University of Victoria | Graduate Studies

Notice of the Final Oral Examination for the Degree of Master of Science

of

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BSc (The Kings University, 2015)

"Cytotoxic Methylthioadenosine Analogues"

Department of Chemistry

Thursday, August 25, 2016
1:00 P.M.
Engineering and Computer Science Building
Room 128

Supervisory Committee:
Dr. Jeremy Wulff, Department of Chemistry, University of Victoria (Supervisor)
Dr. Neil Burford, Department of Chemistry, UVic (Member)
Dr. Tom Fyles, Department of Chemistry, UVic (Member)

External Examiner:
Dr. Peter Constabel, Department of Biology, UVic

Chair of Oral Examination:
Dr. Brendan Burke, Department of Greek and Roman Studies, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

The gene for methylthioadenosine phosphorylase (MTAP) is absent in almost 30% of cancers, opening a door for selective chemotherapy. One strategy to target the absence of MTAP involves the design of a cytotoxic methylthioadenosine (MTA) analogue. Non-cancerous cells would break down the cytotoxic analogue, since they contain MTAP, but cancerous cells would not, since they do not have MTAP. However, before such a compound can be made, we need to better understand the types of substrates accommodated by MTAP. The purpose of this thesis was then to explore a series of MTA analogues, probing the structure function relationships between MTAP and specific structural modifications of MTA.

Nine phenylthioadenosine derivatives bearing *ortho*-, *meta*-, or *para*- methyl carboxylate, carboxylate, and hydroxymethyl substituents were synthesized and tested for substrate activity and cytotoxicity. The biological results of these nine compounds suggested that addition of substituents to the *ortho*-position was not tolerated by MTAP, and substituents similar to the hydroxymethyl might be accommodated by MTAP. None of the compounds were cytotoxic. This informed the design of ten more PTA derivatives, most of which were synthesized and tested for substrate activity and cytotoxicity. The range of functionalities included an amine, an acetamide, a urea, an isovaleramide, and a lomustine group. The amine derivatives of PTA had the best substrate activity of all MTA analogues tested (including PTA). The *meta*-amine derivative and the *meta*isovaleramide showed minor cytotoxicity. The minor substrate activity of the urea derivatives pointed range of functionalities included an amine, an acetamide, a urea, an isovaleramide, and a lomustine group. The amine derivatives of PTA had the best substrate activity of all MTA analogues tested (including PTA). The *meta*-amine derivative and the *meta*isovaleramide showed minor cytotoxicity. The minor substrate activity of the urea derivatives pointed towards nitrosoureas as potential cytotoxic MTAP substrates.