**Abstract**

Heme oxygenase (HO) is a cytoprotective enzyme that gets overexpressed under some pathological conditions, like cancer where it provides growth advantage and protection against radiotherapy, chemotheraphy and photodynamic therapy. Earlier studies on HO inhibition were carried out with metalloporphyrins, which not only inhibit HO‐1 but also other constitutively expressed HOs and other heme‐dependent enzymes. Hence, the present study was aimed at synthesizing highly‐substituted imidazole heterocycles as inhibitors of heme oxygenase‐1 (HO‐1). The synthesized compounds were structurally characterized by IR, 1H, 13C NMR, CHN and single crystal XRD analysis. Among the synthesized compounds,compound6(3‐(4,5‐diphenyl‐1H‐imidazol‐2‐yl)‐6‐methoxy‐1H‐quinoline‐2‐one) showed > 50% HO‐1 inhibitory activity at a least concentration of 9.2 μM and like many pharmaceutically important drugs, it showed competitive inhibition which was confirmed by Lineweaver‐Burk plot. Compound 6 was also tested for cytotoxicity against cancer (A549, MG63, MCF7) and normal cell (HEK293). The compound showed maximum efficacy against A549 cell line and moderate activity against other cell lines. In order to determine the molecular interactions of compound 6 with HO, the molecular docking study was carried out using Schrodinger software, which was in good agreement with experimental observations.