Design, Synthesis and in vitro Anti-Cancer evaluation of Novel Derivatives of 2-(2-Methyl-1,5-diaryl-1H-pyrrol-3-yl)-2-oxo-N-(pyridin-3-yl)acetamide.

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Abstract

OBJECTIVE:

Several anti-tubulin agents were introduced for the cancer treatment so far. Despite successes in the treatment of cancer, these agents cause toxic side effects, including peripheral neuropathy. Comparing anti-tubulin agents, indibulin seemed to cause minimal peripheral neuropathy, but its poor aqueous solubility and other potential clinical problems have led to its remaining in a preclinical stage.

METHODS:

Here in, indibulin analogues were synthesized and evaluated for their in vitro anti-cancer activity using MTT assay (on the MCF-7, T47-D, MDA-MB231 and NIH-3T3 cell lines), annexin V/PI staining assay, cell cycle analysis, anti-tubulin assay and caspase 3/7 activation assay.

RESULTS:

One of the compounds, 4a, showed good anti-proliferative activity against MCF-7 cells (IC50: 7.5 µM) and low toxicity on a normal cell line (IC50 > 100µM). All of the tested compounds showed lower cytotoxicity on normal cell line in comparison to reference compound, indibulin. In the annexin V/PI staining assay, induction of apoptosis in the MCF-7 cell line was observed. Cell cycle analysis illustrated an increasing proportion of cells in the sub-G-1 phase, consistent with an increasing proportion of apoptotic cells. No increase in G2/M cells was observed, consistent with the absence of anti-tubulin activity. A caspase 3/7 assay protocol showed that apoptosis induction by the more potent compounds was due to activation of caspase 3.

CONCLUSION:

newly synthesized compounds exerted acceptable anticancer activity and further investigation on current scaffold would be beneficial.

KEYWORDS:

Apoptosis; Cancer; Caspases 3/7; Indibulin; Pyrrole; Synthesis