

TRI-METHOXY BENZYLIDENE SUBSTITUTED 1, 3-DIHYDRO-INDOL-2-ONE ANALOGS AS ANTI-PROLIFERATIVE, APOPTOSIS INDUCING AND ANTI-MICROTUBULE AGENTS

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Compounds that contain 2-indolinone moiety have been reported to exhibit tyrosine kinase inhibitory activities. For example, SU 6668 and SU 11248 are multitargeted tyrosine kinase inhibitors of VEGFR-1, KDR, PDGFR and FLT-3. SU 11248 which potently inhibits c-KIT is also active against imatinib resistant KIT (V559D/T670I) in GIST, gastrointestinal stromal tumor. Several tyrosine kinase inhibitors (TKIs) have demonstrated effective antitumor activity and are being investigated in clinical trials. In our search for new anti-cancer agents with 2-indolineone moiety, a series of mono, di- and tri-methoxy benzylidene substituted 1, 3-dihydro-indol-2-one analogs were synthesized and tested for their anti-proliferative activity on cancer cell lines. Several of the methoxy (mono, di and tri) benzylidene substituted analogs exhibited good anti-proliferative activity with IC₅₀ values in low nanomolar range against prostate and breast cancer cells^{2,3}. The inhibition of proliferation correlated with cell cycle arrest in G₂/M phase of prostate carcinoma (PC-3) cells and *in vitro* mammalian tubulin polymerization inhibiting activity. These compounds inhibited the polymerization of purified mammalian tubulin to microtubule polymers similar to colchicine and were identified to be colchicine site binder on tubulin. Some of the potent analogs were tested for their anti-microtubule activity on mammalian tubulin and had IC₅₀ values in low micromolar range. From modeling studies it was identified that these compounds were conformationally restricted analogs of combretastatin A-4, a known colchicine site anti-microtubule agent currently in clinical trials for various cancers. These compounds induced apoptosis in PC-3 cells as observed from cytoplasmic histone-associated DNA fragments and caspase-3 activity in cell extracts. We also wanted to see if these compounds could have potential as dual anti-angiogenic and anti-mitotic agents like combretastatin A-4 and also as they were derived from KDR inhibitor, SU 5416². The most active analog of the series was docked in the catalytic pocket of VEGFR-2 (KDR) kinase and tightly occupied the ATP binding site.

Structures and biological activities of the various methoxy benzylidene substituted 1, 3-dihydro-indol-2-one analogs will be presented.

REFERENCES

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