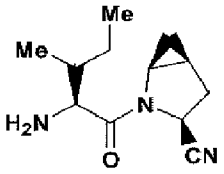
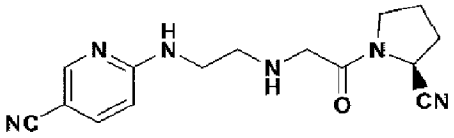
DP4 Chem Sig Events **August 11, 1999**

Executive Summary: 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. Inhibiton of DP4 should prevent the degradation of GLP-1 and potentiate its action in vivo. Recently, BMS-356379 was identified as the first BMS proprietary DP4 inhibitor with high potency against the enzyme (Ki = 28 nM). Future analogs will be directed towards optimization of the N-terminal amino acid residue and the incorporation of other novel prolyl surrogates.

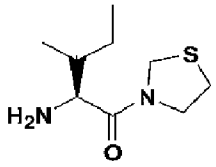


BMS-356379
DP4 Ki = 28 nM

Competitive Update: At the recent ADA meeting in San Diego, Novartis presented data on their phase I DP4 inhibitor, NVP-DPP-728 (IC_{50} = 6 nM, covered in application WO 98/19998). This compound is water-soluble and short-acting (t1/2 = 2 h) and is to be administered at mealtimes. NVP-DPP-728 increases the half-life of endogenous GLP-1 four to five-fold. Acute dosing (10 µmol/kg) led to normalization of glucose tolerance and beta-cell responsiveness in dexamethasone-treated glucose-intolerant rats. Additionally, Prous reports that Probiodrug is in proof-of-principle phase II diabetes studies with the DP4 inhibitor P32/98 (believe to be isoleucine-thiazolidide) and may be seeking licensing partners for development.

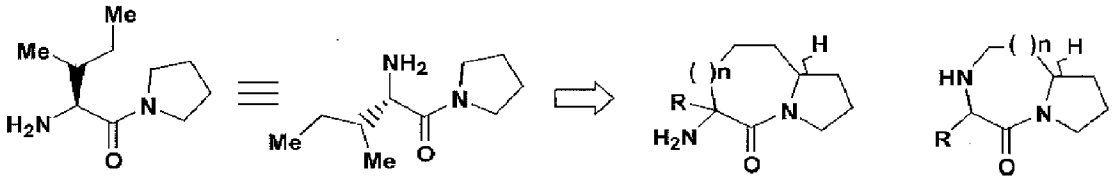


NVP-DPP-728



P32/98
(tentative structure)

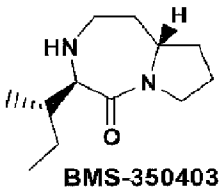
The goal of the program is to discover small molecule inhibitors of dipeptidyl peptidase IV (DP4) for use in the treatment and prevention of diabetes. Inhibiton of DP4 should prevent the degradation of GLP-1 and potentiate its action in vivo. The main thrust of our efforts have been directed towards identifying novel and proprietary conformationally restricted dipeptide scaffolds, two of which are generically represented by structure A and B, which would mimic the binding interaction of the known DP4 inhibitor BMS-326430 (Ile-pyrrolidide).



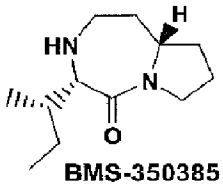
BMS-326430
DP4 Ki = 440 nM

A **B**

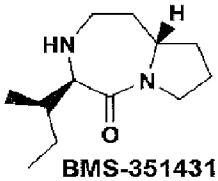
Internal bicyclic amino-lactams BMS-350385, BMS-350403, BMS-351431, BMS-349231, and BMS-355493 were generated to explore the sterochemical requirements for binding in a fully elaborated Ile-pyrrolidide constrained mimetic. Unfortunately, all of these compounds were essentially inactive against DP4. Attempts to generate the corresponding 8,5-fused amino-lactams, predicted by modeling studies to adopt an orientation more favorable to binding, to date have been elusive. In the external bicyclic amino-lactams series, BMS-349054 and its diastereomer BMS-349058 were poorly active vs DP4. Chemical attempts to generate the related 8,5-fused system were not successful but the synthesis of the corresponding 7,5-fused lactam is in progress. A substantial number of compounds have been generated in this program in an effort to explore a variety of binding conformations and substituent orientations required for small molecule inhibition. The SAR suggest that the pyrrolide/thiazolide binding pocket in DP4 is very tight and likely cannot tolerate the incorporation of carbon bridges (a conformational locking element present in all these systems). Thus, new compounds syntheses within the chemotypes related to structures A and B are being de-emphasized.



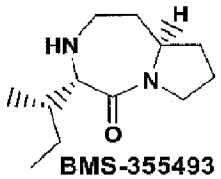
BMS-350403



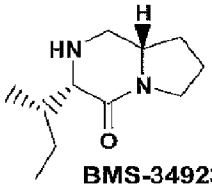
BMS-350385



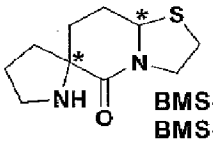
BMS-351431



BMS-355493

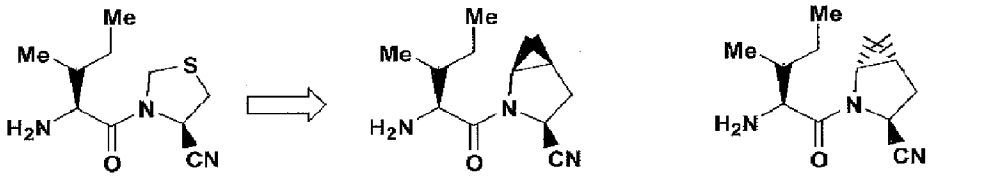


BMS-349231



BMS-349054 (Isomer A)
BMS-349058 (Isomer B)

In an attempt to identify proprietary DP4 inhibitors, structures more closely related to the literature compounds (e.g. BMS-338358) are being explored. The cyclopropyl substituted 2-cyanopyrrolidides BMS-356279 and BMS-357151 were recently found to be the first novel and potent leads in the program, Ki = 28 nM and 1600 nM respectively. Based on this recent information, future efforts will be directed in generating additional cyclopropanated derivatives at both the N- and C-terminus of the molecule. Novel heteroatom substituted prolyl derivatives will also be examined.



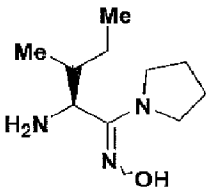
BMS-338358
DP4 Ki = 1 nM

BMS-356379
DP4 Ki = 28 nM

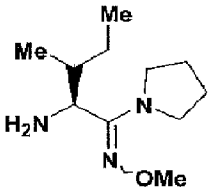
BMS-357151
DP4 Ki = 1600 nM

BMS-355838 and BMS-355839 were generated as novel amide surrogate replacements related to BMS-326430 (DP4 Ki = 440 nM). Although both compounds exhibited activity comparable to BMS-326430 in the screening protocol, Ki determination showed these compounds to be

significantly less potent, indicating an absolute requirement for an amide functionality at this position.



BMS-355838
DP4 Ki =47,000 nM



BMS-355839
DP4 Ki = 173,000 nM