



**Trip Report:
229th ACS National Meeting
San Diego, California
March 13– 17, 2005**

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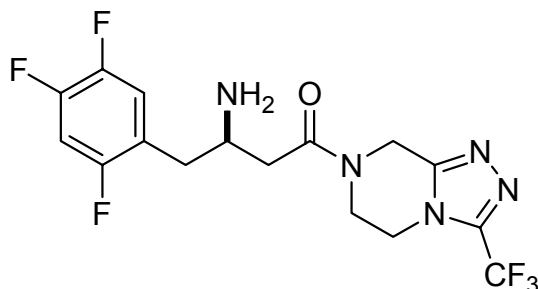
***Abstract.** The 229th ACS National Meeting was held over a five day period from March 13 to March 17 at the San Diego Conventional Center. The Meeting contained all majors of chemistry and many sessions in each major. This report highlights selected presentations and posters in both synthetic chemistry and medicinal chemistry.*

“The Discovery of Potent and Selective Orally Bioavailable β -Substituted Phenylalanine Derived Dipeptidyl Peptidase IV Inhibitors,”

Scott D. Edmondson, (Merck Research Laboratories) Rahway, New Jersey.

Diabetes is a growing public health problem. It was the 6th leading cause of death in the United States in 2000. It is forecasted there will be 210 million cases worldwide by 2010. Over 90% of type 2 diabetes is associated with metabolic syndrome. Dipeptidyl Peptidase IV (DPP-IV) has been shown playing critical role in deactivating two important peptides, glucagons-like peptide 1 and glucose dependent insulinotropic polypeptide, which are responsible for insulin biosynthesis and secretion. Thus, the inhibition of DPP-IV offers a valuable pharmacotherapy to diabetes.

a. Initial hits and backup strategy



Enzyme	IC ₅₀ (nM)
DPP-IV	18
QPP	>100,000
DPP8	48,000
DPP9	>100,000
hERG	78,000

species	t _{1/2} (h)	Cl _p (mL/min/kg)	F (%)
Rat	1.7	60	76
Dog	4.9	6.0	100
Rhesus	3.7	28	68

MK-0431 was the first important hit for this project. It demonstrated promising biological in vitro and in vivo activity. The backup strategies for this lead were:

Identify a DPP-IV inhibitor with

- Increased potency at DPP-IV compared to MK-0431
- Comparable selectivity over counter screens
- Increased half-life
- Structural diversity

b. An efficient route for diversification was developed (Scheme 1)

c. Selected SAR results (Table 1)

d. Phenylalanine Derivative 32 (This number was used by the original presentation. Because I'm not able to change the number in the cited table (Table 2), this number has to be used): a potent and selective orally bioavailable DPP-IV Inhibitor

e. Summary

- (1) Phenylalanine 32 is a structurally diverse, potent ($IC_{50} = 12$ nM) and selective orally active DPP-IV inhibitor with high levels of protein binding.
- (2) Dimethyl amide group is optimal at the β -position
- (3) Tight SAR but small hydrophobic groups are tolerated, changes in this region affects potency and selectivity
- (4) Many biaryl groups tolerated, but the addition of some polar aryl groups affords compounds with suboptimal bioavailability or $t_{1/2}$

Scheme 1

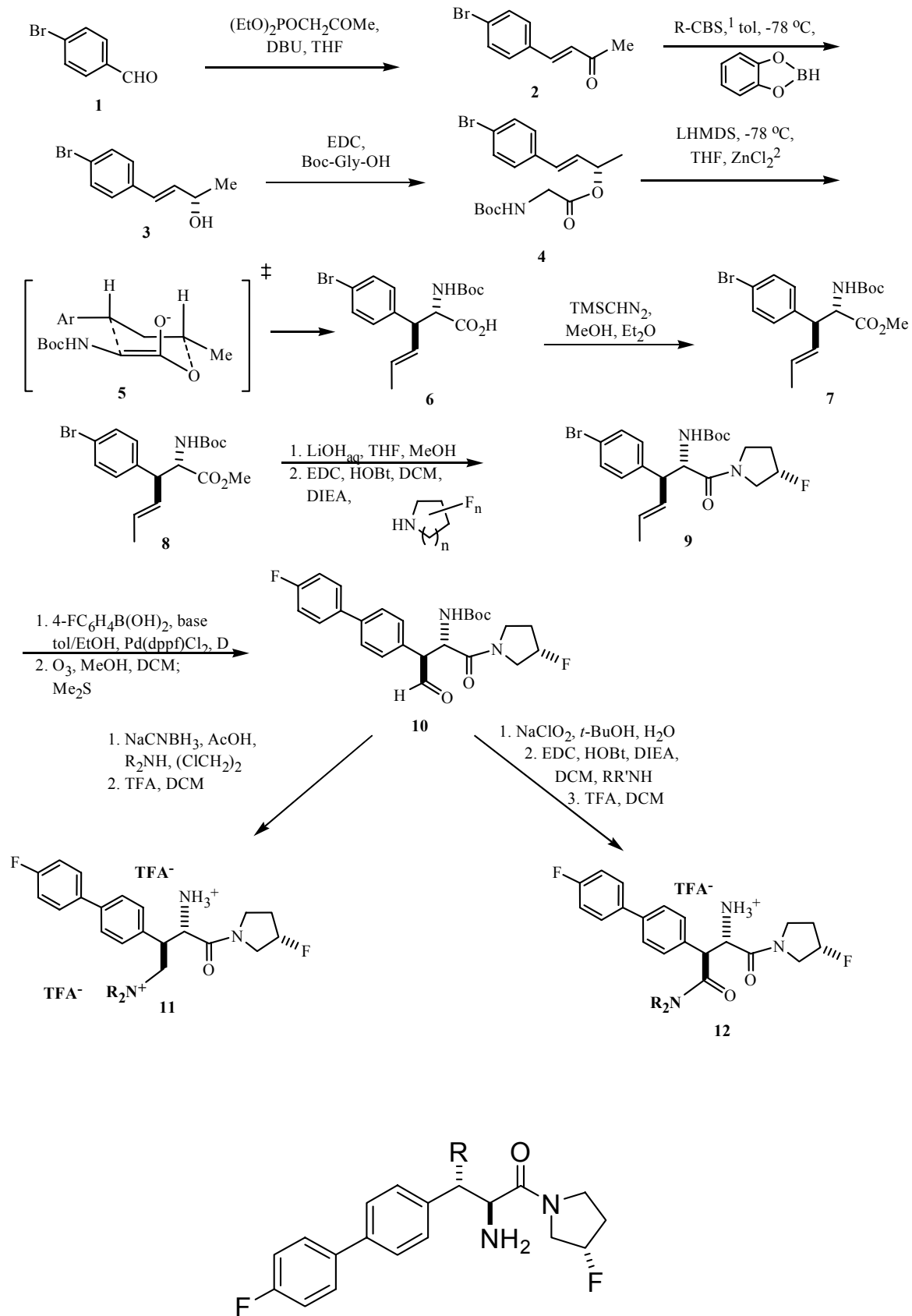
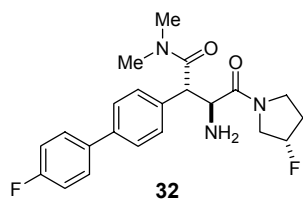


Table 1: β -Polar Substituent Effects of Phenylalanines

Compound	R	IC ₅₀ (nM)				
		DPP-IV	QPP	DPP8	DPP9	hERG
20	H	980	>100,000	>100,000	>100,000	---
21	Me	64	2,700	87,000	86,000	1,100
22	CH ₂ OH	390	15,000	>100,000	>100,000	---
23	CH ₂ NMe ₂	1,600	2,500	16,000	>100,000	---
24	CH ₂ N(CH ₂) ₄	3,500	660	49,000	>100,000	---
25	COOH	6.6	>100,000	>100,000	>100,000	76,000
26	tetrazole	192	>100,000	>100,000	>100,000	---
27	CONH ₂	110	>100,000	>100,000	>100,000	---
28	CONHMe	37	>100,000	41,000	>100,000	5,400

Table 2. Phenylalanine Derivative **32**:
A Potent and Selective Orally Bioavailable DPP-IV Inhibitor**Potency and selectivity:****Pharmacokinetic Profile Comparison:****For MK-0431**

species	t _{1/2} (h)	Cl _b (mL/min/kg)	F (%)
Rat	1.7	60	76
Dog	4.9	6.0	100
Rhesus	3.7	28	68

For 32

species	t _{1/2} (h)	Cl _b (mL/min/kg)	F (%)
Rat	3.5	4.8	67
Dog	6.1	1.5	90
Rhesus	4.7	2.4	56

	IC ₅₀ (nM)	
	MK-0431	Cpd 32
DPP-IV	18	12
QPP	>100,000	45,000
DPP8	48,000	>100,000
DPP9	>100,000	69,000
PEP	>100,000	>100,000
APP	>100,000	>100,000
Prolidase	>100,000	>100,000
FAP	>100,000	>100,000
hERG	78,000	4,600

“Design and Synthesis of Orally Efficacious Melanin Concentrating Hormone (MCH) Receptor Antagonists as Antiobesity Therapeutics,”

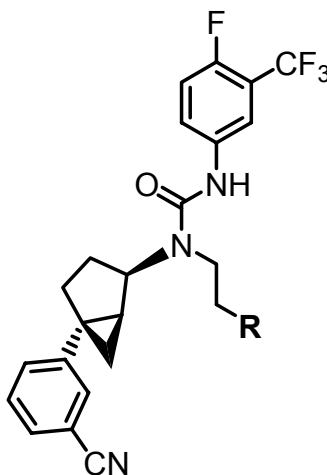
Mark D. McBriar*; Henry Guzik; Ruo Xu; Jaroslava Paruchova; Shengjian Li; Anandan Palani; Sherry Shapiro; John W. Clader; William J. Greenlee; Brian E. Hawes; Timothy J. Kowalski; Kim O'Neill; Brian Spar; Blair Weig.

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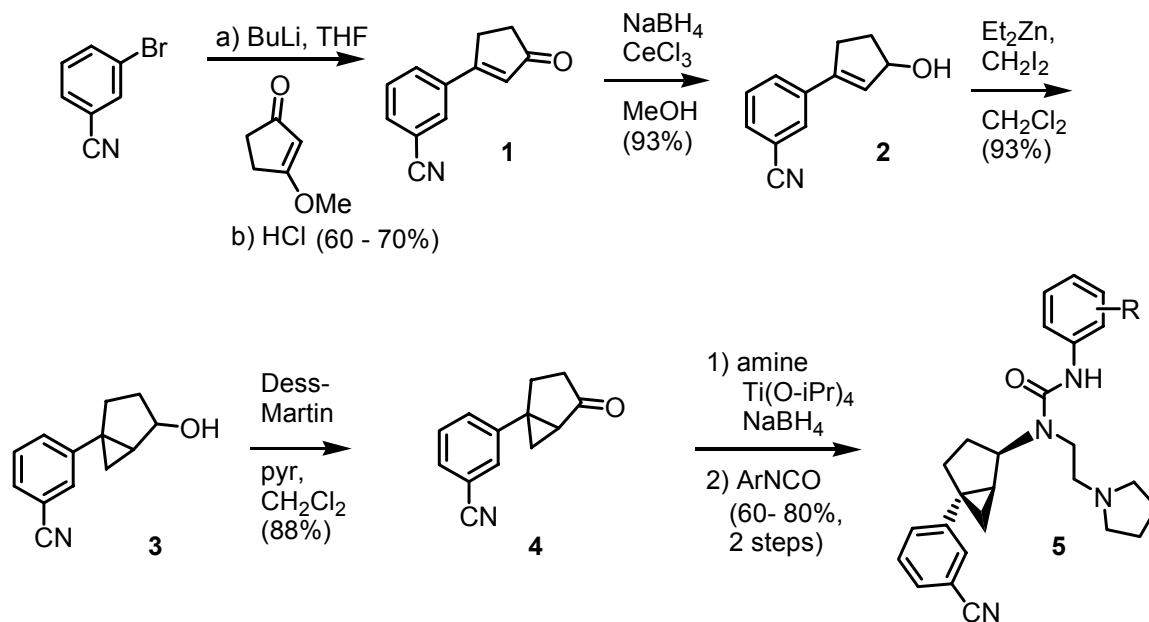
Obesity is recognized by WHO as a top 10 global health problem. It affects over 30% (60 Million) of adults in the U.S., total annual costs in the USA are over 117 billion (direct and indirect). Associated with obesity are morbidities such as type 2 diabetes, hyperlipidemia, stroke, cardiovascular disease, sleep apnea and several types of cancers.

Melanin Concentrating Hormone (MCH) is a 19 residue peptide found in the CNS. MCH regulates feeding and energy homeostasis by interaction with the central melanocortin system. It was found administration (ICV) of MCH increasing feeding, and that MCH null mice display a lean phenotype and are hypophagic. MCH-R1 is a GPCR expressed in the CNS. MCH-R1 null mice exhibit hypermetabolic phenotype, and are resistant to diet induced obesity (DIO). Therefore small molecule antagonists of MCH-R1 are expected to have similar effect.

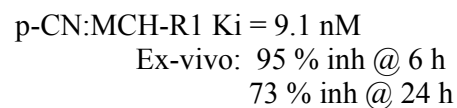
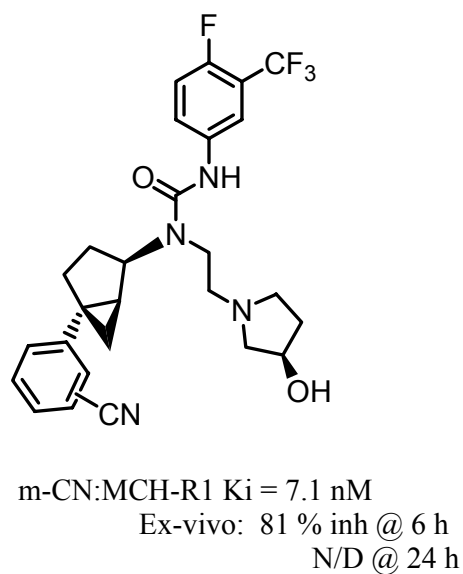
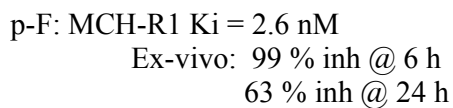
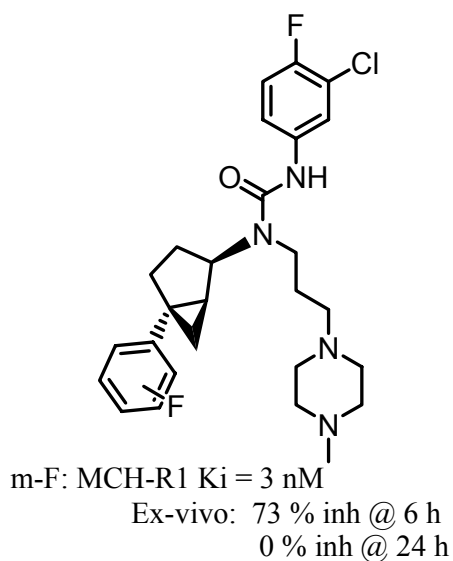
- a. A series of compounds that share the general features of the following structure has been discovered to have potent activity:



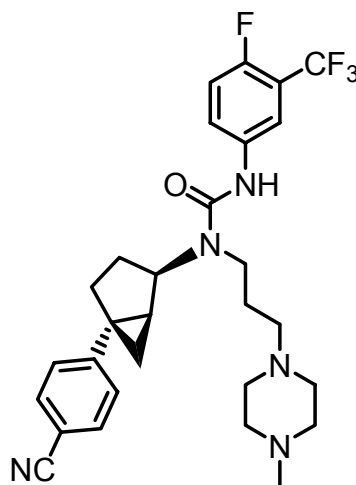
The synthesis of these compounds is achieved through the following route:



b. Representative Ex-vivo Profile of Bicyclohexanes are listed below:



c. In vivo efficacy of representative compound:



MCH K_i = 2.7 nM; K_b = 0.8 nM (cAMP)
Rat AUC (0-24h) (10 mpk, po) = 3.9 mM·h
F = 27%

Mouse:
ex-vivo binding: 99% inh. @ 6 h
58% inh. @ 24 h

d. Summary

- (1) A series of potent and selective MCH-R1 antagonists has been discovered from in-house screening leads.
- (2) Selectivity over M2, MCH-R2 and other receptors has been achieved.
- (3) Ex-vivo binding enables correlation of extent and duration of receptor occupancy with in vivo efficacy.
- (4) Compounds show in vivo efficacy in a DIO mouse model.

“Discovery of Dipeptidyl Peptidase IV (DPP-IV) Inhibitors by Structure-Based de novo Design,”

*Lei Qia**o; Christian A. Baumann; Carl S. Crysler; Nisha S. Ninan; Marta C. Abad; John C. Spurlino; Renee L. DesJarlais; Jukka Kervinen; Mike P. Neeper; Shariff S. Bayoumy; Robyn Williams; Ingrid C. Deckman; Bruce E. Tomczuk; Kevin J. Moriarty.*

**Johnson & Johnson
Pharmaceuticals Research and Development, L.L.C.
665 Stockton Drive
Exton, PA, 19341

Dipeptidyl peptidase IV (DPP-IV or CD26), a serine protease, inactivates glucagons-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) by cleavage of the N-terminal dipeptides. GLP-1 and GIP are gut peptides released in response to food intake. GLP-1 has multiple biological functions, including glucose-induced stimulation of insulin biosynthesis and secretion, inhibition of glucagon secretion, trophic effects on b cells, inhibition of food intake, and

slowing of gastric emptying. GIP has been implicated in the regulation of energy balance. However GLP-1 is rapidly eliminated via DPP-IV mediated metabolism. Inhibition of DPP-IV, which leads to an increased level of GLP-1 in circulation, has been recognized as a potentially valuable therapy for metabolic disorders related to diabetes and obesity. In a variety of studies, treatment with DPP-IV inhibitors has demonstrated the ability to improve glucose tolerance in normal and diabetic animals and humans.

Currently several DPP-IV inhibitors are under clinical evaluation (Figure 1). With few exceptions, DPP-IV inhibitors contain a proline mimic as P1. Incorporation of an electrophile at P1 provides potent reversible or irreversible inhibitors. The other portion of the molecules accepts numerous modifications.

A structure-based drug design strategy was used throughout the discovery process. A published crystal structure³ of human DPP-IV with inhibitor 1 bound in the active site (Figure 2, PDB ID: 1N1M) was used to initiate the discovery efforts. During the course of their work, a porcine DPP-IV in complex with the inhibitor 2 was published by Engel et al. Later efforts were driven by the in-house X-ray structure of compound 3 bound in the active site of human DPP-IV.

Figure 1: Selected inhibitors of DPP-IV

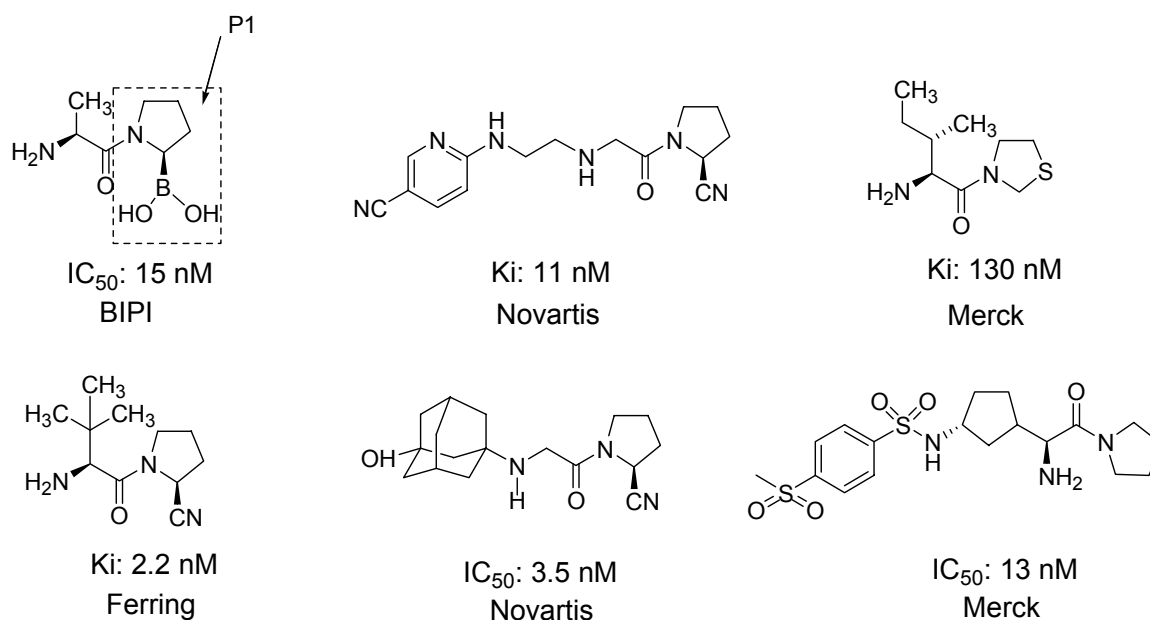
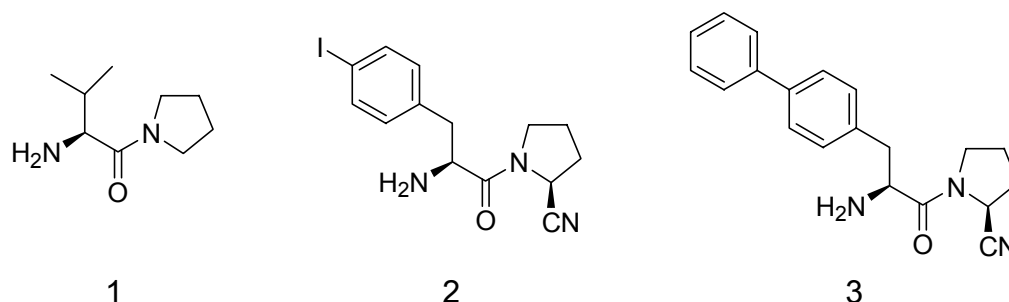
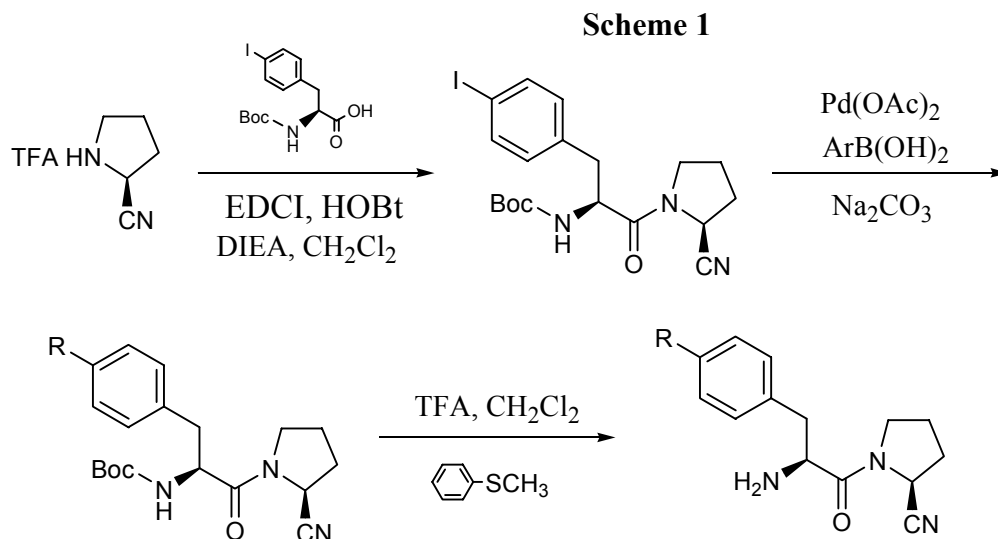


Figure 2: Probe molecules bound to DPP-IV



**Table 1:** SAR results of analogs

1st Group		2nd Group		3rd Group		4th Group	
R	Ki (nM)	R	Ki (nM)	R	Ki (nM)	R	Ki (nM)
	34		26		20		2.2
	13		36		5.3		
			3.1				
			470				

Conclusions:

A novel series of biaryl inhibitor of DPP-IV was identified by structure guided approach. The K_i of the biaryl cyanopyrrolidines reached lower single digit nanomolar range, and a preliminary SAR was established. The SAR was then successfully transferred to non-cyano containing biaryl thiazolidines, and double-digit nanomolar K_i was achieved. A crystal structure of human DPP-IV in complex with inhibitor 3 was obtained, and the structural information is expected to facilitate future lead optimization efforts.

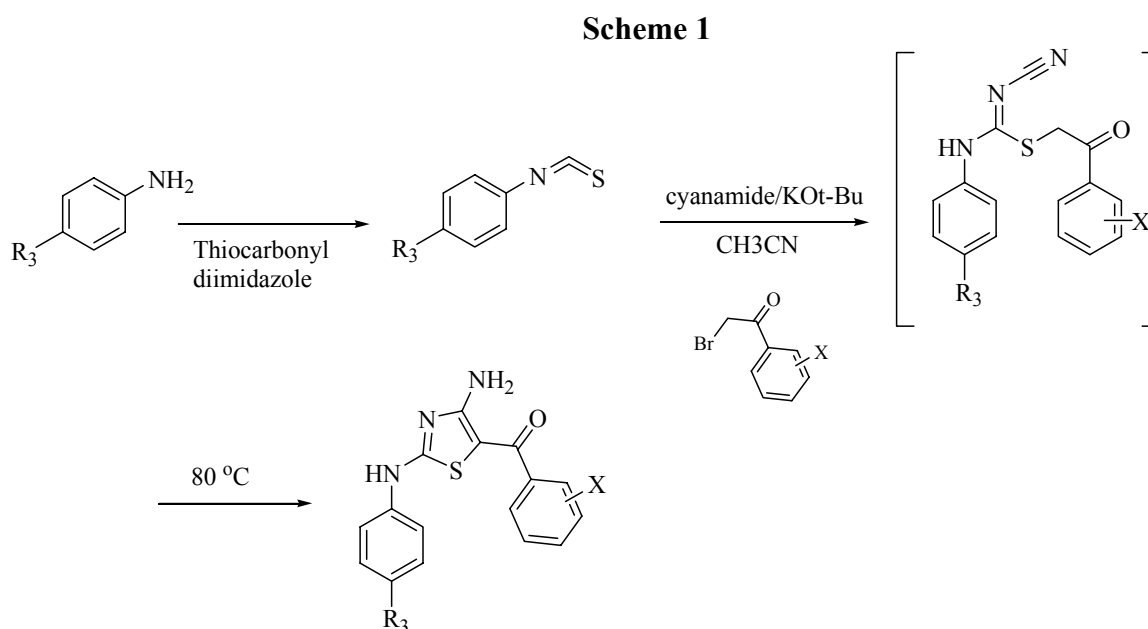
“Design, Synthesis, and Biological Evaluation of Aminothiazoles As Selective Inhibitors of Cyclin-dependent Kinase 4 (CDK4),”

Allen Lovey et al, (Hoffmann-La Roche, Inc.), Nutley, New Jersey.

a. Introduction

It is expected that inhibition of CDK4 by itself could lead to cell cycle arrest at G1 + G2 of the cell cycle rendering the tumor cells susceptible to apoptosis relative to non-transformed cells. Activity of the CDKs allows orderly transitions between phases of the cell cycle. CDK activity is controlled by association with regulatory subunits (Cyclins) and CDK inhibitor proteins, by their phosphorylation state and by ubiquitin-mediated proteolysis. This pathway is complex and knowledge is still emerging.

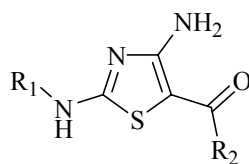
b. A group of inhibitors with low nanomolar K_{i} s have been discovered. The synthesis of the analogs was done using chemistry in Scheme 1.



c. The SAR for these aminothiazoles is listed in Table 1.

d. Conclusions:

Although compound (5) is 200x selective for CDK4 vs CDK2 and 133x selective for CDK1, its cellular activity is modest. There was modest efficacy despite the low exposure. It is expected that similar analogs having greater potency and better exposure can address the question of selective kinase inhibition and the potential for tumor inhibition.

Table 1: Inhibition of CDKs by Aminothiazoles substituted at R1 and R2

comp	R1 group	R2 group	CDK4/ Cyclin D1 Ki (μM)	CDK2/ Cyclin E Ki (μM)	CDK1/ Cyclin B Ki (μM)	HCT116 IC50 (μM)	HCT116 IC90 (μM)
1			0.185	0.140	2.5	0.52	1.01
2			0.032	0.892	0.126	0.52	1.01
3			0.013	0.173	0.270	0.73	1.51
4			0.025	5.4	2.1	2.79	6.75
5			0.015	3.0	2.0	1.07	2.53
6			0.012	2.9	1.3	1.76	3.0
7			0.032	0.860	0.265	1.23	2.00
8			0.018	3.5	0.494	3.48	7.01
9			0.020	4.1	2.4	3.85	6.11
10			0.020	0.930	2.9	0.40	0.82

“Asymmetric Synthesis of 1,2-Diol and Its application to the Synthesis of Flutriafol,”

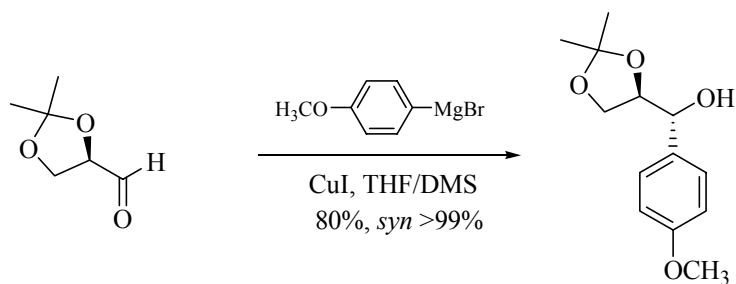
Tae Hyun Kim; Seol Rin Park and Hee-Doo Kim.

Sharpless asymmetric dihydroxylation of alkene is one of the most important strategies for optical active method for chiral 1,2-diols featuring tridentate chelation-controlled asymmetric alkylation of alpha-alkoxyketones. In connection with our asymmetric synthesis of chiral 1,2-diol, we report here the first asymmetric synthesis of triazole fungicide flutriafol.

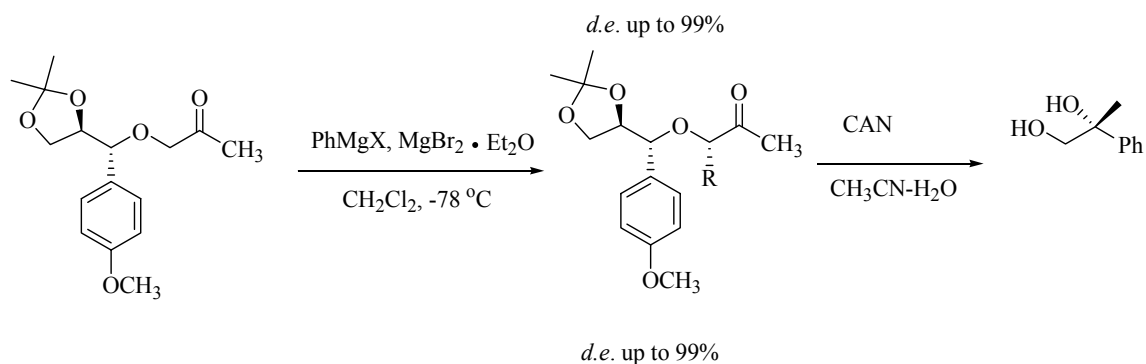
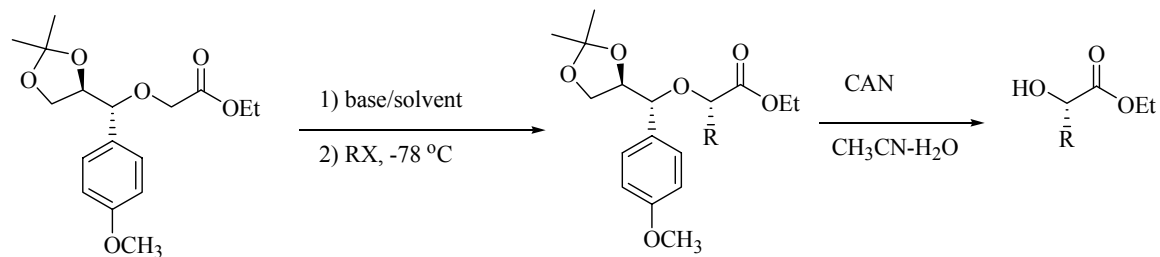
a. Synthesis of Chiral Auxiliary

The chiral auxiliary is synthesized by Scheme 1

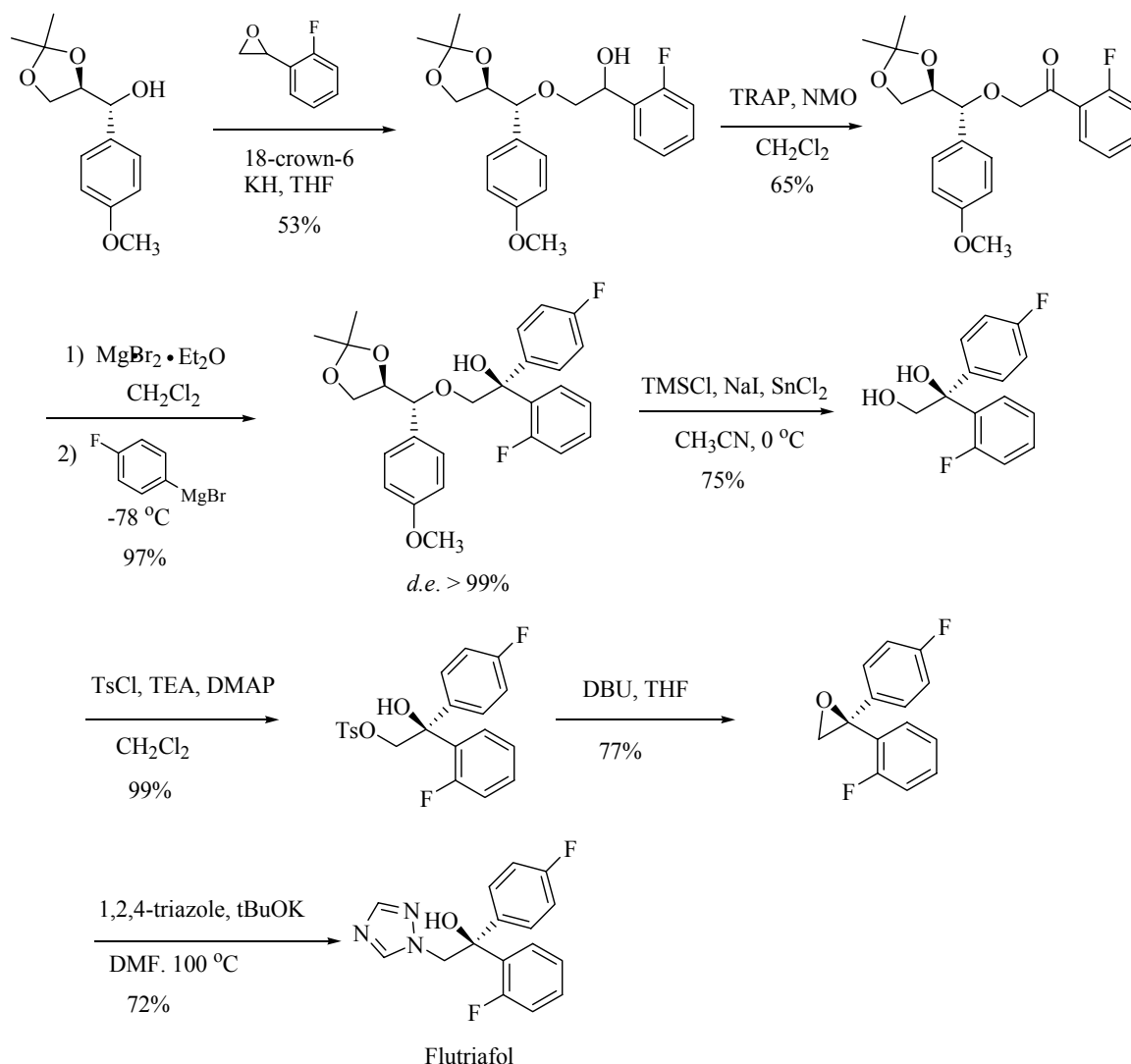
Scheme 1



b. Examples of the application of this auxiliary



c. Synthesis of Flutriafol



d. Summary

This method provides an efficient and alternative way to chiral 1,2-diols with high optical purity, inaccessible from the conventional Sharpless asymmetric dihydroxylation.

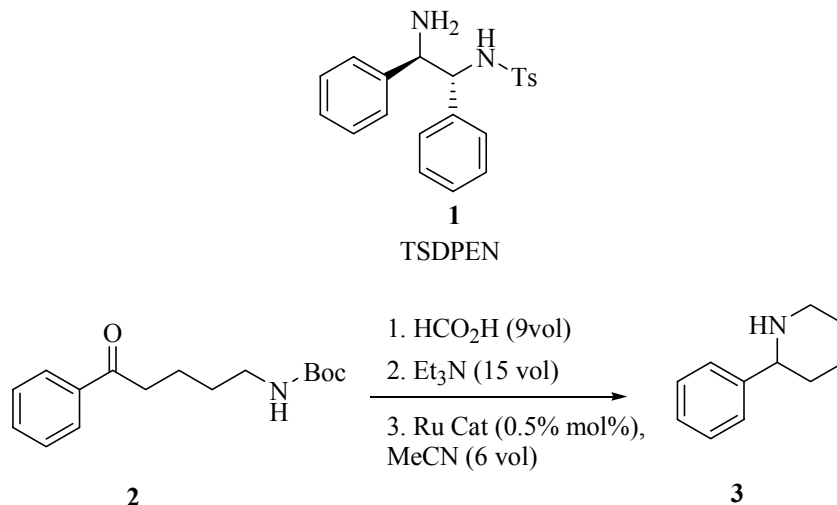
“One-pot Deprotection/Reductive Amination to Form N-Heterocycles,”

Glynn Williams, Martin Wills and Charles Wade.

Chiral alcohols and amines are fundamentally important building blocks for the synthesis of chiral organic molecules. Catalytic asymmetric hydrogenation is one of the most commonly performed operations to introduce new stereocenters. Catalytic asymmetric transfer hydrogenation using 2-propanol or formic acid as a source of hydrogen has recently emerged as an alternative to classic hydrogenation and there has been significant interest in the area, due mainly to the introduction of Noyori's ruthenium (II)-based catalysts. Of particular interest is the monotosylated diamine

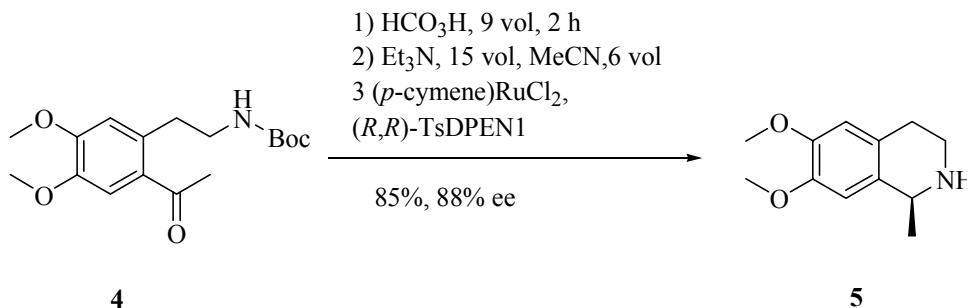
TsDPEN 1 (Scheme 1), which has become the ligand of choice for the catalytic asymmetric hydrogenation of ketones. The Ru(II)/TsDPEN system has been shown to work for the reduction of C=N double bonds in certain systems.

Scheme 1



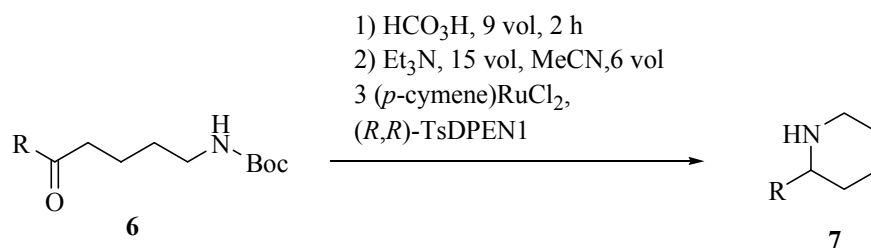
For a tetrahydroisoquinoline type product decent enantioselectivity can be achieved (Scheme 2).

Scheme 2



A number of substrates have been tested for this reaction protocol, and the results show six-membered rings are particularly suited for this reaction (Scheme 3).

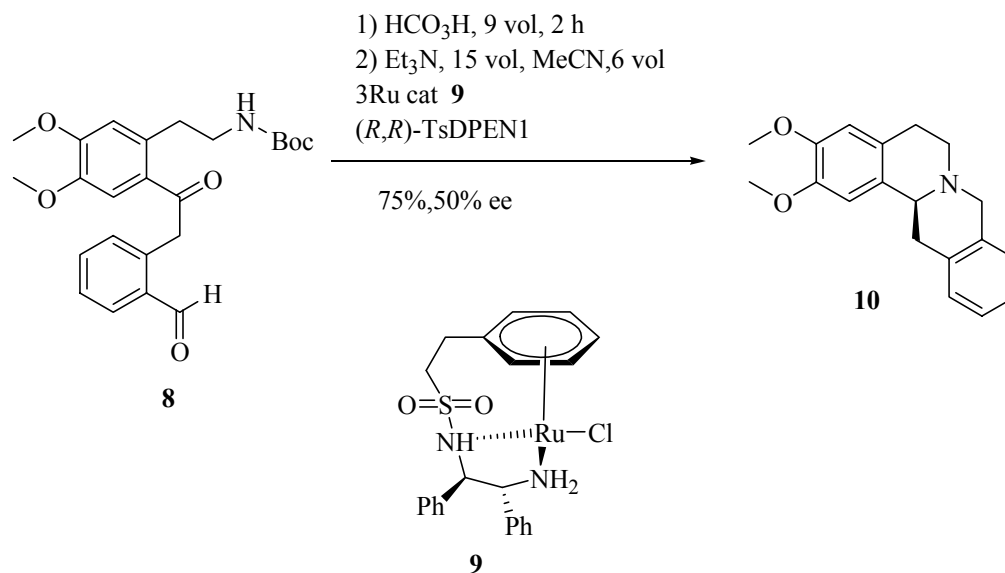
Scheme 3



R	yield	R	yield
<i>o</i> -MeOC ₆ H ₄	78	<i>p</i> -CF ₃ C ₆ H ₄	99
<i>m</i> -MeOC ₆ H ₄	96	2-thiophene	20
<i>p</i> -MeOC ₆ H ₄	94	<i>c</i> -C ₆ H ₁₁	98
<i>m</i> -CF ₃ C ₆ H ₄	98		

This reaction was also applied in complex alkaloid synthesis (Scheme 4).

Scheme 4

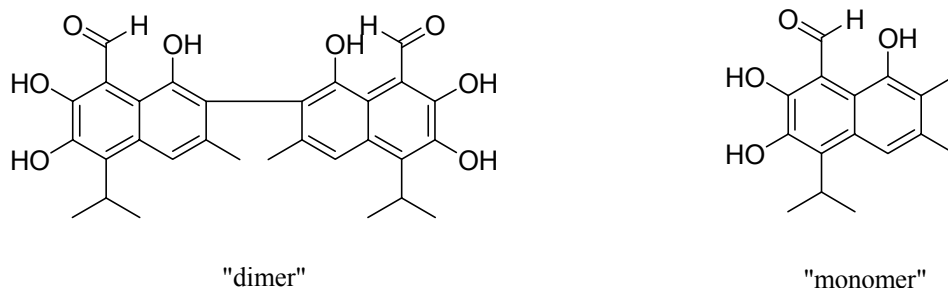


Conclusion: A novel one-pot deprotection, homogeneous catalyzed asymmetric reductive amination that is amenable to the synthesis of six-membered rings in excellent yields with moderate to good enantioselectivities has been developed.

“Synthesis of Methylhemigossypol for Biological Studies,”

Wei, J.; Hunsaker, L. A.; Deck, L. M.; Vander Jagt, D. L.; Royer, R. E.; (University of New Mexico).

The inhibition of human and parasitic isoenzymes of lactate dehydrogenases (LDH) has potential in the development of antimalaria and male antifertility therapeutic agents. Gossypol derivatives and dihydroxynaphthoic acids are found to be inhibitors of LDH with $K_i = 0.1-6 \mu\text{M}$.



Molecular modeling study indicates that gossypol both “dimer” and “monomer” bind tightly to the enzyme Parasitic: *P. falciparum* (pfLDH). To design more potent inhibitor, three different modification strategies were examined: 1. use monomer as a core structure; 2. remove some OH group; 3. use tetralone as a core.

Compounds			
pf-LDH K_i (μM)	7.2	6.6	7.8
LDH-A K_i (μM)	26.7	520	65.5
Compounds			
pf-LDH K_i (μM)	0.02	1.8	2.4
LDH-A K_i (μM)	151.9	>250	6.4

Six compounds were synthesized and tested for their binding affinities with pfLDH and LDH-A. The compounds in tetralone series give good K_i . Some compounds show selectivity between pfLDH and LDH-A. More SAR studies are in progress.

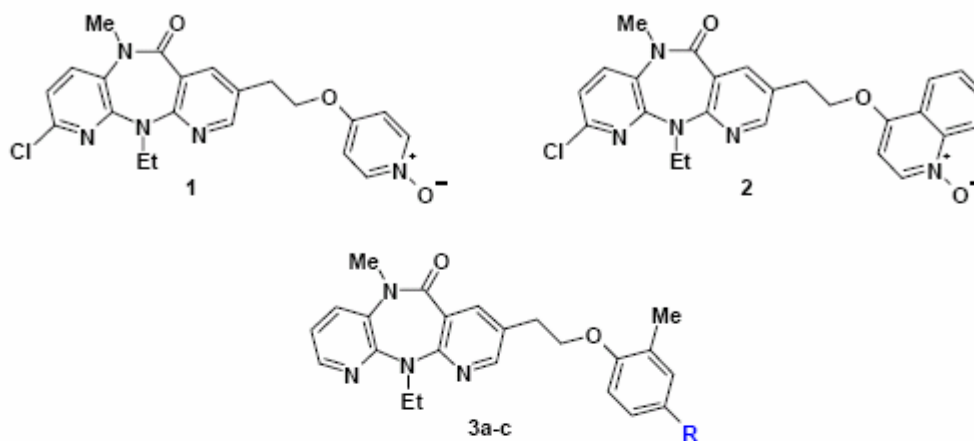
“Novel 8-Substituted Dipyridodiazepinone Derivatives as HIV NNRTIs with Broad Antiviral Potency,”

S. Landry; P.R. Bonneau; J. Bordeleau; L. Doyon; J. Duan; I. Guse; E. Malenfant; J. Naud; J.A. O’Meara; B. Thavonekham; C. Yoakim; B. Simoneau; M. Bös; M.G. Cordingley; (Boehringer Ingelheim (Canada) Ltd. Research and Development), Laval (Québec), Canada.

Since Viramune® (non-nucleoside reverse transcriptase inhibitor (NNRTI), anti-etroviral therapy) was introduced to the market in 1998, more and more drug resistance, which caused the treatment failure, was observed. Therefore a novel NNRTI that displays potent antiviral activity against wild-type and NNRTI-resistant viruses associated with treatment failure is needed incorporating the currently approved NNRTIs.

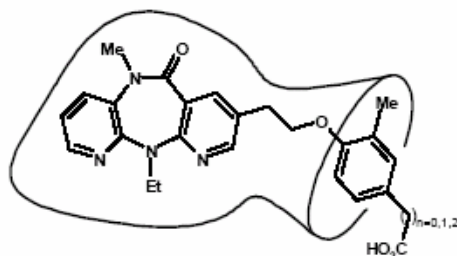
Nevirapine core was used as a starting point to identify inhibitors with activity against WT & NNRTI-resistant HIV-1. Substitution of the position 8 of the dipyridodiazepinone scaffold was proved to be critical in order to obtain inhibitors with a broad antiviral profile.

Background SAR

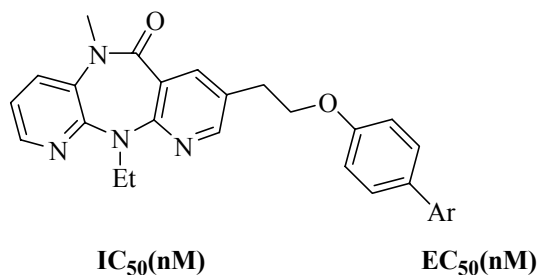


Cpd #	R	IC ₅₀ (nM)		EC ₅₀ (nM)	
		WT	K103N/ Y181C	WT	K103N/ Y181C
1	-	31	250	1.4	14
2	-	12	46	0.7	3.4
3a	CO ₂ H	17	221	1.6	15
3b	CH ₂ CO ₂ H	23	370	12	139
3c	(CH ₂) ₂ CO ₂ H	22	200	5.5	101

Since hydrophilic R groups are well tolerated, C-8 heterocycle was thought to be exposed to solvents. Possible binding mode is listed as below:



Replacement of the alky side chain by more rigid aryl increases potency



Cpd #	Ar	WT	K103N/ Y181C	WT	K103N/ Y181C
5		17	26	3.0	9.0
8		16	36	4.0	8.0
12		9.0	20	0.4	1.0
19		5.5	34	1.0	6.0

C-8 biaryl derivatives show higher potency against a panel of relevant HIV-1 mutants.

ANTIVIRAL PROFILE

Cpd #	EC ₅₀ (nM)								
	WT	K103N	Y181C	Y188L	V106A	K103N/ Y181C	K103N/ P225H	K103N/ V108I	K103N/ L100I
3a	1.6	3	8	189	34	15	4	5	3
5	3	3	9	14	4	9	2	3	4
8	4	5	11	19	7	8	3	4	3
12	0.4	0.4	1	9	3	1	0.9	0.6	0.5
19	1.0	-	-	19	6	6	1.9	1.0	-

Cyp450 profile shows compound 19 is a potent CYP inhibitor.

Cyp450 INHIBITION PROFILE

Cpd #	IC ₅₀ (μM)					
	1A2	2C9	2C19	2D6	3A4-BFC*	3A4-BQ*
3a	>30	10	2	>30	24	>30
5	20	3	3	>30	10	>30
8	26	3	3	>30	16	27
12	>30	7	5	>30	2	5
19	12	0.3	0.5	0.9	0.2	0.5

Pharmacokinetic profile of compound 3a, 5, 8 and 12 is listed below.

IN RAT:

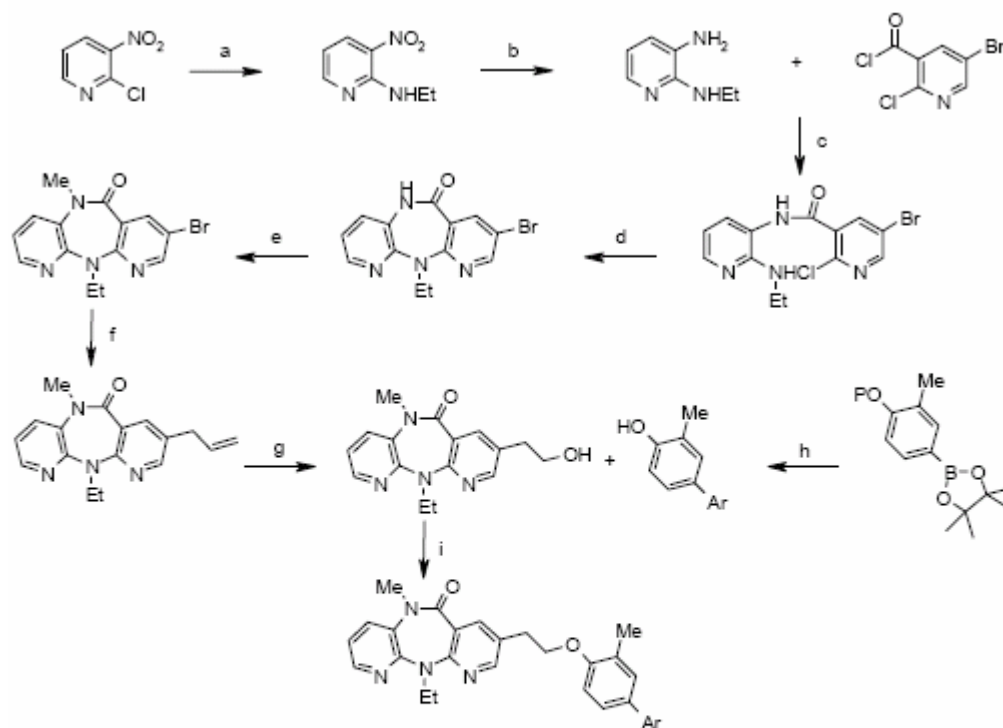
Cpd #	Intravenous			Oral (5 mg/Kg)			Metabolic Stability T _{1/2} (min)
	V ₂₅ (L/Kg)	T _{1/2} (h)	Cl (mL/Kg/min)	C _{max} (μM)	AUC _{0-∞} (μM ² h)	%F	
3a	4.6	11.3	7.1	5.7	17	67	291
5	1.7	3.9	5.9	2.7	12	45	74
8	3	5.1	15.4	3.4	8.7	83	106
12	0.6	0.6	19.3	3.3	5.7	61	23

IN DOG:

Cpd #	Intravenous			Oral (5 mg/Kg)			Metabolic Stability T _{1/2} (min)
	V ₂₅ (L/Kg)	T _{1/2} (h)	Cl (mL/Kg/min)	C _{max} (μM)	AUC _{0-∞} (μM ² h)	%F	
3a	2.5	5.9	10.2	16.2	20.6	~100	253
5	1.9	1.8	26.6	9.8	15.3	304*	65
12	1.2	1.8	14.8	1.4	2.3	18	13

Compound 5, 8 and 12 meet the criteria for next generation NNRTIs

For the syntheses, various C-8 substituents were installed at the last step through Mitsunobu reaction. The synthetic route is shown below:

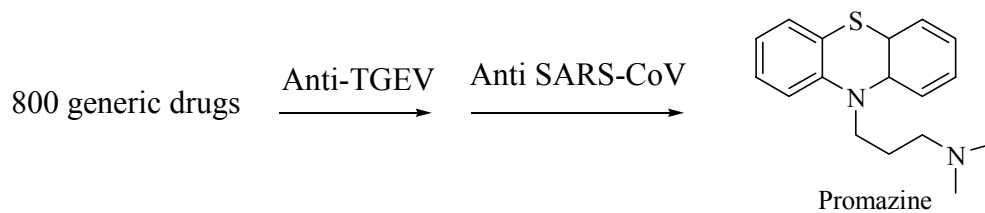


(a) EtNH₂, THF; (b) H₂, Pd(OH)₂/C, MeOH, 88% (2 steps); (c) NaHCO₃, MeCN, 69%; (d) NaHMDS, pyridine, 50°C, 75%; (e) NaH, MeI, DMF, 50°C, 99%; (f) CH₂=CHCH₂SnBu₃, (Ph₃P)₄Pd, DMF, 90°C, 84%; (g) O₃, CH₂Cl₂/MeOH, -78°C followed by NaBH₄, 72%; (h) Br(I)Ar, PdCl₂(dppf), DPPF, K₃PO₄, dioxane, 100°C, deprotection; (i) DEAD, Ph₃P, substituted phenols, THF.

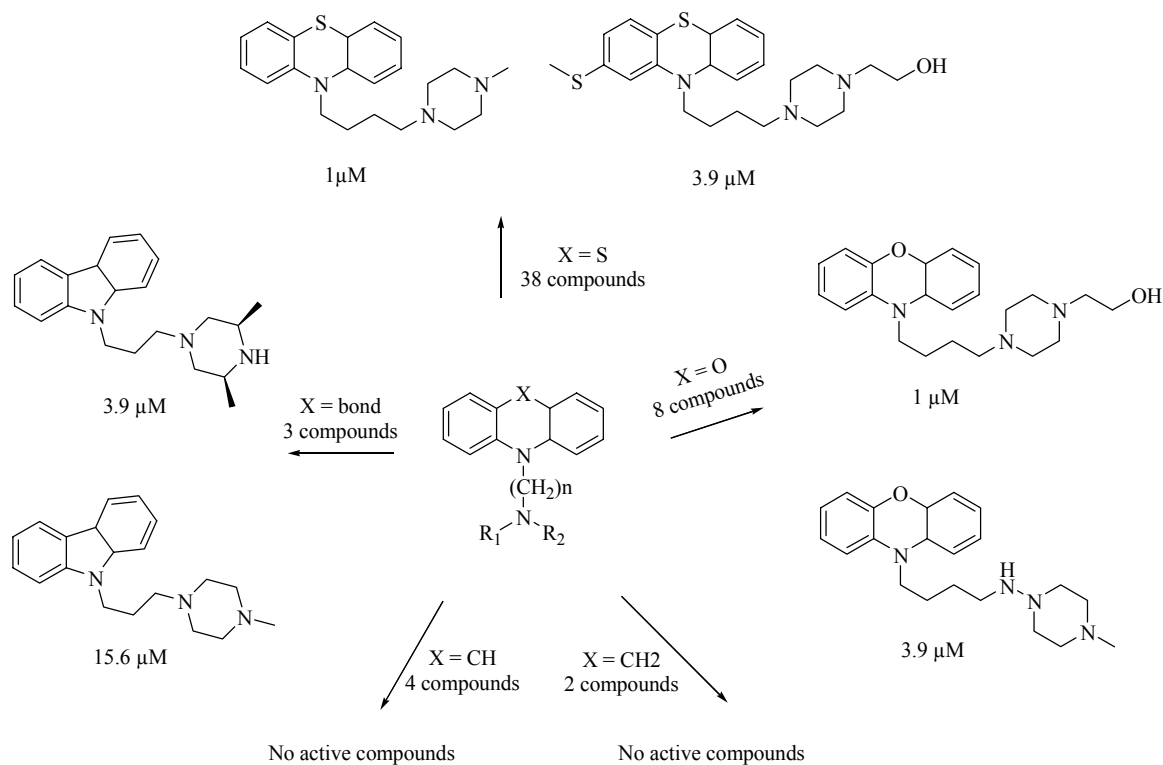
“Promazine Analogues as Potential Anti SARS-CoV Drugs,”

Yu-Shan Wu^a; Ping Hsun Lu^a; Yu-Chan Chao^b; Jia-Tsong Jan^c; Chang-Jer Wu^c; Chi-Min Chen^d; Jing-Ping Liou^a; Huei-Ru Lo^b; Shiou-Hwa Ma^c; Yu-Sheng Chao^a; Tsu-An Hsu^a; Hsing-Pang Hseh^a; (^a Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes; ^b Institute of Molecular Biology, Academia Sinica; ^c Institute of Preventive Medicine, National Defense Medical Center, National Defense University; ^d Animal Technology Institute Taiwan).

The global outbreak of Severe Acute Respiratory Syndrome (SARS) caused by a new coronavirus began in March 2003. The rapid emergence of SARS and the substantial illness and death it caused have made it a critical public health issue. Many efforts were made in finding promising antiviral drugs. Screening from a library of 800 marketed generic drugs using porcine transmissible gastroenteritis virus (TGEV) as a surrogate system, promazine was found to be active against SARS coronavirus (SARS-CoV) *in vitro*. The compound was therefore identified as the lead compound for further SAR study.



The SAR is shown in the scheme below.



In summary, a series of promazine analogues was synthesized and a few analogues showed good activity against baculovirus pseudovirion containing SARS-CoV spike protein.