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Inhibition by Tetrahydroquinoline Sulfonamide Derivatives of the Activity of Human 8-Oxoguanine DNA Glycosylase (OGG1) for Several Products of Oxidatively-induced DNA Base Lesions

Melis Kant[†],

Yu-Ki Tahara[‡],

Pawel Jaruga[†],

Erdem Coskun[†,⸙],

R. Stephen Lloyd[▫],

Eric T. Kool[‡],

Miral Dizdaroglu[†]

[†]Biomolecular Measurement Division, National Institute of Standards and Technology, Gaithersburg, Maryland 20899, United States

[‡]Department of Chemistry, ChEM-H Institute, and Stanford Cancer Institute Stanford University, Stanford, California 94305, United States

[⸙]Institute for Bioscience & Biotechnology Research, University of Maryland, Rockville, Maryland 20850, United States

[▫]Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, Oregon 97239, United States

Abstract

Corresponding Authors Miral Dizdaroglu — Biomolecular Measurement Division, National Institute of Standards and Technology, Gaithersburg, Maryland 20899, United States, miral@nist.gov, **Eric T. Kool** — Department of Chemistry, ChEM-H Institute, and Stanford Cancer Institute Stanford University, Stanford, California 94305, United States, kool@stanford.edu.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at

List of materials used; detailed experimental procedures for the production of human OGG1 and for the analysis of DNA lesions by gas chromatography-tandem mass spectrometry with isotope-dilution; statistical analysis performed.

Authors

Melis Kant — *NIST International Associate at Biomolecular Measurement Division, National Institute of Standards and Technology, Gaithersburg, Maryland 20899, United States*

Yu-Ki Tahara — *Department of Chemistry, ChEM-H Institute, and Stanford Cancer Institute, Stanford University, Stanford, California 94305, United States*

Pawel Jaruga — *Biomolecular Measurement Division, National Institute of Standards and Technology, Gaithersburg, Maryland 20899, United States*

Erdem Coskun — *Institute for Bioscience & Biotechnology Research, University of Maryland, Rockville, Maryland 20850, United States*

R. Stephen Lloyd — *Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, Oregon 97239, United States*

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DNA glycosylases involved in the first step of the DNA base excision repair pathway are promising targets in cancer therapy. There is evidence that reduction of their activities may enhance cell killing in malignant tumors. Recently, two tetrahydroquinoline compounds named SU0268 and SU0383 were reported to inhibit OGG1 for the excision of 8-hydroxyguanine. This DNA repair protein is one of the major cellular enzymes responsible for excision of a number of oxidatively-induced lesions from DNA. In this work, we used gas chromatography-tandem mass spectrometry with isotope-dilution to measure the excision of not only 8-hydroxyguanine, but also that of the other major substrate of OGG1, i.e., 2,6-diamino-4-hydroxy-5-formamidopyrimidine, using genomic DNA with multiple purine- and pyrimidine-derived lesions. The excision of a minor substrate 4,6-diamino-5-formamidopyrimidine was also measured. Both SU0268 and SU0383 efficiently inhibited OGG1 activity for these three lesions, with the former being more potent than the latter. Dependence of inhibition on concentrations of SU0268 and SU0383 from 0.05 μmol/L to 10 μmol/L was also demonstrated. The approach used in this work may be applied to the investigation of OGG1 inhibition by SU0268 and SU0383, and other small molecule inhibitors in further studies including cellular and animal models of disease.

Oxidatively-induced DNA damage caused by free radicals and other DNA-damaging agents lead to the formation of a plethora of modifications in DNA (reviewed in[1, 2]). Many of the DNA base lesions are repaired by the base excision repair (BER) pathway, and some of them are subject to nucleotide excision repair (NER) and nucleotide incision repair (NIR) pathways.[2–7] Unrepaired DNA damage leads to many biological consequences in living organisms, including genotoxicity, mutagenesis and carcinogenesis (reviewed in[8–12]). Over the past two decades, DNA repair pathways, especially BER have become targets for cancer therapy (reviewed in[12–16]). Cancer cells increase their DNA repair capacity by overexpressing DNA repair proteins, leading to drug or radiation resistance in cancer therapy. Several inhibitors of DNA repair proteins are approved or are under development as potential anticancer drugs (reviewed in[17–19]).

Several investigations have suggested that the combined use of antimetabolite-based drugs and small molecule inhibitors of DNA glycosylases NEIL1, OGG1, and NTH1 could enhance therapeutic outcomes in cancer therapy.[20–22] Thus, synthetic lethal relationships between different repair pathways may have the potential to be less toxic in cancer therapy with a high therapeutic outcome (reviewed in[23]). Furthermore, ionizing radiation-induced killing in cells within solid tumors was enhanced by depletion of NEIL1 versus control siRNA treatments.[24] Similarly, RNAi suppression of both mitochondrion- and nucleus-located forms of OGG1 resulted in sensitization of oral squamous cell carcinoma cell lines to ionizing radiation.[25] Three leukemia cell lines with mutated OGG1 or low OGG1 transcript levels were also found to be hypersensitive to ionizing radiation.[26] Moreover, inhibition of NEIL2 in colorectal cancers was shown to enhance the efficacy of radiation therapy.[27] In addition to their relevance to cancer, the activity of certain BER enzymes, and OGG1 in particular, has been linked to inflammation pathways. Inflammation has long been associated with oxidative stress.[28] Mice engineered to lack the OGG1 gene were observed to exhibit attenuated responses to challenge by bacterial lipopolysaccharide (LPS) and by allergens,[29] and experiments with siRNA-mediated reduction in OGG1 expression resulted in reduced airway inflammation in mice exposed to pollen allergens.[30] The

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binding of OGG1 to chromosomal DNA recruits NF-κB to promoter sequences, resulting in upregulation of other proinflammatory factors.[31, 32] In addition, the free excised base 8-OH-Gua itself can upregulate genes essential in experimental asthma.[33] Thus, oxidized DNA binding and repair by OGG1 appear to be important contributors to the innate immune inflammatory response.

On the basis of these discoveries, several laboratories have developed small molecule inhibitors of DNA glycosylases, including NEIL1, NTH1 and OGG1, and tested them using different types of methodologies[34–38] (recently reviewed in[23]). These three BER enzymes are bifunctional, exhibiting both glycosylase and lyase activities, and possess varied substrate specificities (reviewed in[23, 39–41]). Using a high-throughput methodology, Donley *et al.* screened a large number of molecules for the inhibition of the activity of OGG1.[35] Five hydrazide-containing molecules with the IC_{50} values in the range of 0.22 μmol/L to 0.63 μmol/L were identified as effective inhibitors. These inhibitors were also tested using gas chromatography-tandem mass spectrometry with isotope-dilution (GC-MS/MS) and genomic DNA with multiple DNA base lesions. The excision of 8-hydroxyguanine (8-OH-Gua) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua), which are the *in vivo* substrates of OGG1,[39, 40, 42, 43] was efficiently inhibited. No inhibition of the activities of NEIL1 and NTH1 was found. Recently, several other molecules were reported as potent and selective inhibitors of OGG1. A small-molecule inhibitor (TH5487) was developed as a potent selective active-site OGG1 inhibitor with an IC_{50} of 0.342 μmol/L, and did not affect the activity of other DNA glycosylases.[37] TH5487 was also shown to be well tolerated by mice and to suppress proinflammatory gene expression and inflammation. Tahara *et al.* synthesized a large number of compounds with an acyl tetrahydroquinoline sulfonamide skeleton and tested them using a fluorogenic assay of 8-OH-Gua excision.[36, 38, 44, 45] Optimization of the tetrahydroquinoline scaffold yielded a compound, i.e., *4'-(N-(1-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroquinolin-7-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide* (SU0268) with IC_{50} = 0.059 μmol/L. SU0268 was shown to bind OGG1 both in the absence and presence of DNA and to be selective for inhibiting OGG1 over other BER enzymes. This compound recently showed efficacy in reducing inflammation and mortality in a mouse model of bacterial lung infections.[46] Another compound, i.e., *N-(2-((2-Amino-5-methylpyrimidin-4-yl)oxy)ethyl)-4'-(N-(1-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroquinolin-7-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide* (SU0383) exhibited dual inhibition activities for both OGG1 and MTH1 with IC_{50} = 0.49 μmol/L and IC_{50} = 0.034 μmol/L, respectively.[38] Figure 1 illustrates the structures of these compounds. Both SU0268 and SU0383 displayed little or no toxicity in two human cell lines at a concentration of 10 μmol/L. Using liquid chromatography-tandem mass spectrometry with isotope-dilution, inhibition by SU0268 of OGG1 activity in HeLa cells was shown to increase the level of 8-OH-Gua in DNA.[36] Similar results were obtained by using luminescence probes in HeLa and MCF-7 cell lysates.

In the present work, we used a different approach to test the inhibition activities of SU0268 and SU0383 using GC-MS/MS and genomic DNA containing multiple purine- and pyrimidine-derived lesions. This approach simultaneously measures a plethora of DNA base lesions in a given DNA sample, and thus enables the determination of substrate specificities and excision kinetics of DNA glycosylases by identifying which damaged

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DNA bases are or are not excised from DNA (reviewed in[39]). The details of the GC-MS/MS measurements are given in Supporting Information. In control experiments with no inhibitor present, we identified and quantified 8-OH-Gua and FapyGua excised from DNA by OGG1, confirming previous results.[42, 43] Some small excision of 4,6-diamino-5-formamidopyrimidine (FapyAde) was also observed. This lesion is not recognized as one of the main substrates of OGG1. However, the bacterial analogue of OGG1, *i.e.*, *E. coli* Fpg, excises FapyAde from DNA with excision kinetics similar to those of 8-OH-Gua and FapyGua.[47, 48] Despite the low excision, we also measured the inhibition of OGG1 by SU0268 and SU0383 for the removal of FapyAde. First, we used a concentration of 10 μmol/L of both SU0268 and SU0383 to test whether any significant inhibition of the excision by OGG1 of 8-OH-Gua, FapyGua and FapyAde occurs. In the previous work, both inhibitors exhibited little or no toxicity at concentrations up to 10 μmol/L in HEK293T and HeLa cells, and moderate toxicity at the highest concentration of 100 μmol/L.[36] Figure 2 illustrates the excised levels of the three lesions by OGG1 alone, OGG1 plus DMSO, and OGG1 plus DMSO and SU0268 or SU0383 at a concentration of 10 μmol/L, along with the *p*-values indicating the statistical significance between the data points. The control levels of the lesions in DNA samples incubated without the enzyme are also shown. DMSO was added to check its effect on excision because the inhibitors were dissolved in DMSO before addition to the reaction mixture. Some small insignificant increase of excision by addition of DMSO in the case of 8-OH-Gua and FapyGua was observed. SU0268 strongly inhibited the excision of 8-OH-Gua with its level decreasing almost to the control level. A significant inhibition by SU0383 was also observed; however, its effect of inhibition was not as potent as that of SU0268, consistent with prior reports of the relative *in vitro* activities of the two compounds.[36] In the case of FapyGua, approximately 60% inhibition by SU0268 was observed. However, the inhibition by SU0383 was lower, at approximately 30%. Excision of FapyAde was also quite significant with both inhibitors exhibiting almost the same effect.

Next, we measured the inhibition at increasing concentrations of SU0268 or SU0383 from 0.05 μmol/L to 10 μmol/L to measure the effects of lower concentrations of the inhibitors. A concentration dependence of inhibition was observed as shown in Figure 3, where the decreasing excised levels of 8-OH-Gua, FapyGua and FapyAde correspond to the increased levels of inhibition. The *p*-values indicate the statistical significance between the inhibition by SU0268 and SU0383 at each inhibitor concentration. The data point at 0 μmol/L shows the levels of the lesions excised by OGG1 in the presence of DMSO without the inhibitors. A sharp increase in the inhibition was observed at concentrations up to 1 μmol/L. Subsequently, the inhibition increased with a slower rate. Starting from 1 μmol/L, the inhibition by SU0268 of both 8-OH-Gua and FapyGua was significantly greater than that by SU0383. In the case of FapyAde, this effect was not as pronounced.

Our data show the potent inhibition of OGG1 for the excision of three purine-derived lesions from DNA by SU0268 and SU0383. This work is unique in that DNA containing multiple purine- and pyrimidine-derived lesions as a substrate was used and the excision of all three lesions and, thus, the inhibition of OGG1 activity was measured simultaneously. In the case of 8-OH-Gua, the results confirmed the previous results obtained using a different experimental approach, a fluorogenic assay.[36, 45] Furthermore, SU0268 being a more potent inhibitor than the dual inhibitor SU0383 was also confirmed. The previous work was

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limited to 8-OH-Gua excision only. However, the other major physiological substrate of human OGG1 and other eukaryotic OGG1s is FapyGua as determined over two decades ago.[42, 43, 49–52] These proteins remove 8-OH-Gua and FapyGua from DNA with similar excision kinetics. When compared to 8-OH-Gua, FapyGua is formed in DNA *in vitro* and *in vivo* with comparable yields following challenges by various DNA-damaging agents (reviewed in[39]). Furthermore, it is as mutagenic as 8-OH-Gua, leading to the same G → T transversion mutations (reviewed in[53]). These facts make the simultaneous measurement of both lesions essential in investigations of DNA damage and DNA repair. For these reasons, biologically active small molecules as possible drug-precursors, such as the two compounds studied in this work should be fully characterized with respect to their scope of inhibition, including analyses of all the known substrates of their presumed DNA repair target enzyme under study. The mechanism through which OGG1 initiates repair of its DNA base lesion substrates is complex, involving non-specific DNA binding, specific substrate binding via nucleotide flipping, an activated water-mediated release of the damaged base and the potential for a subsequent abasic site lyase activity that cleaves the phosphodiester bond (reviewed in[23, 54]) As such, small molecule inhibitors have the potential to inhibit at any of these steps and thus a full characterization of the enzyme inhibition on different substrates must be provided. For example, prior literature that characterized the inhibition of OGG1 by hydrazide molecules revealed that in addition to inhibition of the glycosylase activity, IC_{50} values for inhibition of AP lyase activity was ~10-fold lower.[35] Germane to this study, prior literature has only reported on the inhibition of OGG1 concerning the excision of 8-OH-Gua. However, such analyses only characterize one of the two major substrates of OGG1, as noted above and thus, leaves the scope of this inhibition open to speculation and conjecture. Therefore, reporting only data for the inhibition on the release of 8-OH-Gua is only telling half of the story. Our work provides a more comprehensive analysis of the inhibition of OGG1 for its physiological substrates, providing a broader basis for understanding their biological effects. These analyses should become routine in the development of anticancer drugs for the inhibition of OGG1. Our methodology is the only one at present that can simultaneously measure enzyme-catalyzed excision of 8-OH-Gua and FapyGua from genomic DNA. Our work has uncovered a second major potential site of action for these inhibitors, which will be important in directing future preclinical studies. Further, such investigations are consistent with meeting regulatory requirements for preclinical and clinical trials.

These new results also have significant implications in the relevance and mechanism of OGG1 inhibition in suppressing inflammatory responses. Our observation that inhibitors of OGG1 increase levels of not only 8-OH-Gua, but also FapyGua in DNA may introduce a second important factor in the mechanism of such responses. The OGG1 enzyme has been shown to bind DNA at 8-OH-Gua sites and is reported to recruit NF-κB to chromosomal DNA, leading to proinflammatory signaling.[31–33, 54] Further, the excised base 8-OH-Gua has been shown to act as a separate proinflammatory signaling agent. However, it is not known whether FapyGua, either in DNA or as the released small molecule, also can mediate such effects or not. Recent studies of OGG1 inhibitors in mice have confirmed anti-inflammatory effects; for example, the compound TH5487 reduced inflammation in mice challenged with LPS and allergens.[37] A recent study of SU0268 in mice infected

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with *Pseudomonas aeruginosa* revealed that the compound reduced both inflammation and proinflammatory cytokines, and improved animal survival from the infection.[46] It would be of significant interest to study whether the biological effects of such inhibitors are the result of action at only 8-OH-Gua sites or at FapyGua as well; no data yet exist on the latter. Further studies including cellular and animal models, both in cancer and inflammation, are warranted for the application of SU0268 and SU0383, and the methodology used in this work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Certain commercial equipment or materials are identified in this paper in order to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

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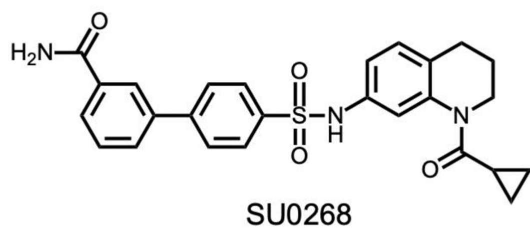

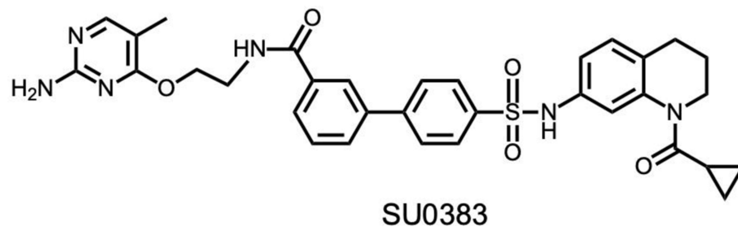

Figure 1.
Structures of SU0268 and SU0383.

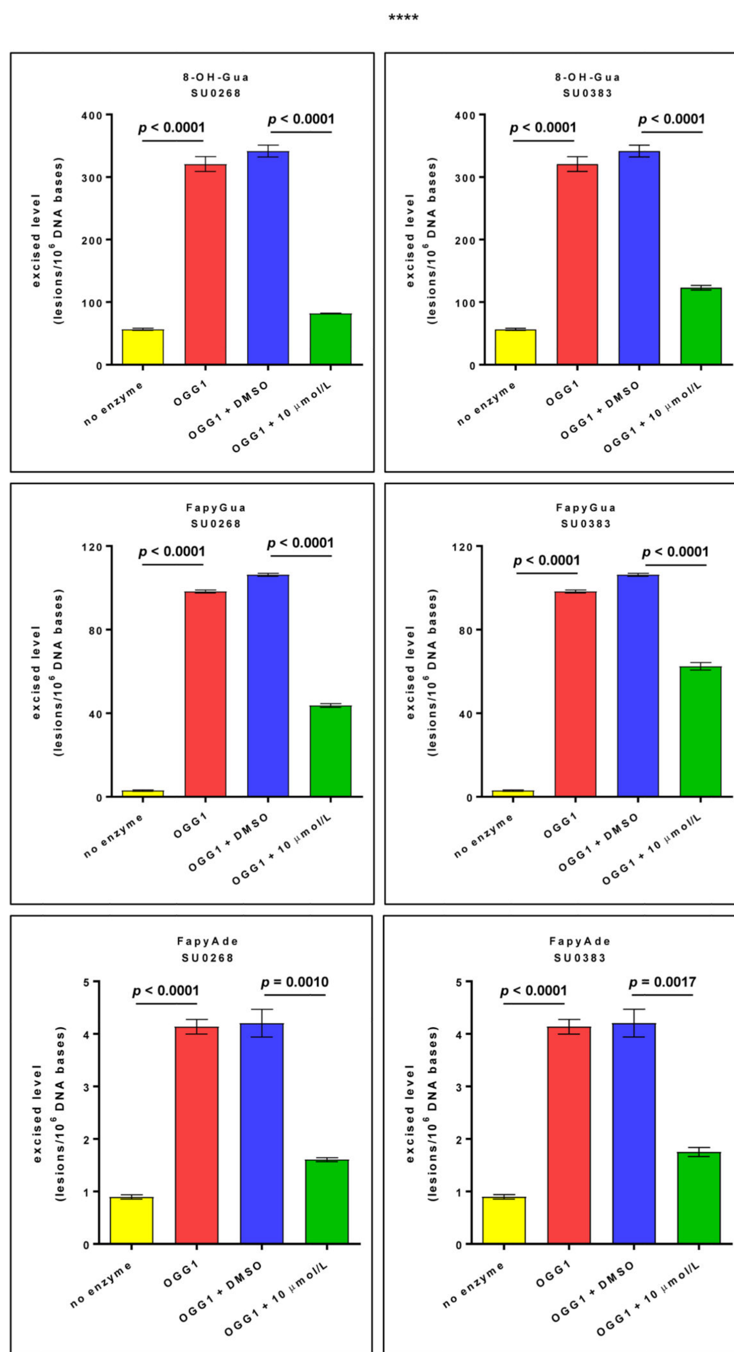

Figure 2.

Excised levels of 8-OH-Gua, FapyGua and FapyAde from DNA by OGG1, OGG1 plus DMSO, and OGG1 plus either SU0268 or SU0383 at a concentration of 10 μmol/L. Control levels without OGG1 are also shown. Uncertainties are standard deviations. The *p*-values < 0.05 show the statistical significance.

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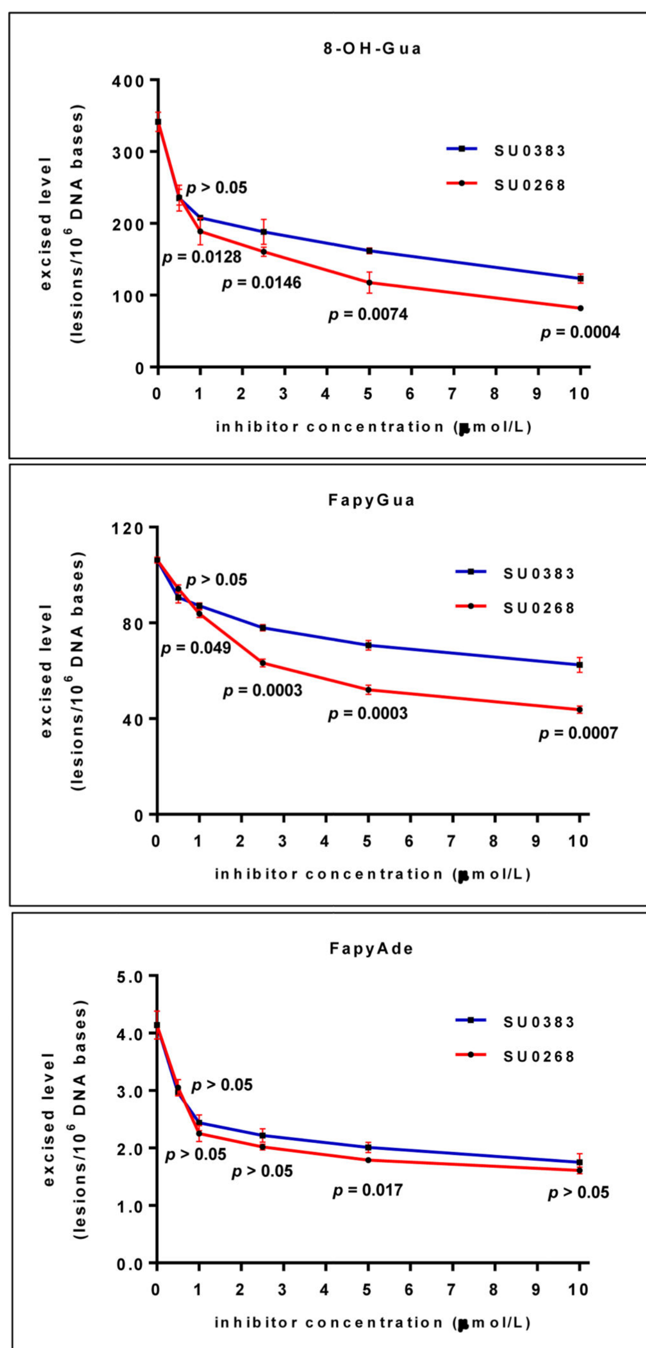

Figure 3.

Dependence of the excised levels of 8-OH-Gua, FapyGua and FapyAde on the concentration of SU0268 or SU0383. Uncertainties are standard deviations. The *p*-values < 0.05 show the statistical significance.