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Imidazopiperidine amides as dipeptidyl peptidase IV inhibitors for the treatment of diabetes

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Abstract—A series of substituted imidazopiperidine amides has been prepared and evaluated for inhibition of dipeptidyl peptidase IV (DPP-4). Substitution at the 1- and 3-positions produced increased selectivity for DPP-4 relative to DPP-8 and DPP-9. Compounds in this series had IC_{50} values as low as 5.8 nM for inhibition of DPP-4.
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Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are important incretin hormones released from intestine in response to nutrient ingestion. They both stimulate insulin secretion in a glucose-dependent manner. In addition, GLP-1 also suppresses glucagon secretion, slows gastric emptying, and reduces food intake, while stimulating pancreatic β-cell growth.[1,3] Continuous subcutaneous infusion of GLP-1 in diabetic patients for six weeks resulted in reduction of blood glucose and hemoglobin A_{1c} levels.[2]

GLP-1 and GIP are rapidly inactivated in the circulation by the enzyme dipeptidyl peptidase IV (DPP-4), a serine peptidase which cleaves an N-terminal dipeptide from polypeptides having a proline or alanine residue at the P_1 site.[1] Inhibition of DPP-4 prevents the degradation of GLP-1 and GIP, resulting in enhancement of their physiological effects.[1,3] Clinical studies have shown that small molecule DPP-4 inhibitors reduce both prandial and fasting glucose levels significantly, leading to lowering of hemoglobin A_{1c} levels in type 2 diabetics.[3] Thus, DPP-4 inhibition has emerged as a new therapeutic approach for treatment of type 2 diabetes.

Among the structurally novel β-amino acid-based DPP-4 inhibitors reported from these laboratories, the triazolopyrazine sitagliptin phosphate (**1**), also called Januvia, is a potent, selective, orally active DPP-4 inhibitor recently approved for treatment of type 2 diabetes.[4] In a related series of piperazine derivatives, represented by structures **2**–**4**, introduction of a 2-methyl substituent improved DPP-4 potency by more than two fold, while the benzyl group of compound **4** gave a 27-fold increase

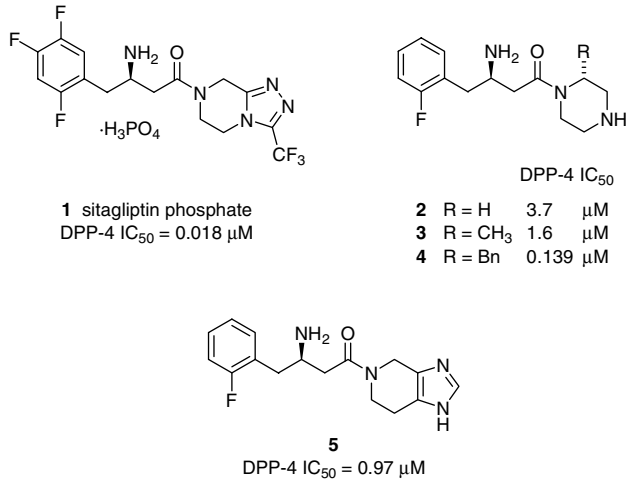

Figure 1. β-Amino acid DPP-4 inhibitors.

Keywords: Dipeptidyl peptidase IV inhibitors; Diabetes; Glucagon-like peptide-1 (GLP-1); Incretin hormones; Imidazopiperidine amides.
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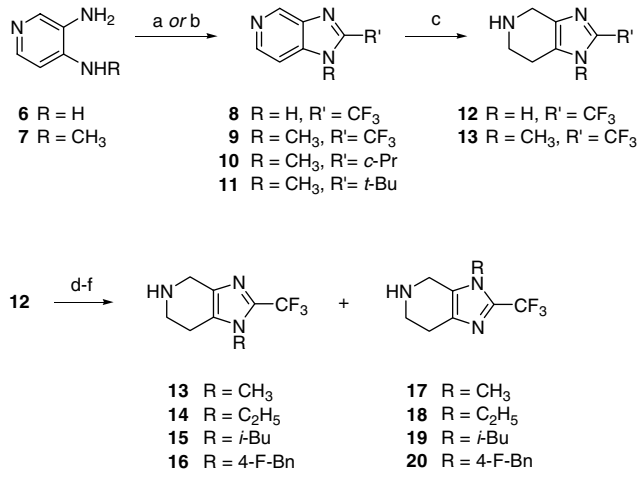


Scheme 1. Reagents and conditions: (a) TFA, reflux (R′ = CF_3); (b) R′COCl, Et_3N, CH_2Cl_2, then TsOH, xylene (R′ = *t*-Bu) or AcOH (R′ = *c*-Pr); (c) H_2 (1000 psi), PtO_2, EtOH, 40 °C; (d) $(Boc)_2O$, CH_2Cl_2; (e) R-I, NaH, THF; (f) HCl, CH_3OH.

in potency.[5] The first imidazopiperidine analog we prepared was the unsubstituted derivative **5**, which showed modest potency as a DPP-4 inhibitor (Fig. 1). We initiated an investigation of the effect of substitution in this series of heterocyclic compounds. The work described here involves the synthesis and biological evaluation of imidazopiperidine-based β-amino acid derivatives.

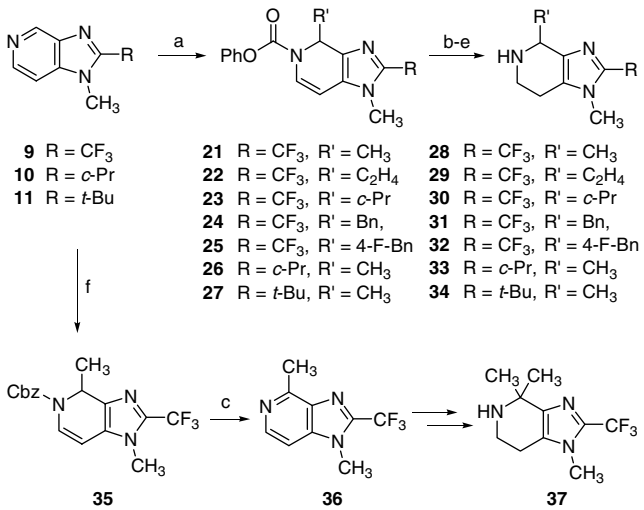
Determinations of IC_{50} values for inhibition of DPP-4 and quiescent prolyl peptidase (QPP/DPP-II) were carried out as described previously.[6] Compounds were also tested against DPP-8 and DPP-9, two enzymes which have been associated with significant toxicity in animal studies.[7]

An initial synthetic route to imidazopiperidine intermediates having substitution at the 1-, 2- or 3-position is depicted in Scheme 1. Chemistry began with 3,4-diaminopyridine (**6**) and 3-amino-4-(methylamino)pyridine (**7**).[8] Treatment with trifluoroacetic acid as described by Threadgill yielded the 2-(trifluoromethyl)imidazopyridines **8** and **9**.[9] Hydrogenation then generated imidazopiperidine intermediates **12** and **13**. Protection of the piperidine nitrogen, alkylation on the imidazole ring, and removal of the Boc protecting group produced 1- and 3-alkyl imidazopiperidines **13**–**16**, and **17**–**20**.

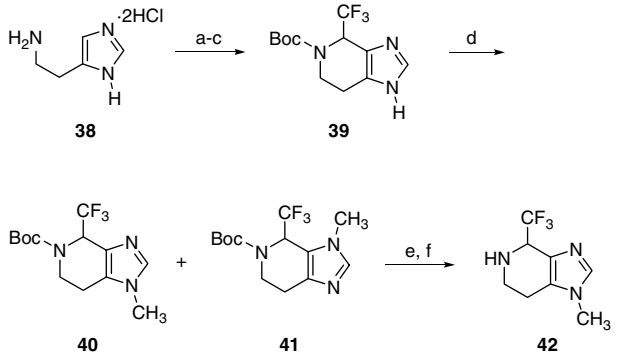
Synthesis of the 2-cyclopropyl and 2-*tert*-butyl substituted imidazopyridines **10** and **11** was accomplished by acylation of **7** followed by acid-catalyzed cyclization of the intermediate amides (Scheme 1). These derivatives, as well as the 2-trifluoromethyl analogs described above, were used in acylpyridinium reactions[10] to produce the 4-substituted 4,5-dihydro intermediates **21**–**27** (Scheme 2). Treatment with potassium *tert*-butoxide converted the *N*-phenoxycarbonyl group of these intermediates into a Boc group prior to hydrogenation.[11] In most cases, enantiomers of the Boc-protected hydrogenation products were separated using a chiral HPLC column. Finally, removal of the *N*-Boc group using methanolic HCl gave imidazopiperidine intermediates **28**–**34**. An early attempt to synthesize **28** using a one-pot hydrogenation and deprotection of the *N*-Cbz intermediate **35** resulted in formation of aromatization product **36**. Imidazopyridine **36** was later converted into 4,4-dimethyl analog **37** following a reaction route similar to that used to prepare imidazopiperidine **28** from intermediate **9**.

Introduction of a trifluoromethyl group at the 4-position was accomplished by a condensation reaction of histamine (**38**) with trifluoroacetaldehyde ethyl hemiacetal (Scheme 3).[12] The mono-protected intermediate **39** was generated by reaction with 2 equiv of di-*tert*-butyl dicarbonate, followed by treatment with ammonia to remove the more reactive imidazole Boc group. Methylation, HPLC separation, and deprotection gave the enantiomers of intermediate **42**.

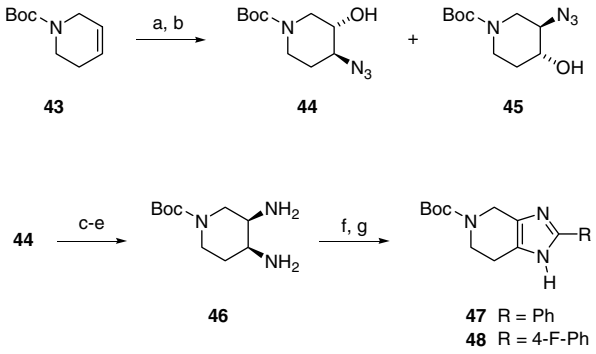
Synthesis of imidazopiperidines **47** and **48** via 3,4-diaminopiperidine intermediate **46** is outlined in Scheme 4. Epoxidation of 1,2,3,6-tetrahydropyridine derivative **43**[13] followed by opening with sodium azide afforded



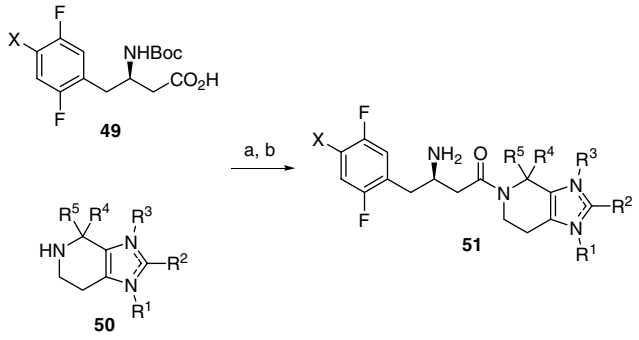
Scheme 2. Reagents: (a) PhOCOCl, R′MgX, THF; (b) *t*-BuOK, THF; (c) H_2, 10% Pd/C, EtOH; (d) HPLC resolution; (e) HCl, CH_3OH; (f) Cbz–Cl, CH_3MgBr, THF.



Scheme 3. Reagents and conditions: (a) $CF_3CH(OH)OC_2H_5$, NaOH, H_2O, reflux; (b) 2 equiv $(Boc)_2O$, CH_2Cl_2, THF; (c) NH_3, CH_3OH; (d) CH_3I, $KN(TMS)_2$, THF, −20 °C; (e) separate isomers; (f) HCl, CH_3OH.



Scheme 4. Reagents and condition: (a) *m*-CPBA, CH_2Cl_2; (b) NaN_3, NH_4Cl, EtOH, H_2O; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaN_3, DMF; (e) H_2, 10% Pd/C, EtOH; (f) PhC(=NH)OEt HCl or 4-FC_6H_4C(=NH)SMe HCl, EtOH, reflux; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2.



Scheme 5. Reagents: (a) EDC, HOBt, Et_3N, DMF; (b) HCl, CH_3OH.

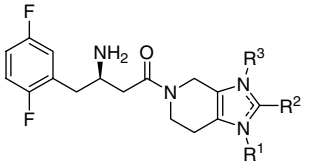
separable azido alcohols **44** and **45**. Conversion of **44** into the corresponding mesylate,[14] displacement by azide, and hydrogenation afforded diamine **46**. Cyclization with benzimidate (for R = Ph)[15] or thiobenzimidate (for R = 4-C_6H_4F)[16] produced an imidazoline which was oxidized to the imidazole using Swern conditions.[17]

Finally, in most cases EDC-mediated coupling of Boc-protected β-amino acids **49** (X = H or F) with imidazopiperidine intermediates **50** was successful, providing DPP-4 inhibitors **51** after removal of the Boc group. For the less reactive imidazopiperidines leading to *gem*-dimethyl derivative **66** and the 4-trifluoromethyl derivatives **67a**–**b**, it was preferable to activate acid **49** as a mixed anhydride with pivaloyl chloride prior to condensation with **50** in the presence of 4-(dimethylamino)pyridine and *N*-methylmorpholine in dichloromethane (Scheme 5).

Table 1 lists data for an initial series of DPP-4 inhibitors having substitution on the imidazole ring. While all of these compounds have submicromolar IC_{50} values as DPP-4 inhibitors, relatively little variation in potency is observed. It is noteworthy that compounds **52** and **61**, the two examples lacking N-substitution on the imidazole ring, show the lowest selectivity for DPP-4 over DPP-8 and DPP-9. *i*-Butyl and 4-fluorobenzyl groups at the 3-position produce high levels of selectivity (e.g., **58** and **60**), but these analogs are slightly less potent as DPP-4 inhibitors. The 1-methyl derivative **53**, with its balance of activity and selectivity as a DPP-4 inhibitor, was selected for further modification to examine the effects of substitution at the 4-position.

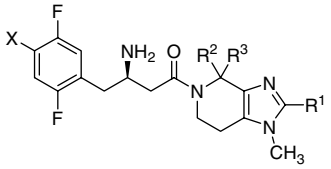
Table 2 displays enzyme assay data for 1-methylimidazopiperidine derivatives having substitution at 2- and 4-positions. For diastereomeric isomers **63a**–**b**, **65a**–**b**, and **67a**–**b** to **72a**–**b**, one stereoisomer is 2- to 130-fold more potent than the other as a DPP IV inhibitor. X-ray crystal structure determination of these active diastereomers was not conducted in this series. However, a related analog having 2-substituted triazolopiperazine subunit on the right-hand side was studied and the absolute stereochemistry of 2-methyl triazolopiperazine derivative was determined by X-ray crystal structure,[18] in which *R*-isomer (IC_{50} = 25 nM) is 120-fold more potent than *S*-isomer (IC_{50} = 274 nM). We assume that the active stereoisomer of **63b**, **65b**, **67b**–**72b** have (*R*) configuration while **63a**, **65a**, **67a**–**72a** have (*S*) stereochemistry. The 2,4,5-trifluorophenyl analog **64** is the *R*-diastereomer, prepared from the same enantiomer of

Table 1. Substitution on the imidazole ring



Compound	R^1	R^2	R^3	DPP-4 IC_{50} (μM)	QPP IC_{50} (μM)	DPP-8 IC_{50} (μM)	DPP-9 IC_{50} (μM)
52	H	CF_3	—	0.14	>100	9.4	51
53	CH_3	CF_3	—	0.15	92	68	>100
54	—	CF_3	CH_3	0.13	80	50	50
55	C_2H_5	CF_3	—	0.18	>100	58	>100
56	—	CF_3	C_2H_5	0.23	76	77	63
57	*i*-Bu	CF_3	—	0.22	49	54	>100
58	—	CF_3	*i*-Bu	0.26	85	>100	>100
59	4-F–Bn	CF_3	—	0.25	64	23	>100
60	—	CF_3	4-F–Bn	0.25	56	>100	>100
61	H	Ph	—	0.13	33	6.6	9.4
62	CH_3	4-C_6H_4F	—	0.28	58	26	73

Table 2. Substitution at the 4-position



Compound	X	R^1	R^2	R^3	DPP-4 IC_{50} (μM)	QPP IC_{50} (μM)	DPP-8 IC_{50} (μM)	DPP-9 IC_{50} (μM)
63a	H	CF_3	CH_3	H	0.19	>100	64	>100
63b	H	CF_3	CH_3	H	0.065	>100	77	>100
64	F	CF_3	CH_3	H	0.045	39	58	>100
65a	F	CF_3	C_2H_5	H	0.61	93	>100	>100
65b	F	CF_3	C_2H_5	H	0.060	45	55	89
66	F	CF_3	CH_3	CH_3	0.57	28	4.0	15
67a	F	H	CF_3	H	0.38	76	>100	>100
67b	F	H	CF_3	H	0.050	38	39	>100
68a	F	CF_3	*c*-Pr	H	0.34	>100	>100	>100
68b	F	CF_3	*c*-Pr	H	0.11	37	85	>100
69a	F	*c*-Pr	CH_3	H	0.49	90	65	ND
69b	F	*c*-Pr	CH_3	H	0.25	30	33	ND
70a	F	*t*-Bu	CH_3	H	0.63	37	80	ND
70b	F	*t*-Bu	CH_3	H	0.37	19	21	ND
71a	F	CF_3	Bn	H	0.57	46	100	>100
71b	F	CF_3	Bn	H	0.0084	20	70	>100
72a	F	CF_3	4-F–Bn	H	0.78	39	100	>100
72b	F	CF_3	4-F–Bn	H	0.0058	15	46	>100

Table 3. Pharmacokinetic properties in rats

	64	**67b**	**71b**
Dosage			
iv (mg/kg)	1	1	1
po (mg/kg)	2	2	2
Cl_p (ml/min/kg)	81	93	64
Vd_{ss} (L/kg)	8.0	8.3	6.5
$t_{1/2}$ (h)	1.2	1.4	1.5
C_{max} (po dosage, μM)	0.098	0.050	0.072
Oral bioavailability (%)	40	16	16

piperidine **28** used in the synthesis of the 2,5-difluorophenyl compound **63b**. Relative to **63b**, the 2,4,5-trifluorophenyl analog **64** shows a small increase in potency as a DPP-4 inhibitor, but is less selective versus QPP. Introduction of an ethyl or cyclopropyl group at the 4-position (samples **65b** and **68b)** does not result in an improvement relative to the 4-methyl derivative **64** (DPP-4 IC_{50} = 45 nM). A benzyl or 4-fluorobenzyl substituent at the 4-position (samples **71b** and **72b**), however, produces compounds having DPP-4 IC_{50} values below 10 nM. The 4,4-dimethyl compound **66** shows increased potency against DPP-8 and DPP-9 while losing activity against DPP-4. The 4-trifluoromethyl analog **67b** is a DPP-4 inhibitor with an IC_{50} value of 50 nM.

Compounds **64**, **67b**, and **71b**, having methyl, trifluoromethyl, and benzyl groups at the 4-position, were selected for evaluation in rat pharmacokinetic studies (see Table 3). While the 4-methyl compound **64** showed moderate oral bioavailability, the clearance was high and half-life was modest. The trifluoromethyl analog **67b** showed a decrease in oral bioavailability and no improvement in other parameters. The more potent benzyl derivative **71b** had similar pharmacokinetic properties.

In conclusion, a series of substituted imidazopiperidine amides has been prepared and evaluated as DPP-4 inhibitors. Substitution at the 1- and 3-positions produced increased selectivity for DPP-4 relative to DPP-8 and DPP 9, although improved potency against DPP 4 was not observed. Introduction of a substituent at the 4-position of the imidazopiperidine unit significantly improved DPP-4 inhibition, resulting in compounds with IC_{50} values as low as 5.8 nM.

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References and notes

1. (a) Holst, J. J. *Diabetogoia* **2006**, *49*, 253; (b) Drucker, D. J. *Expert Opin. Investig. Drugs* **2003**, *12*, 87; (c) Vahl, T. P.; D'Alessio, D. A. *Expert Opin. Investig. Drugs* **2004**, *13*, 177.
2. Zander, M.; Madsbad, S.; Madsen, J. L.; Holst, J. J. *Lancet* **2002**, *359*, 824.
3. (a) Holst, J. J.; Deacon, C. F. *Curr. Opin. Pharmacol.* **2004**, *4*, 589; (b) Weber, A. E. *J. Med. Chem.* **2004**, *47*, 4135; (c) Deacon, C. F.; Ahren, B.; Holst, J. J. *Expert*

Opin. Invest. Drugs **2004**, *13*, 1091; (d) Mentlein, R. *Expert Opin. Investig. Drugs* **2005**, *14*, 57.
4. (a) Kim, D.; Wang, L.; Beconi, M.; Eiermann, G. J.; Fisher, M. H.; He, H.; Hickey, G. J.; Kowalchick, J. E.; Leiting, B.; Lyons, K.; Marsilio, F.; McCann, M. E.; Patel, R. A.; Petrov, A.; Scapin, G.; Patel, S. B.; Sinha Roy, R.; Wu, J. K.; Wyvratt, M. J.; Zhang, B. B.; Zhu, L.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2005**, *15*, 141; (b) Thornberry, N. A.; Weber, A. E. *Curr. Top. Med. Chem.* **2007**, *7*, 557; (c) Gallwitz, B. *Drugs Today* **2007**, *43*, 13.
5. Brockunier, L. L.; He, J.; Colwell, L. F., Jr.; Habulihaz, B.; He, H.; Leiting, B.; Lyons, K. A.; Marsilio, F.; Patel, R. A.; Teffera, Y.; Wu, J. K.; Thornberry, N. A.; Weber, A. E.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4763.
6. Leiting, B.; Pryor, K. D.; Wu, J. K.; Marsilio, F.; Patel, R. A.; Craik, C. S.; Ellman, J. A.; Cummings, R. T.; Thornberry, N. A. *J. Biochem.* **2003**, *371*, 525.
7. Lankas, G. R.; Leiting, B.; Sinha Roy, R.; Eiermann, G. J.; Beconi, M. G.; Biftu, T.; Chan, C.-C.; Edmondson, S.; Feeney, W. P.; He, H.; Ippolito, D. E.; Kim, D.; Lyons, K. A.; Ok, H. O.; Patel, R. A.; Petrov, A. N.; Pryor, K. A.; Qian, X.; Reigle, L.; Woods, A.; Wu, J. K.; Zaller, D.; Zhang, X.; Zhu, L.; Weber, A. E.; Thornberry, N. A. *Diabetes* **2005**, *54*, 2988.
8. 3-Amino-4-(aminomethyl)pyridine was prepared from 4-ethoxy-3-nitropyridine by analogy to the literature preparation of 3,4-diaminopyridine: Campbell, J. B.; Greene, J. M.; Laragnino, E. R.; Gardner, D. N.; Pike, A. J.; Snoddy, J.; Taylor, E. C. *J. Heterocycl. Chem.* **1986**, *23*, 669.
9. Jones, B. G.; Branch, S. K.; Thompson, A. S.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2685.
10. Khanna, I. K.; Weier, R. M. *Tetrahedron Lett.* **1991**, *34*, 1885.
11. Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.
12. Habermehl, G. G.; Ecsy, W. *Heterocycles* **1976**, *5*, 127.
13. Zhao, S.; Ghosh, A.; D'Andrea, S. V.; Freaman, J. P.; VonVoigtlander, P. F.; Carter, D. B.; Smith, M. W.; Blinn, J. R.; Szmuszkovicz, J. *Heterocycles* **1994**, *39*, 163.
14. Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
15. Dauwe, C.; Buddrus, J. *Synthesis* **1995**, 171.
16. Matsuda, K.; Yanagisawa, I.; Isomura, Y.; Mase, T.; Shibanuma, T. *Synth. Commun.* **1997**, *27*, 2393.
17. Zimmerman, S. C.; Cramer, K. D.; Galan, A. A. *J. Org. Chem.* **1989**, *54*, 1256.
18. Kowalchick, J. E.; Leiting, B.; Pryor, K. D.; Marsilio, F.; Wu, J. K.; He, H.; Lyons, K. A.; Eiermann, G. J.; Petrov, A.; Scapin, G.; Petel, R. A.; Thornberry, N. A.; Weber, A. E.; Kim, D. *Bioorg. Med. Chem. Lett.*, in press. doi:10.1016/j.bmcl.2007.07.100.