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Notes

Cytotoxic and Antioxidant Activities of Benzohydroxamic Acid Analogues

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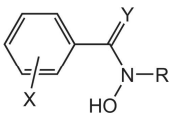
Hydroxamic acids (R-CO-NH-OH) are a class of chemical compounds sharing the same functional group wherein a hydroxylamine (NH_2OH) is inserted into a carboxylic acid (R-COOH). They are used as chelating agents in industry.[1] Hydroxamates are essential growth factors, or vitamins, for some microbes and function as iron-binding compounds that solubilize iron and transport it into cells.[2]

Many kinds of hydroxamic acid (HA) derivatives have been reported to exhibit cytotoxicity, *e.g.* diaryl ether HAs against four cancer cell lines,[3] suberoylanilide HA analogues against breast cancer cells,[4] *O*-alkylated HAs against pancreatic cancer,[5] halogenated HAs against specific tumor cells,[6] hydrophillic hydroxamates and 2-aminobenzamide containing derivatives against human fibroblast cells,[7] pyrimidyl-5-HAs as histone deacetylase inhibitors,[8] bis(*N*-phenyl) HAs as doxorubicin sensitivity modulators,[9] and isoindoledione ring containing HA against human leukemia cell line.[10] However, benzohydroxamic acid analogues containing *N*-alkyl substituents as well as electron-donating or -withdrawing groups in their benzene ring structure have not been thoroughly studied.

Several HA derivatives have been studied for their antioxidant activities; caffeoyl-amino acidyl-HAs,[11] cycloalkyl-*N*-aryl-HAs,[12] glucuronic acid-substituted HAs,[13] simple HA derivatives hydroxyurea or hydroxycarbamide,[14] HA derivatives of NSAIDs (ibuprofen, fenoprofen, ketoprofen, indomethacin, and diclofenac),[15] and galacturonyl HAs[16] all exhibit DPPH radical and/or hydroxyl radical scavenging activities. Further, 3-substituted phenyl groups bearing propene HAs[17] and *O*-alky/benzyl-NSAID HAs[18] have been shown to inhibit lipid peroxidation. However, the compounds prepared in this report have not yet been investigated. Therefore, to search new clinical agents or lead compounds associated with cytotoxicity and/or antioxidant activity, the biological properties of other synthetic HA derivatives should be investigated.

In the present study, 20 benzohydroxamic acid analogues, including three new compounds *N*-isopropyl-benzohydroxamic acids (**1-13**), *N*-isopropyl-thiobenzohydroxamic acids (**14-17**), and *N*-methyl-benzohydroxamic acids (**18-20**) were synthesized and evaluated for their *in vitro* cytotoxicities against mouse mammary tumor cells as well as antioxidant activities. The aim of this paper was to derive predictive structure-activity relationships for the purpose of improved compound design.



No	X	Y	R	No	X	Y	R
1	H	O	*i*Pr	11	4-$OCH_2C_6H_5$	O	*i*Pr
2	3-NO_2	O	*i*Pr	12	4-F	O	*i*Pr
3	4-NO_2	O	*i*Pr	13	4-Cl	O	*i*Pr
4	4-CN	O	iPr	14	H	S	*i*Pr
5	3-CH_3	O	*i*Pr	15	3-CH_3	S	*i*Pr
6	4-CH_3	O	*i*Pr	16	3-OCH_3	S	*i*Pr
7	4-*tert*-butyl	O	*i*Pr	17	2-$OCH_2CH{=}CH_2$	S	*i*Pr
8	2,4,6-trimethyl	O	*i*Pr	18	4-NO_2	O	Me
9	3-OCH_3	O	*i*Pr	19	4-Cl	O	Me
10	4-OCH_3	O	*i*Pr	20	2,4,6-trimethyl	O	Me

Figure 1. Chemical structures of synthetic benzohydroxamic acid analogues.

All synthetic benzohydroxamic acid derivatives (**1-20**) (Fig. 1) were evaluated for their *in vitro* cytotoxicities in a mouse mammary tumor cell line (FM3A). Among the compounds tested, **17** showed the most potent cytotoxicity with a value of EC_{50} 3.2×10^{-7} M (Table 1).

The next order of potency was compounds **16** > **15** > **14**, which belong to the series of *N*-isopropyl-substituted thiohydroxamic acids. Analogues (**14-17**) containing a C=S group exhibited greater cytotoxicities than their corresponding C=O-substituted compounds; especially, in the case of no substituents (**14** > **1**), 3-methyl (**15** > **5**), and 3-methoxy substituents (**16** > **9**), drastic differences were observed. *N*-Methyl-substituted analogues (**18-20**) possessed relatively weak activities compared to *N*-isopropyl derivatives (**1-17**). Among the most active compounds (**14-17**), those containing alkoxy groups showed increased cytotoxicity due to the