



**Trip Report:  
Annual Meeting of American Chemical Society  
Washington, D.C.  
August 28 – September 1, 2005**

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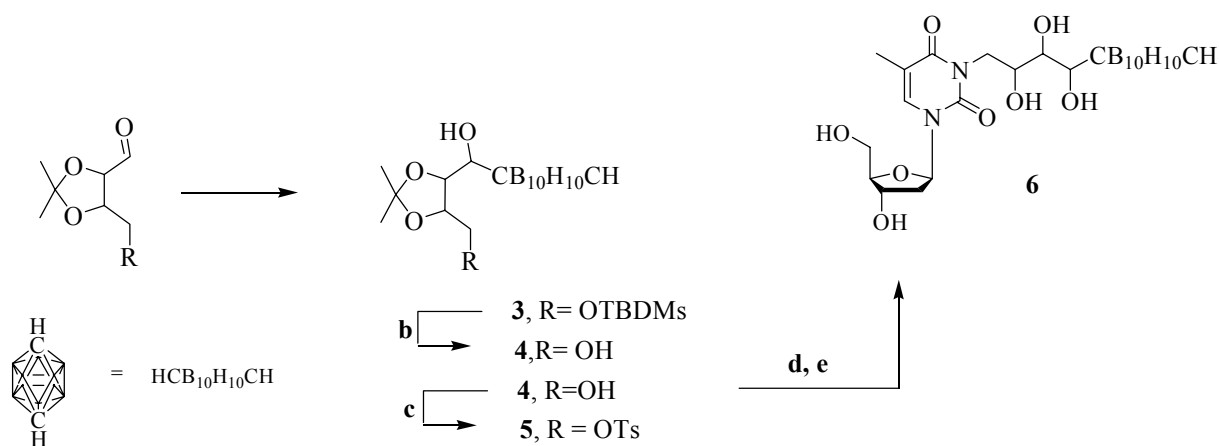
***Abstract:** Annual Meeting of American Chemical Society was held August 28-September 1, 2005 in Washington, DC. This symposium covered a variety of problems in all fields of modern chemistry. This report highlights select material from the seminars presented at the conference.*

## “Hydrophilic 3-Carboranyl Thymidine Analogues (3CTAs) for Boron Neutron Capture Therapy (BNCT),”

S. Naraynasamy, B. T. S Thirumagal, J. Johnsamuel, C. Carnrot, A. S. Al-Madhoun, G. Y. Cosquer, Y. Byun, A. K. Bandyopadhyaya, S. Eriksson, W. Tjarks (Ohio State University), Columbus, Ohio; (Swedish University of Agricultural Sciences) Uppsala, Sweden; (University of Ottawa, Heart Institute) Ottawa, Canada.

BNCT is a chemo-radio therapeutic method for treatment of cancer. The principal of the method is based on capture of thermal neutrons by atom of  $^{10}\text{B}$ . This capture produces cytotoxic alpha-particles ( $\text{He}^2$ ),  $\text{Li}^7$  and  $\gamma$ -quant. The energy of  $\gamma$ -quant is relatively low (about 17%), therefore the tumor is mainly affected by interaction with alpha-particles and a nuclei of  $^7\text{Li}$ . The big advantage of this process is that both particles have path length  $\sim 10\ \mu\text{m}$  which is close to the cell diameter. Also boron atoms have a capture diameter for heat neutrons 4-7 fold higher than carbon, nitrogen, oxygen and hydrogen atoms normally found in cells. For success of the BNCT method the crucial issue is transport of boron containing compound into tumor cells. Tumor cells contain elevated levels of cytosolic thymidine kinese-1 (TK1) compared to quiescent cells. It was suggested that 3CTAs could be excellent carriers of boron to the tumor cell due to their metabolic potential for incorporation into tumor cells. The key step is phosphorylation of 3CTAs by TK1 to the corresponding monophosphates, which will be trapped inside tumor cells. Further phosphorylation to the di- and triphosphates incorporation into tumor cell DNA could lead to localization of boron-containing units in close proximity to DNA, the most critical target for  $^2\text{He}$  and  $^7\text{Li}$  ions. The synthesis of various types of 3CTAs containing an additional nucleoside moiety and acyclic alcohol functions is presented on Schemes 1 and Scheme 2.

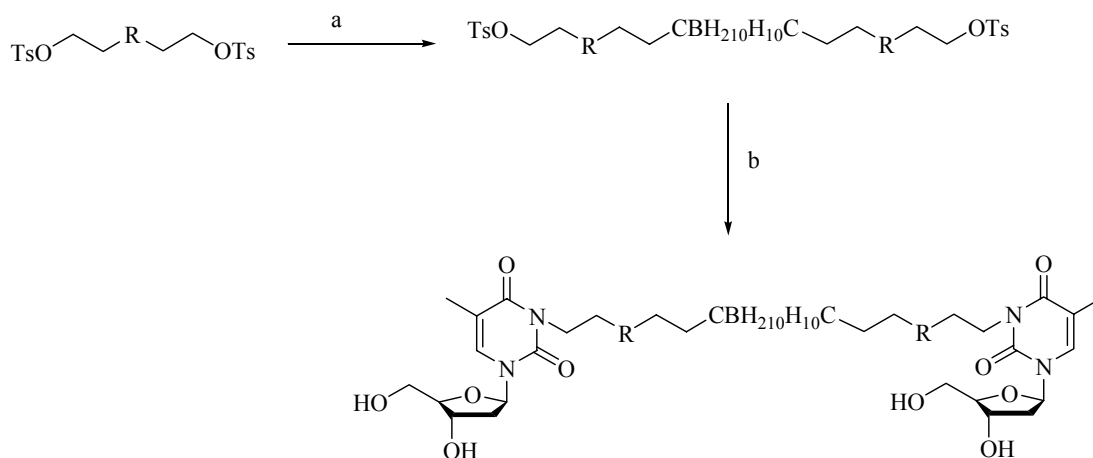
**Scheme 1**



p-carborane

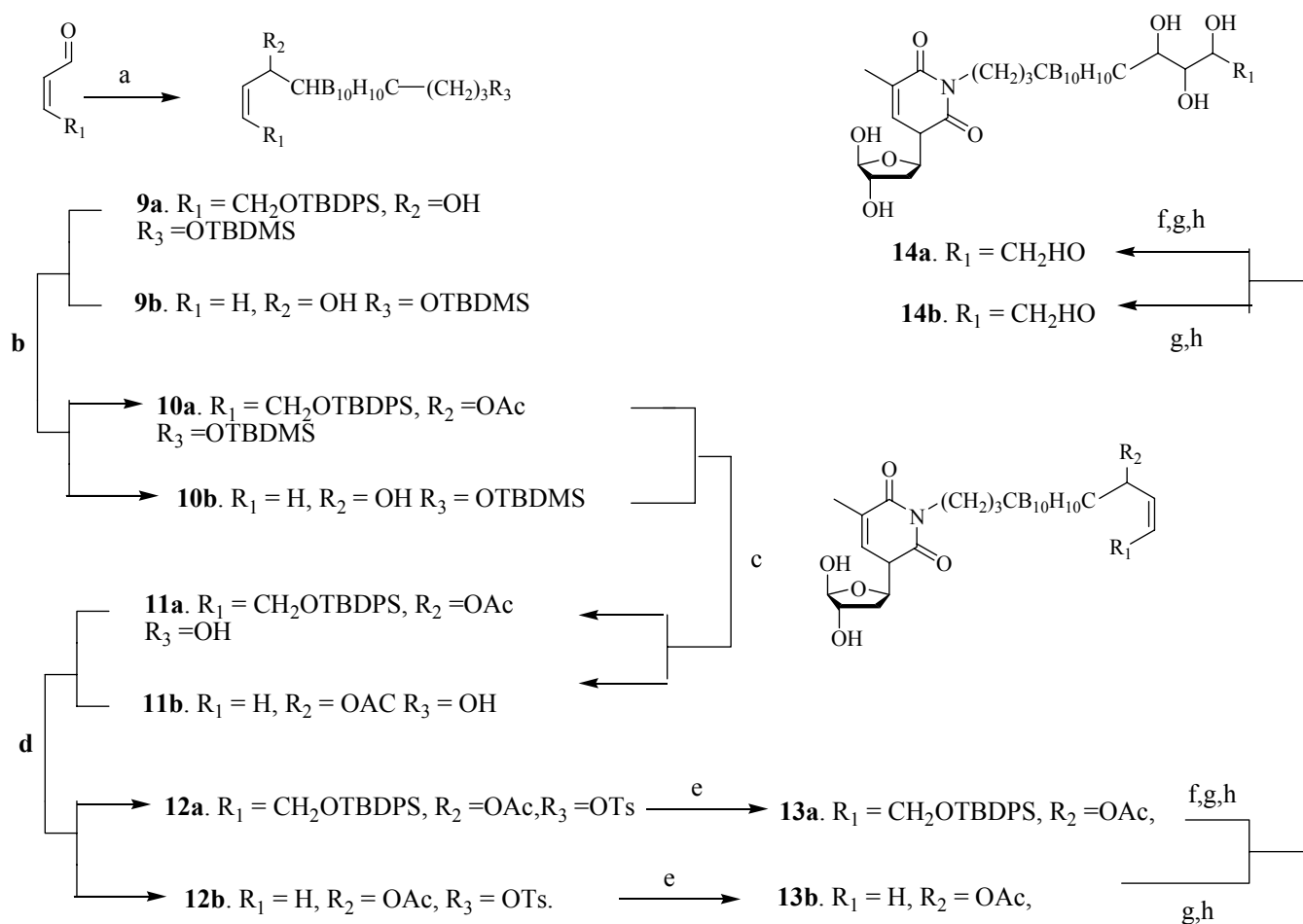
Conditions: a: p-carborane/ $\text{BuLi}$ / $\text{THF}$ , 12 h, 85%; b:  $\text{TBAF}$ / $\text{THF}$ ,  $-78\ ^\circ\text{C}$ , 95%; c:  $\text{TsCl}$ / $\text{Py}$ / $\text{DCM}$ , 12 h, 55%;  $\text{Thdk}/\text{K}_2\text{CO}_3/\text{acetone}/\text{DMF}$ , 75%; e: 17%  $\text{HCl}$  in methanol, 14 h, RT, 65%.

**Scheme 2**



Conditions: a: p-carborane/BuLi/THF, 12 h, 85%; b: Thdk/K<sub>2</sub>CO<sub>3</sub>/acetone/DMF, 24-48 h, 50 °C, 75 %;

## Scheme 3



Conditions: a: 1-(tert-Butyldimethylsilyloxy)-3-(p-carboran-1-yl)propane, BuLi/THF, RT, 12h, 60%; b: AcCl/pyridine/DCM, 3h, RT, 85%; c: CCl<sub>4</sub>/MeOH, ultrasonic bath, 10 h, 80%; d:

TsCl/Py/DCM, 12 h, 80%; e: Thdk/K<sub>2</sub>CO<sub>3</sub>/acetone/DMF, 24-48 h, 50 °C, 60%; f: TBAF/THF, -78 °C, 70 %; g: MeOH, K<sub>2</sub>CO<sub>3</sub>, RT, 78%; h: OsO<sub>4</sub>, acetone/water, RT, 12h, 75%.

The relative TK1 phosphorylation rates of 3CTAs were determined and results are presented in the Table 1.

**Table 1. Relative TK1 Phosphorylation rates of 3CTAs**

Compound	Relative phosphorylation rates (%)
THd	100
14a	47
14b	61
6	65
19	4
20	15

It was found that compounds **6**, and **14a,b** are good substrates for TK1, which is over expressed in most tumors. The superior substrates activity of 3CTA with multiple hydroxyl groups indicates that hydrophilicity is essential for phosphorylation by TK1.

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#### **“SAR for a Novel Series of Indazole and Indole Ureas as TRPV1 Antagonists,”**

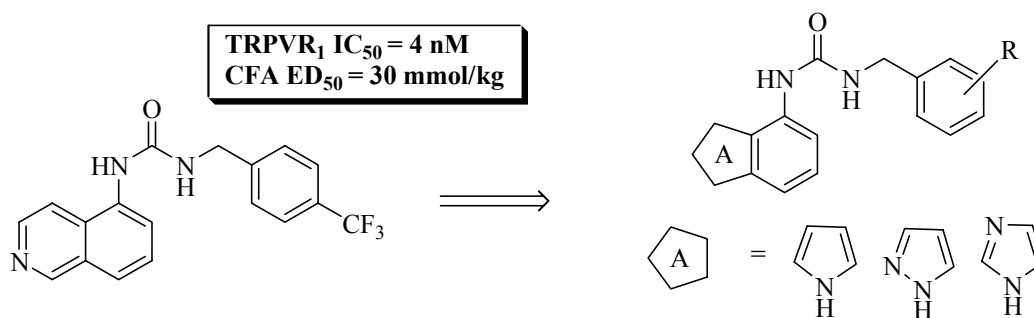
*Irene Drizin, Arthur Gomtsyan, Erol K. Bayburt, Richard Perner, Stanley DiDomenico, John R. Koenig, Heath McDonald, Prisca Honore, Carol T. Wismer, Kennan C. Marsh, Jill Wetter, Michael F. Jarvis, Connie R. Faltynek, Chih-Hung Lee (Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories), Abbott Park, Illinois.*

The capsaicin sensitive TRPV1 receptor is a member of the mammalian transient receptor potential (TRP) channel family and is highly expressed on small diameter (C-fiber) nociceptive sensory neurons. It is also expressed at lower levels in other non-neuronal tissues such as skin and bladder. This receptor has been called a polymodal detector of noxious stimuli since it can be activated in several ways. Low pH, heat, and naturally occurring ligands such as capsaicin and resiniferotoxin activate TRPV1 causing a burning pain sensation.

Interest in the TRPV1 receptor as a therapeutic target can be supported by the fact that “knock-out” mice lacking this receptor did not develop thermal hyperalgesia after acute inflammation. Until recently, agonists were the major focus of research due to the analgesic effect resulting from receptor desensitization, but use of such agents was compromised by the fact that they cause an initial burning effect. Attempts to separate analgesic and excitatory effects were unsuccessful. To avoid this problem there is a significant interest in the development of competitive TRPV1 antagonists as therapeutic agents for pain.

Authors recently published an article devoted to identification of TRPV1 antagonists among a series of 6,6 fused heteroaromatic ureas<sup>1</sup>. Presented work described the replacement of 6,6-fused heteroaromatic rings with 5,6-heteroaromatic rings, such as indole, indazole and benzimidazole, (Figure 1).

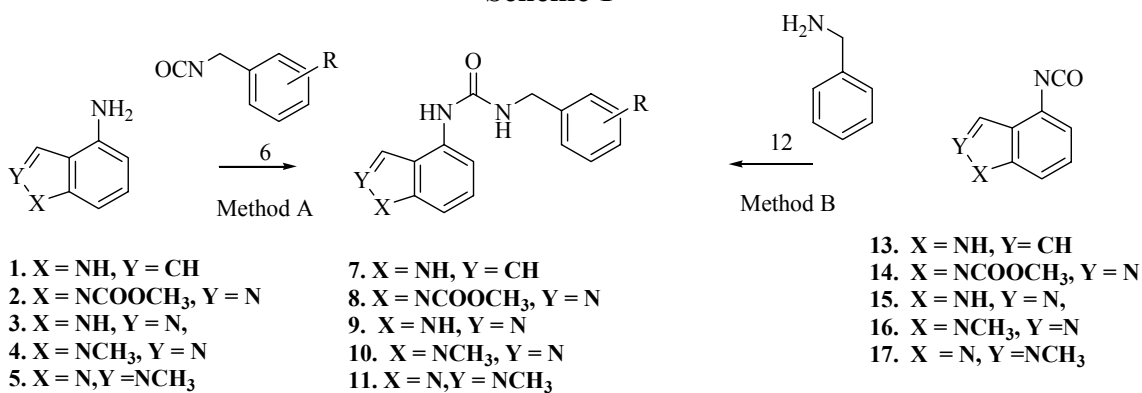
Figure 1



The synthesis of urea derivatives was accomplished either via method **A** (Scheme 1) where the aminoindole **1** or aminoindazoles **2-5** were reacted with the various commercially available isocyanates **6**. Reaction of 4-aminoindazoles **3** with isocyanates **6** resulted in a mixture of products, generated by the addition of isocyanate to the nitrogen of the ring. To circumvent it, the urea formation was carried out on the protected indazole **2**.

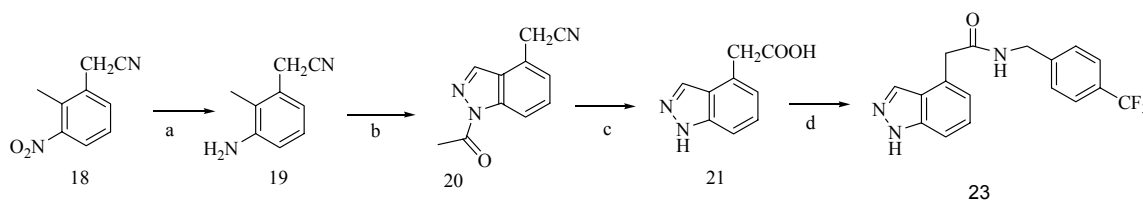
Method **B** (Scheme 1) entailed the utilization of the isocyanates **13-17** prepared by the reaction of the corresponding heterocyclic amines with 20% phosgene solution in toluene. The isocyanates **13-17** were subsequently reacted with the corresponding amines **12**, that were either available commercially or synthesized by literature procedures to form the ureas **7-11**.

Scheme 1



Urea linker replacement required synthesis of indazole **21** (Scheme 2) and indole **22** carboxylic acids. They were converted to the corresponding amides **23** and **24** by standard coupling methods. The carbamate **25** was formed by the reaction of indole isocyanate **13** with the corresponding alcohol.

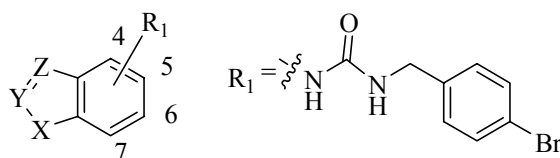
Scheme 2



Conditions: a: NaBH<sub>4</sub>, BiCl<sub>3</sub>, EtOH, rt 1h; b: isoamylnitrite, (CH<sub>3</sub>CO)<sub>2</sub>O, CH<sub>3</sub>CN, 80°C, 16 h;  
c: NaOH, H<sub>2</sub>O<sub>2</sub>, CH<sub>3</sub>CN, reflux 16h; d: EDCI, HOAT, THF, rt.

The activity of synthesized compounds in vitro and in vivo was determined. Results obtained for in vitro activity are presented in Tables 1 and 2.

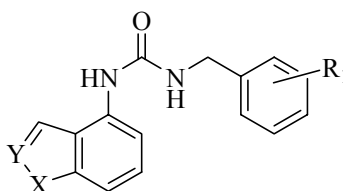
**Table 1. SAR of Heterocyclic Ureas Regioisomers**



Compound	Point of Attachment for R <sub>1</sub>	X	Y	Z	IC <sub>50</sub> (nM)
<b>26</b>	4	NH	CH	CH	0.11
<b>27</b>	5	NH	CH	CH	5.85
<b>28</b>	6	NH	CH	CH	> 10
<b>29</b>	7	NH	H	CH	0.18
<b>30</b>	4	NH	N	CH	0.013
<b>31</b>	5	NH	N	CH	3.54
<b>32</b>	4	N	NCH <sub>3</sub>	C-CH <sub>3</sub>	1.47
<b>33</b>	4	N-CH <sub>3</sub>	N	CH	0.076
<b>34</b>	4	N	NCH <sub>3</sub>	CH	1.39
<b>35</b>	4	NH	CH	N	2.47

The results from Table 1 clearly show that the attachment of urea moiety is very important for retention of potency. 4-Substituted ureas are clearly the most preferred compounds. Indoles and indazoles are the preferred 5,6 fused heterocycles, as benzimidazole (**35**) was a very weak compound. Indazole **30** is 10-fold more potent than the analogous indole **26**. Introduction of methyl groups is tolerated only in the 1-position (**33** versus **34**). Addition of a second methyl group on the indazole core leads to loss of activity (**32**).

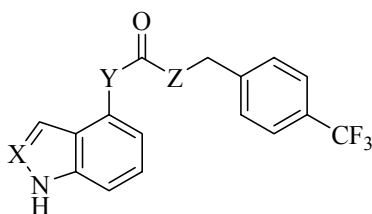
**Table 2. SAR of Indole and Indazole Ureas**



Compound	X	Y	R1	IC50 (nM)

26	NH	CH	4-Br	0.11
36	NH	CH	3,4-diCl	0.22
37	NH	CH	4-CF <sub>3</sub>	0.059
38	NH	CH	4-OCF <sub>3</sub>	0.084
39	NH	CH	3-F, 4-CF <sub>3</sub>	0.038
40	NH	CH	4-Cl, 3-CF <sub>3</sub>	0.07
41	NH	CH	4-Cl	0.15
42	NH	N	3,4-diCl	0.021
30	NH	N	4-Br	0.012
43	NH	N	4-CF <sub>3</sub>	0.009
44	NH	N	4-OCF <sub>3</sub>	0.011
44	NH	N	3-OCF <sub>3</sub>	0.046
45	NCH <sub>3</sub>	N	4-OCF <sub>3</sub>	0.035
46	NCH <sub>3</sub>	N	4-chloro	0.062
47	NCH <sub>3</sub>	N	4-fluoro	0.72
48	NCH <sub>3</sub>	N	3,4-diCl	0.12

**Table 3. SAR of Urea Replacement**



Compound	X	Y	Z	IC <sub>50</sub> (nM)
23	N	CH <sub>2</sub>	NH	10.2
24	CH	CH <sub>2</sub>	NH	0.52
25	CH	NH	O	0.94

The results presented in Table 2 indicate that large electron withdrawing groups in the 4 or 3,4-position are the preferred substituents as was previously discovered for 6,6 fused analogs. Indazoles consistently display higher potency than indoles. Methyl-substituted indazoles are only slightly less potent than desmethylated analogs.

The data from Table 3 demonstrates the importance of the urea linker for activity and shows that replacement of the urea with an amide group leads to 5-fold less active compounds in the indole case (**24**) and total loss of activity in indazole series (**23**). Carbamate **25** was found to be significantly less potent than the corresponding ureas.

The most potent of the indole and indazole ureas were evaluated *in vivo* for their activity in animal pain models. It was found that compounds **37**, **39**, **42** and **43** reduced thermal hyperalgesia in the CFA (complete Freund's adjuvant) model of chronic inflammatory pain. Also compound **42** was

tested in several pain models upon oral administration and demonstrated activity in all of them. The best effects were observed in the (CFA) inflammatory and visceral pain models.

1. Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koenig, J. R.; Turner, S.; Jinkerson, T.; Drizin, I.; Hannick, S. M.; Macri, B. S.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J.; Stewart, K. D.; Oie, T.; Jarvis, M. F.; Surowy, C. S.; Faltynek, C. R.; Lee, C. H. *J. Med. Chem.* **2005**, *48*, 744-752.

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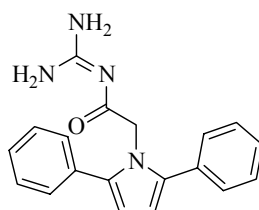
### “Acylguanidines as a small molecule BACE1 inhibitors: exploration of S1 pocket,”

*P. Zhou, R. Chopra, J. Condon, D. Cole, R. Cowling, K. Y. Fan, Y. Hu, L. Jennings, G. Jin, W. Liu, F. Lowering, M. Malamas, E. Manas, K. Morris, A. J. Richardson, M. Suhkhdeo, J. Turner, E. Wagner, J. Wu, J. Bard (Chemical and Screening Sciences and Neurosciences, Wyeth Research), Princeton, New Jersey.*

It is known, that Alzheimer’s disease could be attributed in part to the aggregation and neurotic properties of amyloid  $\beta$ -peptide-42 ( $A\beta$ -42) in the brain.  $A\beta$ -42 is produced by sequential processing of the amyloid precursor protein (APP) by two proteases  $\gamma$ - and  $\beta$ -secretases. The novel aspartyl protease BACE1 has been identified as enzyme responsible for processing APP at  $\beta$ -secretase cleavage site. The goal of reported study was to develop small molecule to inhibit  $A\beta$ -42 production.

Compound WY-25105 (Figure 1) was found to be active inhibitor with  $IC_{50} = 3.7 \mu M$ .

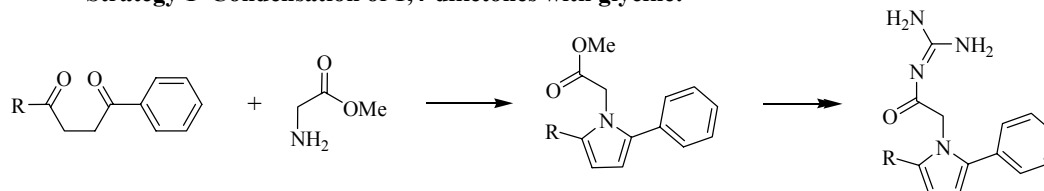
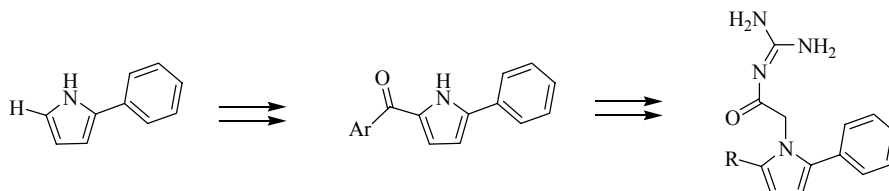
**Figure 1**



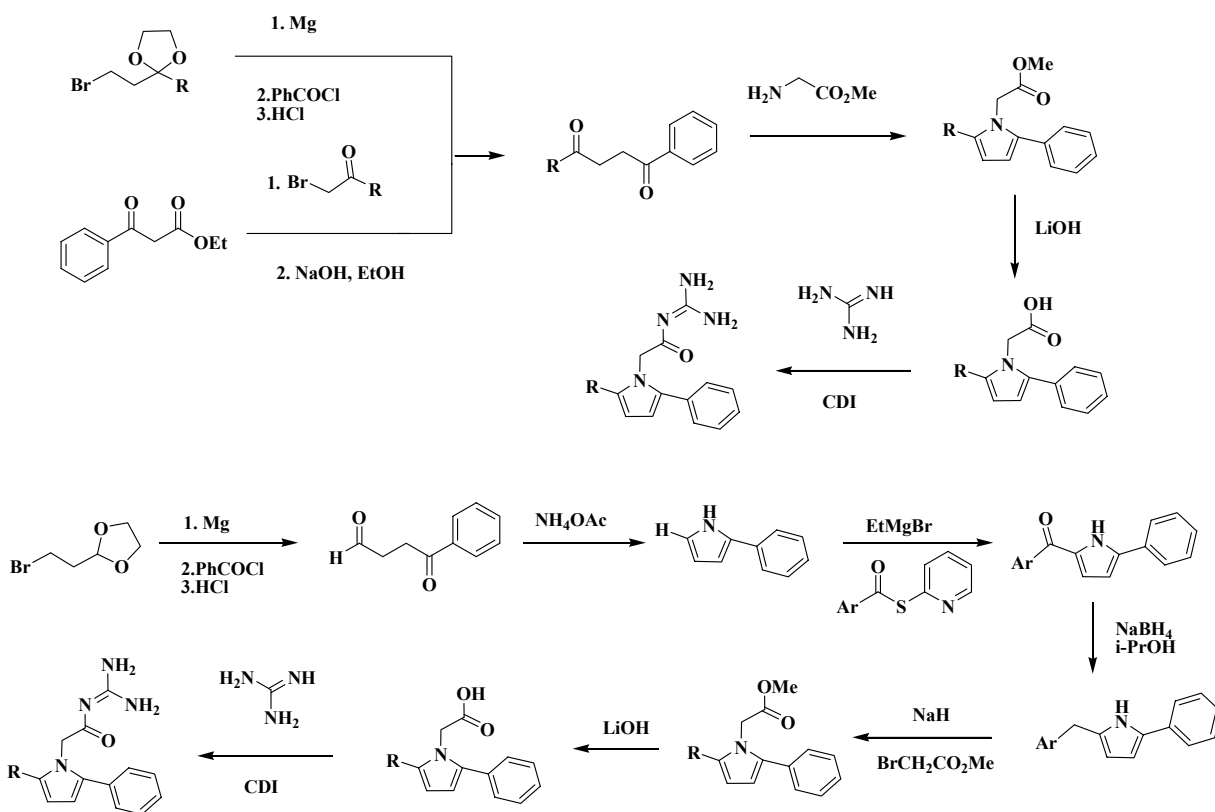
WY-25105

The main idea to design active compounds for exploring the hydrophobic S1 pocket included replacement 2-phenyl group with more hydrophobic substituents. The author proposed two synthetic strategies for synthesis of WY-25105 analogs (Scheme 1).

**Scheme 1**

**Strategy 1 Condensation of 1,4-diketones with glycine:****Strategy 2. Derivatization from 2-phenyl pyrrole:**

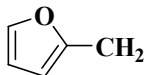
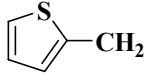
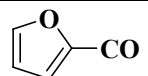
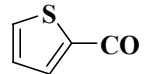
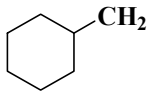
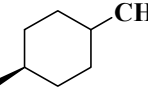
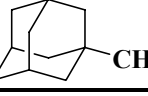
WY-25-105 Analogs were prepared in accordance with Scheme 3.

**Scheme 3**

The activity of prepared analogs is presented in Table 1.

**Table 1**

R	IC <sub>50</sub> (μM)
Ph	3.7
Me	76

PhCH <sub>2</sub>	22
	24
	80 @ 50 μM
PhCO	19
	22
	18
	4.9
	2.0
	0.6

The results show that replacement of 2-phenyl with an adamantly group increased activity ~ 5 fold. This finding supported the original hypothesis of the importance of hydrophobic interactions at the S1 pocket for high affinity.

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### “A-784168, A Novel TRPV1 Receptor Antagonist as Analgesic Agent,”

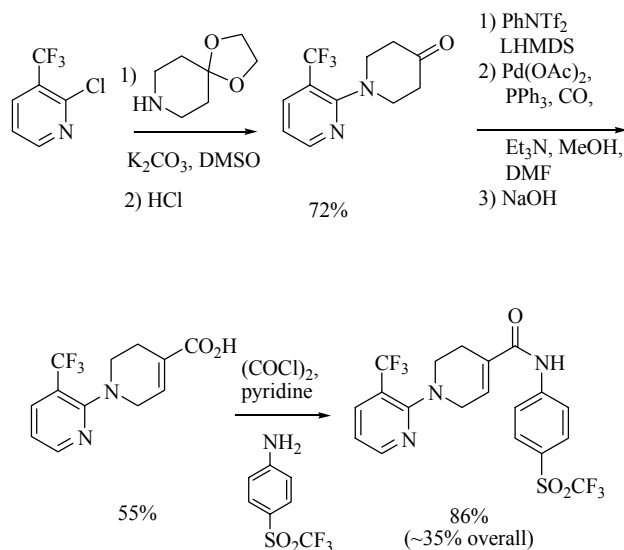
Brian Brown, Guo Zhu Zheng, Robert G. Schmidt, Ryan Keddy, John R. Koenig, Tammie Jinkerson, Heath McDonald, Minglei Cui, Marie Honore, Kennan Marsh, John Darbyshire, Carol Suowy, Robert Moreland, Michael Jarvis, Connie Faltynek and Chih-Hung Lee (Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories), Abbott Park, Illinois.

The presented work was devoted to *in vitro* studies, SAR studies of A-784168 analogs as TRPV1 receptor antagonists. The main goal was to reduce nociception in models of chronic inflammatory pain.

Nociceptors are primary sensory afferent (C and A $\delta$  fibers) neurons that are activated by a wide variety of noxious stimuli including chemical, mechanical, thermal, and proton (pH < 6) modalities. 1,2-Capsaicin activates primary sensory fibers via a specific cell surface capsaicin receptor, cloned as vanilloid receptor 1 (TRPV1). The TRPV1 receptor has been called a “polymodal detector” of noxious stimuli since it can be activated in several ways. The TRPV1 receptor channel is activated by capsaicin and other vanilloids and thus is classified as a ligand-gated ion channel. The TRPV1 channel can also be activated by protons. Under conditions of mild acidity (pH 6-7), the affinity of capsaicin for the receptor is increased, while at pH <6 direct activation of the channel occurs.

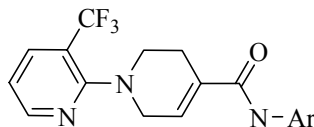
The synthesis of tested compounds is presented on Scheme 1.

**Scheme 1**



The results of SAR study are presented in Table 1.

**Table 1**  
**SAR studies A-784168**



Ar	IC50	F (%)	Cl	Ar	IC50	F (%)	Cl
	2100	NT	NT		23	33	27
	8	2	382		43	2	315
	21	NT	100		53	NT	NT
	21	2	221		3100	NT	NT

IC50 (nM); F% (oral); Cl (rat): ml/min/mg

Based on the data from Table 1 the authors concluded that varying lipophilic substitutions yielded improved *in vitro* potency but decreased oral bioavailability. This observation was corroborated by the short half lives in a microsomal stability assay, and it was confirmed that they were mainly metabolized through a first pass metabolism pathway. From the results, a trifluoromethylsulfonyl group at the 4-position provided adequate rat microsomal stability and yielded higher oral bioavailability.

It was found that A-784168 is a novel, potent, TRPV1 receptor antagonist that is orally effective at relieving nociception in a spectrum of well characterized animal models of pain, including acute and chronic inflammatory pain. The evaluation of A-784168 in these diverse pain models significantly expands the antinociceptive profile for selective TRPV1 antagonists.