAYS INDEPENDENT OF COX-2 INHIBITION

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Prostaglandin E2 (PGE2), the major product of cyclooxygenase-2 (COX-2), stimulates aromatase gene expression via protein kinase A and C signaling pathways. This biochemical mechanism may explain epidemiological observations of the beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on breast cancer. Previous studies demonstrate that COX-2 inhibitors decrease aromatase activity at the transcriptional level. However, COX-2 inhibitors which have similar IC50 values for COX-2 inhibition, differ significantly in their ability to suppress aromatase activity. This observation suggests differences in the mechanisms by which COX-2 inhibitors suppress aromatase activity in breast cancer cells. It is noteworthy that the COX-2 selective inhibitor NS-398 inhibits aromatase activity more prominently than other COX-2 inhibitors. *N*-Methyl NS-398, which does not have COX-2 inhibitory activity, can decrease aromatase activity and transcription in MCF-7 and MDA-MB-231 breast cells similarly as NS-398. Further investigations find that the compounds only decrease aromatase activity stimulated by forskolin/phorbol ester from the transcriptional level in breast cells. It does not affect aromatase stimulated by dexamethasone. The compounds can also suppress MCF-7 cell proliferation stimulated by testosterone. Microsomal aromatase inhibition studies proves that the compounds have very weak aromatase inhibitory activity. These results suggest that NS-398 suppresses aromatase activity by interfering with adenosine 3',5'-cyclic monophosphate (cAMP) driven aromatase transcription in breast cells and this suppression is independent of its COX-2 inhibitory activity.

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