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Amino- and fluoro-substituted quinoline-4-carboxylic acid derivatives: MWI synthesis, cytotoxic activity, apoptotic DNA fragmentation and molecular docking studies

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Cancer is one of the leading causes of death worldwide and is ranked second after cardiovascular diseases. It is a complex and evolving disease with the formation of defects at multiple genetic steps in a cell. In continuation of our research work on amino substituted quinoline-4-carboxylic acid derivatives, microwave irradiated and conventional heating methods were used for synthesis of target compounds, 6-fluoro-2-phenyl-7-substituted amino-quinoline-4-carboxylic acid derivatives. Benzaldehyde, pyruvic acid, and 3-chloro-4-fluoroaniline in absolute ethanol media condensed, and cyclized to form intermediate 7-chloro-6-fluoro-2-phenyl-quinoline-4-carboxylic acid. This intermediate reacted with various substituted amines attaining desired products. Products obtained by microwave synthesizer showed short reaction time and good yield. All compounds were characterized by spectral and elemental analysis and were tested for effect on cellular viability against various carcinoma cell lines viz. MCF-7, HELA, Hep-2, NCI, HEK-293, and VERO by XTT bioassay at 24 h of drug exposure using doxorubicin and methotrexate as standard drugs. Majority of the compounds proved to be more potent than doxorubicin and few compounds exhibited significant anticancer activity. Apoptotic DNA fragmentation was carried out on MCF-7 and HEK-293 cell lines and found that few compounds exhibited excellent DNA fragmentation pattern confirming apoptosis. Docking study was performed by Surflexdock to establish probable mechanism of action of synthesized compounds using X-ray crystallographic structure of the ATPase domain of hTopoIIa. Docking experiments confirmed good correlation between calculated interactions with the hTopoIIa and the observed IC50 values. The present study of quinoline-4-carboxylic acid derivatives may be considered as promising lead for future design of potent hTopoIIa inhibitors as novel anticancer agents.

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Integrative studies with multidisciplinary approach from standardized extracts in the treatment of peptic ulcer disease

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The increase in human life expectancy has required the development of new drugs to treat several chronic diseases such as peptic ulcer disease (PUD). The PUD is a complex and multifactorial process including bacterial infections, the increase of acid secretion, generation of reactive oxygen species (ROS), inhibition of the endogenous PGs, and the degradation of the extracellular matrix. This disease has been increasing in elderly people because of the intrinsic weak mucosal barrier induced by aging and also the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs). The last decade has offered new insights in the preventative therapy and also the healing of PUD. The synergistic efficiency of standardized herbal drugs could be the new perspective for treatment of this disease. In our project entitled "Standardized extracts for the treatment of chronic disease", our research group realized integrative studies with multidisciplinary approach with phytochemical, pharmacological and toxicological assays. Based on these integrative studies we evaluated more than 20 medicinal species according to the pharmacopeial standard and evaluated the ensured efficacy and safety of these herbal medicines as antiulcer drug. The antiulcer studies of these extracts were investigated against different ulcerogenic agents including NSAID, HCl, pyloric ligature, absolute ethanol and ischemia–reperfusion procedure. We evaluated the gastroprotective effect of extracts by analyzing the gastric juice secretion, mucus, nitric oxide (NO), sulfhydryl compound, vanilloid receptor, glutathione (GSH) levels, and myeloperoxidase (MPO) activity in the gastric and duodenal mucosa. We also evaluated the gastric and duodenal healing effects of extracts and evaluated the effect of matrix metalloproteinase activity (MMP-2 and MMP-9) and roles of VEGF, PCNA, and COX-2 in cell proliferation.

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