SUMMARY

We have discovered a novel series of potent and dual A2A/A2B adenosine receptor antagonists. Our best compounds present high in vitro activity not only in low adenosine conditions but also in tumor like adenosine rich environment. We have observed rescue of adenosine-suppressed cytotoxicity of NK cells and reversal of NECA-induced CREB phosphorylation in in vivo murine model (up to 24 hours). Additionally the A2B activity is key factor in restoring of the adenosine agonist-impaired functional activity of moDC (cytokine release assays). To sum up, presented compounds show improved pharmacological profile in comparison to A2A inhibitors currently tested in clinical trials.

INTRODUCTION

Adenosine is the key immunomodulator responsible for immune tolerance in tumors. It is present in normal tissue in low concentrations, having various physiological functions. In the tumor, its concentration increases rapidly, as a result of overexpression of enzymes producing adenosine, additionally enhanced by hypoxia and inflammation. Adenosine inhibits the biological functions of T lymphocytes infiltrating the cancer tissue by binding to the A2A receptor. The affinity to A2A receptor is believed to attenuate the response of dendritic cells and other parts of innate system. Thus blocking simultaneously the effects mediated by both receptor subtypes with dual inhibitor seems to be a viable approach for cancer immunotherapy in comparison to A2A inhibitors currently tested in clinical trials.

SEL330-584 AND SEL330-639 ARE HIGHLY POTENT IN ADENOSINE-RICH TUMOR MICROENVIRONMENT

SEL330-639 OUTPERFORMS COMPETITORS IN DOWNREGULATION IN VIVO OF CREB PHOSPHORYLATION

SEL330-584 AND SEL330-639 RESTORE NK CELLS CYTOTOXIC FUNCTION