



**Figure S1. Detection of hemin and hematin as 616.18 m/z ion.** (A-B). K562 cells were treated with 50  $\mu$ M hemin in presence and absence of NAC (2mM) for 24 h. Extraction of the LMW metabolites ( $5 \times 10^6$  cells) and LC-MS/MS analysis took place, as described in Materials and Methods. Ion chromatograph of the 616.18 m/z ( $M-Cl$ )<sup>+</sup> ( $C_{34}H_{32}ClFeN_4O_4$ ) ( $M$ , hemin) is shown. (C-D) RBCs ( $\sim 2 \times 10^9$ ) were subjected to the same extraction protocol, immediately after their isolation or incubated with 20  $\mu$ M hemin (RPMI, 37°C, 30 min). Ion chromatograph of the 616.18 m/z ( $M'-OH$ )<sup>+</sup> ( $C_{34}H_{32}OHFeN_4O_4$ ) ( $M'$ , hematin) is shown. The area under (AA) the curve of hemin is shown and compared between K562 cells-treated with both NAC and hemin and hemin-only treated cells is less, as found recently by direct measurements of hemin intracellular content (pyridine hemochromagen assay) [31].

Hemin-treated RBCs yielded a more abundant peak at 616.18 m/z, compared with untreated RBCs. A possible explanation for the partially diffused LC ion chromatograph peaks is the high quantity of the molecular ions. The slightly different RTs between hemin and/or hematin between the four samples is justified, since each sample was run separately.