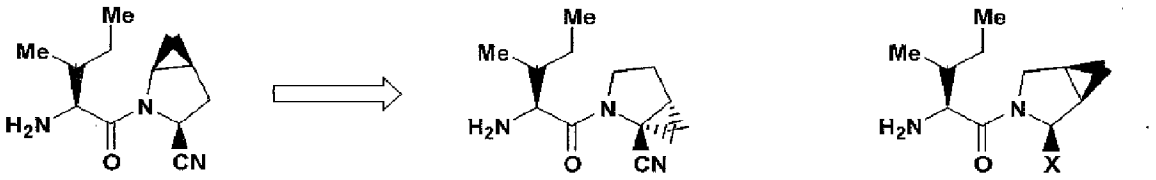
DP4 Chemistry Significant Events **October 1 ,1999**

Competitive Update: Nothing new to report

Current FTE's: 3

Monthly Summary: None

The goal of the program is to discover small molecule inhibitors of dipeptidyl peptidase IV (DP4) for use in the treatment and prevention of diabetes. Inhibition of DP4 should prevent the degradation of GLP-1 and potentiate its action in vivo. BMS-356379 was previously identified as a novel and proprietary inhibitor with an inhibitory constant of 28 nM vs pig kindey DP4. Rat oral bioavailability of this compound is in progress as well as studies related to in vitro metabolism and P450 inhibition. It was recently demonstrated that the Caco-2 permeability of this compound is 114 mn/sec, which would predict good oral absorption. The cyano substituted cyclopropanated pyrrolidine precursor is currently being scaled up for future analoging in this series. In an attempt to uncover other suitable chemotypes related to BMS-356379, the generation of additional cyclopropanated analogs are in progress. In contrast to BMS-356379 (a 4,5-fused analog), the 2,3-fused analog BMS-378736 exhibited only marginal activity in the screening assay (20% inhibition @ 10 uM) while the related 3,4-fused analog, BMS-378738 (X = H) exhibited significant potency in this screen (80% inhibition @ 10 uM). Ki values will be determine shortly. Efforts are currently directed towards generation of the related cyano derivative (X = CN) in hopes of further enhancing potency with this chemotype.



BMS-356379
DP4 screen:
97% inhib. @ 10 uM
DP4 Ki = 28 nM

BMS-378736
DP4 screen:
20% inhib. @ 10 uM

BMS-378738 (X = H)
DP4 screen:
80% inhib. @ 10 uM