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Synthesis and characterization of quinoline-based thiosemicarbazones and correlation of cellular iron-binding efficacy to anti-tumor efficacy

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ABSTRACT

Iron chelators have emerged as a potential anti-cancer treatment strategy. In this study, a series of novel thiosemicarbazone iron chelators containing a quinoline scaffold were synthesized and characterized. A number of analogs show markedly greater anti-cancer activity than the 'gold-standard' iron chelator, desferrioxamine. The anti-proliferative activity and iron chelation efficacy of several of these ligands (especially compound **1b**), indicates that further investigation of this class of thiosemicarbazones is worthwhile.

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Iron (Fe) chelators are commonly used to treat diseases connected with altered iron metabolism, for example, β-thalassaemia major.[1] However, considering the marked anti-proliferative activity of this group of agents, recent investigations have focused on the anti-cancer efficacy of iron chelators.[2,3] In fact, there are many reports of the anti-proliferative activity of desferrioxamine (DFO), Triapine® and other ligands based on the (thio)urea moiety.[2]

The cytotoxic mechanisms of chelators include: (**1**) the inhibition of cellular iron uptake from the iron-binding protein, transferrin (Tf);[4–7] (**2**) mobilization of iron from cells;[4–7] (**3**) the inhibition of the iron-containing enzyme involved in the rate-limiting step of DNA synthesis, ribonucleotide reductase;[8] and (**4**) the formation of redox-active iron complexes that generate reactive oxygen species (ROS).[5,7] The latter mechanism is significant, especially in the context of recent reports demonstrating the role of ROS generation in increasing the anti-proliferative activity of chelators against tumor cells.[5,7,9]

Alterations in the metabolism of iron[10–13] and copper[14,15] are known to occur in cancer cells and may play a role in angiogenesis[16] and metastasis.[17] The rationale behind the potential application of iron chelators for cancer treatment is due to the higher demand for iron in rapidly proliferating tumor cells in comparison to their normal counterparts.[10–12] The greater requirement for iron in tumor cells results in high levels of the transferrin receptor (TfR1) on the cell surface which binds Tf.[13] Furthermore, the expression of ribonucleotide reductase is markedly higher in neoplastic cells relative to their normal counterparts.[2] Hence, this also increases the sensitivity of cancer cells to iron-depletion.

Although DFO was investigated as an anti-cancer agent, interest in this compound was diverted in favor of more effective ligands such as aroylhydrazones that show greater iron chelation efficacy and cellular permeability.[3] Some of these compounds were shown to have moderate anti-tumor activity that was significantly greater than that of DFO for example, 2-hydroxy-1 naphthylaldehyde isonicotinoyl hydrazone (311; Fig. 1).[18,19] Further structural modifications of this series produced the 2-hydroxy-1-naphthylaldehyde thiosemicarbazone (NT)[20] and di-2-pyridyl ketone isonicotinoyl hydrazone (PKIH) series[21] of chelators (Fig. 1), which showed superior activity.

Abbreviations: Bp44mT, 2-benzoylpyridine-4,4-dimethyl-3-thiosemicarbazone; BpT, 2-benzoylpyridine thiosemicarbazone; DFO, desferrioxamine; DpT, dipyridyl thiosemicarbazone; Dp44mT, di-2-pyridyl ketone-4,4-dimethyl-3-thiosemicarbazone; NT, 2-hydroxy-1-naphthylaldehyde thiosemicarbazone; PKIH, di-2-pyridyl ketone isonicotinoyl hydrazone; ROS, reactive oxygen species; Tf, transferrin; TfR1, transferrin receptor 1; QCIH, 2-quinolinecarboxaldehyde isonicotinoyl hydrazone; QT, quinoline thiosemicarbazone.

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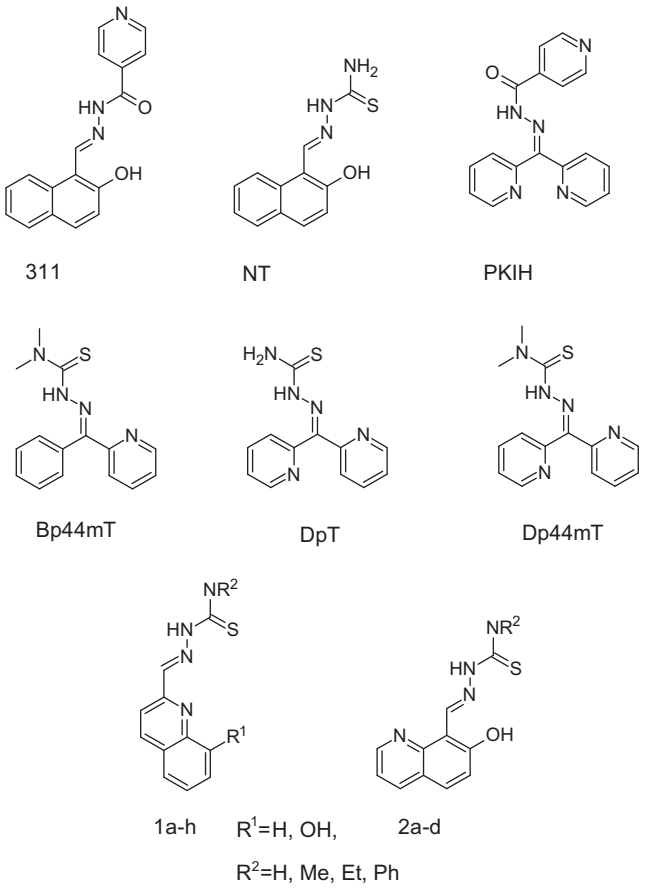
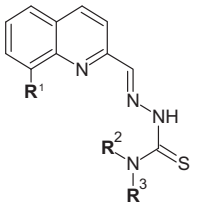
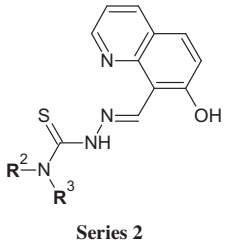


Figure 1. Representative structures of the hydrazones and thiosemicarbazones used to design the quinoline thiosemicarbazone (QT) analogs, **1a**–**h** and **2a**–**d**.

Table 1
The quinoline-based thiosemicarbazones examined in this study





Compd	R^1	R^2	R^3
1a	8-OH	Me	Me
1b	H	Me	Me
1c	8-OH	Me	H
1d	H	Me	H
1e	8-OH	Et	H
1f	H	Et	H
1g	8-OH	Ph	H
1h	H	Ph	H

Compd	R^2	R^3
2a	Me	Me
2b	Et	H
2c	Me	H
2d	Ph	H

The di-2-pyridyl ketone thiosemicarbazone (DpT; Fig. 1) class of chelators are essentially hybrids of these two latter classes of chelators.[7,22] The DpT series, and in particular the chelator, di-2-pyridyl ketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT; Fig. 1), have shown potent and selective anti-tumor activity both in vitro and in vivo against a variety of murine and human xenografts.[7,22,23] For example, Dp44mT has demonstrated marked activity in vivo, reducing the growth of a murine M109 lung cancer by approximately 50% within 5 days of treatment, while at the same time having little effect on normal hematological indices.[7] In addition to the ability of Dp44mT to effectively induce cellular iron-deprivation in vitro, initial studies revealed that the iron complex was redox-active within cells.[5,7] Hence, it was proposed that the anti-tumor activity of these compounds relates both to their ability to bind intracellular iron and to form redox-active iron complexes that generate cytotoxic ROS.[5,24]

More recent studies have led to the 2-benzoylpyridine thiosemicarbazone (BpT) series of ligands (e.g., 2-benzoylpyridine-4,4-dimethyl-3-thiosemicarbazone; Bp44mT; Fig. 1) that show selective anti-tumor activity in vitro and in vivo and which are effective via the intravenous or oral routes.[9,25] Additionally, thiosemicarbazones are more stable in plasma and are advantageous over aldehyde-derived aroylhydrazones (such as 311) which undergo hydrolysis of the hydrazone bond.[26]

In the current study, a series of novel thiosemicarbazones were synthesized as potential anti-cancer agents. These compounds were designed to contain a quinoline scaffold (quinoline thiosemicarbazones; QTs; compounds **1a–h** and **2a**–**d**; Fig. 1 and Table 1). In fact, the quinoline moiety is often a fragmental motif in the design of novel anti-cancer agents[27] (e.g., the clinically used camptothecin derivatives, topotecan and irinotecan)[28] and it was of interest to assess its effect on the biological activity of thiosemicarbazones. In series **1**, the four-atom moiety (N=C–C=N), which is found in the DpT and BpT ligands is maintained (Fig. 1). In contrast, in series **2**, a five-atom fragmental construct (N=C–C=C–OH) similar to 311 or NT (Fig. 1) was preserved, while the four-atom moiety (N=C–C=N) of the DpT and BpT series was extended (N=C–C–C=N). Of the two series of QTs described herein, several analogs acted similarly to Dp44mT, markedly preventing cellular iron uptake and promoting iron mobilization.[5,7,22]

All the QTs herein were synthesized as shown in Figure 2 by reacting the respective quinolinecarbaldehyde (**3**) and thiosemicarbazide (**4**) in a microwave reactor (experimental details for all procedures in this study are described in the Supplementary data). We confirmed the iron chelating ability of these QTs by titrating the two most biologically active analogs (see below), **1b** and **2a** with Fe^{3+} to generate their Fe^{3+} complexes in situ at the following ligand to Fe ratios: 2:1, 2.5:1, 3.3:1, 5:1, and 10:1 (Supplementary Fig. 1). This was carried out in comparison to the well characterized iron chelator, Dp44mT.[5] As previously observed, the electronic spectrum of the Fe^{3+} complex of Dp44mT displayed characteristic intense transitions (400 nm) that spanned into the visible region (Supplementary Fig. 1A).[5] Additionally, isosbestic points were observed at 310 and 365 nm (Supplementary Fig. 1A). The Fe^{3+} complexes of **1b** and **2a** exhibited a similar shift into the visible region in comparision to that of the free ligands. The Fe^{3+} complex of compound **1b** displayed an intense band at 430 nm, with an isosbestic point found at 375 nm (Supplementary Fig. 1B). Similarly, the Fe^{3+} complex of **2a** showed a transition at 450 nm, while isosbestic points were observed at 330 and 385 nm (data not shown). The electronic spectra of the Fe^{3+} complexes of **1b** and **2a** display characteristics that are typical of Fe^{3+} thiosemicarbazone complexes[5,9,29] and confirm their ability to act as iron chelators.

The anti-proliferative activity of the QT analogs was assessed against cancer and non-neoplastic cells, including the human SK-N-MC neuroepithelioma, HCT116 colon cancer cell lines, and normal human dermal fibroblast (NHDF) cells by standard methods.[5,9,19] The SK-N-MC cell line was chosen as the effects of iron chelators are well characterized in this cell line.[5,9] Additionally, we examined whether the p53 status of HCT116 cells altered their response to the QT analogs. The protein, p53, is an important tumor

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