Research in Pharmaceutical Sciences, 2012;7(5)
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Synthesis and cytotoxic evaluation of bidentate 3-hydroxypyridin-4-ones Iron chelating agents

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Background and Aims: All cells require iron, and neoplastic cells have a high iron requirement related to their proliferation. In the absence of iron, cells are unable to progress in the cell cycle. Previous studies have shown that desferrioxamine (DFO), as an iron chelator, is able to inhibit DNA synthesis and cell proliferation in a number of hepatoma and neuroblastoma. DFO has been proposed for the multi-agents chemotherapy of neuroblastoma. Base on this strategy, a range of 3-hydroxypyridin-4-one derivatives (HPOs) as orally active iron chelators were synthesized. The partition coefficient (Kpart) and in vitro cytotoxic activity of these liands were also determined..

Methods: For the synthesis of HPOs, the hydroxyl group of 3-hydroxypyran-4-one (maltol) was protected by using benzyl chloride and then it was reacted with suitable primary amines to produce the benzylated HPOs. Subsequently, the protecting group was removed by using hydrogenation method to yield the corresponding bidentate 1-substituted-3-hydroxypyridin-4-ones. The Kpart values of compounds were determined in aqueous/octanol system buffer (pH=7.4). The cytotoxic effects of synthesized compounds were also evaluated against HeLa cancer cells and IC50 of HPOs was determined using MTT assay.

Results: In this work, six final of HPO derivatives were synthesized. Identification and structural elucidation of compounds were achieved by elemental analysis, 1H-NMR, Mass and IR spectra. Among synthesized HPOs, two compounds with Kpart values of 5.02 and 1.52 were shown to possess the lowest IC50 of 30 and 45 µM respectively.

Conclusions: 3-hydroxypyridin-4-ones with high partition coefficients were found to be more hydrophobic which renders them to enter the cells much easier and showed more cytotoxic activity. These bidentate iron chelators are potential cytotoxic agents against cancer cells.

Keywords: 3-Hydroxypyridin-4-ones; Orally active iron chelators; Cytotoxicity; HeLa cell line