Highly active and selective JAK2 inhibitor CPL-407-220 as a new drug candidate for myeloproliferative disorders

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) include a diverse group of cell disorders such as chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytemia (ET) and primary myelofibrosis (PMF). The deregulated signaling of the JAK/STAT pathway plays an important role in the pathogenesis of MPNs. JAK2 is important for hematopoietic growth factors signalling and JAK2V617F mutation occurs in the majority of patients with PV, ET, and PMF.

METHODS and RESULTS

Activity of CPL-407-220 was measured with ADP-Glo™ Kinase Assay (Promega). Recombinant kinase were purchase from Carna Biosciences Inc. Our compound shows great potency against JAK2 kinase with IC50=0.69 nM and has a good selectivity over other JAK family kinases: JAK1, JAK3 and TYK2 with IC50 of 35.37nM, 30.71nM and 6.04nM, respectively.

CPL-407-220 inhibitory effect was studied with JAK2-dependent HEL921.7(JAK2V617F), cell line purchased from ATCC. Cells were treated with tested compound for 1 hour and Western Blot analysis was performed. Our compound inhibits phosphorylation of STAT3 with IC50=59.06nM.

The inhibition of cancer cells viability was examined with SET-2 cells (JAK2V617F), and the cytotoxicity with Human Embryonic Kidney 293 cells, both lines were purchased from ATCC. The viability assays were performed after 72 hours of compound treatment by ATPlite™ Luminescence Assay (PerkinElmer). CPL-407-220 shows good inhibition of JAK2-dependent SET-2 cells (IC50=64.8nM) and moderate cytotoxicity against HEK293 cells (IC50=4.8uM).

CONCLUSIONS

- A novel highly potent JAK2-selective inhibitor CPL-407-220 was developed
- CPL-407-220 significantly reduces viability of JAK2-dependent cell line and shows moderated HEK293 cytotoxicity
- Our compound is promising for further development in therapy of myeloproliferative disorders

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