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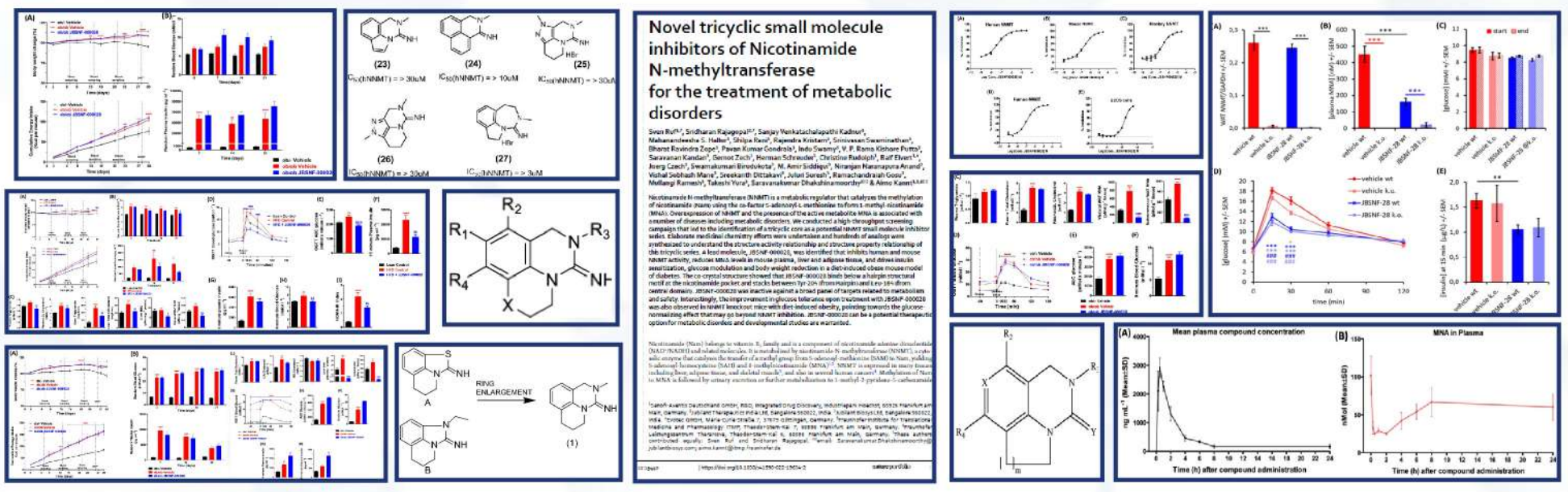
Novel tricyclic small molecule inhibitors of Nicotinamide N-methyltransferase for the treatment of metabolic disorders



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A Successful IDD Collaboration with Sanofi

Nicotinamide N-methyltransferase (NNMT) is a metabolic regulator that catalyzes the methylation of nicotinamide (Nam) using the co-factor S-adenosyl-L-methionine to form 1-methyl-nicotinamide (MNA). Overexpression of NNMT and the presence of the active metabolite MNA is associated with numerous diseases, including metabolic disorders

The molecule

A lead molecule, JBSNF-000028, was identified that inhibits human and mouse NNMT activity, reduces MNA levels in mouse plasma, liver and adipose tissue, and drives insulin sensitization, glucose modulation and body weight reduction in a diet-induced obese mouse model of diabetes.

The co-crystal structure showed that JBSNF-000028 binds below a hairpin structural motif at the nicotinamide pocket and stacks between Tyr-204 (from Hairpin) and Leu-164 (from central domain). JBSNF-000028 was inactive against a broad panel of targets related to metabolism and safety.

Investigations

A high-throughput screening campaign that led to the identification of a tricyclic core as a potential NNMT small molecule inhibitor series. Elaborate medicinal chemistry efforts were undertaken and hundreds of analogs were synthesized to understand the structure activity relationship and structure property relationship of this tricyclic series.

Insights

Interestingly, the improvement in glucose tolerance upon treatment with JBSNF-000028 was also observed in NNMT knockout mice with diet-induced obesity, pointing towards the glucose-normalizing effect that may go beyond NNMT inhibition. JBSNF-000028 can be a potential therapeutic option for metabolic disorders and developmental studies are warranted.

Results

- *Disorders of energy utilization and storage leading to metabolic syndrome are a predisposing factor for Type 2 Diabetes and liver diseases*
- *NNMT is reported to be a regulator of adiposity and energy expenditure and is involved in modulating adipose SAM and NAD+, the metabolites for energy metabolism*
- *NNMT is touted as an attractive target for developing small molecule inhibitors to treat obesity and type 2 diabetes. In this work, we describe a novel series of potent and selective tricyclic NNMT inhibitors that are active on the recombinant NNMT enzymes from several species and on the native, endogenous enzyme in human cells.*

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