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# C8-Substituted Temozolomide Analogs Overcome O6-Methylguanine-DNA Methyltransferase and Mismatch Repair Precipitating Apoptotic Cancer Cell Death

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## Abstract

Temozolomide (TMZ) is the standard of care chemotherapeutic agent used in the treatment of glioblastoma multiforme. O6-methylguanine lesions mainly formed by TMZ are repaired by O6-methyl-guanine DNA methyltransferase (MGMT), a DNA repair protein that removes alkyl groups located at the O6-position of guanine. Response to TMZ requires low MGMT expression and functional mismatch repair. Resistance to TMZ conferred by MGMT, and tolerance to O6-methylguanine lesions conferred by deficient MMR severely limit TMZ clinical applications. Therefore, development of new TMZ derivatives which can overcome TMZ-resistance is urgent. In this study, we investigated the anti-tumor mechanism of action of two novel TMZ analogs: C8-imidazolyl (377) and C8-methyl imidazole (465) tetrazines. We found that analogs 377 and 465 display good anticancer activity against the MGMT-overexpressing glioma T98G and MMR deficient colorectal carcinoma HCT116 cell lines with IC<sub>50</sub> value of 62.50 μM, 44.23 μM and 33.09 μM, 25.37 μM respectively. Analogs induce cell cycle arrest at G2/M; DNA double strand break damage was detected, preceding apoptosis irrespective of MGMT and MMR status. It was established that analog 377 can ring-open and hydrolyze like TMZ under physiological conditions and its intermediate product is more stable compared to that of TMZ. The following DNA adducts of 377 with calf thymus DNA were identified - N3-methyladenine, N7-methylguanine, O6-methylguanine, N3-methylguanine thymine, N3-methylcytidine deoxynucleotides and N3-methyladenine deoxynucleotides.

**Keywords:** Glioblastoma; Colorectal carcinoma; O6-Methylguanine-DNA methyltransferase; Mismatch repair; Apoptosis; DNA adducts

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The article entitled "C8-Substituted Temozolomide analogs Overcome O6-Methylguanine-DNA Methyltransferase and Mismatch Repair Precipitating Apoptotic Cancer Cell Death," has been accepted for publication in the Journal of Neuro-Oncology and Neuroscience considering the statements provided in the article as personal opinion of the author which was found not having any conflict or biasness towards anything. As the article was a research article one, information provided by the author was considered as an opinion to be expressed through publication. Publisher took decision to make the article online solely based on the reviewers suggestion which considered the article not but a personal opinion of the author. However, it is found that the author have some personal concerns and issues, therefore, being retracted from the journal.

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